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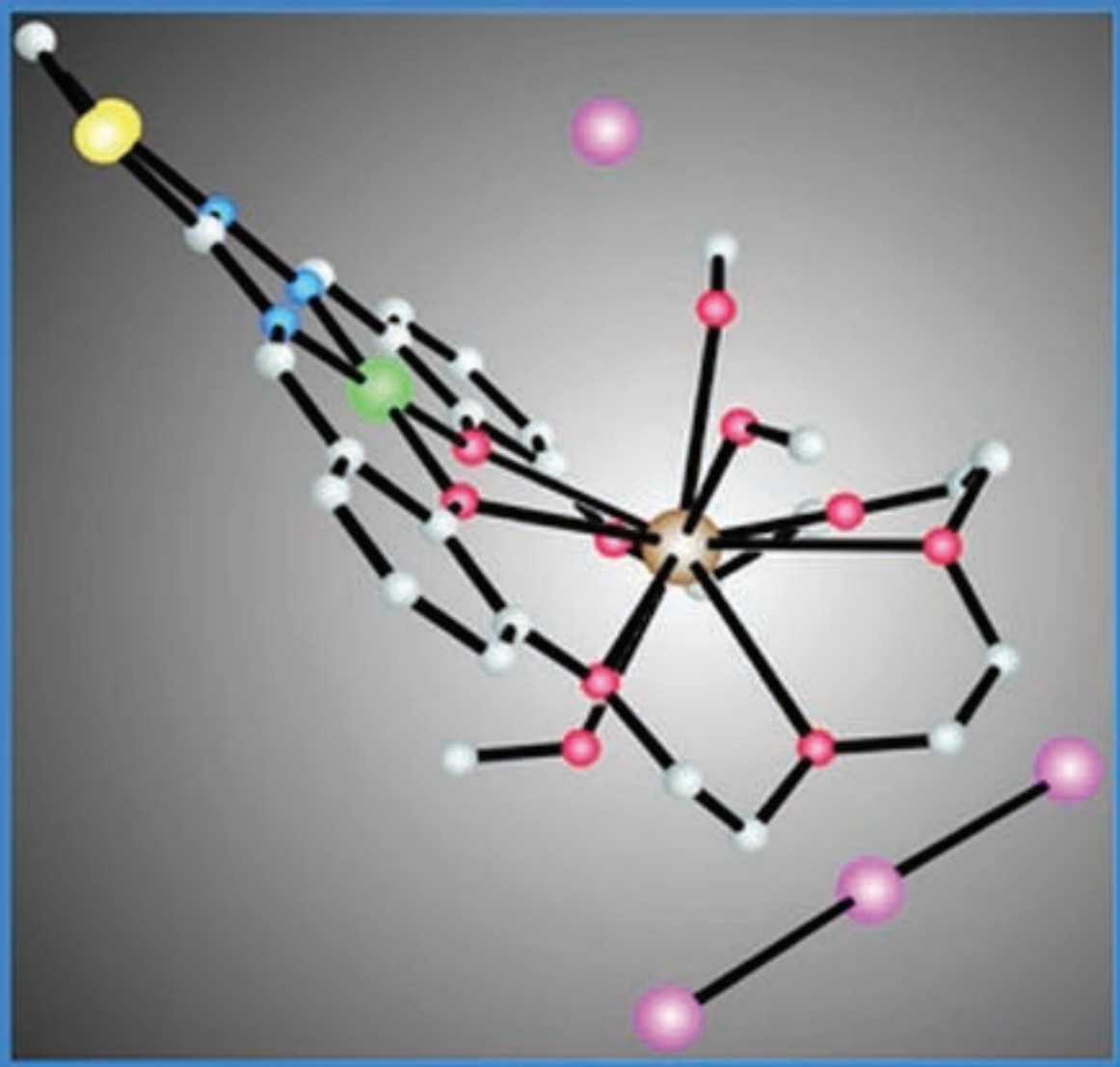

Nicolai V. Gerbeleu
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Preface

The synthesis of substances or creation of molecules by means of chemical transformations is the basis of progress in almost all domains of chemistry. The level of chemical understanding in any epoch, as well as practical scientific achievements, depend on what substances can be obtained and what properties they have. The modern facilities available to science, including apparatus, instruments, devices and methods of studying matter and its properties, tend to overshadow the importance of synthesis. Moreover, obtaining compounds and materials with predefined properties depends significantly on the power of the synthetic tools deployed.

Since the mid 1960s the employment of template processes (reactions on matrices) has been of great significance. They allow us to obtain compounds that are difficult or even impossible to synthesise from their components by traditional methods. In particular, template reactions provide the basis of the synthesis of macroheterocyclic compounds, whose systematic preparation, wide research investigation, and applications are well-known. The features of the template synthesis of macrocyclic systems have been discussed in various aspects and to different extents in various monographs and reviews. However, the fast development of this fascinating area of synthetic chemistry has provided new results, which are related to the theory and practice of template synthesis itself and which need special consideration and generalisation.

This book describes template processes, their mechanisms, the 'centres' used for their realisation, and the basic classes of compounds synthesised by means of these reactions. Detailed consideration is given to ways of constructing macrocyclic systems. The main classes of substances examined are polyazamacrocyclic compounds, crown ethers and their hetero-analogues, and other products such as cryptands, sepulchrates, sarcophagines, catenanes, rotaxanes and knots. The conditions for carrying out such reactions, which are sometimes very specific in character, are also considered. Taking into account the recent achievements in the field of the template processes, the trends of research in this domain have been analysed.

It is a particular pleasure to acknowledge our colleagues, who have contributed in one way or another to this work. We wish particularly to thank Dr. V.N. Cebotari and V.G. Levitsky for technical assistance and S.A. Kostyuk for helping us to produce the text.

We should like to express our special gratitude to Professor K.B. Yatsimirskii and Dr. Ya.D. Lampeka from the Institute of Physical Chemistry of the Ukrainian Academy of Sciences for their advice and assistance during the period of writing. Special thanks go to many colleagues from different countries for kindly making available their recent research results. They are too numerous to name individually. We have tried to incorporate these works into our book. V.A. is greatly indebted to Professor M.T. Reetz of Max-Planck-Institut für Kohlenforschung who was an excellent host during the sabbatical in 1998, where the work on the manuscript was concluded and to the Alexander von Humboldt foundation for financial support. Where structural data have been presented, we wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury.

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John Burgess

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Chapter 1

Template processes

1.1 Introduction

The various aspects of template synthesis of macrocyclic compounds have been discussed in a series of monographs and reviews [1–21]. However, there is no strict definition of what can be called a template reaction. A synthetic chemist who takes advantage of the template effect in synthesis will have his own view of what constitutes a template process. It is therefore appropriate to commence here with a general definition, which is that the template effect is the enhancement of chemical reaction by complementary surfaces [22, 23]. One of the first examples was connected with the discovery of the double helix structure of DNA (Figure 1-1) by Watson and Crick in 1953 [24]. The template effect is operative in its replication. Each chain of the DNA double helix serves as template, or mould, for the formation of the second chain.

"A chemical template organises an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms." [16]. A mechanistically simple S_N2 alkylation of an amine (L1) by an alkyl halide (L2) in the presence of a template is shown in Scheme 1-1 [25]. In the first step of this templated synthesis the template binds simultaneously two substrates via hydrogen bonding, placing the reactive functionalities in close proximity to each other, so that their interaction becomes possible. This results in a new product appearing due to formation of a C–N bond. It remains temporarily bonded to the mould, and the dissociation of the complex gives the template-free product. The template can be then used again in later synthetic cycles. This is a general illustration of the template effect operating in a chemical reaction.

In this book we do not embrace the topic in a very broad sense. Rather, our aim is to try to show the exploitation of the template effect in a specific field – macrocyclic chemistry.

Macrocyclic compounds, various classes of which have been known for a long time, have attracted great attention in respect of the synthesis, physico-chemical and physical investigation of various new representatives of these substances. The search for applications has solved or made it possible to solve many significant

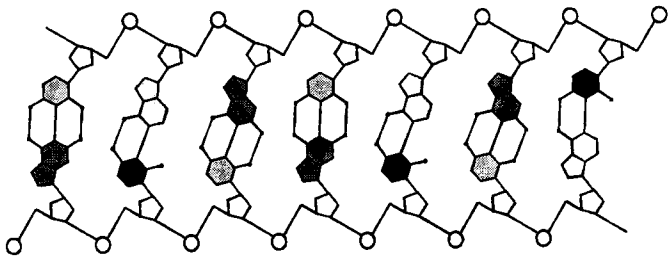


Figure 1-1. Schematic representation of the complementary strands in the double helix structure of DNA.

practical tasks in different fields of science and engineering (e.g. chemistry, electrochemistry, biophysics, metallurgy, catalysis, preparative organic synthesis, medicine, agriculture and ecology) [1, 4, 13].

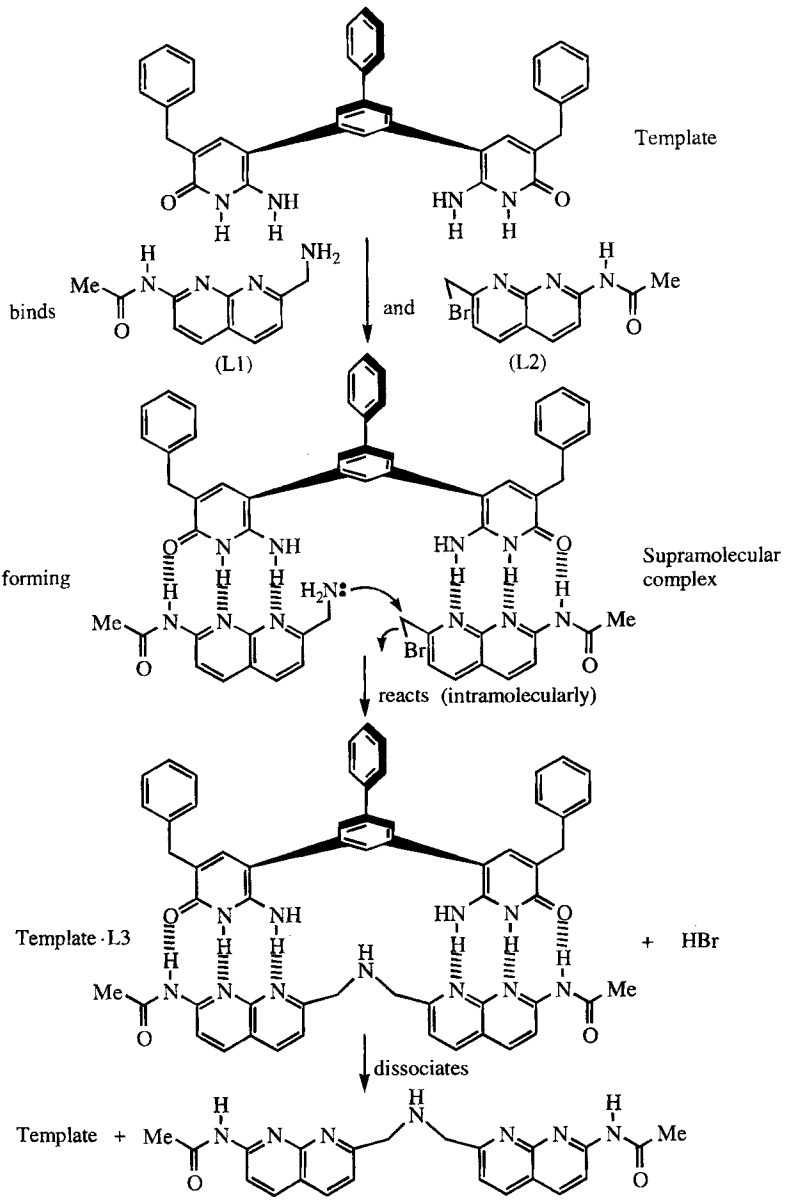
The use of template effects in the synthesis of new compounds was first demonstrated by the pioneering work of Busch, on metal template effect exploration in the synthesis of macrocyclic compounds in the 1960s. This then led to the renaissance of the chemistry of macrocyclic compounds in general. It is not an overstatement to say that the emergence of supramolecular chemistry, whose importance in life processes cannot be overestimated, was largely due to the exploration of template methodology. It is sufficient to remember that in the serendipitous discovery of Pedersen's crown polyethers, actively used in host–guest chemistry, the template effect of alkali metal ions played a paramount role. Moreover, self-assembly, as another conceptual category in supramolecular chemistry, can be considered as an extension of the template effect in both chemistry and biology.

As the discussion will focus mainly on metal template processes, the following definition of template processes seems to be appropriate:

Template processes are those in which the metal ion, or another centre that has a definite stereochemistry and electronic state, serves as a mould, pattern, form, or matrix for forming, from appropriate building blocks, reaction products whose synthesis is either difficult or totally impossible under other conditions [2, 11]. Put another way, template reactions may be called the transformations in which the interaction of initial ligands is either conditioned or considerably facilitated by their suitable spatial orientation as a result of coordination. This is dictated by the metal ion, or another centre, by its organising and sequestering role as well as by its effect on reactivity.

In addition, template synthesis has an advantage over other methods in that, in the majority of cases, it leads to the appearance of additional metallocycles and, in the process, to the tailoring of these metallocycles.

It is well known [26, 27] that coordination of one bidentate ligand to a metal ion is energetically more advantageous than the coordination of two monodentate ligands with analogous donor atoms, due to formation of a chelate or metallocyclic ring. This phenomenon is known as the **chelate effect** [28]. Moreover, in a series of related compounds, stability constants increase with an increase in the number of



Scheme 1-1. Template S_N2 alkylation of an amine by an alkyl halide.

chelate rings. In turn, the greater stability observed for the complexes of cyclic ligands, over those of open-chain analogues of similar structure, has been termed the **macrocyclic effect** [29]. Stability constants increase by several orders of magnitude on going from mono- to bidentate ligands, with further enhancement of the stability of cyclic ligand complexes over their linear counterparts [29–31]. The stability constants of metal complexes with crown ethers also appear to be several orders of magnitude higher in comparison with their corresponding open-chain analogues. As with the chelate effect, the macrocyclic effect manifests itself to a different degree, depending upon the nature of the metal as well as upon the nature, number and arrangement of donor atoms and other parameters of the macrocycle. The physico–chemical factors at the basis of the macrocyclic effect have been examined thoroughly in a series of sources [1, 32].

The use of template synthesis procedures makes it possible to carry out a wide range of reactions of either a stoichiometric or a catalytic nature. In all cases this pathway facilitates the preparation, from simple starting blocks, of more complex organic compounds, which are as a rule isolated as coordination compounds of the metal centre used as template. It should be emphasised that the use of template processes constitutes the basic strategy for the synthesis of macrocyclic compounds with nitrogen donor atoms, as well as of a number of crown ethers and of other cyclic systems containing various donor atoms. This is because, when building macrocyclic systems by non-template procedures, the entropy of the condensing fragments, related to the decrease of the number of rotational and vibrational degrees of freedom, decreases markedly. As a result the probability of formation of the cyclic products is reduced. In contrast, in the presence of the template, the starting ligands are coordinated. This results in a preliminary entropy lowering, which facilitates the following stages necessary for the final assembly of the macrocyclic product [4, 33, 34]. At present the reactions on matrices are so dominant in the synthesis of macrocyclic compounds, that in cases where the latter are obtained without using the template effect, the authors make special mention of this fact [5].

1.2 Fundamental terms and notions

The term "template" has been widely used since 1964 [35]. Daryle Busch introduced the template notion in coordination chemistry in 1963 [36]. Since 1968 the synonym of this term – matrix – has also been widely used [2, 10, 37]. The concept of a template or mould first appeared in 1953 in molecular biology, which, in turn, had borrowed the term from engineering (polygraphy, punching). It is worth noting that "template" in the *Oxford English Dictionary* is defined as "an instrument used as a guide in bringing any piece of work to the desired shape". Matrix, as a synonym of template, is also used in many other languages.

In the literature devoted to template synthesis several specific terms and expressions are used. Some have become generally accepted while others, though not as

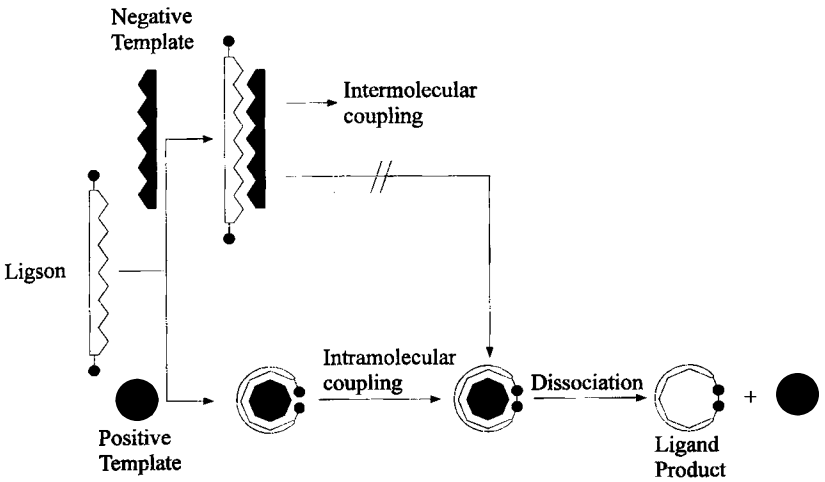


Figure 1-2. Schematic illustration of positive and negative template effects in directed synthesis of chemical species.

widely used, are necessary for the following discussion on the synthesis of macrocyclic systems, e.g. [1, 4, 38–42]:

- **Template centre** (template, matrix, mould, form, model, pattern) – the metal ion or another particle (molecule, anion) which can orientate and activate the ligands for their subsequent interaction.
- **Positive template** – a template which brings together the reactive end groups of a molecule (molecules) facilitating intramolecular coupling.
- **Negative template** – template which prevents the reactive end groups of a molecule (molecules) coming together suppressing intramolecular coupling and favouring intermolecular reactions. A schematic illustration of both kinds of templating is shown in Figure 1-2 [42].
- **Template bonds** – forces by means of which the corresponding template orients (and/or activates) the reacting ligands, organising their preparation for the reaction. Metal-ligand binding, hydrogen bonding, and π–π interactions can be successfully exploited with a high degree of control in syntheses of macrocycles.
- **Ligand synthon or ligson** – a polyfunctional, usually chelating, ligand that takes part in the assemblage reactions at the template centre (a building block for the template synthesis).
- **Chelant (chelator)** – the open-chain ligand which occupies several coordination places in the inner sphere (coordination shell) of the template centre.
- **Assemblage reaction** – the organic reaction at the template centre, by means of which coupling of ligands occurs.
- **Construction (chelatogene) bonds** – covalent bonds formed as a result of assemblage reactions and providing the skeleton of the appearing chelatocycles.

- **Ligand product** – the final organic product (ligand) which is formed as a result of ligsons interaction.
- **Template information** – the totality of coordinative-stereochemical characteristics of the template centre which stipulates a definite spatial arrangement of ligsons.
- **Template complementarity** – a matching between the template information of the matrix and the geometrical (conformational) and electron donor-acceptor parameters of the ligsons and of the ligand product.

As this book deals mainly with macrocyclic systems we include here the following definition:

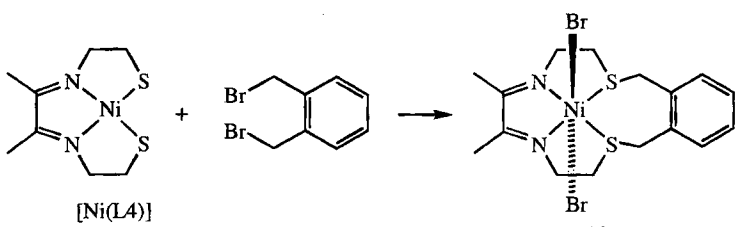
- **Macrocyclic compound** – a cyclic compound with nine or more atoms in the ring, of which not less than three are electron pair donors.

1.3 Mechanistic aspects of the template effect

The template centre plays the key role in matrix reactions. If the steric course of macrocyclisation, or other multistep reaction, is directed and facilitated by the ligsons' spatial structures, and their activation by coordination to the metal ion or another centre, then the process is controlled by the **kinetic coordination template effect**. If the metal ion (or another centre) sequesters one of the components from an equilibrium mixture (starting ligsons and other competing molecular species) and, as a consequence, shifts the position of the equilibrium towards the formation of the desired product in the form of its metal complex, then the **thermodynamic (or equilibrium) coordination template effect** is considered to be operative for the reaction.

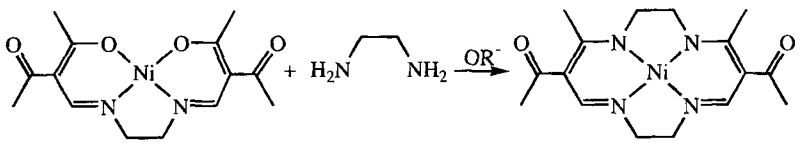
Two distinct classes of template effect have been distinguished since 1964 [39]. Both types of effect are, chemically, manifestations of molecular organisation by means of coordination to the template centre [14]. This is their common feature.

Reactions with a pronounced kinetic coordination template effect are found, in particular, in cases of preparation of macrocyclic compounds by ring-closure of chelate precursors. For example, when the complex [Ni(L4)] is electrophilically alkylated with 1,2-bis(bromomethyl)benzene, the macrocyclic product $[Ni(L5)Br_2]$ is isolated (Eq. 1.1).



[Ni(L4)] $[Ni(L5)Br_2]$ (1.1)

A kinetic study of this reaction showed [39] that the interaction of the starting chelate with the difunctional alkylating agent proceeds in two steps. The first, slow, step consists of 1,2-bis(bromomethyl)benzene attack at the coordinated mercaptide group, followed by the very fast step of macro-ring closure. Note that reaction of the initial complex [Ni(L4)] with benzyl bromide or methyl iodide, unlike the process just described, occurs in two slow consecutive steps. In this case the reaction with the first mole of alkyl halide is much faster than with the second. As a result, in the formation of the monoalkylated intermediate with 1,2-bis(bromomethyl)benzene, the potential reacting functions are, owing to their coordination to the nickel ion, held in close proximity to each other, poised for the reaction between them to occur. Thus the first step is rate-determining.

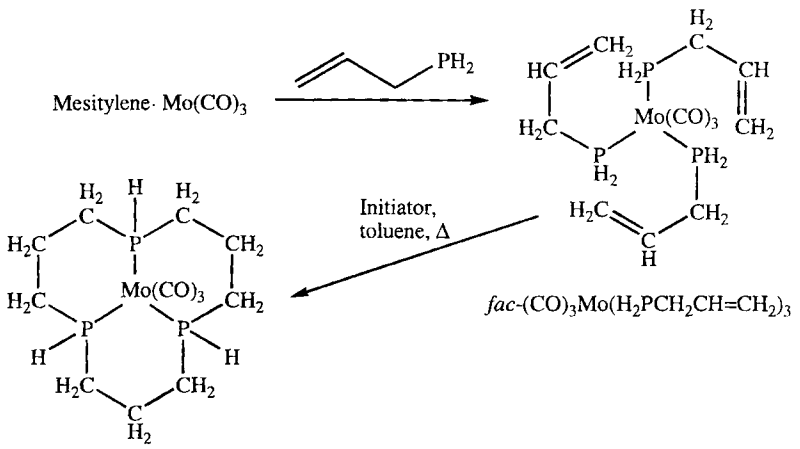


[Ni(L6)] [Ni(L7)] (1.2)

During template condensation of chelate [Ni(L6)] with 1,2-diaminoethane (en) in the presence of base, the kinetic coordination effect is also revealed (Eq. 1.2) [41]. In this case it resides in the spatial structure of the reacting components as well as in their considerable activation. Kinetic measurements confirm formation in the initial step of the six-coordinate adduct Ni(L6)·2en with the molecules of en axially arranged. The central ion thus polarises the amino-groups of coordinated en molecules and carbonyl groups of $(L6)^{2-}$. A proton dissociates from the polarised coordinated 1,2-diaminoethane $-NH_2$ group under the influence of hydroxide or ethoxide ion, and the highly reactive nucleophile $^{-}NH-(CH_2)_2-NH_2$ grouping is formed. Polarisation of the CO groups of the tetradentate ligand in turn increases the electrophilicity of these carbon atoms. This facilitates the condensation of a deprotonated amino-group of en with one of the coordinated CO groups. This sluggish step is followed by a rapid process of ring closure by the second $-NH_2$ group interacting with another coordinated CO-group of the tetradentate ligand. It should be noted that the topology of the intermediate is undoubtedly of major importance for the ring closure reaction to occur. It is obvious that steric factors must also contribute to the realisation of the reaction [14].

In the above examples of the kinetic coordination template effect, the metal ion serves to transfer information to interacting compounds, so the structure of the reaction product is predetermined. In such cases the strict geometry of the metal ion coordination sphere [2, 11] may be considered as an information source.

Mesitylene·$Mo(CO)_3$ reacts with allylphosphine in benzene to produce *fac*-$(CO)_3Mo(H_2PCH_2CH{=}CH_2)_3$, which under the action of a free-radical initiator {2,2′-azobis(isobutyronitrile)} in toluene is converted into the macrocyclic triphosphine complex *fac*-$(CO)_3Mo(L8)$ [43] (Eq. 1.3).



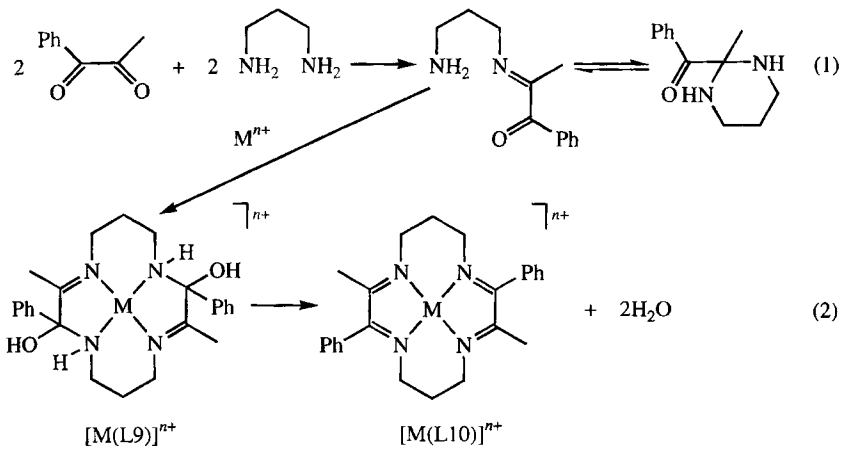
(1.3)

It should be noted that uncoordinated allylphosphine does not cyclise when treated with initiator. This gives evidence for the kinetic coordination template effect operating in this process. In conditions of kinetic control (enforced by spatial effects resulting from coordination to the metal), macrocyclic product formation by addition of P–H to the C=C double bond of a neighbouring coordinated allylphosphine proceeds contrary to Markovnikov's rule (phosphorus as a more electronegative element bonded to a less substituted carbon atom). This template process is notable for its exceptional regiospecific character in that the formation of Markovnikov addition products is not detected.

The following reactions provide examples of the thermodynamic coordination template effect.

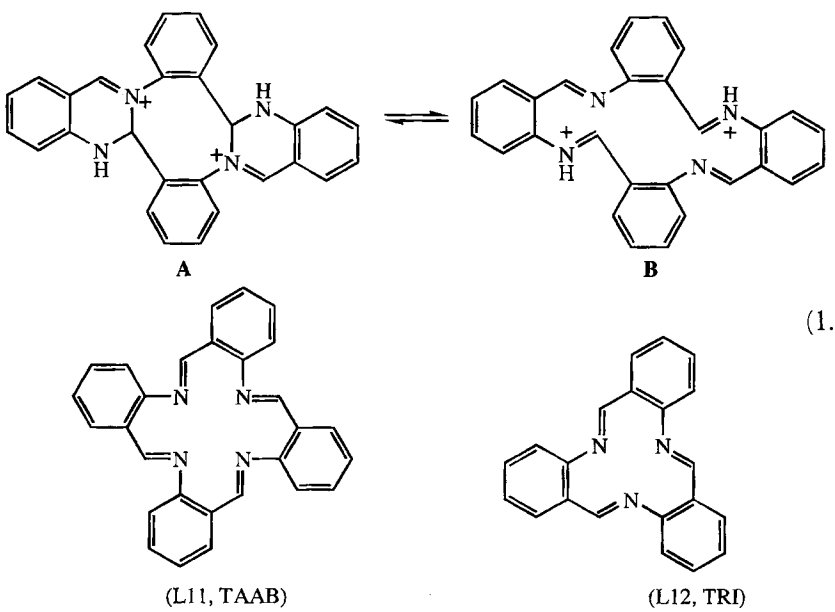
The template synthesis of macrocyclic complexes *trans*-$[M(L9)]^{n+}$ ($M^{n+} = Ni^{2+}$, Co^{3+}, Fe^{2+}) from 1-phenyl-1,2-propanedione and 1,3-diaminopropane occurs [44] according to Scheme 1-2. Reaction (1) represents the "organic" reaction prior to addition of a metal salt. When a methanolic solution of the latter is added to the reaction mixture, the metal-directed condensation is realised, producing the carbinolamine and final products. It is obvious that reaction (2) is a consequence of shifting the position of tautomeric equilibrium under the influence of a metal ion exclusively towards $[M(L9)]^{n+}$, the latter subsequently being transformed into $[M(L10)]^{n+}$. That the condensation reaction actually takes place within the metal coordination sphere has been demonstrated by the isolation of the corresponding cobalt(III) macrocyclic complexes with L9.

The self-condensation of *o*-aminobenzaldehyde may be taken as another example where the thermodynamic template effect is suggested to be operative [4, 45]. In the absence of metal salts it gives various products either of macrocyclic or non-cyclic nature. If there are strong mineral acids in the solution, a doubly protonated tetramer product A is formed, which is in equilibrium with its isomeric form B. In the presence of metal ions, *o*-aminobenzaldehyde gives (TAAB) or (TRI), bound in the corresponding complexes. Transition metal (3d) ions introduced into the equi-



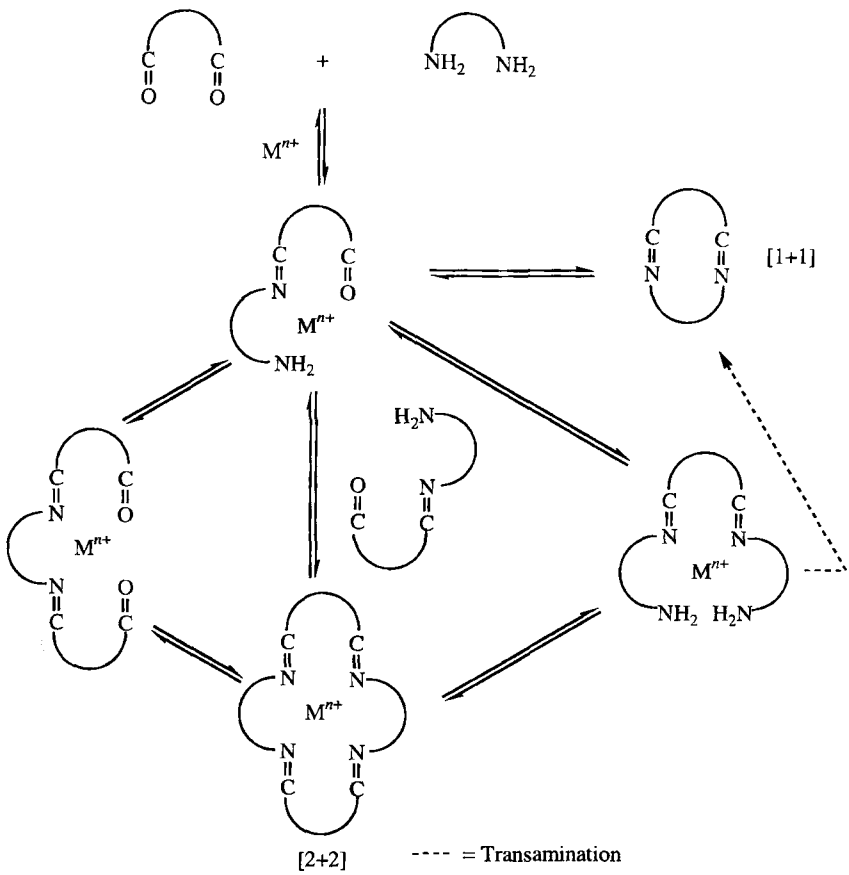
Scheme 1-2. Template synthesis of $[M(L10)]^{n+}$.

librated system A ⇌ B give only [M(L11)] (Eq. 1.4). Hence the kinetic coordination template effect, which could cause a transformation of L11 into L12, cannot manifest itself. These observations affirm the prevalence of the thermodynamic coordination template effect in the synthesis of L11.



(1.4)

In the above-mentioned cases attention is intentionally paid to two different ways of conducting reactions on matrices. In one case the topological factor is empha-



Scheme 1-3. Possible synthetic routes for template assembly of [2 + 2] macrocycles.

sised, and in the other the sequestration of the desired product by means of coordination to the metal ion is outlined.

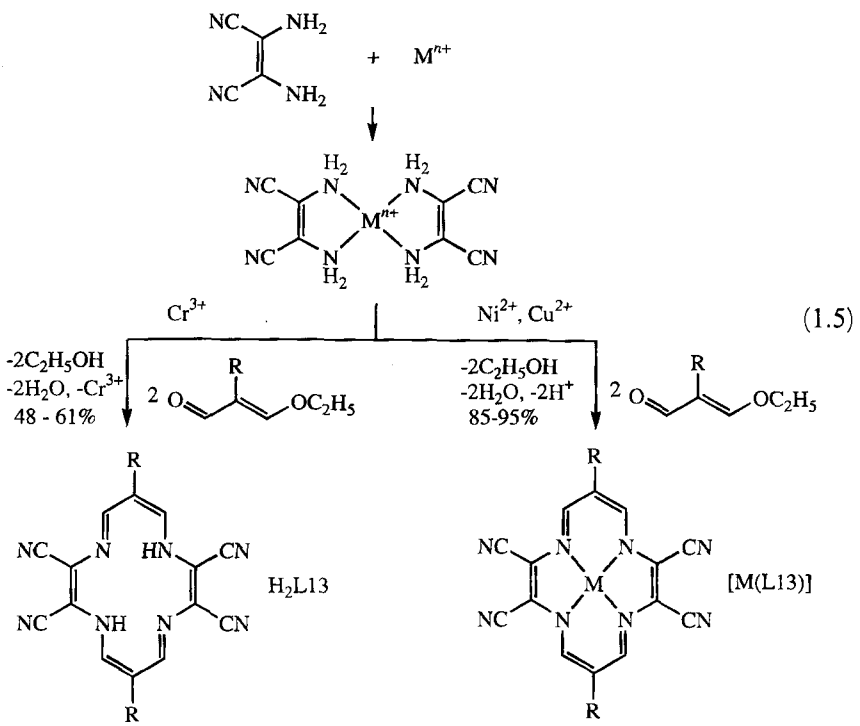
As a rule, template processes have a more complicated nature. They often involve several steps and alternative sequences may also occur. Scheme 1-3 represents the case of [2 + 2] building of macroheterocyclic compounds, described in detail in corresponding sections of this book. This diagram, adapted from [46], shows how a shift of the equilibrium in any direction implies participation of one of the two initial ligsons. Formation of systems of [1 + 1] type is possible if one of the building blocks contains at least one extra donor atom suitable for chelation. It should be noted that appearance of the [2 + 2] template condensation product by synchronous interaction between four corresponding ligsons is scarcely probable, and has therefore been omitted from Scheme 1-3. The substances that result from template transformations depend, among other factors, on the kinetic lability and thermodynamic stability of every species participating in the equilibria. In particular, at

any reaction step either kinetic or thermodynamic factors play the key role but, for the overall process, only one of them may be of prevailing significance.

Thus, when we say that, for instance, a kinetic coordination template effect is responsible for the production of some product, it does not mean that a possible contribution from the thermodynamic coordination template effect is ruled out. The role of the matrix does not depend on one or other of the two coordination template effects prevailing. It consists not only in the strict suppression of side effects, but also in directing the process to its most favourable pathway [2, 4].

1.4 Generation of metal-free macrocycles

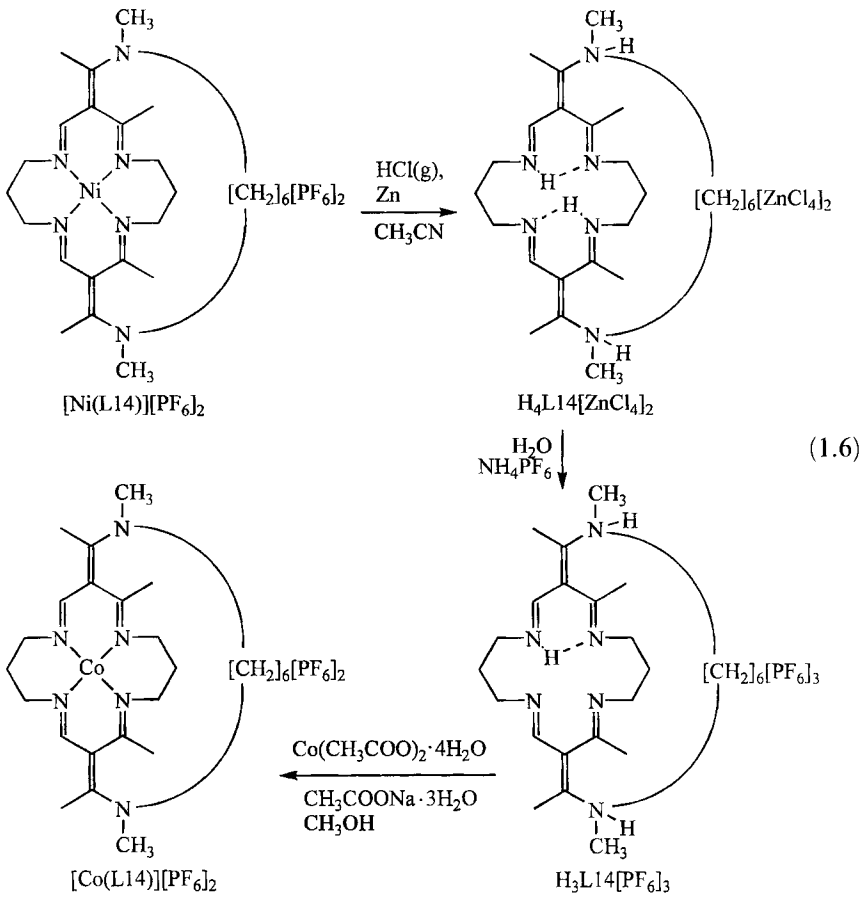
In the examples described so far, where a metal ion is used as template, macrocyclic organic compounds are isolated as complexes. There are also many template processes in which the organic product formed is isolated in the metal-free state. Frequently different templates allow the building up of the same product from the same ligsons, which may then be isolable as a coordination compound or in the metal-free state, depending on the nature of the metal ion. This is illustrated by the assembly of the macrocyclic system H_2L10 from diaminomaleodinitrile and 3-ethoxyacroleins in the presence of nickel(II), copper(II), or chromium(III) (Eq. 1.5) [47–49].



(1.5)

It should be noted that a metal complex is most commonly the final product when synthesising polyazamacrocyclic compounds. However, as a rule, crown ethers synthesised by template procedures are isolated in the metal-free state.

In some cases the macrocyclic metal complexes may be demetallated through the action of appropriate reagents, such as HCl, HBr, cyanides, H_2S, OH^- or ethylenediaminetetraacetate ion, leaving the metal-free macrocycle in solution. Thus on passing dry hydrogen chloride through an acetonitrile solution of $[Ni(L14)][PF_6]_2$, with the subsequent addition of the solution obtained from the reaction of metallic zinc with dry HCl in CH_3CN, $H_4L14[ZnCl_4]_2$ is isolated (Eq. 1.6).



(1.6)

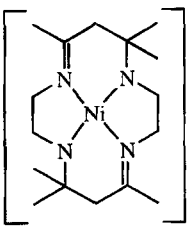
After dissolving this salt in water and adding NH_4PF_6, the metal-free compound $H_3L14[PF_6]_3$ can be isolated. This readily forms complexes with other metals [50].

The possibility of demetallating complexes is of special importance in cases where only one or a limited number of centres may be used for the synthesis of the macrocycle in the form of a complex. The isolation of free ligands enables coordination

compounds to be obtained with metal ions which are normally reluctant to act as matrices.

1.5 Transmetallation

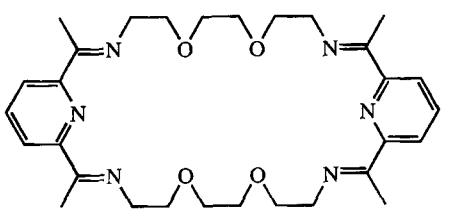
Situations are known when demetallation results in the formation of a macroheterocyclic organic compound which is unstable in the metal-free state. This is the case, for instance, when $[Ni(L15)](ClO_4)_2$ interacts with aqueous NaCN [51] (Eq. 1.7).



$[Ni(L15)](ClO_4)_2$

$$(ClO_4)_2 + 4NaCN + 4H_2O \longrightarrow Na_2[Ni(CN)_4] + 2NaClO_4 + 2 \text{ (acetone)} + 2\ H_2N(CH_2)_2NH_2 \quad (1.7)$$

This restricts possibilities of obtaining complexes of the corresponding ligand with metals unable to act as templates. One solution is transmetallation, namely, the treatment of a kinetically labile complex with a metal ion to form inert complexes. Thus it is possible to synthesise complexes of nickel(II), copper(II), iron(II), cobalt(II) and cobalt(III) with the unstable ligand L16 from the corresponding $[Pb(L16)]X_2$ or [Ag(L16)]X, themselves assembled with the use of lead(II) or silver(I) as templates [46] (Eq. 1.8).



L16 (1.8)

There are also many situations where demetallation of coordination compounds obtained by template pathways is impossible. The reason for this is the high thermodynamic and kinetic stability of these metal complexes according to the **principle of maximal correspondence between the cavity and the metal ion** (PMCCMI). This principle requires a number of conditions [32] to be fulfilled:

- matching of the macrocycle cavity size to the corresponding metal ion, i.e. the average cavity diameter must be equal to the diameter of the central metal ion;

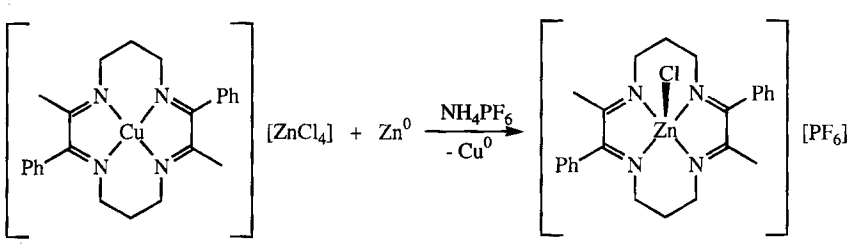
- certain electron donor characteristics of the atoms of the cavity, interacting with the central transition metal ion to form a donor-acceptor bond, i.e. the presence of electron pairs in orbitals of high energy (usually HOMO) overlapping the acceptor orbitals of the central ion;
- for central ions with partly filled d-orbitals, the LUMO of the ligand, capable of π-acceptor interaction, should have the lowest possible energy;
- the electrostatic characteristics of hard donor atoms and groups (effective charges, dipole moments, polarisability) should ensure the maximal value of the energy of interaction with alkali and alkaline earth metal ions, lanthanides and actinides;
- the correspondence of the number of donor atoms within the cavity to the optimal coordination number of the metal ion;
- the spatial arrangement of ligand binding sites within the cavity which should match the optimal coordination polyhedron for the given cation;
- macrocycle conformation flexibility (or rigidity) allowing the donor atoms to satisfy the metal ion stereochemical demands with a minimum strain energy.

Among complexes of the first row transition metals most often used as templates, copper(II) macrocyclic complexes demetallate least readily as the energy of vacant d-orbitals decreases along the d^5, d^6, d^7, d^8, d^9 ion series [4, 44]. In this case, reductive transmetallation may be used [4, 44]. Thus, by treatment of the copper(II) complexes with metallic zinc or zinc amalgam, it is possible to replace Cu by Zn [52] (Scheme 1.4).

On going from copper to zinc, PMCCMI requirements are perturbed significantly because the preferred stereochemistry (tetrahedral) and electron configuration (d^{10}) of zinc(II) differ from those of copper(II) (square-planar, d^9). As a result, it becomes possible to transmetallate zinc complexes with ions of other metals.

1.6 Template particle types for obtaining different ligand products

In all the examples described above, except for the synthesis of L8, metal ions are used as template centres. Most commonly they play the role of matrices, condi-



[Cu(L17)][$ZnCl_4$] [Zn(L17)Cl][PF_6]

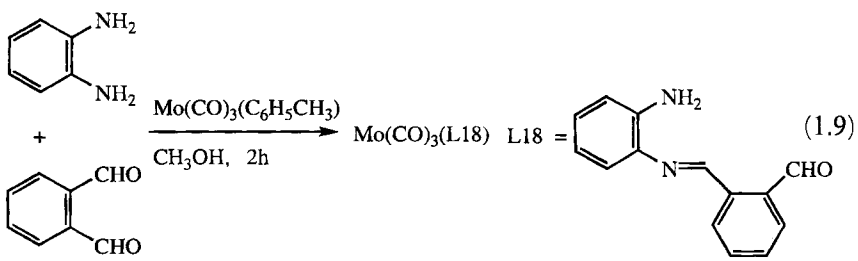
Scheme 1-4. Transmetallation.

tioned by one of the main criteria for template processes realisation – the ability to orient and activate interacting ligsons by means of coordination. No less important is the fact that ligand products generated are often isolated as metal complexes. In addition, depending on the nature of metal and ligand precursors, the template bonds formed may be of various kinds – donor–acceptor [38], hydrogen bonding [25], single- or multi-centre π-bonds [53], covalent [54], ion-dipole [3], π–π^*-interactions [19], or metal–carbon σ-bonds [55].

Metal ions with closed electron shells, such as s^2p^6, d^{10} or $d^{10}s^2$, serve mainly to obtain crown ethers – with the exception of small ions of comparatively high charge, such as Be^{2+}, Mg^{2+}, Zn^{2+}, Cd^{2+}, Al^{3+} and Sc^{3+}. To assemble poly-azamacrocyclic systems, 3d cations with either filled or incomplete electron shells are suitable.

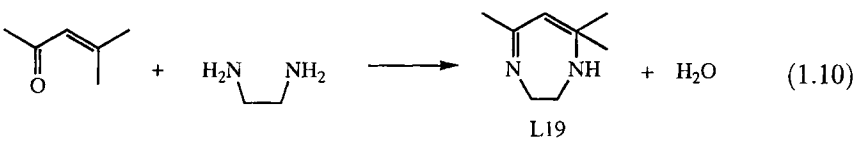
The ions of cobalt(III), rhodium(III) and iridium(III) are the best templates for assembling octahedral complexes with ligands of the sepulchrate type. To obtain macrocyclic polylactones and polylactams, templates with covalent character bonds, such as Sn, Si, Sb, or B, are used. Copper(I) is the most convenient centre for the synthesis of catenanes.

Metals in the zero oxidation state may also act as matrices. This is illustrated by the above-mentioned example [39] of assembling L8, where Mo(0) was used as a pattern, and by the $Mo(CO)_3(C_6H_5CH_3)$ reaction with *o*-phenylenediamine and *o*-phthalic aldehyde (in the ratio 1:1:1) in dry methanol [56] to form L18 (Eq. 1.9). This last reaction stops at the intermediate stage in the macrocyclisation process.



(1.9)

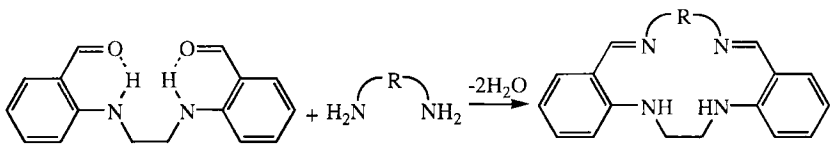
The proton is often used as an effective template centre for obtaining metal-free macrocyclic systems. Its role is not always obvious, so reactions with its participation are sometimes classified as "non-template" [57]. Thus, interaction of 1,2-diaminoethane monohydroperchlorate with acetone yields H_2(*trans*[14]diene)$(ClO_4)_2$ [51, 58]. The template role of H^+ here follows from evidence given in ref. [59], where it was shown that the reaction of dry unprotonated 1,2-diaminoethane with mesityl oxide gives the substituted dihydrodiazepin L19 (Eq. 1-10).



L19

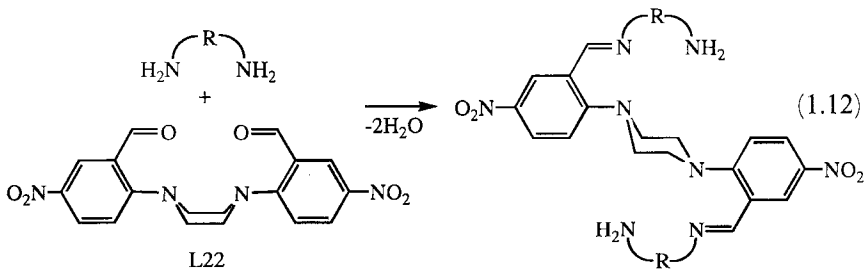
(1.10)

In the case of ligsons having elements capable of self-organisation through intramolecular hydrogen-bonding, new chelate bonds are formed at the expense of their own protons and without extra protonation from outside [57], as in the formation of H_2L21 (Eq. 1.11).



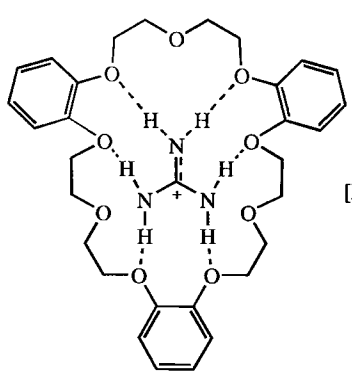
H_2L20 $\quad$ $R = (CH_2)_n$, $n = 2\text{-}4$ $\quad$ H_2L21 (1.11)

If there are no hydrogen atoms of secondary amino-groups in the starting material, as with L22, then macrocyclisation is impossible (Eq. 1.12) [57]. It is also clear that the conformation of the diazahexane ring in L22 may influence the course of reaction.



L22 $\quad$ L23 (1.12)

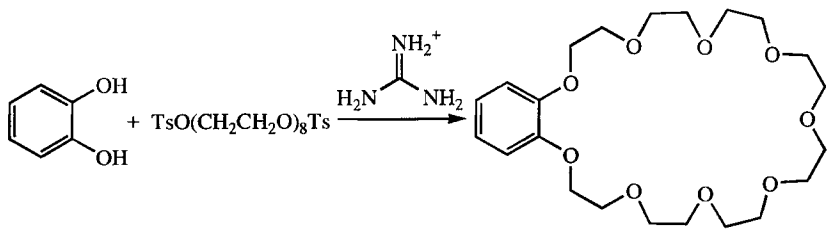
Processes using the proton as matrix are described as H-template. Ammonium ion, quaternary cations, or related species may be used as template centres in H-template reactions [11, 35]. Thus, tribenzo-27-crown-9 is obtained in the presence of guanidinium ion (Eq. 1.13) [60].



$[L24\{C(NH_2)_3\}]^+$ (1.13)

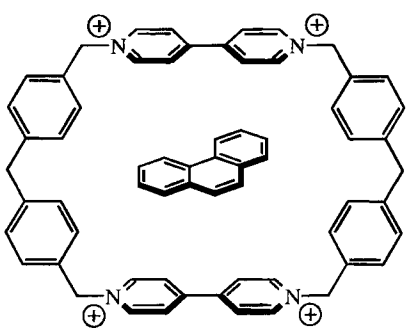
The guanidinium ion plays an important topological role in the last example. Owing to its shape, which is derived from its primary covalent structure, it favourably arranges protons for participating in hydrogen bonding. In this case a kind of tandem template is involved, where one of the partners predetermines the spatial arrangement of the another. The latter in its turn organises the corresponding ligsons for their subsequent interaction by virtue of the corresponding hydrogen bonds.

The guanidinium ion acts analogously in the process of synthesis of L25 (Eq. 1.14) [59]. Steric and functional complementarity between the guanidinium ion, ligsons and ligand product predetermine the success of the synthesis of 27-membered macrocycles L24 and L25.



L25 (1.14)

As previously mentioned, π–π^* aromatic forces can also be exploited for carrying out template macrocyclisation reactions. Thus the formation of L26 proceeds more effectively in the presence of π-donor species like phenanthrene (Eq. 1.15) [61]. The π-donor–π-acceptor interaction between the template and bipyridinium ions leads to a favourable arrangement of the latter for their subsequent reaction with the second molecule of the dibromoderivative.



$(L26)^{4+}$·Template (1.15)

Stoddart and co-workers also made use of aromatic electron donor-acceptor (EDA) interactions for highly effective synthesis of catenanes and rotaxanes (Figure 1-3) [62]. In this case, however, one of the ligsons acts as template, which is subsequently incorporated in the covalent structure of the ligand product (catenane or rotaxane).

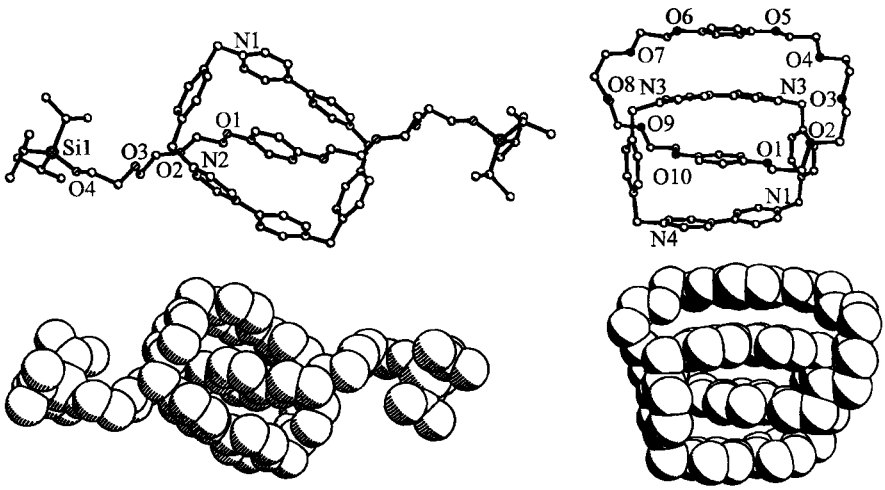
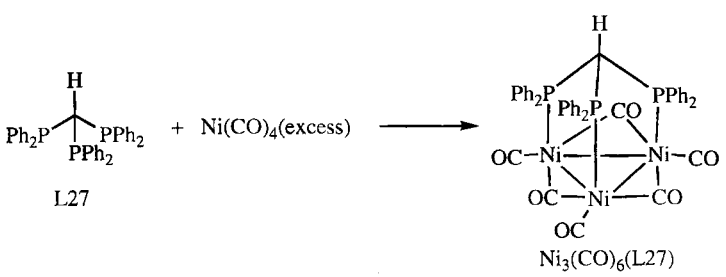


Figure 1-3. The molecular structures of a rotaxane (left) and catenane (right), the syntheses of which were promoted by aromatic π–π^* interactions between complementary hydroquinone and bipyridinium dication units of the corresponding ligsons [62].

The application of EDA aromatic interactions in the directed syntheses of various catenanes and rotaxanes is considered in more detail in Chapter 4.

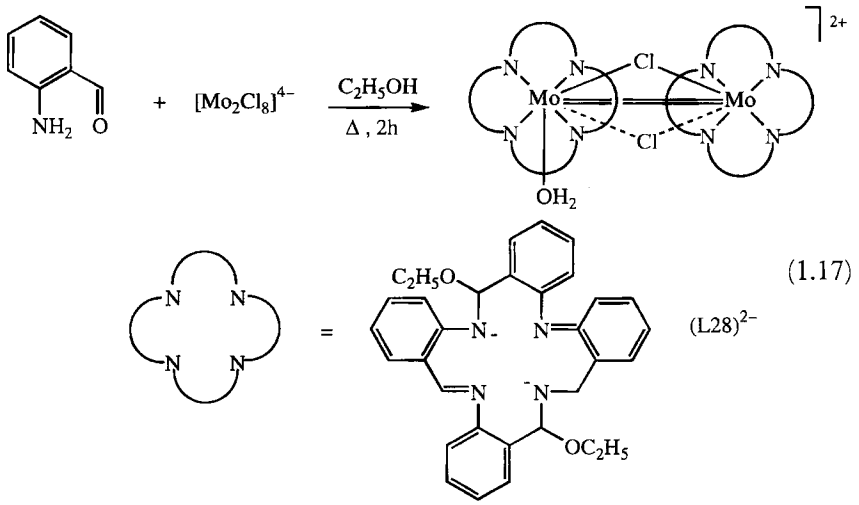
A number of other organic compounds have been shown to play a template role in some reactions. Thus, the tripodal ligand $HC(PPh_2)_3$, L27, when used as matrix [63, 64] promotes simultaneous binding of three nickel atoms in a triangular disposition when treated with excess of $Ni(CO)_4$. As a result, a trinuclear nickel(0) compound is formed (Eq. 1.16).



(1.16)

Although a metal ion usually serves as a matrix for the synthesis of organic products, in this case there is a kind of functional work exchange between partners, with L27 assembling the trinuclear metal carbonyl cluster from mononuclear $Ni(CO)_4$. The cluster is isolated as a nickel complex incorporating the L27 template.

Examples are also known where anions are used as templates. For instance, *o*-aminobenzaldehyde self-condensation on the $[Mo_2Cl_8]^{4-}$ binuclear anion matrix results in the construction of $[(Mo^{IV})_2(L28)_2(H_2O)Cl_2]Cl_2$, together with other products (Eq. 1.17) [65].

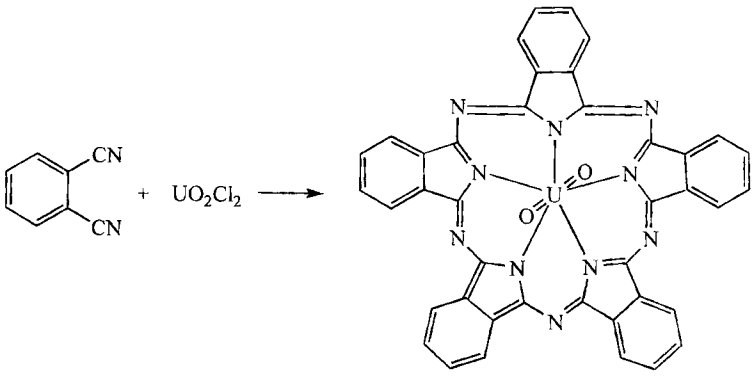


(1.17)

The specific character of this template involves not only an anion complex being an active centre, but also provides an example of a multicentre matrix. In this case, as in the aminoguanidinium example, a kind of tandem effect operates, in which, however, each partner shows its "independence".

The possibility of carrying out reactions on matrices depends essentially on the rate of template information transmission and its reception by ligsons and ligand products, i.e. the extent to which the spatial organisation and electron state of the donor atoms [66] and reacting groups coincide with the demands of the template [35].

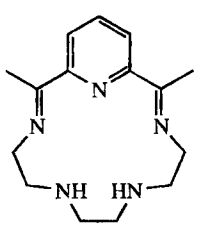
Thus, in examples of synthesis of tetraazamacrocyclic compounds on nickel ions (mainly) and on copper(II), square-planar system assembling is realised [38, 47–49]. Guanidium ion promotes building of 27-crown-9-ether [60]. *o*-Aminobenzaldehyde self-condensation on the copper ion as matrix results exclusively in forming a complex with TAAB [67]. When using nickel(II) or cobalt(II) as templates under the same conditions, two types of macrocyclic azomethine systems – TAAB and TRI – may be synthesised [67–71]. Macrocyclisation of phthalonitrile on the anisotropic matrix O=U=O ends with obtaining the so-called superphthalocyanine product $[UO_2(L29)]$ [72, 73], rather than with the isolation of the corresponding complex with the phthalocyanine (Pc), as observed for other metal ions (Eq. 1.18) [11, 74].



(1.18)

$[UO_2(L29)]$

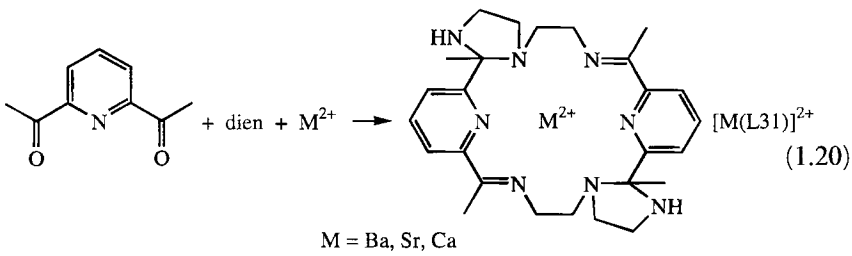
Without complementarity a template reaction does not proceed at all or stops at an intermediate step. This explains, for example, the difficulty or even impossibility of obtaining polyazamacrocyclic compounds on alkaline metals as matrices or crown ethers in the presence of 3d ions. Further, when *o*-phenylenediamine condenses with *o*-phthalic aldehyde on molybdenum(0), the template reaction stops at the open-chain compound stage, as a result of lack of complementarity between template requirements and the hypothetical macrocyclisation product of 2 + 2 type [56]. In some processes a certain compromise is achieved between the template and the ligsons' initial demands, resulting in the synthesis of substances with the central ion in untypical or unusual stereochemistry. This may lead to unexpected regroupings, ring contraction, addition reactions on azomethine bonds, or other unexpected changes. Thus template condensation of 2,6-diacetylpyridine with triethylenetetramine (trien) on iron(II) or manganese(II) yields macrocyclic complexes in which, untypically for 3d ions, pentagonal coordination of L30 to iron(II) and manganese(II) is achieved (Eq. 1.19) [75, 76].



L30

(1.19)

In contrast, when 2,6-diacetylpyridine interacts with diethylenetriamine (dien) in the presence of alkaline earth metal ions, other than magnesium, contraction of a 24-membered macrocyclic ligand to an 18-membered system takes place (Eq. 1.20). This is caused by mismatch between the demands of the template and of the ligand products abilities to satisfy them [77].

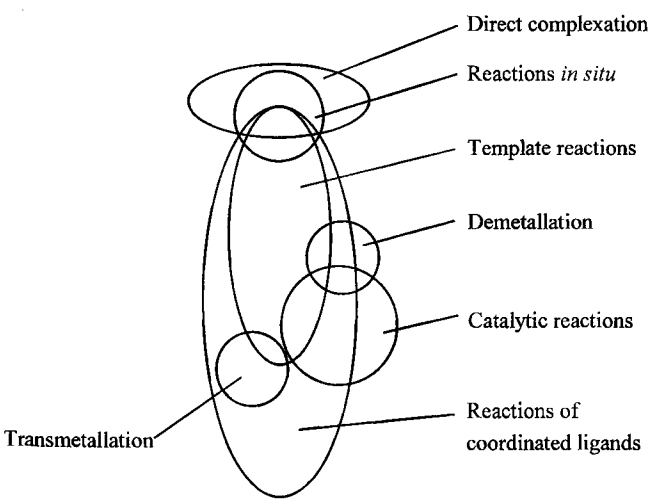


(1.20)

1.7 The place of metal template processes among other chemical reactions with participation of metal ions

Template processes and reactions of coordinated ligands, *in situ*, direct complexation, demetallation, transmetallation and catalytic transformations all exhibit similar features. This sometimes leads to unjustifiable classification of such reactions as template processes and vice versa. To define the relationships between template reactions and other coordination chemistry processes, Scheme 1-5 is proposed, constructed on the principle of Venn logic diagrams [78].

Template reactions and reactions of coordinated ligands occupy similar positions in the Scheme. Almost all template transformations fall into the category of coordinated ligand reactions. At the same time, it needs to be noted that not every chemical transformation of ligands may be classified as a template process. In the case of reactions of coordinated ligands, the metal ion plays an electronic role in



Scheme 1-5. Interrelations of template reactions with other processes of coordination chemistry.

modifying ligand reactivity. The electronic factor in template reactions is also of importance, but the metal coordination geometry is paramount. As a rule, in such reactions, new chelate rings are formed. For example, $M(TAAB)^{2+}$ (M=Ni, Cu) interactions with the trifunctional reagents $HO(CH_2)_2X(CH_2)_2OH$, where X=S or NCH_3, resulting in the formation of complexes with the macrobicyclic ligands ([M(L32)]), may be ranked among template reactions (Eq. 1.21) [79, 80]. However, chemical changes resulting from nucleophilic attack at $M(TAAB)^{2+}$ by α,ω-polymethylenediamines [80] are reactions of coordinated ligands which cannot be strictly classified as template processes.

$$[M(TAAB)]^{2+} + HO(CH_2)_2X(CH_2)_2OH \longrightarrow \text{[(M(L32)]} \qquad (1.21)$$

M = Ni, Cu
X = S, NCH_3

The chelate [Ni(L4)] transformation into the macrocyclic product $[Ni(L5)Br_2]$ [36, 37] belongs to those coordinated ligand reactions which are also template transformations. The latter are realised as a result of the kinetic coordination template effect with formation of a new chelate ring, whereas the alkylation of [Ni(L4)] with methyl iodide or benzyl bromide is merely a reaction of a coordinated ligand.

As is clear from Scheme 1-5, marked overlap is observed for *in situ* and template reactions. For instance, in cases where the coordination thermodynamic factor predominates in template processes [40, 41, 43, 45], reactions *in situ* are the obligatory constituent part and precede sequestering of the final ligand product from the equilibrium mixture by the appropriate template. Situations are also known where an organic compound being synthesised from the appropriate ligsons in the presence of metal ions is also generated by mixing the reagents in the absence of a metal ion (without using a high-dilution procedure). This sometimes gives even better yields. For instance, synthesis of L33–L35 proceeds irrespective of whether metal ions (Ag^+) are used or not (Eq. 1.22) [81].

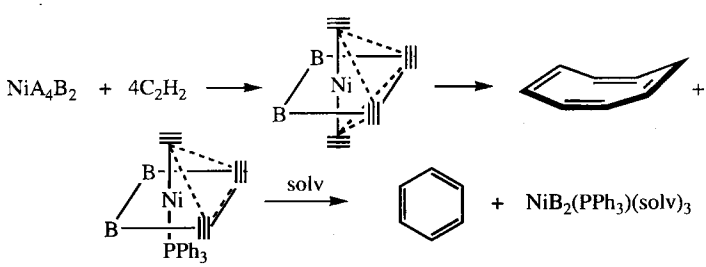
$$\text{R} = (CH_2)_2S(CH_2)_2, \quad \text{L33}$$
$$\text{R} = (CH_2)_2NH(CH_2)_2, \quad \text{L34} \qquad (1.22)$$
$$\text{R} = (CH_2)_3NH(CH_2)_3, \quad \text{L35}$$

Naturally, such processes cannot be classified as template ones. In such a case, as

with situations where there is no unequivocal evidence for the template effect, it seems more correct to use the term *in situ*.

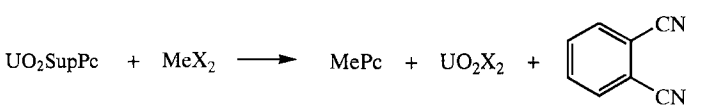
Template and *in situ* processes overlap with direct complexation reactions. The last-named involve complexation between a presynthesised ligand and metal ions. If the ligand is stable in solution, then complex formation proceeds without interference from side reactions, and synthesis is achieved out of the zones of the reactions on matrices or *in situ*. However, when the corresponding ligand used in the reaction, because of hydrolysis or other reason, decomposes in solution into simpler entities, which are in equilibrium with it, a new situation arises. This looks like an *in situ* reaction in some ways, with the role of the metal ion consisting of sequestering the starting ligand (the thermodynamic coordination template effect is realised).

The overwhelming majority of template reactions carried out to date have been stoichiometric. However, many catalytic processes are known which have been realised by the template approach. The classic example of a template catalytic process is Reppe's cyclooctatetraene and benzene synthesis, in which a nickel atom brings together four and three acetylene molecules, respectively, prior to cyclotetra(tri)merisation (Eq. 1.23) [34].



(1.23)

Transmetallation reactions have a template nature in some cases, as in the above-mentioned transformation of UO_2SupPc or [UO_2(L29)] (see p. 20) into MePc on interaction with salts of transition metals (Eq. 1.24) [73, 74, 82].



(1.24)

Numerous examples of transmetallation are given in the following chapters.

When examining interrelations between demetallation reactions and template processes, three main steps may be distinguished for the latter:

- ligsons preparation by matrix coordination (to obtain template precursors);
- reaction between coordinated ligsons themselves or with the attacking agent, which results in assemblage of the ligand product;
- removal of the template (demetallation) followed by the isolation of matrix-free organic product.

If the final step is performed, demetallation becomes a constituent part of the template reaction, as described in refs [47–49]. If, however, the ligand product cannot exist in the free state or is bound to the template centre as a stable complex, the third step is not realised. As shown above [50], demetallation may be performed out of the domain of template synthesis by the action of a number of agents on the corresponding metal complexes.

It should be noted that the reactions shown in Scheme 1-5 may overlap with template processes and between themselves as well. Thus, demetallation reactions are necessarily included in catalytic template transformations. From Scheme 1-5 it also follows that reactions *in situ* mutually overlap with direct complexation processes. The same applies to transmetallation processes and the reactions of coordinated ligands.

Template processes are complex, have a multistep nature, and depend on many factors. Taking this and other above-mentioned factors into account, it is readily seen that the frontiers of template processes overlap with the other reactions given in Scheme 1-5 and are by no means clear-cut. It is also quite obvious that, in the non-intersecting zones, each of the reactions under consideration has strictly individual features. This must be taken as a basis when classifying template reactions and considering their place among other transformations in the chemistry of coordination compounds.

1.8 Classification of macrocyclic compounds

Variants of macrocyclic compound classification, based on various features, are given in a number of works [1, 4, 32]. The clearest and most complete is that proposed in ref. [32]. The availability of donor atoms and the ability of the corresponding macrocyclic compounds to form complexes are taken into account to a certain extent in the variants. In the light of this, it seems reasonable to proceed by considering the following two main factors when classifying such compounds: ligand denticity and the nature of the donor atoms. These, together with a number of other features given below, may be regarded as necessary and sufficient for their classification. If the denticity corresponding to the macroring donor atoms is taken as a starting point, and account is then taken of the number of metal ions that may be complexed when using all the functional groups of the corresponding ligand suitable for coordination, then macrocyclic compounds can be subdivided (irrespective of the nature of donors) into the following classes:

1. Mononucleating macrocyclic ligands capable of forming complexes with only one metal ion. In turn this class can be subdivided as follows:
   - 1.1 Bidentate macrocyclic ligands
   - 1.2 Tridentate ligands
   - 1.3 Tetradentate ligands
     - 1.3.1 Planar rigid systems
     - 1.3.2 Three-dimensional systems
   - 1.4 Pentadentate ligands

- 1.4.1 Planar systems
- 1.4.2 Three-dimensional systems

1.5 Hexadentate ligands
- 1.5.1 Rigid, coordinating in a single plane
- 1.5.2 Flexible, capable of forming six-coordinate species approximating to both octahedral and trigonal prismatic coordination geometries
- 1.5.3 Other three-dimensional systems, for example, pseudorotaxanes, rotaxanes etc.

1.6 Higher multidentates

2. Bi- and polynucleating macrocycles, which are capable of coordinating to two or more ions within the macrocyclic system

2.1 Binucleating (or compartmental) ligands
- 2.1.1 With one common macrocycle
  - 2.1.1.1 With two equivalent cavities
  - 2.1.1.2 With two non-equivalent ring cavities (differing at least by the set of donors)
- 2.1.2 With two separated macrocycles
  - 2.1.2.1 Two macrorings joined by a single bridging unit
  - 2.1.2.2 Two macrorings joined by more elaborate linkages
  - 2.1.2.3 Binucleating systems which incorporate more than one linkage between the cyclic subunits
  - 2.1.2.4 Catenanes
  - 2.1.2.5 Trefoil knots and other topologies

2.2 Trinucleating species
- 2.2.1 With one common macrocycle
- 2.2.2 With three separated macrorings

2.3 Tetranucleating systems
- 2.3.1 With one common macroring
- 2.3.2 Capable of forming a cubane core

2.4 Pentanucleating systems etc.

Proceeding from the nature of donors, macrocyclic systems can be classified as follows:

1. Macrocycles containing donors of one type
   - 1.1 Polyazamacrocycles
   - 1.2 Polythiamacrocycles
   - 1.3 Polyoxamacrocycles
   - 1.4 Polyphosphamacrocycles
   - 1.5 Polyarsamacrocycles
   - 1.6 Cyclotriynes (with acetylene groups as donors)
2. Macrocycles containing two types of donor atoms
   - 2.1 Polyazapolythiamacrocycles
   - 2.2 Polyazapolyoxamacrocycles
   - 2.3 Polyoxapolythiamacrocycles
   - 2.4 Polyazapolyphosphamacrocycles etc.
3. Macrocycles with more than two types of heteroatoms.

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Chapter 2

Template synthesis of polyazamacrocyclic compounds

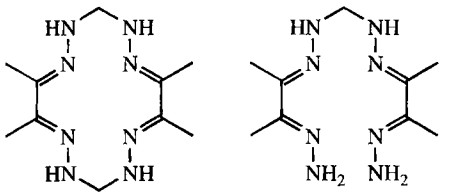
Compounds containing nitrogen in their cyclic backbone are one of the most representative groups of macrocyclic systems, and are very often synthesised by template reactions. The ligsons participating in the construction of ligand products must have certain groups or positions in molecules – which are sometimes concealed, revealing themselves when coordinated and activated by the template.

Building up polyazamacrocyclic systems on the appropriate matrices is carried out by the interaction of compounds containing amine or imine groups with aldehydes, ketones, organic halogen derivatives, substituted malonic esters and ligsons containing unsaturated C–C bonds. The process may also be performed by interaction of the appropriate blocks, containing both functional groups necessary for obtaining the final product. Among such template reactions the most frequent is the formation of azomethine construction bonds, then C–N and C–C and in some cases, N=N chelatogene bonds.

2.1 Cyclic hydrazines and hydrazones

In this section examples of polyazamacrocyclic products synthesised by the interaction of simple ligsons, such as hydrazine and its derivatives with mono- and dicarbonyl compounds, are discussed. The main feature of hydrazines as ligsons is the presence of two lone pairs of electrons in the functional groups. Coordination of hydrazines to the metal ion leads to the loss of nucleophilic properties of only one functionality, because steric restraints will not permit the second nitrogen donor to coordinate to a metal at the same time. As a result the nucleophilic properties of the non-coordinated amino groups can be exploited to carry out ring-closure reactions.

For example, by template condensation of 2,3-butanedione dihydrazone with formaldehyde, a series of nickel(II), cobalt(II) and copper(II) complexes with the neutral macrocyclic ligand L36 were obtained (Eq. 2.1) [1–4].



L36 L37 (2.1)

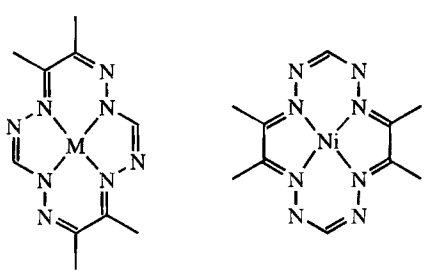
The iron(II) complex of L36 is synthesised directly by interaction of stoichiometric amounts of 2,3-butanedione, hydrazine and formaldehyde on the iron(II) matrix [2]. $[Co(L36)(CH_3CN)_2](ClO_4)_3$ is synthesised by oxidation of $[Co(L36)](ClO_4)_2$ with molecular oxygen in acetonitrile in the presence of perchloric acid [2].

It is possible to carry out 2,3-butanedione dihydrazone interaction with acetaldehyde, propionaldehyde, acetone or cyclohexanone on the nickel(II) matrix, forming macrocycles similar to L36 [2].

Attempts to synthesise manganese(II) and zinc(II) octaazamacrocyclic compounds had no success. Complexes of these metals with 2,3-butanedione dihydrazone react with formaldehyde, but in this case products containing the acyclic tetradentate ligand L37 are isolated [2].

Manganese(II) and zinc(II) do not promote macrocyclisation, possibly because of greater radii of d^5 and d^{10} electron systems in comparison with the ions of other d-elements, as well as their restricted stereochemical capabilities.

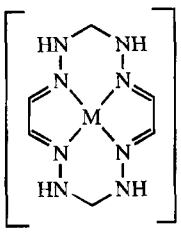
Template reaction of 2,3-butanedione, formaldehyde, and hydrazine in the presence of nickel(II) or cobalt(II) and molecular oxygen results in the isolation of [M(L38)] [3], in which the macrocyclic ligand is a product of oxidative dehydrogenation of L36 (Eq. 2.2). Isomer B is obtained by oxidation of an acetonitrile solution of [Ni(L36)] with molecular oxygen in the presence of hydrazine as a base. The structure of both A and B isomers of [Ni(L38)] has been confirmed by X-ray diffraction studies [3, 4]. Isomer A is the more stable. This assertion is supported by the fact that, when heated or ultraviolet irradiated, isomer B turns irreversibly into A.



[M(L38)], M = Ni, Co (isomer A) [Ni(L38)] (isomer B) (2.2)

Attempts to prepare octaazamacrocyclic systems similar to L36 but derived from

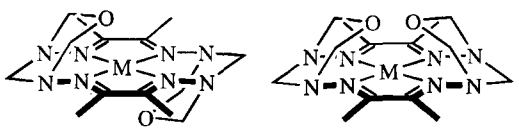
other α-diketones failed [2]. (For instance, glyoxal gives the dihydrazone but, when interacting with formaldehyde in the presence of nickel(II), it yields polymeric products.) It was reported [5] that in conditions of moderate dilution, nickel(II) and cobalt(II) complexes with glyoxal dihydrazone interact with formaldehyde, forming macrocyclic products $[M(L39)]X_2$, but the authors did not provide convincing evidence for the macrocyclic nature of the ligand (Eq. 2.3).



X_2 $[M(L39)]X_2$ (2.3)

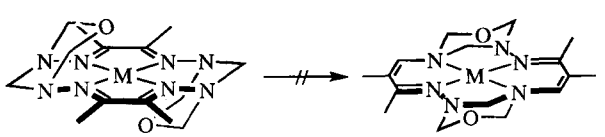
M = Ni, Co;
X= Cl^-, Br^-, I^-, SCN^-, BF_4^-, NO_3^-

Macrocycle L36 in the coordinated state contains four secondary nitrogen atoms, capable of further attack on carbonyl electrophiles. For example, the interaction of [M(L36)], M = Fe^{II}, Co^{II}, Co^{III}, Ni^{II} or Cu^{II}, with formaldehyde in acetonitrile gives complexes with the tricyclic ligand L40 [1, 7]. In this case formaldehyde molecules attack secondary nitrogen atoms, forming $-CH_2-O-CH_2-$ bridges, situated either on the same or opposite sides of the MN_4 plane (Eq. 2.4).



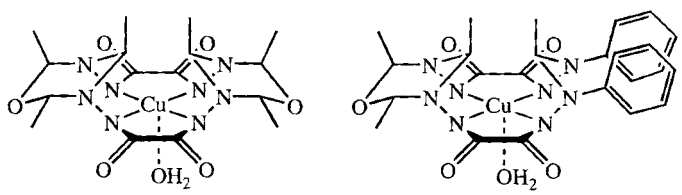
[M(L40A)] [M(L40B)] (2.4)

Existence of the *syn* and *anti* isomer structures is confirmed by ^1H NMR spectra of the two products, isolated by fractional crystallisation of the compound $[Co(L40)(CH_3CN)_2](ClO_4)_3$. Isomer $[Co(L40B)(CH_3CN)_2](ClO_4)_3$ was also studied by X-ray analysis [6]. Cobalt(III) octahedral coordination is realised by means of the four nitrogen atoms of L40B in the equatorial plane and of the two axially arranged CH_3CN molecules. In $[M^{II}(L40)(H_2O)](ClO_4)_2$ with M = Cu or Co, X-ray diffraction study showed [6] that the ligand also adopts the L40B conformation. The complex cation has a square-pyramidal structure. A molecule of water is coordinated in the apical position and on the MN_4 plane side, opposite to the ether bridges. Attempts to perform *syn* and *anti* isomerisation of the imine bonds by extended heating of the metal complexes with L40 or by ultraviolet irradiation failed (Eq. 2.5) [6].



(2.5)

Complexes $(NH_4)_2[Cu(L41)H_2O]\cdot 3/4NH_4ClO_4$ and $(NH_4)_2[Cu(L42)(H_2O)]\cdot 4H_2O$ are obtained by reaction of oxalyldihydrazide (or its *N*-phenyl derivative) with an ammoniacal solution containing copper(II) ions, followed by addition of an excess of acetaldehyde to the cooled solution in the presence of atmospheric dioxygen (Eq. 2.6) [7–9].



$[Cu(L41)(H_2O)]^{2-}$ $[Cu(L42)(H_2O)]^{2-}$ (2.6)

The copper atom in $[Cu(L41)(H_2O)]^{2-}$ and $[Cu(L42)(H_2O)]^{2-}$ is coordinated by four nitrogen atoms of the macrocyclic ligand (Cu–N 18.5–18.8 and 18.86–18.97 nm for the first and second complex anions, respectively) and the oxygen atom of H_2O in a square pyramid [8]. The copper atom is displaced by 1.5 and 1.7 nm from the mean plane of the nitrogen atoms towards the H_2O molecule for the $[Cu(L41)(H_2O)]^{2-}$ and $[Cu(L42)(H_2O)]^{2-}$ anions respectively. In $[Cu(L41)(H_2O)]^{2-}$ the water molecule is disposed between oxygen atoms of $CH(CH_3)OCH(CH_3)$ ether bridges. Chemical and spectroscopic evidence for diamagnetism of $(NH_4)_2[Cu(L41)(H_2O)]\cdot 3/4NH_4ClO_4$ in solution indicates an oxidation state of +3 for the central atom in the complex, and for coordination of hydroxy ion rather than H_2O in the apical position at pH 8 [10, 11].

If an excess of acetaldehyde is avoided and $[C_2H_5NH_3]^+$ used as cation precipitant, then $[C_2H_5NH_3][Cu^{III}(L43)]\cdot H_2O$ is isolated as a result of the reaction with oxalyldihydrazide and molecular oxygen in the presence of copper(II) as template [12]. X-Ray data indicate square-planar coordination of the ligand to the central atom in the complex anion $[Cu(L43)]^-$ (Figure 2.1). Short Cu–N distances of 18.96, 18.83, 18.81 and 18.85 nm, as well as an absence of signals in the ESR spectra of both the solid sample and its solution, indicate an oxidation state of +3 for the copper (Eq. 2.7).

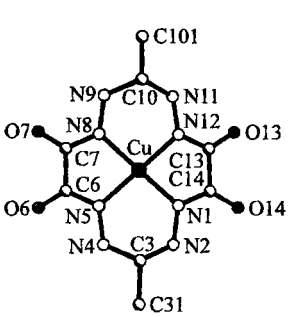
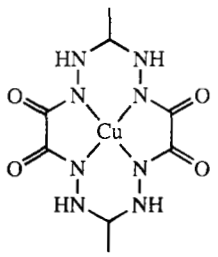
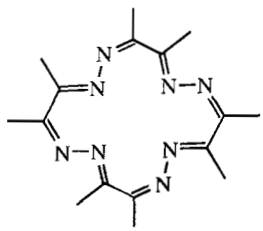


Figure 2-1. The structure of the $[Cu(L43)]^-$ anion.

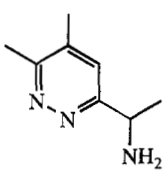


$[Cu^{III}(L43)]^+$



L44 (2.7)

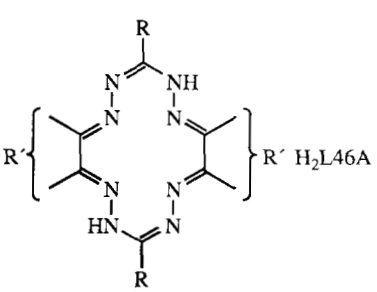
Attempts to obtain complexes with the 16-membered octaazamacrocycle L44 by interaction of diacetyl with hydrazinium halides, followed by the subsequent addition of nickel(II) or copper(II) salts and prolonged heating of the reaction mixture, led to the isolation of $[M(L45)]X_2 \cdot nH_2O$, where $X = Cl^-$, Br^-, NO_3^-, ClO_4^- or BF_4^- and $n = 0, 2$ (Eq. 2.8) [13].



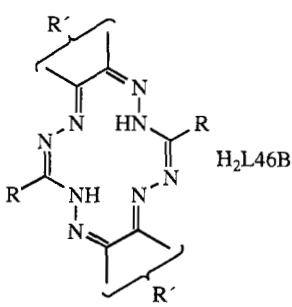
L45 (2.8)

The formation of L45 is proved by X-ray analysis of the $[Ni(L45)](ClO_4)_2 \cdot 2H_2O$ product.

Reactions of 1,2-dihydrazones of cyclic α-diketones with orthoethers in the presence of catalytic amounts of sulphuric acid result in macrocyclic systems H_2L46 [14–18], for which the two isomer structures H_2L46A and H_2L46B can be suggested (Eq. 2.9).

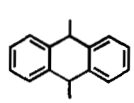


H_2L46A

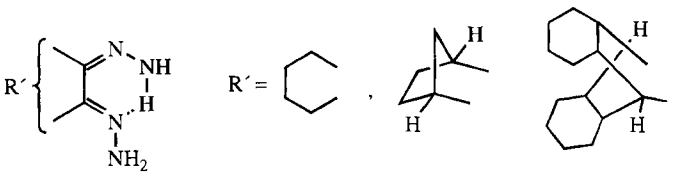


H_2L46B (2.9)

R = H, CH_3, C_2H_5, n–C_3H_7, n–C_4H_9, $(CH_2)_7CH_3$, C_6H_5, 4–CH_3–C_6H_4, 2-naphthyl

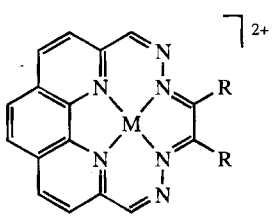
R′ = $-(CH_2)_{2-}$, $-(CH_2)_{3-}$, $-(CH_2)_{4-}$, , 

These macrocyclic compounds interact with nickel(II), cobalt(II) and iron(II) salts, yielding neutral complexes [M(L46)] [16]. The ^{1}H NMR spectra of H_2L46 and of its nickel(II) complex, and the X-ray structure analysis of [Fe(L46)], where R = $-(CH_2)_7CH_3$, R′ = $-C_{14}H_{10}$, showed that the L46B structure is present both in complexes and in the metal-free macrocycle [18]. Attempts to carry out thermal isomerization of L46B into the so far undiscovered isomeric structure L46A failed [16]. Also of note is that the initial 1,2-dihydrazones of cyclic α-diketones (from ^{1}H NMR spectra evidence) have *syn, anti* structures (Eq. 2.10) [16].



(2.10)

The existence of only one form of the dihydrazone, stabilised by intramolecular hydrogen-bonding, indicates its considerable thermodynamic stability and seems to predetermine the structure of the final macrocyclic product. Hexaazamacrocyclic products $[M(L47)]^{2+}$ are obtained by template condensation of dihydrazones of α-diketones with 1,10-phenanthroline-2,9-dicarbaldehyde on nickel(II), cobalt(II) and iron(II) matrices in methanol (Eq. 2.11) [19]. Manganese(II) and zinc(II) are not effective for building up macrocycles of the L47 type.

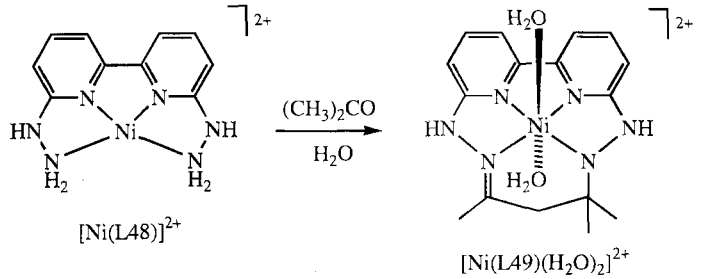


$[M(L47)]^{2+}$

R = C_6H_5, $C_6H_4OCH_3$, $C_6H_4CH_3$

(2.11)

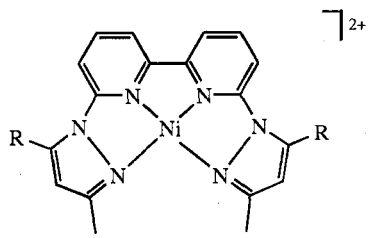
The compound 6,6′-dihydrazino-2,2′-bipyridyl (L48) can be used as ligson for production of hexaazamacrocyclic systems. On coordination to a metal ion, it forms quite strong bonds with the α-diimine nitrogen atoms and weaker bonds with the terminal amino groups. The latter are characterised by increased lability. The presence of an equilibrium between species containing the free and the coordinated amino groups is paramount in displaying nucleophilic properties. It permits the generation of a sufficient concentration of non-coordinated primary amines, necessary for condensation reaction with carbonyl compounds to proceed at a reasonable rate. Thus $[Ni(L48)](ClO_4)_2$ reacts with boiling aqueous acetone forming $[Ni(L49)(H_2O)_2](ClO_4)_2$ in almost quantitative yield (Eq. 2.12) [20, 21].



(2.12)

It needs to be noted, however, that the presence of water promoting macrocyclisation is not typical [22]. Metal-free L49 is obtained by demetallation of the $[Ni(L49)(H_2O)_2](ClO_4)_2$ with sodium cyanide in methanol [21]. Cobalt(II) complexes are obtained similarly. Iron(II) does not work as a template when one attempts to assemble L49 from the corresponding ligsons by their direct interaction with one of its salts.

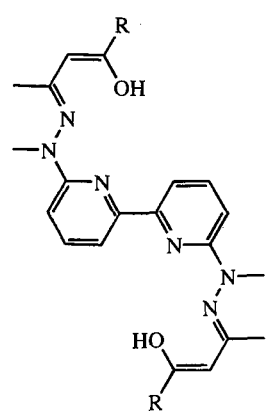
Acetylacetone and benzoylacetone react with the nickel(II) complex of 6,6′-dihydrazino-2,2′-bipyridyl, forming pyrazole derivatives [Ni(L50)] and [Ni(L51)], respectively (Eq. 2.13) [21, 22].



$[Ni(L50)]^{2+}$, R = CH_3
$[Ni(L51)]^{2+}$, R = C_6H_5

(2.13)

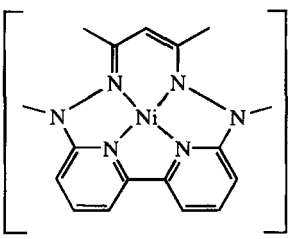
Formation of the latter can be prevented by using 6,6′-di(*N*-methylhydrazino)-2,2′-bipyridyl as the starting compound [23]. It reacts with two moles of β-diketone and gives the product L53 (Eq. 2.14).



L52, R = CH_3
L53, R = C_6H_5

(2.14)

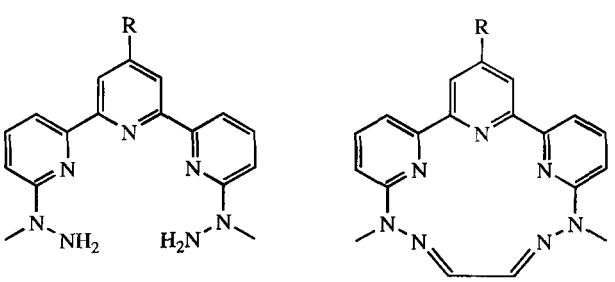
The macrocyclic product [Ni(L54)]I is isolated through refluxing an aqueous solution of L52 and nickel(II) acetate with the subsequent addition of an aqueous solution of NaI (Eq. 2.15) [23]. The diamagnetism and electronic absorption spectrum of $[Ni(L54)]^+$ indicate that it has a square-planar structure. The peak with the maximal m/z in the mass spectrum of the iodide corresponds to the $[Ni(L54)]^+$ cation. It should be noted that, in the mass spectra of a number of other macrocyclic coordination compounds of the [ML]X type, the most intense peak in the high-mass number range is $[ML]^+$ as, for example, in case of the nickel(II) complex with the 13-membered macrocycle derived from 3,7-diaza-1,9-diaminononane [24].



I [Ni(L54)]I (2.15)

Synthesis of [Ni(L54)]I occurs at pH 5. The formation rate for this macrocycle decreases substantially for pH < 5. This suggests that acid hydrolysis of the imine bond is necessary for reaction initiation. The amino group formed attacks at a carbon atom of the bound acetylacetone fragment, which is suitably positioned for metal–template interaction. The latter is likely to be decisive, if it is kept in mind that macrocyclisation does not occur when the template centre is absent. Also of note is that the L54 system is not formed in the presence of Cu^{2+}. Analysis of a molecular model of this 13-membered ring ligand gives evidence of strain in the macro-ring, due to insufficient complementarity of the interacting ligsons. The impossibility of obtaining the phenanthroline analogue of L54, even in the presence of nickel(II) [25], confirms such a suggestion, as phenanthroline is not flexible, in contrast to 2,2′-bipyridyl.

The respective complexes with L56 are obtained by template reactions of 6′,6″-bis(methylhydrazino)-4′-phenyl-2,2′:6′,2″-terpyridine (L55) with glyoxal in the presence of nickel(II) and manganese(II) ions in methanol (Eq. 2.16) [26, 27].



(2.16)

L55, R = C_6H_5
L57, R = H

L56, R = C_6H_5
L58, R = H

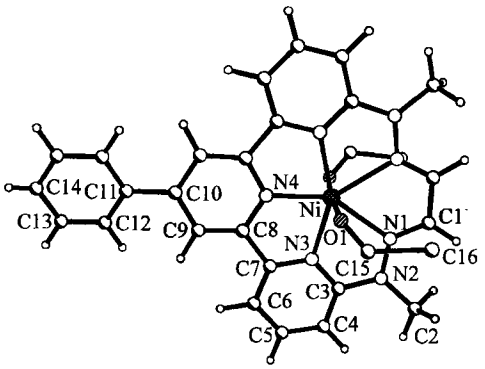


Figure 2-2. The molecular structure of the $[Ni(L56)]^{2+}$ cation.

Single crystals of $[Ni(L56)(C_2H_5OH)_2](BF_4)_2$ were isolated by recrystallisation of $[Ni(L56)(CH_3OH)_2](BF_4)_2$ from ethanol. As their X-ray analysis revealed [26], nickel(II) pentagonal-bipyramidal coordination is realised in the complex via the five nitrogen atoms of L56 in the equatorial plane and the two ethanol molecules in the axial positions (Figure 2-2).

The precursor L55 condenses with glyoxal in the presence of cobalt(II) through only one of the terminal amino groups [27] rather than through both of them, as was originally assumed [28]. Ions such as Ba^{2+}, Ca^{2+}, Sr^{2+}, Cd^{2+}, Zn^{2+}, Hg^{2+}, Rh^{3+}, Ru^{3+}, Fe^{2+} or Cu^{2+} are unsuitable for synthesis of L56 [27]. Dihydrazine derivatives L55 and L57 interact with $Sn(CH_3)_2Cl_2$ in chlorobenzene, 1,2-dichloroethane or chloroform, forming $[Sn(CH_3)_2L55]Cl_2$ and $[Sn(CH_3)_2L57]Cl_2$, respectively [28–30]. The metal-free macrocyclic products $[H_2L56](PF_6)_2$ and $[H_2L58](PF_6)_2$ are synthesised by heating methanol solutions of the corresponding complexes with glyoxal in the presence of a trace of acid, followed by removal of the SnO_2 precipitate formed and addition of NH_4PF_6. This is confirmed by mass spectra, which show intense peaks corresponding to $[L56]^+$ and $[L58]^+$ ions, as well as by the results of the X-ray structural analysis of $[H_2L56](PF_6)_2$ [27]. The metal-free macrocycle L56 is also formed in good yield as a result of reaction of L55 with glyoxal in methanol in the presence of $[Cr(H_2O)_6]Cl_3$ [27].

It should be noted that L55 reacts with glyoxal in the presence of HCl or HPF_6 by both of the end $-NH_2$ groups, even in the absence of metal ions. In this case, however, a polymeric product is isolated together with $[H_2L56](PF_6)_2$. In the light of this, the template role of the tin(IV) and chromium(III) becomes indisputable in these macrocyclisation processes, which seem to proceed through the equilibrium (2.17) [27].

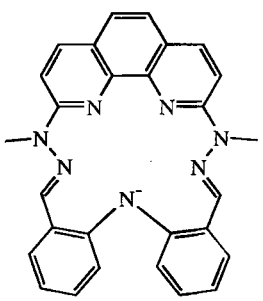
$$[M(L55)]^{n+} \rightleftharpoons [M(L56)]^{n+} \rightleftharpoons L56 + M^{n+} \qquad (2.17)$$

$$M = Sn(IV)(CH_3)_2, Cr(III)$$

According to X-ray data [29], when passing from $[Sn(CH_3)_2(L55)]^{2+}$ to $[Sn(CH_3)_2(L56)]^{2+}$, there is a considerable change in the ligand cavity size, from

23.2 to 21.0 nm. In addition, the "fit parameter" [31] decreases considerably. This seems to be one of the reasons for the kinetic destabilisation of the complex, which facilitates isolation of the synthesised macrocycle L56 in a metal-free state. Another (perhaps the main) reason, which is undoubtedly thermodynamic in origin, may be SnO_2 formation. Such behaviour, in which dimethyltin(IV) directs the course of cyclisation without tin being incorporated into the macrocyclic product, has been termed the "transient template effect" [29, 32]. It should be mentioned that the above example is one of the extremely rare cases of tin acting as template for the construction of polyazamacrocyclic products. In the case of chromium(III), the reasons are not so obvious. Nevertheless, it must be taken into account, that for chromium(III) an octahedral O_6 environment is thermodynamically more favourable than pentagonal-planar N_5 or pentagonal-bipyramidal N_5O_2 [27]. The isolated ligands L56 and L58 interact readily with nickel(II), cobalt(II), manganese(II), copper(II) and zinc(II), forming their respective complexes [27, 30].

The complexes $[Co(L59)Py_2]X$ ($X = BPh_4$ or PF_6) are obtained by reaction of 2,2′-iminobenzaldehyde with 2,9-bis(1-methylhydrazino)-1,10-phenanthroline in aqueous ethanolic solution in the presence of cobalt(II) ions and pyridine, with the subsequent addition of $NaBPh_4$ or NH_4PF_6 [33]. The macrocyclic nature of L59 was proved by an X-ray diffraction study of $[Co(L59)Py_2]BPh_4$. The cobalt(II) has distorted pentagonal-bipyramidal coordination, which is achieved through the five nitrogen atoms of the ligand (including the deprotonated one) in the equatorial plane and of the two molecules of pyridine in the axial positions (Eq. 2.18).



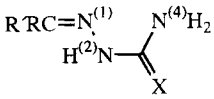
(L59)⁻ (2.18)

2.2 Hexa- and pentaazamacrocyclic systems based on chalcogensemicarbazides

Among the hydrazine derivatives, chalcogensemicarbazides $H_2N^{(1)}-N^{(2)}H-C^{(3)}(X)-N^{(4)}H_2$ (X = S, Se), containing non-equivalent terminal $-NH_2$ groups, as well as chalcogen donor atoms, and isochalcogensemicarbazides $H_2N-N=C(XR)-NH_2 \cdot HI$, substituted at the sulphur (selenium) atom, are of special interest for the synthesis of macrocyclic compounds.

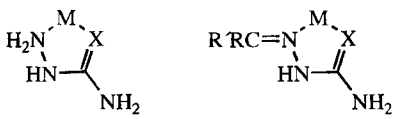
Chalcogensemicarbazides participate in condensation reactions with aldehydes and ketones solely via the nitrogen atom $N^{(1)}$. As a result, the Schiff bases –

chalcogensemicarbazones are formed (Eq. 2.19) [34–36].



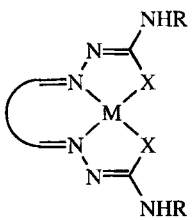
(X = S, Se) (2.19)

The chalcogenamide group is less active and does not condense with aldehydes or ketones under the usual conditions. In their metal complexes the chalcogensemicarbazides and chalcogensemicarbazones use the sulphur (selenium) atom for coordination, yielding chelate rings where X = S, Se (Eq. 2.20) [34, 37–41].



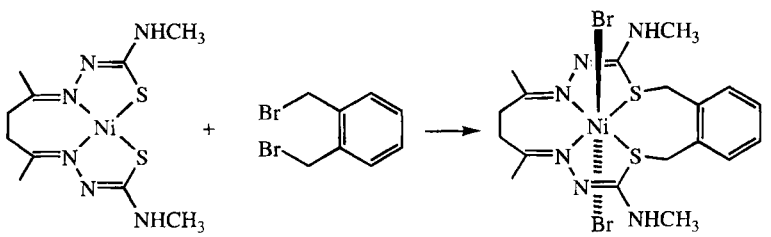
(2.20)

With dicarbonyl compounds, the chalcogensemicarbazides form a number of products. Among them are the corresponding bis-thio(seleno)semicarbazones, which give square-planar chelates (Eq. 2.21) [42–47].



[M(L60)]
R = H or alkyl
X = S, Se (2.21)

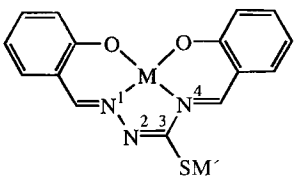
Owing to their geometry, such inner complex compounds may serve as suitable precursors for the synthesis of macrocyclic systems. At present, however, only one product of this type is known; it proved possible to perform a macrocyclisation template reaction employing 1,2-bis(bromomethyl)benzene as ring closure agent (Eq. 2.22) [48].



[Ni(L61)Br2] (2.22)

It was postulated earlier [49], that thiosemicarbazide cannot use its nitrogen atom $N^{(4)}$ for coordination to a d metal ion. But in 1971–1973, the condensation of 2-hydroxybenzaldehyde thiosemicarbazone with 2-hydroxybenzaldehyde in the

presence of oxovanadium(IV), nickel(II), and copper(II) as matrices in alkaline medium was carried out. On the basis of elemental analysis, electronic spectra, magnetic measurements [50–52] and the results of mass spectrometric research [53–55] it was concluded that all complexes isolated have the composition and structure given in Equation (2.23).

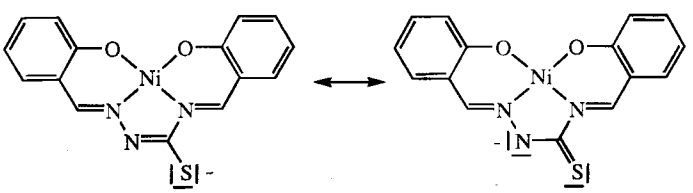


M′[M(L62)], where M = VO, Ni, Cu,
M′ = NH_4, Na, K (2.23)

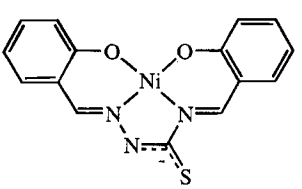
This was an unexpected result for these ligands, on the basis of normal behaviour of chalcogensemicarbazides. It showed clearly that, under certain conditions, the thioamide nitrogen instead of the sulphur atom can be involved in coordination. Furthermore the condensation via N^4 with 2-hydroxybenzaldehyde takes place. Quite recently the structure of K[Ni(L62)]·1/3H_2O·1/3DMF was established by X-ray diffraction [56], revealing that the crystal consisted of K^+ cations, three crystallographically independent complex anions $[Ni(L62)]^-$ (A, B, C), molecules H_2O and DMF in the ratio 3:3:1:1. The structure of the complex anion A is shown in Figure 2-3.

The ligand in K[Ni(L62)] acts as tetradentate (N_2O_2), triply deprotonated. The sulphur atom, as suggested [50–55], is not involved in coordination to the nickel ion. The interatomic distances N1–N2, C1–N3, N2–C1 and C1–S (14.4(2), 14.7(2), 13.0(3) and 16.5(2) nm, respectively) indicate the distribution of the excess negative charge over the fragment N2–C1–S in $[Ni(L62)]^-$. The structure of the complex anion can be represented by two canonical forms (Eq. 2.24), which may be expressed as shown in Equation (2.25). Spreading of the charge leads to enhanced stabilisation of the resonance hybrid structure of $[Ni(L62)]^-$.

Template synthesis of the chelates M′[M(L62)] , which proceeds according to Scheme 2-1, is achieved in aqueous alkaline medium, being performed more easily



(2.24)



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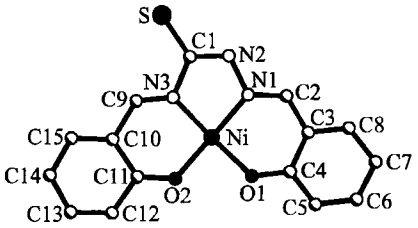
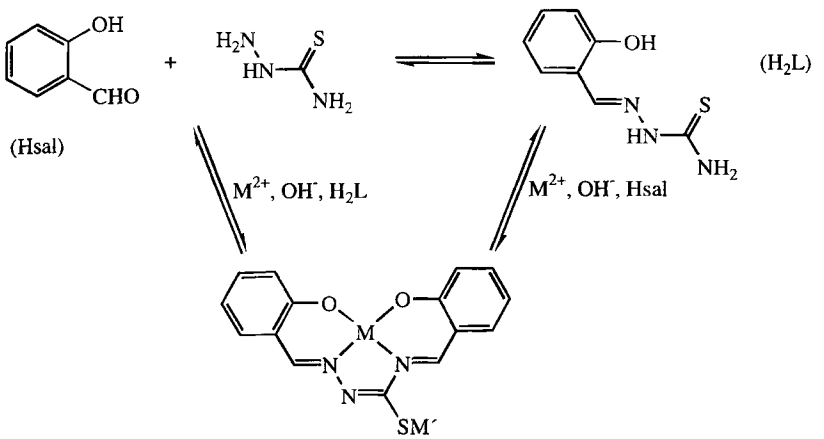
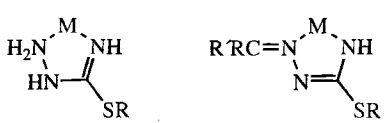


Figure 2-3. The structure of the crystallographically independent anion $[Ni(L62)]^-$ (A) in the crystal of $K[Ni(L62)]\cdot\frac{1}{3}H_2O\cdot\frac{1}{3}DMF$; anions B and C have very similar structural parameters.



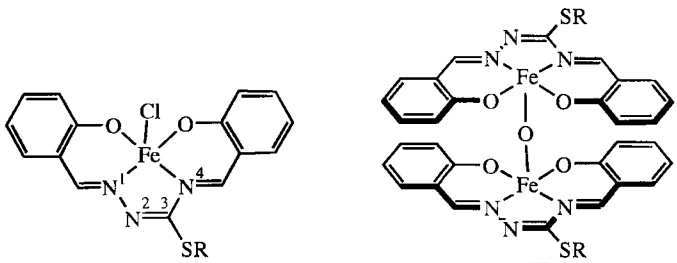
Scheme 2-1. Template synthesis of chelates M′[M(L62)], where M′ = NH_4, Na, K; M = VO, Ni, Cu.

for VO^{II} and Ni^{II} and with relatively more difficulty for Cu^{II} [50–55]. Other 3d elements have proved to be non-effective as templates under analogous conditions. Complexes M′[M(L62)] can be readily alkylated at the sulphur atom or oxidised with iodine with formation of dimers connected via an S–S bond [50–56]. These results clearly demonstrate that the traditional mode of coordination of chalcogensemicarbazides and/or chalcogensemicarbazones (through the hydrazine amino group and sulphur atom) can in principle be varied. According to the hard and soft acids and bases (HSAB) principle 3d metal ions as borderline intermediate acids should form bonds both to soft and hard bases (sulphur and nitrogen, respectively). A kind of competitive behaviour of both sulphur and nitrogen atoms of the thioamide group toward coordination to a d metal ion is a special feature of this kind of ligson. Isothiosemicarbazides, obtained by alkylation of thiosemicarbazide and isothiosemicarbazones (the products of condensation of isothiosemicarbazides with aldehydes or ketones), coordinate to the 3d metal ions through terminal nitrogen atoms (Eq. 2-26) [57–61].



(2.26)

This can easily be explained by taking into account the weaker donor properties of thioether sulphur atoms as compared to thiol or thione sulphurs [62]. This mode of coordination of isothiosemicarbazones was later used for carrying out similar condensation reactions in the presence of other metal ions as templates. Thus by interaction of equimolar amounts of 2-hydroxybenzaldehyde *S*-methylisothiosemicarbazone, anhydrous iron(III) chloride, and 2-hydroxybenzaldehyde in a mixture of absolute ethanol and DMF the template reaction became possible, giving rise to the formation of [Fe(L62)Cl] (Eq. 2.27) [63]. The synthesis of dimers $[Fe(L62)]_2O$ (R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9) was performed by reaction of 2-hydroxybenzaldehyde *S*-alkylisothiosemicarbazone and 2-hydroxybenzaldehyde with anhydrous $FeCl_3$ in absolute ethanol or *n*-butanol, followed by addition of triethylamine as base [64]. For these complexes the possibility was established of mutual transformations (Eq. 2.28).



[Fe(L62)Cl] [Fe(L62)]$_2$O (2.27)

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9

$$[Fe(L62)Cl] \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} [Fe(L62)]_2O \qquad (2.28)$$

The third type of complex, $[Fe(L62)(NCS)H_2O]$, was obtained by acid hydrolysis of the μ-oxodimer in the presence of LiNCS. By interaction with pyridine $[Fe(L62)(NCS)H_2O]$ was transformed into [Fe(L57)(NCS)Py] [65].

Under the conditions given in ref. [64] and by using the corresponding metal perchlorate as template salt, the zinc(II) chelate with H_2L62 was isolated from absolute methanol solution [66]. In a similar template fashion, cobalt(II) and manganese(II) complexes have been synthesised using sodium acetate as base in an inert atmosphere from methanol solutions of the corresponding acetates, 2-hydroxybenzaldehyde *S*-alkylisothiosemicarbazones and 2-hydroxybenzaldehyde [67, 68]. The chromium(III) coordination compound with H_2L62 has been obtained starting from Reinecke's salt in ethanol [69].

The structures of the coordination compounds of copper(II), manganese(III), iron(III) and zinc(II) with H_2L62 have been established by X-ray diffraction [61, 63–65, 68, 70, 71].

The UO_2^{2+} ion, which is bigger than 3d metal ions, was also used as template. The synthesis was carried out [72] by adding 2-hydroxybenzaldehyde to a hot

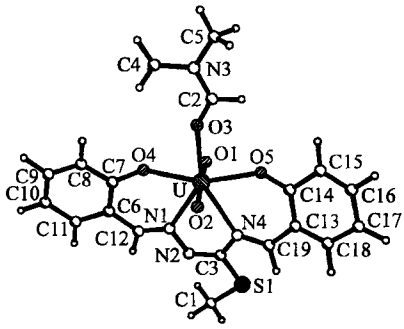
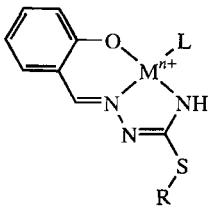


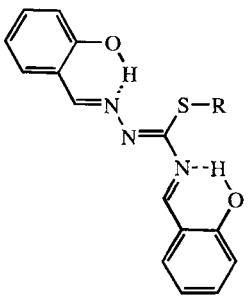
Figure 2-4. The molecular structure of $[UO_2(L62)DMF]$.

methanol or ethanol solution of $UO_2(CH_3COO)_2 \cdot 2H_2O$ and 2-hydroxybenzaldehyde *S*-methylisothiosemicarbazone. In so doing $[UO_2(L62)CH_3OH]$ and $[UO_2(L62)C_2H_5OH]$ were isolated. Recrystallisation of the latter from DMF afforded $[UO_2(L62)DMF]$. Its structure has been shown by X-ray diffraction to be a distorted pentagonal bipyramid with the tetradentate ligand and the molecule of DMF coordinated in the equatorial plane of the uranyl moiety (Figure 2-4) [72]. It is obvious that when passing from iron(III), manganese(III) or zinc(II) complexes [58, 63, 71] to $[UO_2(L62)DMF]$ [72], distances between the central atom and donor atoms of $(L62)^{2-}$ are considerably increased, to 22.0(2), 22.7(2) nm for U–O and 25.4(2), 25.9(2) nm for U–N.

The presence of a template metal ion and of a base is crucial for the success of the condensation of 2-hydroxybenzaldehyde *S*-alkylisothiosemicarbazone with 2-hydroxybenzaldehyde via the terminal $-NH_2$ group of isothiosemicarbazone. In principle, coordination of an amine to a metal ion leads to the loss of the nucleophilicity of the ligand as the non-bonded pair of the nitrogen atom is involved in metal-ligand interaction. However, the acidity of isothiosemicarbazones increases upon coordination due to the polarisation effect of metal ions. The higher the metal ion oxidation state, the stronger is its polarisation effect. The deprotonation of the terminal amino group takes place easily in the presence of highly charged Fe^{3+} and a weak base (DMF) or in the presence of doubly charged Zn^{2+} and a strong base (NEt_3). It results in generation of a deprotonated nucleophilic intermediate (Eq. 2-29), where L is a molecule of solvent or other monodentate ligand, R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, capable of further interaction with electrophilic 2-hydroxybenzaldehyde with the formation of the new chelate ring. The complementarity between the stereochemical demands of the template metal ion and the ability of the assembled ligand product to satisfy them (fully or in part) by square-planar coordination around the metal centre should be mentioned as well. The final step of a template process ends with a release of the matrix used for assembly of the final product. The demetallation of [Ni(L62)], where R = alkyl, was performed by reaction with dry hydrogen chloride in acetone [71]. X-Ray diffraction of the metal-free ligand product H_2L62 (R = CH_3) revealed its *E*-configuration (the groups of higher precedence are on opposite sides of the N=C double bond) to be stabilised by two intramolecular hydrogen bonds (Eq. 2.30).



(2.29)

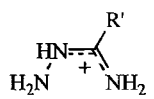


H_2L62 (R = CH_3)

(2.30)

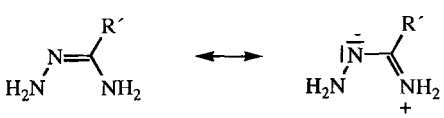
Several publications [50–55, 61, 63–71] have now demonstrated the practicality of condensation of *S*-alkylisothiosemicarbazide via the end N^4 atom with carbonyl compounds, and have given an impetus to further investigations on template synthesis of complexes with chelating ligands. At the same time, possibilities for assembling macrocyclic systems by means of various carbonyl building blocks and *S*-alkylisothiosemicarbazides have emerged. In particular pentan-2,4-dione and its derivatives have proved to be suitable partners in such processes.

Before considering template reactions involving isothiosemicarbazides, their structure and general properties deserve special comment. *S*-Alkylisothiosemicarbazides, like other isochalcogensemicarbazides and amidrazones, are monoacid bases, which form salts with inorganic acids (Eq. 2.31).



X^-, where R' = SR, SeR, OR, R (R = alkyl); X = I, Br, Cl, NO_3 (2.31)

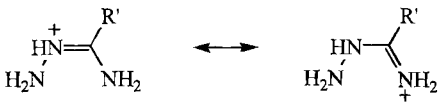
All these derivatives are unstable as free bases and hydrolyse in alkaline solution. The difference in stability of the free bases and monoacid salts can be explained in terms of resonance theory. The structure of the free base can be looked on as shown in Equation (2.32).



(2.32)

However, the charge separation in the second canonical form does not contribute greatly, if at all, to the true structure. For the cation, the structure can also be rep-

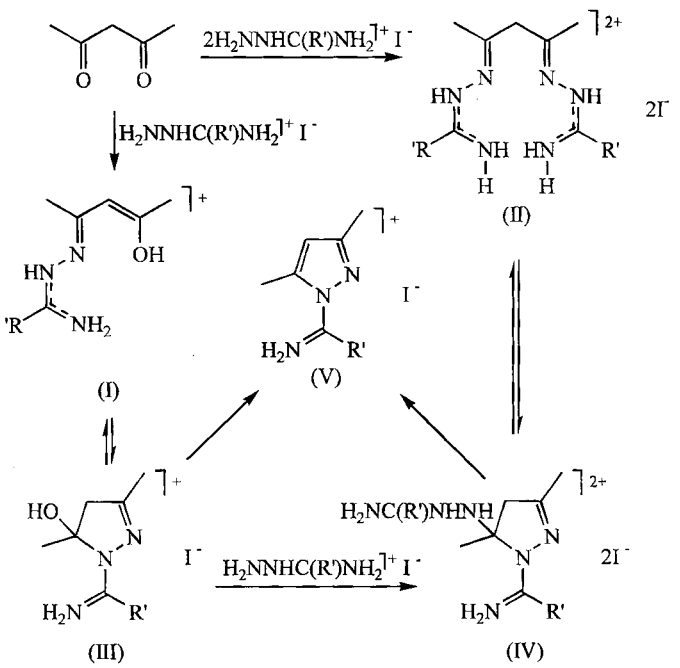
resented by two canonical forms (Eq. 2.33), but their contributions to the hybrid structure are now nearly equal.



(2.33)

Spreading the charge increases the stability of the cation with respect to the free base. This suggestion has been supported by the distribution of bond lengths in the crystal structure of *S*-methylisothiosemicarbazidium nitrate [73]. It should be also noted, that all these derivatives should exhibit reducing properties like hydrazine itself. We mention here the very stable complexes $[Pt^{II}\{HN{=}NC(R){=}NH\}_2]$, where R = *t*-$C_4H_9$ or 3,4-dimethoxyphenyl [74, 75]. Like dithiolene derivatives [76], isochalcogensemicarbazones and amidrazones should be considered as potentially "non-innocent" ligands [77]. New evidence of the complicated, but extremely interesting, behaviour of these kinds of ligands is given in the following discussion.

Pentan-2,4-dione reacts with isochalcogensemicarbazides and amidrazones yielding as a rule the corresponding pyrazole (V) as a final product (Scheme 2-2) [78–81]. The reaction proceeds via the formation of either open-chain mono- (I) or bis-(isochalcogensemicarbazones) and/or amidrazones (II), or the cyclic hydroxy-

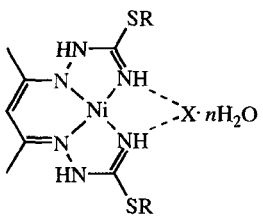


Scheme 2-2. Possible routes of reaction of pentan-2,4-dione with isochalcogensemicarbazones and amidrazones.

pyrazoline intermediates (III and/or IV). The mono-*S*-methylisothiosemicarbazone of pentan-2,4-dione has been successfully synthesised using a twofold excess of pentan-2,4-dione [82].

Attempts to isolate pentan-2,4-dione bis-(*S*-alkylisothiosemicarbazones) or bis-amidrazones in the solid state have been unsuccessful [78, 81].

The course of the multistep process depicted in Scheme 2-2 can be controlled to a great extent by metal coordination. Thus the reaction of equimolar amounts of *S*-alkylisothiosemicarbazonium salts with pentan-2,4-dione in methanol or ethanol in the presence of nickel(II) acetate is directed toward the formation of pentan-2,4-dione bis-(*S*-alkylisothiosemicarbazones), which have been isolated as $[Ni(H_2L63)]X{\cdot}nA$, where X = I, Cl, NO_3 or PF_6 and A = H_2O or CH_3OH (Eq. 2.34) [83, 84]. Note that repeated heating of the filtrate after the isolation of the precipitated product affords further portions of the nickel(II) complex; a nearly quantitative yield of the desired material may be reached.



$[Ni(H_2L63)]X \cdot nH_2O$

R = alkyl, X = I
R = $CH_2C_6H_5$, X = Cl
R = CH_3, X = NO_3, Cl, PF_6 (2.34)

Varying the ratio of interacting ligsons does not affect the general pathway of the reaction. No other products have been detected. An X-ray diffraction study of the iodide salt, methylated at the sulphur, confirmed the formation of pentan-2,4-dione bis-(*S*-methylisothiosemicarbazone) [84]. The latter, as can be seen from Figure 2-5, acts as a monodeprotonated tetradentate ligand coordinated in square-planar mode to the nickel(II). Obviously, the coordination of two imine groups to the nickel(II) ion results in higher acidity of adjacent methylene protons of the β-diketonate moiety. It is likely that CH_3COO^- acts as a base here, facilitating the deprotonation of the ligand.

It is worth noting that the formation of the same ligand product occurs, if the

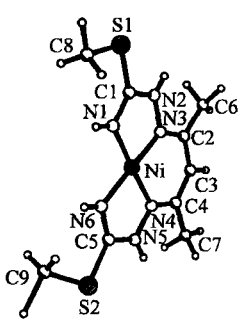


Figure 2-5. The structure of the cation $[Ni(H_2L63)]^+$.

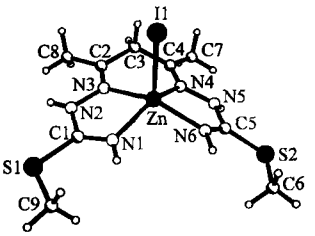


Figure 2-6. The structure of the cation $[Zn(H_3L63)I]^+$.

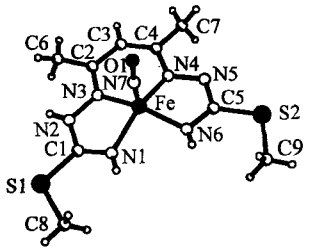


Figure 2-7. The structure of $[Fe(HL63)NO]^+$.

metal ion is added to the equimolar mixture of the corresponding ligsons after their prior heating under reflux in the presence of Na_2CO_3. Thus, using cobalt(II) and copper(II) as templates and carrying out the reaction under an inert atmosphere, $[Co^{II}(H_2L63)]I\cdot 1/2CH_3OH$ and $[Cu(H_2L)]I$ methylated at sulphur atoms have been prepared [85]. These results indicates that the metal ion plays a stabilising and sequestering role in the above condensation process, shifting the equilibrium towards the formation of the desired pentan-2,4-dione bis-(*S*-alkylisothiosemicarbazone). The thermodynamic template effect seems to be dominant in these reactions.

The methyl derivative of $[Co^{II}(H_2L63)]I\cdot 1/2CH_3OH$ has also been prepared [86] by reaction of Hacac with *S*-methylisothiosemicarbazonium iodide in the presence of $Co(CH_3COO)_2\cdot 4H_2O$ in methanol in an inert atmosphere. Zinc(II) and iron(II) also proved to be effective templates for generation of bis-adduct species. In this case, however, the corresponding ligand product is coordinated in the neutral form, and isolated as $[M(H_3L63)I]I$, where M = Zn or Fe [85]. Note that, as template salts, the corresponding iodides have been employed. The structure of the cation $[Zn(H_3L63)I]^+$ is shown in Figure 2-6.

The complex $[Fe(HL63)NO)]NO_3$ with R = CH_3 has been synthesised by template interaction of *S*-methylisothiosemicarbazidium nitrate, sodium acetylacetonate monohydrate, and $Fe(NO_3)_3\cdot 9H_2O$ in ethanol. An X-ray diffraction study has revealed that the cation $[Fe(HL63)NO)]^+$ has a square-pyramidal structure (Figure 2-7) with the corresponding twice deprotonated quadridentate ligand $(HL63)^{2-}$ around the central ion in the basal plane (iron deviation from this plane is 4.77 nm) and the NO in the apical position [87, 88].

The iron complexes [Fe(L63)I] have been obtained using *S*-alkylisothiosemicarbazidium iodide as the starting material [89]. An X-ray diffraction study of

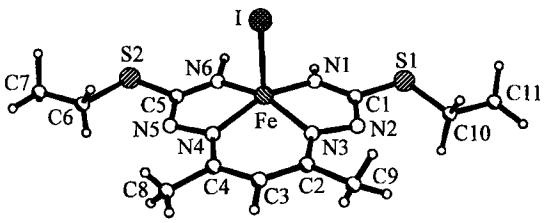
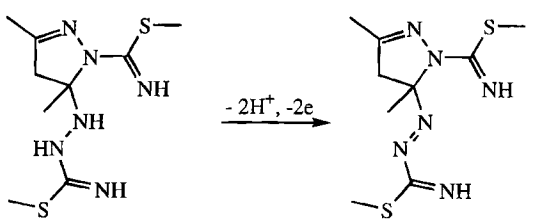


Figure 2-8. The molecular structure of [Fe(L63)I].

the compound with R = C_2H_5 was undertaken. As for the previous complex, the structure (Figure 2-8) is a square pyramid with the donor atoms of the thrice deprotonated organic ligand $(L63)^{3-}$ in its base, iodide ion in the apical position, and the iron atom displaced from the basal plane by 3.89 nm towards I^-. Structural data for this thioethyl derivative, as well as results of mass-spectrometric and Mössbauer and magnetic measurements on the four substances, indicated that the central atom in these complexes has the unusual +4 oxidation state.

In light of this, it should be noted that in $[Fe(HL63)NO]NO_3$, within the framework of the classical valence description, the fragment Fe–NO corresponds to the state $Fe^{IV}NO^- \leftrightarrow Fe^{III}NO$, significantly displaced to the right. In this way, ligand H_3L63 manifests a tendency to stabilise iron in the high valence state [87, 88].

The course of the process shown in Scheme 2-2 can be directed towards a cyclic pyrazoline intermediate tautomer (IV), if the reaction is controlled by manganese(II). An X-ray diffraction study [90] has shown that the complex $[Mn^{II}(L64)]I_2 \cdot 2CH_3OH$ is formed in this case. The ligand product can be regarded as a deprotonated cyclic pyrazoline species IV shown in Scheme 2-2 oxidised by two electrons (Eq. 2.35).



(Deprotonated tautomer IV) L64 (2.35)

Two tridentate ligands L64 are coordinated to manganese(II) meridionally. The coordination polyhedron around the central atom is a compressed octahedron with two short Mn-N distances of 18.9(1) nm *trans* to each other, and with four longer equatorial Mn-N bonds of average length 19.85 nm [90]. The above oxidation reaction is thought to be driven by the tendency to achieve maximal complementarity between stereochemical demands of the matrix, and the possibilities of the ligand product (conformational and electronic) to satisfy them.

This aspect of the fascinating chemistry of bis-isothiosemicarbazones is also connected with using redox-active metal ions as templates. It results in a change of

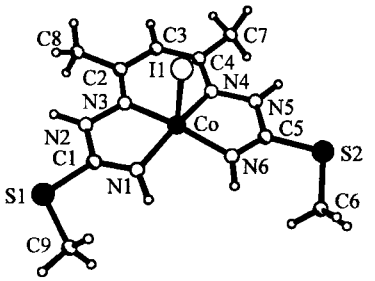
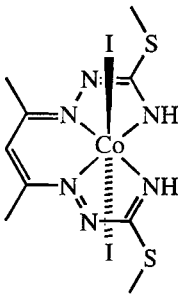


Figure 2-9. The structure of the cation $[Co^{III}(H_2L63)I]^+$.

the oxidation state of the metal ion involved, or as we have just seen, of the ligand product. This additional dimension to the chemical behaviour of templately stabilised bis-isothiosemicarbazones is most evident for cobalt and iron.

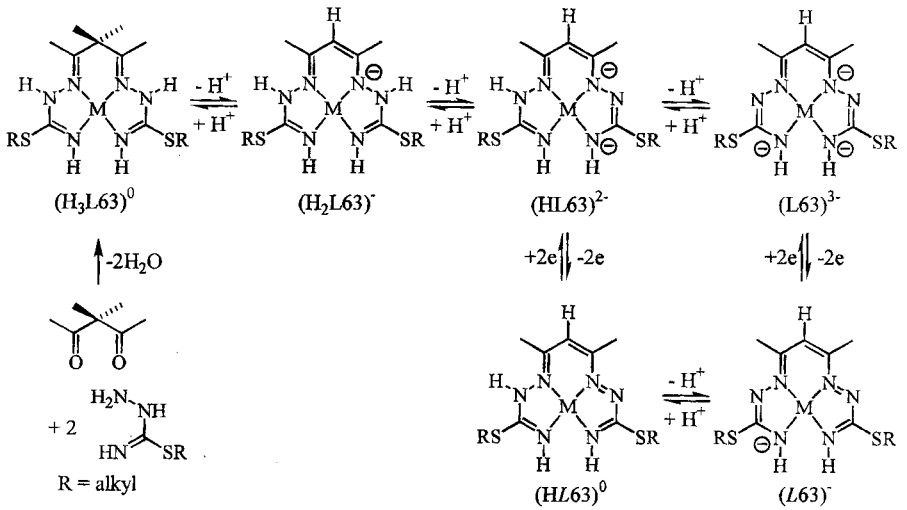
As previously pointed out, the reaction of equimolar quantities of Hacac and *S*-methylisothiosemicarbazonium iodide in the presence of $Co(CH_3COO)_2 \cdot 4H_2O$ under an inert atmosphere affords $[Co^{II}(H_2L63)]I \cdot 1/2CH_3OH$. If, however, the above reaction mixture prepared in an inert atmosphere is allowed to react with atmospheric oxygen, oxidation of cobalt(II) to cobalt(III) occurs. This results in the formation of diamagnetic $[Co^{III}(H_2L63)I]I \cdot CH_3OH$ [91]. As revealed by X-ray diffraction, the latter consists of cations $[Co^{III}(H_2L63)I]^+$, anions I^- and molecules of CH_3OH, joined together by a network of hydrogen bonds. As is seen from Figure 2-9, square-pyramidal cobalt(III) is present, which is an unusual geometry for cobalt(III).

Nitrogen atoms of the quadridentate ligand form the base of the pyramid. The terminal NH groups are 0.40 nm further from the cobalt(III) than the inner ones. The cobalt ion is above the plane of the N_4 fragment, displaced by 2.08 nm towards the apical iodide. Recrystallisation of this complex from ethanol gives a hexacoordinate complex with the two-electron-oxidised monodeprotonated form of pentan-2,4-dione bis-(*S*-methylisothiosemicarbazone) $[Co(L63)I_2]$ (Eq. 2.36) [85, 86]. The short N-N bonds (average 13.26 nm) in this complex give evidence of



$[Co(L63)I_2]$ (2.36)

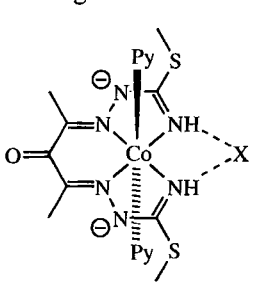
their predominantly double bond character and rule out the assignment of the ligand as the trianion $(L63)^{3-}$ [86]. Note that the corresponding bond distances in the methylated derivative $[Fe^{IV}(L63)I]$ are 13.6(1) and 13.7(1) nm respectively, [92]. The anion $(L63)^{3-}$ is formally a 14 π-electron system and $(L63)^-$ is a 12 π-electron



Scheme 2-3. Protonation steps for the 14 π-electron system $(L63)^{3-}$ and its oxidized 12 π-electron system $(L63)^{-}$.

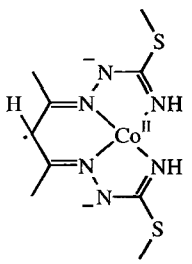
system. The "non-innocent" behaviour of this kind of ligand has also been convincingly demonstrated by the reaction of the square-pyramidal complex $[Fe^{IV}(L63)I]$ with cyanide, which gives reversibly the octahedral iron(II) species $[Fe^{II}(L63)(CN)_2]^-$ [92]. Thus the pentan-2,4-dione bis-(*S*-alkylisothiosemicarbazones) manifest complicated coordination behaviour in reactions with inactive and active transition metal ions because (i) they can exist in various protonated forms such as $(H_3L63)^0$, $(H_2L63)^-$, $(HL63)^{2-}$ or $(L63)^{3-}$ (Scheme 2-3), or (ii) they can be oxidised by two electrons, where again two different protonated forms have been identified $(HL63)^0$ and $(L63)^-$ [92, 93].

The presence of the reactive γ-carbon centre in the systems under consideration makes the chemistry of the latter even more complicated, but much more interesting as well. It has been discovered [93] that the reaction of Hacac, S-methylisothiosemicarbazonium salt and $Co(CH_3COO)_2 \cdot 4H_2O$, taken in 1:2:1 ratio and carried out in the presence of pyridine and atmospheric dioxygen, results in oxidation of the ligand product at the γ-carbon atom of the Hacac residue with generation of the complex $[Co^{III}(L65)Py_2]X$, where X = I, Cl or NO_3. An X-ray diffraction study of $[Co^{III}(L65)Py_2]NO_3$ showed [94] that it has an octahedral structure (Eq. 2.37), in which the nitrogen donor atoms of the quadridentate ligand lie in a equatorial plane



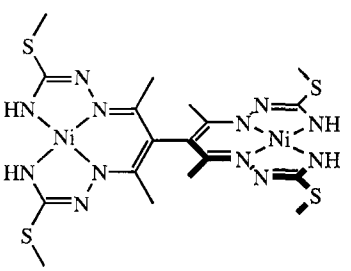
[Co(L65)]X,
where X = I, Cl, NO_3 (2.37)

and the nitrogen atoms of the pyridine molecules are in the axial positions. The distribution of electron density over the ligand indicates that the negative charges are localised on non-coordinated hydrazine nitrogen atoms. The mechanism of this particular oxidation has not been studied yet, but radical intermediates of the type shown in Eq. (2.38) are presumably involved as has been found for related transformations [95, 96].



(2.38)

Base-promoted oxidation, which leads to oxidative dimerisation products, is another viable pathway for complexes based on pentan-2,4-dione bis-(*S*-alkylisothiosemicarbazones). It has been discovered [97, 98] that the mononuclear nickel(II) complex methylated at sulphur $[Ni^{II}(H_2L63)]I \cdot 1/2CH_3OH$ reacts in an ethanol/ammonia mixture with dioxygen with formation of a dinuclear species formulated as $[Ni_2(L66)]$ (Eq. 2.39).



$[Ni_2(L66)]$ (2.39)

According to X-ray crystallographic data [93, 97] the ligand is a hexaanion $(L66)^{6-}$ and the nickel ions are formally trivalent. The unit cell contains two crystallographically independent neutral dinuclear molecules $[Ni_2(L66)]$ per unit cell. Figure 2-10 shows the structure of the independent molecule A. Each of these two crystallographically independent dinuclear molecules may be considered to be composed of two geometrically very similar halves connected by a single $C(sp^2)$–$C(sp^2)$ bond (C3–C12 in molecule A) at 15.07(7) and 14.92(8) nm (in molecule B). The carbon atoms involved in formation of these bonds are clearly sp^2 hybridised. The dihedral angle between the two mean planes defined by atoms N1, N3, N4 and N6, and N7, N9, N10 and N12 is 76.8° in A and, analogously, 71.6° in B. On the basis of electronic and NMR spectra, magnetic and electrochemical studies, and chemical properties of $[Ni_2(L66)]$, the non-innocent character of the ligand was convincingly demonstrated [93]. This complex reacts with concentrated HCl in ethanol giving the diamagnetic $[Ni^{II}_2(H_4L66)]Cl_2 \cdot 1/2C_2H_5OH$ (Eq. 2.40).

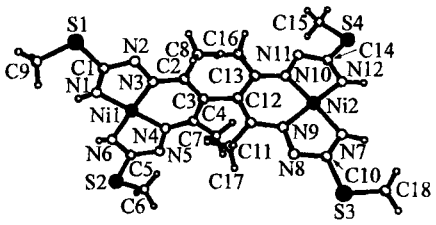
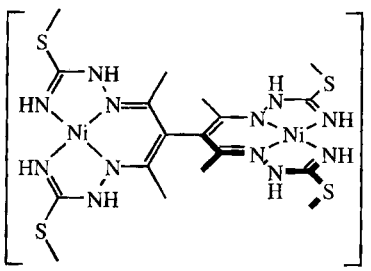


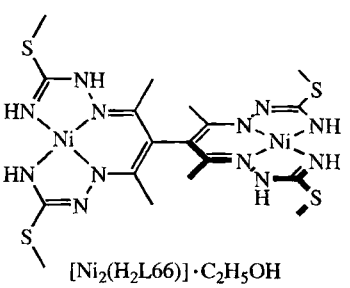
Figure 2-10. Structure of the molecule $[Ni_2(L66)]$ (A).



$[Ni_2(H_4L66)]Cl_2 \cdot 1/2C_2H_5OH$

$Cl_2 \cdot 1/2C_2H_5OH$ (2.40)

The reaction is a two-electron reduction of $[Ni_2(L66)]$ with concomitant protonation at the ligand. Deprotonation of the latter in ethanol/ammonia under argon affords the complex $[Ni^{II}{}_2(H_2L66)] \cdot C_2H_5OH$ (Eq. 2.41) [93], which is very sensitive to dioxygen.

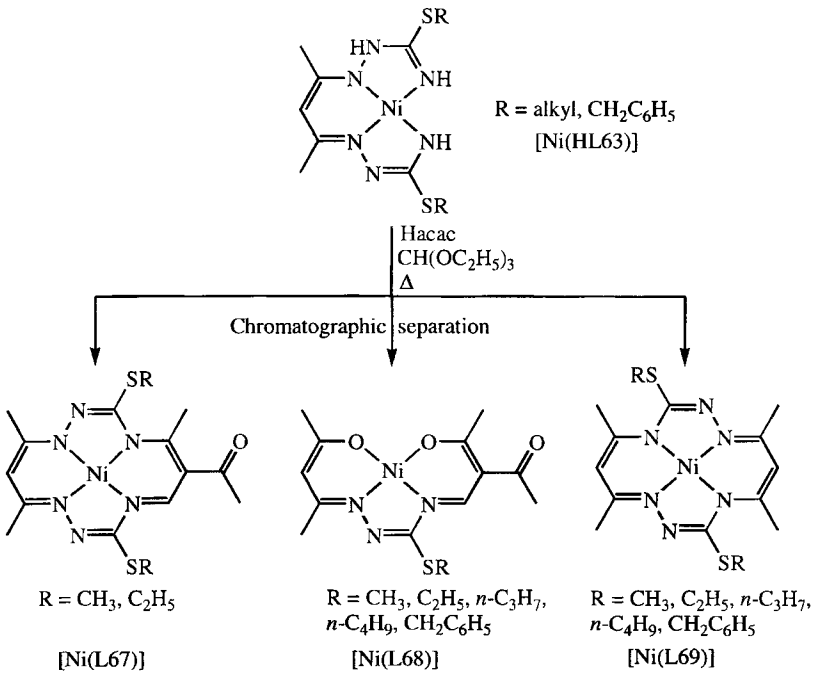


$[Ni_2(H_2L66)] \cdot C_2H_5OH$

$\cdot C_2H_5OH$ (2.41)

Thus, the template approach demonstrates the interesting behaviour of complexes based on pentan-2,4-dione bis-(*S*-alkylisothiosemicarbazones). Some are also suitable precursors for constructing macrocyclic compounds. Of these open-chain complexes, the most useful have proved to be complexes of the $[Ni^{II}(HL63)]$ family. These have been prepared by deprotonation of the species $[Ni^{II}(H_2L63)]I$ in ethanol/ammonia [93] or by template synthesis directly from the corresponding ligsons and a nickel salt in ethanol/water (1:1) in an inert atmosphere, followed by the addition of KOH [83].

Substances of three types – [Ni(L67)], [Ni(L68)] and [Ni(L69)] – were obtained by a template reaction of [Ni(HL63)] with a large excess of acetylacetone. The reaction was carried out by prolonged heating of the reaction mixture in an inert



Scheme 2-4. Template synthesis of three different types of macrocyclic and open-chain chelates.

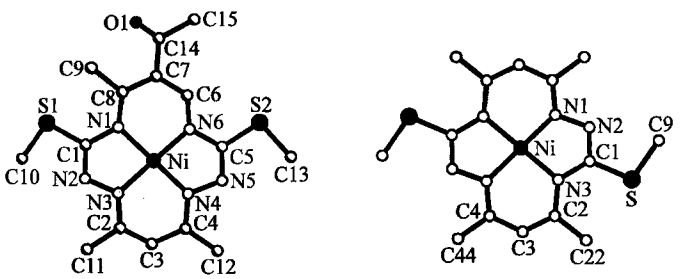


Figure 2-11. The molecular structure of [Ni(L67)] and [Ni(L69)].

atmosphere in a sealed tube, with triethyl orthoformate as a dehydrating and formylating agent, followed by the chromatographic separation (Scheme 2-4) [99–103].

The structures of [Ni(L67)] and [Ni(L69)] were established by means of X-ray diffraction [100–102]. Figure 2-11 shows the structures for R = CH_3.

Both substances have square-planar structures. It is noteworthy that complex [Ni(L67)] has a *cis* and [Ni(L69)] a *trans* disposition of –SR groups. Correlation of data concerning the lengths of the Ni–N bonds in these two compounds shows the following patterns:

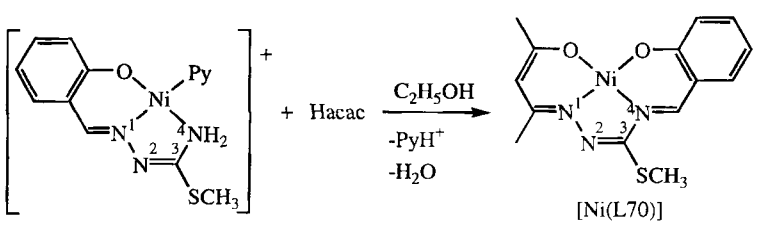
- all Ni–N bonds in [Ni(L69)] are shorter than those in [Ni(L67)];
- the *trans* arrangement of the bonds Ni–N with the amide and hydrazine nitrogen atoms results in the relative elongation of the former;
- the amide and hydrazine nitrogen atoms in [Ni(L67)] have different environments, suggesting different Ni–N bond character in this complex;
- differences in the Ni–N (amide) bond lengths in the latter (18.40 and 18.72 nm) are likely to be determined by the presence of the acetyl group in the γ-position of one of the acetylacetone residues.

Complexes [Ni(L67)] and [Ni(L69)] are characterised by molecular ion peaks of high intensity in their mass spectra, and fragmentation of the parent (molecular) ion ($P^{+\cdot}$) proceeds mainly at the expense of the peripheral groups. As to chelates [Ni(L68)], their structures follow from a number of properties, such as diamagnetism and ^1H NMR spectra as well as from the mass-spectrometric behaviour resembling [Ni(L62)] fragmentation under electron impact.

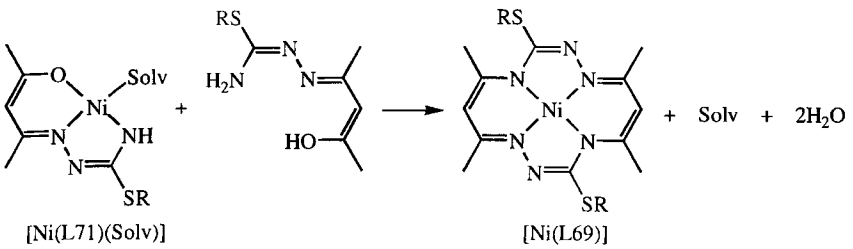
Thus N_4-chelates [Ni(HL63)] play the role of templates during the synthesis of [Ni(L67)]–[Ni(L69)]. They serve as the topological centres of orientation for the reagents interacting with them, and as the sources for the formation of fragments necessary for building up the final complexes. Both starting materials and products are coordination compounds with the low-spin square-planar configuration common in nickel(II) macrocyclic complexes. This seems to be one of the reasons why N_4-chelates have proved to be good patterns for forming the three reaction products under discussion – different in composition but similar in central atom geometry.

Synthesis of each type of complex needs a number of directed transformations, and sequestering of the desired product from equilibrium. Thus, to obtain [Ni(L68)], the hydrolysis of one of the azomethine bonds in the initial complex, followed by the 3-ethoxymethylene-pentane-2,4-dione (or 3-formylacetylacetone) condensation by the $N^{(4)}$ nitrogen atom of the isothiosemicarbazide fragment is necessary. In addition, it seems that the tricarbonyl compound condenses with the isothiosemicarbazide fragment only through the ethoxymethylene (or aldehyde) group, as this is more reactive than the ketone group [104].

The preference of the nitrogen atom of the fragment $=C(SR)NH_2$ to condense with an aldehyde rather than a ketone was also clearly shown in the case of a template reaction (Eq. 2.42) [105]. The course of this reaction implied hydrolysis of the aldimine bond of the starting complex, with the subsequent condensation of the aldehyde formed by the $N^{(4)}$ nitrogen atom and of the acetylacetone ketogroup by the isothiosemicarbazide $N^{(1)}$ nitrogen atom.



[Ni(L70)] (2.42)



Scheme 2-5. A possible way of assembling [Ni(L69)].

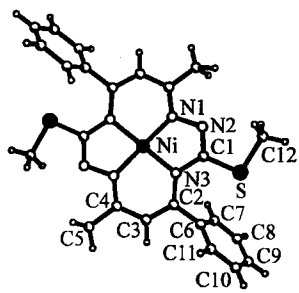


Figure 2-12. Molecular structure of [Ni(L73)].

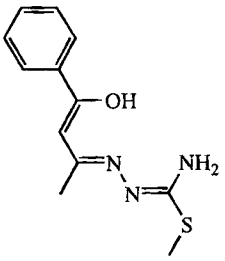
There are two ways to generate the *cis* hexaazamacrocyclic complexes [Ni(L67)]:

a) the initial complex [Ni(HL63)] is condensed with the 3-ethoxymethylene-pentane-2,4-dione (or 3-formylacetylacetone) generated in the course of reaction by the nitrogen atoms $N^{(4)}$ of the both isothiosemicarbazide residues;
b) [Ni(L68)], formed as described above, interacts with the isothiosemicarbazide, present in the solution, at both the terminal nitrogen atoms.

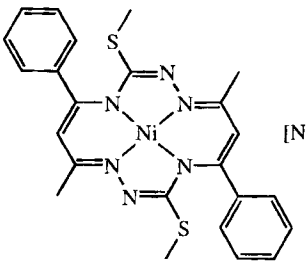
Carrying out template conversions of a mixture of [Ni(HL63)] and its $-SCD_3$ analogue showed that products are formed whose mass spectra contain peaks of ions with *m/z* values of 422 and 428, corresponding to $[Ni(L67)]^+$ and its deuterium analogue. At the same time, the peak with *m/z* 425, which would correspond to species containing both $-SCH_3$ and $-SCD_3$ groups, is absent from the mass spectra. This evidence excludes variant b) for obtaining [Ni(L67)].

Macrocyclic compounds with *trans* arrangements of *S*-alkyl groups, which have a higher degree of symmetry than [Ni(L69)], can be formed, presumably, by the template reaction of the two necessary blocks (Scheme 2-5).

It has also been shown that the formation of [Ni(L69)] proceeds in a low yield by self-condensation of pentan-2,4-dione mono-*S*-methylisothiosemicarbazonium iodide [82] in the presence of $Ni(CH_3COO)_2 \cdot 4H_2O$ in methanol. Quite recently, it has been discovered that using the even more sterically demanding benzoylacetone mono-*S*-methylisothiosemicarbazone (H_2L72) as the starting ligson, instead of its protonated salt, self-condensation in the presence of $Ni(CH_3COO)_2 \cdot 4H_2O$ in methanol proceeds in significantly higher yield (Eq. 2.43). The structure of [Ni(L73)] is shown in Figure 2-12 [106].



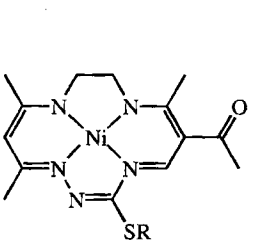
H_2L72



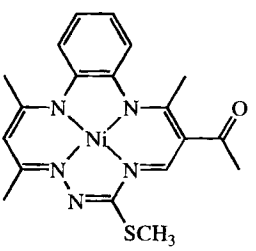
[Ni(L73)] (2.43)

For building up [Ni(L68)] the presence of [Ni(L71)(Solv)] in a reaction mixture is also necessary, in that an interaction of the latter with 3-ethoxymethylene-pentane-2,4-dione (or 3-formylacetylacetone) is the most probable way for obtaining [Ni(L68)]. The proposed assembly pathway for [Ni(L68)] and [Ni(L69)] has been supported [103] by direct template reaction of $[Ni(L71)(NH_3)]\cdot 6H_2O$ with acetylacetone and triethyl orthoformate, yielding both products. The compound $[Ni(L71)(NH_3)]\cdot 2H_2O$ is obtained by the reaction of $Ni(NO_3)_2\cdot 6H_2O$ with pentan-2,4-dione mono-*S*-methylisothiosemicarbazonium iodide ($H_3L71^+I^-$) in aqueous solution followed by addition of ammonia [82]. As follows from its X-ray structure determination, the central ion lies in a square-planar environment of the N, N and O donor atoms of the organic ligand and the nitrogen atom of the NH_3.

Pentaazamacrocyclic complexes [Ni(L74)] and [Ni(L75)] (Eq. 2.44) are synthesised by template interaction of [Ni(L68)] with anhydrous 1,2-diaminoethane or with molten *o*-phenylenediamine (*o*-phda) [107].



[Ni(L74)]



[Ni(L75)] (2.44)

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9

An X-ray diffraction study of [Ni(L74)] (R = *n*-C_4H_9) showed [108] square-planar coordination of the ligand through atoms N1, N3, N4 and N5 (Figure 2-13).

The metallocycles form angles $\leq 7.11°$ with the plane of the coordinated nitrogen donors. Both six-membered metallocycles have the *twist* conformation, which is more marked for NiN3C2C3C4N4. The ethylenediamine chelate ring adopts the *chair* conformation, whereas the isothiosemicarbazide cycle is practically planar.

Interaction of [Ni(L68)] with 1,4-diaminobutane leads to the complex [Ni(L76)] (Eq. 2.45). In this case, macrocyclisation of the starting chelate at the expense of both the diamine nitrogen atoms is not effected [107].

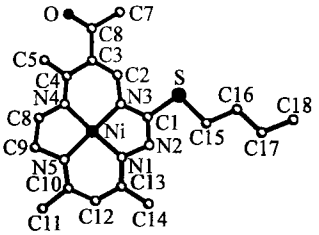
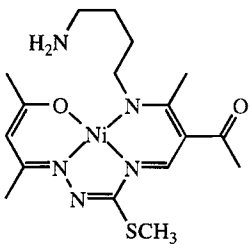


Figure 2-13. The molecular structure of [Ni(L74)] (R = *n*-C_4H_9).

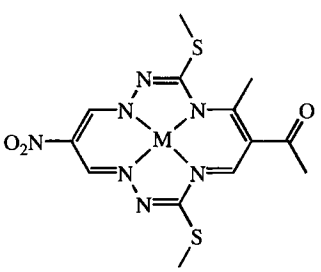


[Ni(L76)] (2.45)

The suggested formula of [Ni(L76)] is in conformity with data from IR, ^{1}H NMR spectra and mass-spectrometry. In particular, as distinct from [Ni(L74)] and [Ni(L75)], whose fragmentation proceeds at the expense of the *S*-alkylisothiosemicarbazide fragment and does not involve cleavage of the diamine metallocycle, the [Ni(L76)] mass-spectrum peaks were found corresponding to losses from the pendant 'diaminobutane' uncoordinated function [107].

Selenium analogues of [Ni(H_2L63)]I·*n*H_2O, [Ni(HL63)], [Ni(L67)] and [Ni(L68)], whose properties are very similar to those of the thio derivatives, have also been obtained by template reactions [109].

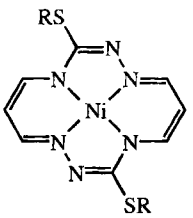
The reference data [50–61, 63–73, 78, 82–94, 97–103, 105–109] indicate that condensation of isochalcogensemicarbazides with bifunctional carbonyl compounds is a general reaction, which can be realised in the case of other aldehydes or ketones containing a second functional group in a position suitable for chelation. Thus the condensation of nitromalondialdehyde bis-(*S*-methylisothiosemicarbazone) with acetylacetone in the presence of triethyl orthoformate has been performed on nickel(II) and copper(II) matrices [110]. (Unlike Hacac, nitromalondialdehyde as its sodium salt forms the corresponding bis-(*S*-methylisothiosemicarbazone), permitting its use as starting ligson). Macrocyclic complexes [Ni(L77)] and [Cu(L77)] (Eq. 2.46) were prepared in this way.



[M(L77)], where M = Ni, Cu (2.46)

The respective $P^{+\cdot}$ are observed in the mass spectra of [Ni(L77)] and [Cu(L77)], the fragmentation of which proceeds similarly to that of the macrocyclic complexes [Ni(L67)]. The presence of the $-NO_2$ group in the [M(L77)] complexes leads to the formation of the $[M\text{-}NO]^+$ ion, a result of the molecular ion nitrate-nitrite rearrangement [111], which is familiar in the mass-spectrometry of organic nitro derivatives.

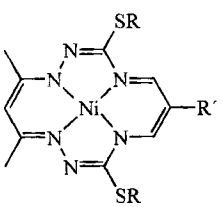
The complexes [Ni(L78)] (Eq. 2.47) can be obtained from the ligsons *S*-alkylisothiosemicarbazide hydroiodide and 1,1,3,3-tetraethoxypropane, with $Ni(CH_3COO)_2 \cdot 4H_2O$ as template source [112]. The ligand's structure is confirmed by X-ray diffraction study of the methyl derivative.



[Ni(L78)] (2.47)

R = CH_3, C_2H_5, n-C_4H_9

When 1,1,3,3-tetraethoxypropane or the sodium salt of nitromalonedialdehyde are used as ring closure agents for macrocyclisation of the precursor $[Ni(H_2L63)]I$, the complexes [Ni(L79)] and [Ni(L80)] have been obtained, respectively (Eq. 2.48) [113]. The structures of [Ni(L79)] (R = C_2H_5) and [Ni(L80)] (R = n-C_3H_7) have been reported [114].



[Ni(L79)], where R′ = H; R = CH_3, C_2H_5, n-C_3H_7, C_3H_5, n-C_4H_9
[Ni(L80)], where R′ = NO_2; R = C_2H_5, n-C_3H_7, C_3H_5, n-C_4H_9 (2.48)

It should be noted that on comparative mass-spectrometric investigation of macrocyclic complexes with *trans* (NiL69) and *cis* (NiL67) arrangements of –SR groups (R = CH_3 or CD_3) a distinct behaviour difference is observed. This consists of the exchange between the hydrogen atoms of the alkylthio groups and the hydrogen at the γ-carbon atoms of the β-diketonate fragment, which was observed for compounds with *trans* –SR groups. In contrast, the molecular ions of the complexes with *cis* –SR groups selectively eliminated the radical R· [115]. This fact can be used for analytical purposes to determine the relative arrangement of SR groups in related complexes. Recently binuclear nickel(II) complexes $[Ni_2(L81)]$ have been prepared [98] by reaction of Ni_2L66 with ethoxyacrolein in DMF/H_2O mixture

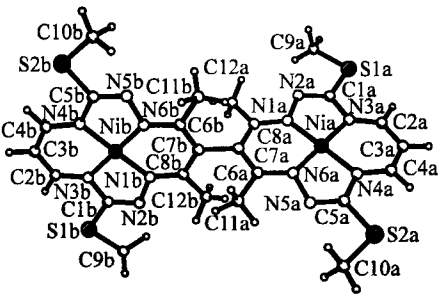
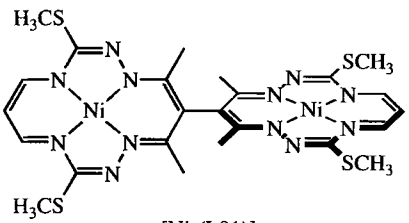


Figure 2-14. The molecular structure of $[Ni_2(L81)]$.

(Eq. 2.49). The proposed structure is confirmed by the presence of the molecular ion peak with m/z 732 in the mass spectrum of the product and by X-ray crystallography [98] (Figure 2-14).



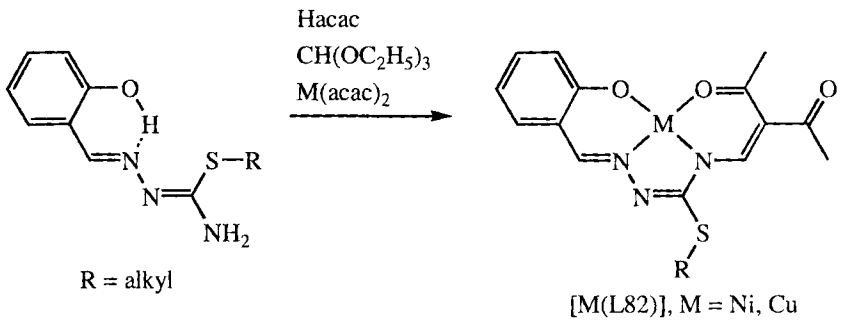
$[Ni_2(L81)]$ (2.49)

On refluxing a methanolic solution of freshly prepared $[Co(H_2L63)]I \cdot 1/2CH_3OH$ with the sodium salt of nitromalondialdehyde monohydrate, the macrocyclic complex [Co(L80)] (R = CH_3, R′ = NO_2) is formed. In its mass spectrum the peak with m/z 412 corresponding to $P^{+\cdot}$ is present [86]. This product is low spin ($\mu_B = 2.28$), like the starting compound, but in contrast to the former it is stable in air.

By refluxing a methanol solution of $[Co(H_2L63)]I \cdot 1/2CH_3OH$ with ethoxyacrolein the five-coordinate species [Co(L79)I] has been obtained. This assignment is confirmed by the presence in its mass spectrum of the peak corresponding to $[Co(L79)I]^+$ [86].

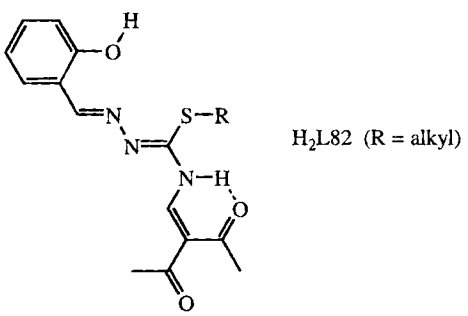
Template synthesis has also been used to construct complexes of other nonsymmetrical quadridentate ligands. Thus [M(L82)], where M = Ni or Cu, have been prepared following Scheme 2-6 from the corresponding 2-hydroxybenzaldehyde *S*-alkylisothiosemicarbazone by prolonged heating with Hacac used as ligson and solvent, and triethyl orthoformate in the presence of $M(acac)_2$, where M = Ni or Cu [116, 117].

X-Ray diffraction studies of [Ni(L82)] (R = CH_3) and [Cu(L82)] (R = n-C_3H_7) revealed their square planar structures [116, 117]. Passing hydrogen chloride into chloroform solutions of [Ni(L82)] leads to demetallation and isolation of metal-



Scheme 2-6. Template assembly of [M(L82)], where M = Ni or Cu.

free Schiff bases H_2L82 (Eq. 2.50). According to X-ray crystallographic data for the propylated derivative [118], the metal-free ligand product is stabilised in the *E*-configuration.

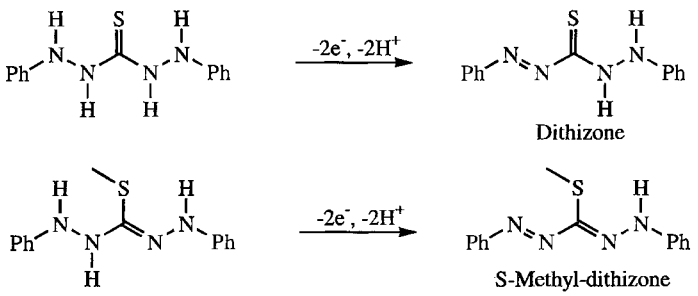


(2.50)

It is noteworthy that only one intramolecular hydrogen bond is present in the structure. Presumably, the formation of a second would destabilise to some extent the favourable π-delocalisation of electron density over the covalent backbone of H_2L82. Attempts to prepare these Schiff bases in the absence of metal ions failed. However, using $Zn(acac)_2$ and $VO(acac)_2$ as matrix sources allows one to obtain metal-free products, avoiding the supplementary demetallation step [119]. So the reaction in this case is enhanced by stabilisation of the transition state by coordination. The formation of Zn^{II} and VO^{II} complexes with H_2L82 in the presence of an excess of Hacac is not observed. The kinetic coordination template effect is likely to be dominant in this reaction. Iron(III) proved to be non-effective in promoting the above reaction. However, it easily forms octahedral complexes $[Fe^{III}(L82)(NCS)(CH_3OH)]$ by direct interaction with previously synthesised Schiff base [120]. The corresponding oxovanadium(IV) and zinc(II) complexes have also been synthesised and characterised by X-ray diffraction [119].

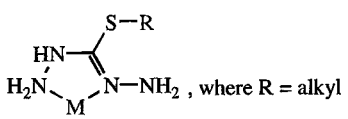
2.3 Nickel(II) octaazamacrocyclic complexes based on thiocarbohydrazide

S-Alkylisothiocarbohydrazides NH_2–NH–C(SR)=N-NH_2 are closely related to the *S*-alkylisothiosemicarbazides considered in Section 2.2. Like the latter, isothiocarbohydrazides are expected to exhibit properties of non-innocent ligands when complexed with metal ions. For example, dithizone (1,5-diphenylthiocarbazone), a well known analytical reagent, and its S-methylated derivative [121, 122] can be regarded as oxidised by two electrons to 1,5-diphenylthiocarbohydrazide and 1,5-diphenyl-3-methylthiocarbohydrazide respectively (Eq. 2.51).



(2.51)

Another resemblance is the tendency of S-alkylisothiocarbohydrazides to form five-membered rather than six-membered chelate rings by coordination to metal ions (Eq. 2.52).



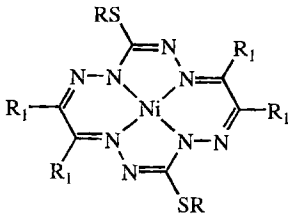
(2.52)

It is noteworthy that non-coordinated *S*-methylisothiocarbohydrazidium iodide adopts the same *cis,trans* conformation in the solid state [123]. This peculiarity, as discussed below, predetermines to a great extent the structure of the final ligand product when assembled templately.

However, in contrast to isothiosemicarbazides, where coordination to the metal ion leads to the loss of nucleophilicity of end aminogroups, isothiocarbohydrazides on binding to the metal ion still have one non-coordinated amino group, which bears a non-bonded electron pair capable of nucleophilic attack on electrophiles. Another distinction is the chemical equivalence of the end amino groups towards condensation reactions with aldehydes and ketones. This difference is displayed advantageously in the one-pot template synthesis of octaazamacrocyclic systems.

Thus macrocyclic coordination compounds of the tetradecine type are synthesised from alkylated isothiocarbohydrazidium iodides and α-dicarbonyl com-

pounds on a matrix of nickel(II) in dry ethanol, followed by the neutralisation of the reaction mixture by pyridine. By using symmetric α-diketones, it proved possible to isolate the products given in Equation (2.53) [124].



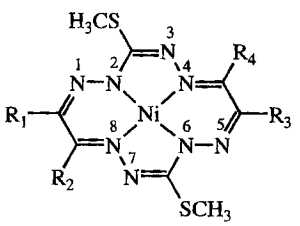
(2.53)

$R = R_1 = CH_3$	[Ni(L83)]
$R = CH_3$, $R_1 = C_6H_5$	[Ni(L84)]
$R = CH_3$, $R_1 + R_1 = [CH_2]_4$	[Ni(L85)]
$R = C_2H_5$, $R_1 = CH_3$	[Ni(L86)]
$R = C_2H_5$, $R_1 = C_6H_5$	[Ni(L87)]
$R = CH_2C_6H_5$, $R_1 = CH_3$	[Ni(L88)]

In the ^1H NMR spectra of [Ni(L83)], [Ni(L86)] and [Ni(L88)] in CF_3COOH, the methyl groups of the diacetyl fragment give two signals of the same intensity at 2.47 and 2.64, 2.43 and 2.58, 2.22 and 2.34 ppm, to confirm the suggested structure of the complexes. Mass spectra of [Ni(L83)]–[Ni(L88)] are characterised by very intense peaks of the molecular ions $P^{+\cdot}$ and peaks of the doubly charged molecular ions P^{2+}. This indicates high stability of the compounds to electron impact (EI) in the gaseous state.

The intensely coloured compounds [Ni(L83)]–[Ni(L88)] are stable when heated in air to relatively high temperatures, despite the presence of N–N bonds. Such properties are conditioned by the high degree of conjugation in the macrocycle and by the consequent decrease in the internal energy of the molecule.

Template condensation of *S*-methylisothiocarbohydrazide with methylglyoxal, with subsequent chromatographic separation of the reaction products, affords three diamagnetic metal-containing isomers [Ni(L89)] (A, B, C) differing in colour and retention factor (R_f). All species shown in Equation (2.54) give peaks for molecular ions in the EI mass spectra [125, 126].



[Ni(L89)]

A	$(R_1 = R_3 = CH_3; R_2 = R_4 = H)$
B	$(R_1 = R_4 = CH_3; R_2 = R_3 = H)$
C	$(R_1 = R_3 = H; R_2 = R_4 = CH_3)$

(2.54)

Similar results have been obtained when using *p*-tolylglyoxal as ligson. The corresponding isomers differ significantly in their ^1H NMR spectra, making it possible to identify clearly the structure of each of them.

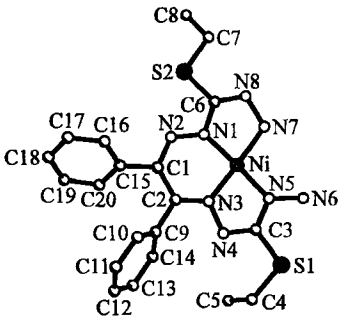
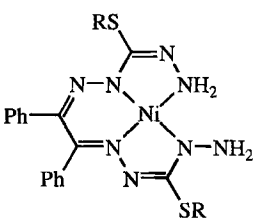


Figure 2-15. The structure of [Ni(L90)] ($R = C_2H_5$).

Mass-spectrometric study of the isomers of [Ni(L89)] showed [125, 126] that all give an intense peak for $P^{+\cdot}$ in the spectra and for the doubly charged ions P^{2+} as well. Products of $P^{+\cdot}$ fragmentation were not detected for low ionisation energies (8–13 eV) [127, 128]. Increasing ionisation energy (to 70–100 eV) causes further fragmentation of $P^{+\cdot}$.

Complexes [Ni(L90)] were obtained by adding a warm aqueous solution of *S*-methylisothiocarbohydrazide hydroiodide and nickel(II) chloride to a solution of diphenylglyoxal in ethanol at 70°C (in the reagent molar ratio 2:1:1) with subsequent addition of aqueous ammonia (Eq. 2.55) [129].



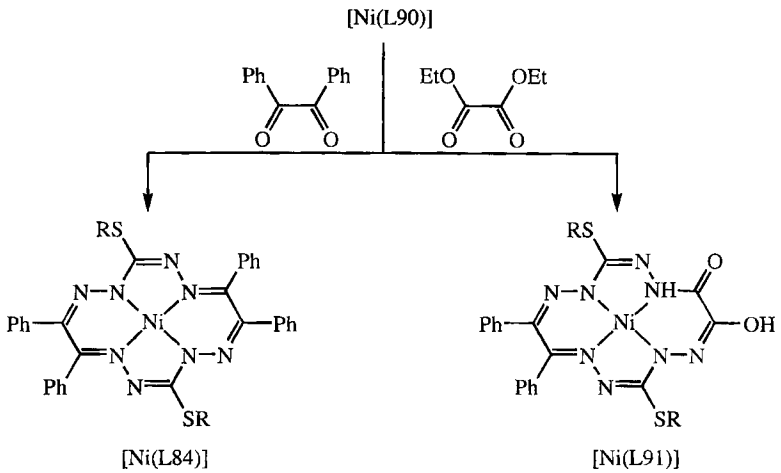
[Ni(L90)]

($R = CH_3, C_2H_5$) (2.55)

An X-ray diffraction study of [Ni(L90)]·C_2H_5OH ($R = C_2H_5$) has been reported [129]. The structure of the complex is given in Figure 2-15.

Square-planar coordination of the central atom is found in this complex. Interatomic distances for Ni-N1, Ni-N3, Ni-N5 and Ni-N7 are 17.98(4), 18.34(3), 18.49(4) and 18.88(5) nm, respectively. In this case, both isothiocarbohydrazide fragments of the ligand are again in a *cis,trans* conformation.

Complex [Ni(L90)] is structurally and electronically preorganised for cyclocondensation with bifunctional agents by the terminal $-NH_2$ groups. The fact that one of the $-NH_2$ groups is not fixed by coordination to the nickel atom, thus preserving its nucleophilicity, makes it possible to use the above-mentioned active centre in [Ni(L90)] for condensation reactions with appropriate ligsons. The second nucleophilic centre required for ring closure reaction to occur emerges presumably via deprotonation of the donor group of the ligand, due to the metal ion polarisation effect. This results in formation of a new chelate ring without any conformational transformations.



Scheme 2-7. Synthetic route to symmetric and non-symmetric octaazamacrocyclic ligand products.

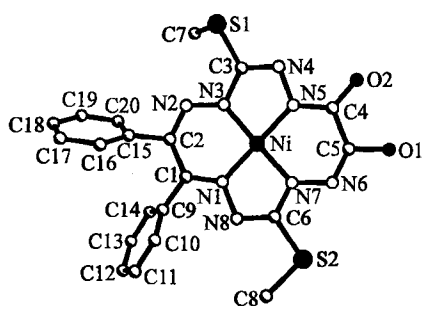


Figure 2-16. The structure of the $[Ni(L91)]^-$ anion.

This compound was used [130] as a precursor for template building of symmetric [Ni(L84)] and non-symmetric [Ni(L91)] species through interaction with diphenylglyoxal and diethyl oxalate, respectively, according to Scheme 2-7.

Thus [Ni(L90)] can be regarded as an intermediate in the synthesis of symmetric octaazamacrocyclic products [Ni(L84)]. It is also a suitable precursor for building up other non-symmetric systems, such as [Ni(L91)]. The coordinated ligand in [Ni(L91)] is rather acidic. An X-ray diffraction study, carried out on recrystallised product from acetonitrile-pyridine mixture [Ni(L91)] (R = CH_3), showed that the complex consists of the cation PyH^+ and the anion $[Ni(L91)]^-$. The structure of the latter is given in Figure 2-16 [130].

The coordination environment of the central atom in $[Ni(L91)]^-$ is square-planar. The bond lengths Ni–N1 = 18.10(5), Ni–N3 = 17.91(5), Ni–N5 = 18.11(5) and Ni–N7 = 18.06(6) nm are within the normal range for nickel(II) complexes of tetradentate 14-membered polyazamacrocyclic ligands.

The species [Ni(L90)] has proved to be an extremely suitable template-closure precursor for both α- and β-dicarbonyl compounds. Thus by refluxing [Ni(L90)]

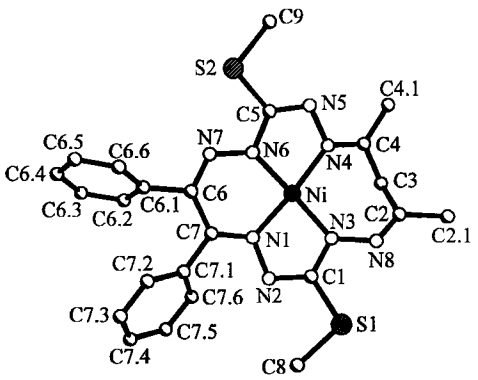


Figure 2-17. The structure of [Ni(L92)] ($R = CH_3$).

($R = CH_3$, C_2H_5) in pentane-2,4-dione, red diamagnetic products [Ni(L92)] have been obtained [131]. X-Ray diffraction has showed that both substances have similar structures with 5–6–5–7 alternation of chelate rings. Figure 2-17 shows the structure of [Ni(L92)] $R = CH_3$.

For the four nitrogens surrounding the central atom, a very small tetrahedral distortion is observed. The deviations of coordinated nitrogen atoms from the mean plane are within 1.2 nm; the central atom is displaced from the plane by 0.7 nm. The presence of the seven-membered ring has a small but significant effect on the bond lengths: Ni–N3 = 18.75(7) and Ni–N4 = 19.01(9) nm, which are noticeably longer than Ni–N1 = 18.56(9) and Ni–N6 = 18.04(7) nm, whose length is normal for five- and six-membered metallocycles. Note that the ring closure reaction and formation of a new six- or seven-membered ring involves one coordinated nitrogen atom and one non-coordinated nitrogen. The kinetic template effect is likely to be dominant in the final macrocyclisation step.

The properties of non-innocent ligands (redox-activity) for the open-chain and macrocyclic ligand products have not been revealed yet, but the research is only in its infancy. Employment of redox-active metal ions as templates should create conditions for displaying this special behaviour.

2.4 Hexaazacyclotetradecine compounds containing azo groups

Another important reaction involved in the synthesis of macrocyclic compounds is the nucleophilic displacement of halide as the leaving group in the ring-closure step. For most systems considered here, the nucleophile is a nitrogen donor, which might be coordinated to a metal ion.

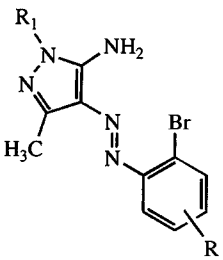
Synthesis of 5,12- or 1,8-dihydro [1, 2, 5, 8, 9, 12] hexaazacyclotetradecine compounds, in which a macrocyclic backbone is formed by aromatic or heterocyclic

nuclei and two azo groups, instead of two azomethine, may be carried out by template pathways according to two schemes:

- by the self-cyclisation of an *o*-halide-*o'*-aminoazo compound;
- by an *o,o'*-dihalideazo compound reacting with an *o,o'*-diaminoazo compound.

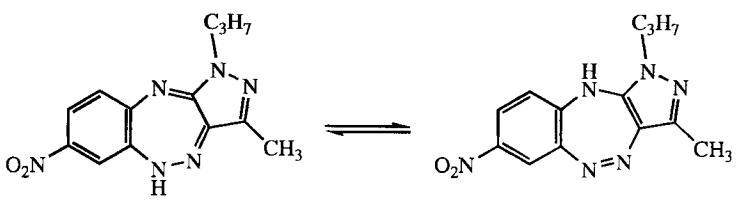
At the end of this section the synthesis of related systems is discussed. The most frequently encountered final stage in these macrocycle template syntheses is the formation of single C–N bonds.

The above-mentioned synthetic schemes for synthesis of hexaazacyclotetradecines can be successfully realised, if the reactions are controlled by the presence of suitable metal ions acting as templates. Thus, *o*-halide-*o'*-aminoazo compounds of the L93 type (Eq. 2.56; like L101, L103, L105 below) do not self-condense to give macrocycles in the absence of metal salts [132, 133].



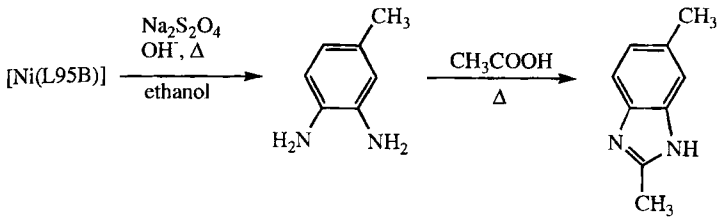
L93 (2.56)

For instance, when refluxing L93 (R = NO_2, R_1 = *n*-C_3H_7) in DMF in the presence of potassium carbonate, intramolecular cyclisation takes place with the isolation of L94. This exists in solution in tautomeric forms L94a and L94b (Eq. 2.57) [132].

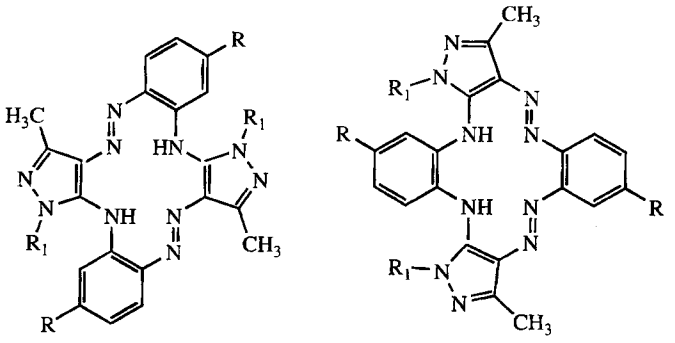


L94a L94b (2.57)

Macrocyclisation can be achieved, however, if self-condensation of ligsons L93 is carried out in the presence of nickel(II), palladium(II) or copper(II) salts [133–139]. All three metals, in DMF in the presence of K_2CO_3, promote formation of hexaazamacrocyclic compounds of the type H_2L95A, which are isolated as the appropriate complexes with doubly deprotonated ligands (Eq. 2.58) [133–137, 139]. The cases for nickel(II) are: R = H, R_1 = *iso*-C_3H_7, *n*-C_3H_7, *n*-C_6H_{13}, *n*-C_8H_{17}; R = CH_3, R_1 = CH_3, *iso*-C_3H_7, *n*-C_3H_7, C_6H_5; R = NO_2, R_1 = *iso*-C_3H_7. For copper(II) and palladium(II), R = NO_2, R_1 = *n*-C_3H_7.



Scheme 2-8. Chemical transformations of [Ni(L95B)] leading to 2,6-dimethylbenzimidazole.



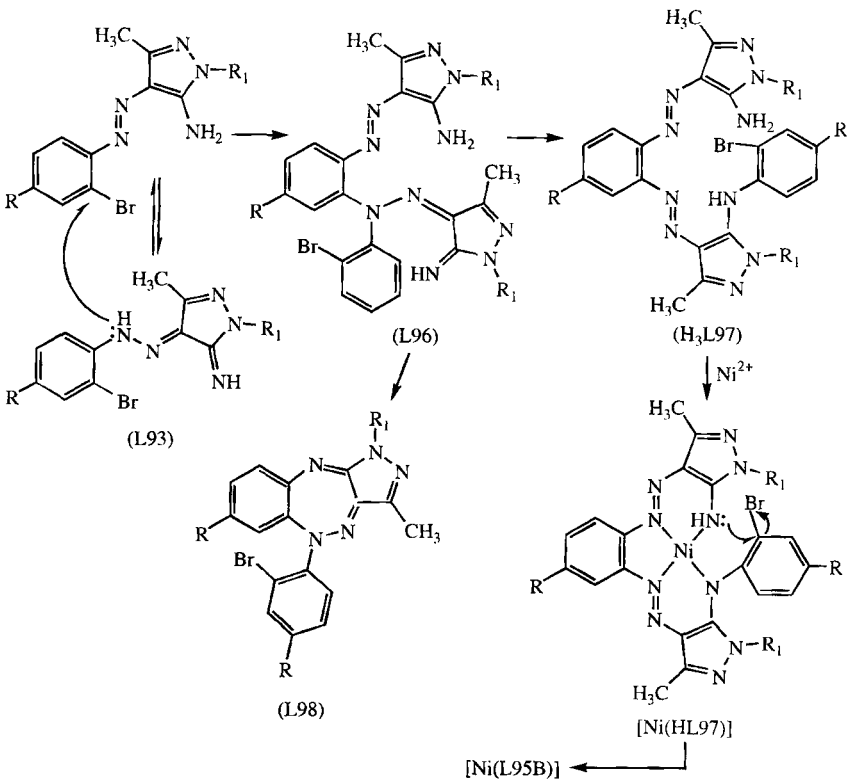
(2.58)

Regardless of the substituents in the starting ligson, palladium(II) always forms only compounds of the H_2L95A type. By way of contrast, under the conditions of the above synthesis, other ligands may be produced on nickel(II) and copper(II) matrices. For example, in the cases when R = CH_3, R_1 = CH_3, *iso*-C_3H_7 or *n*-C_3H_7 isomeric complexes of nickel(II) with H_2L95B were obtained [136, 137].

The structural isomerism of [Ni(L95A)] and [Ni(L95B)] was established by ^1H NMR, by mass spectrometry (including isotopic labelling in the latter case) and by chemical means [136, 137]. Thus on reduction of [Ni(L95B)] (R = CH_3, R_1 = *n*-C_3H_7) with sodium hydrosulfite, 3,4-diaminotoluene was isolated in alkaline medium. By heating the latter with glacial acetic acid, 2,6-dimethylbenzimidazole was obtained (Scheme 2-8) [136].

All the above-mentioned transformations can only be realised when two $-NH_2$ groups are located in the *ortho* positions of the benzene ring, as in H_2L95B. Heating the corresponding nickel(II) complexes of H_2L95A or H_2L95B in DMF in the presence of K_2CO_3 does not result in ligand isomerisation [136].

Template transformation of H_2L93 into H_2L95A presumes mutual nucleophilic attack by *o*-amino groups on halogen-bearing carbon atoms in a pair of identical ligsons, with the consequent isolation of H_2L95A. Obtaining less-symmetrical H_2L95B seems unlikely, and the mechanism of formation of this series of macrocycles must be more complicated. A method of building H_2L95B through a multistep template sequence allowing interaction of the iminohydrazone and azo forms, to yield diarylhydrazone L96, has been proposed [136]. After the intramolecular



Scheme 2-9. A possible mechanism for building up [Ni(L95B)].

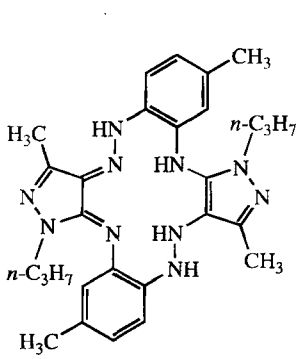
migration L96 → H_3L97 the cyclisation of H_3L97 is realised in the presence of nickel(II) (Scheme 2-9). (Although the nickel ion is explicitly indicated at the crucial ring-closure step of the diagram, its template role from the very beginning of the sequence of transformations has been supposed [132]).

Isolation of the byproduct L98 (R = CH_3, R_1 = *n*-C_3H_7) gives evidence in favour of the proposed mechanism. It is difficult to imagine its formation without the existence of the intermediate diarylhydrazone L96 [134, 136], which transforms into [Ni(L95B)] through the intermediate nickel(II) chelate of H_3L97 (R = H, R_1 = *iso*-C_3H_7) [137].

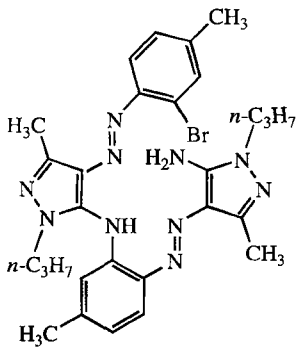
The role of Ni^{II} in the early steps is unclear. However, a kinetic template effect at the key macrocyclisation step is likely to be operative. The metal ion provides conditions for intramolecular reaction to occur by holding the leaving group and the nucleophile in suitable orientations and facilitating the deprotonation of the coordinating amine with formation of a nucleophile. The intramolecular reaction should involve nucleophilic attack by coordinated aminopyrazol on bromoaryl electrophile.

Copper(II) promotes the self-condensation of L93, along with the formation of H_2L95A (R = CH_3, R_1 = *n*-C_3H_7), yielding H_2L99 and H_2L100 (Eq. 2.59).

These are isolated as the corresponding metal complexes [139]. Since the rate of the final ring-closure reaction is relatively slow, the intermediate open-chain species accumulates during the synthesis, which allows its isolation from solution. So, the kinetic template effect of copper(II) in building up H_2L95A from H_2L100 is not pronounced. The reason for this may be the mismatch (to some extent) between the stereochemical demands of the template and the possibilities of the final ligand product (H_2L95A) to optimise the metal–ligand interaction. This suggestion is supported by the synthesis of [Cu(L99)], where complementarity is achieved by two-electron reduction of the ligand product, which increases to some extent its flexibility. Another reason is possibly the relatively low lability of a halide atom in the aryl ring in the reaction of nucleophilic substitution.



H_2L99



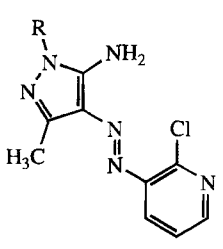
H_2L100

(2.59)

The ions Zn^{2+} [133], Fe^{2+}, Co^{2+}, Mn^{2+}, Cd^{2+} and Pb^{2+} were ineffective [136] for the assembly of H_2L95A, H_2L95B and H_2L99.

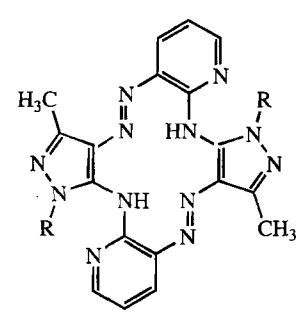
Nickel(II), palladium(II) and copper(II) coordination compounds of H_2L95A, H_2L95B and H_2L99 cannot be demetallated by concentrated mineral acids, strong complexing agents, or even by a solution of metallic lithium in dry ethylenediamine [135, 136]. The compound [Cu(L100)], which contains a chelating ligand, easily liberates copper ions under the influence of mineral acids [138].

By template self-condensation of L101 ($R = C_2H_5$) in the presence of nickel(II), cobalt(II), copper(II), palladium(II) or platinum(II) salts, hexaazamacrocyclic complexes [M(L102)] were obtained (Eq. 2.60) [140, 141].



L101

$R = C_2H_5, C_6H_5$

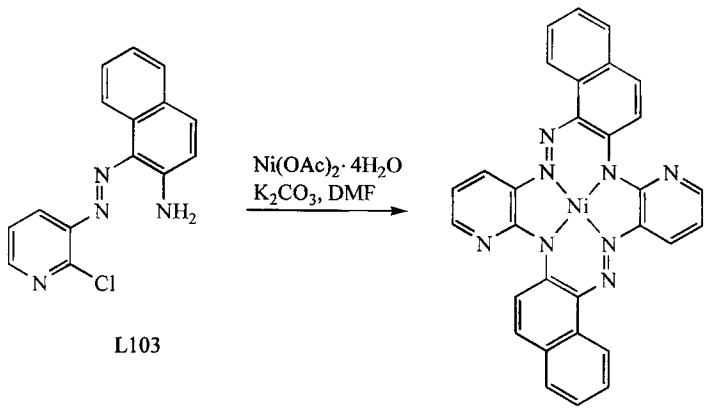


H_2L102

(2.60)

Formation of H_2L102 is confirmed by ^1H NMR spectra as well as by the presence of 100% peaks for $[P]^{+\cdot}$ in the spectra of all the isolated [M(L102)] products. Iron(II), manganese(II), lanthanum(III) and oxovanadium(IV) ions do not promote macrocyclisation of *o*-halogen-*o'*-aminoazocompounds of the L101 type [140].

By bimolecular self-cyclisation of ligson L103 in the presence of nickel(II) as template, the complex [Ni(L104)] was obtained (Eq. 2.61) [142].



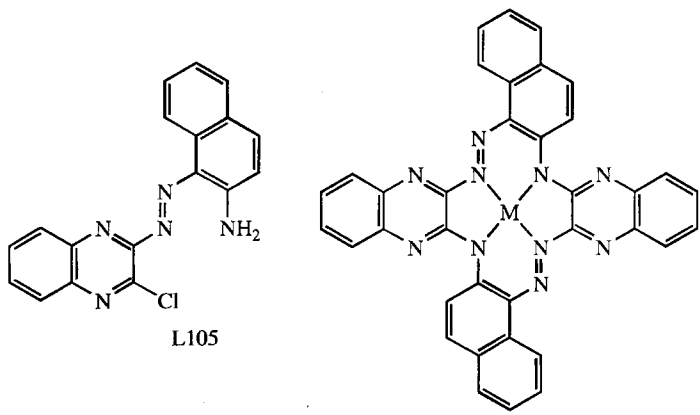
L103

[Ni(L104)]

(2.61)

Synthesis of H_2L104 cannot, however, be carried out in the presence of K^+, Ca^{2+}, Mg^{2+}, Zn^{2+}, Cd^{2+} or Pd^{2+} ions, or in the presence of boric acid salts.

Hexaazatetradecine systems [M(L106)] have been obtained from the *o*-halogen-*o'*-amino derivative L105 on nickel(II) and palladium(II) matrices (Eq. 2.62) [143].



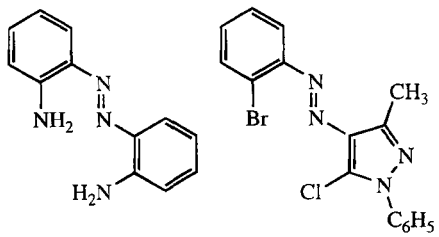
L105

[M(L106)] (M = Ni, Pd)

(2.62)

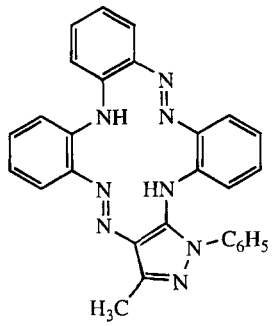
For constructing macrocyclic compounds such as hexaazatetradecine derivatives, another scheme has also been widely used. This results in building up less symmetrical macrocyclic systems. Thus, reaction of 2,2'-diaminoazobenzene (L107) with 4-[(2'-bromophenyl)azo]-5-chloro-3-methyl-1-phenylpyrazole (L108) in a polar aprotic solvent on a nickel(II) or palladium(II) matrix in the presence of potassium

carbonate, gives the macrocycle H_2L109 (Eq. 2.63). This is isolated as the corresponding chelate [142, 144, 145]. The $[P]^{+\cdot}$ peaks confirming formation of H_2L109 are the most intense in the mass spectra of the corresponding complexes.



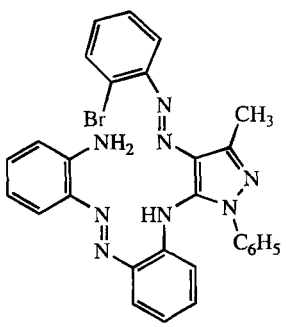
L107

L108



H_2L109 (2.63)

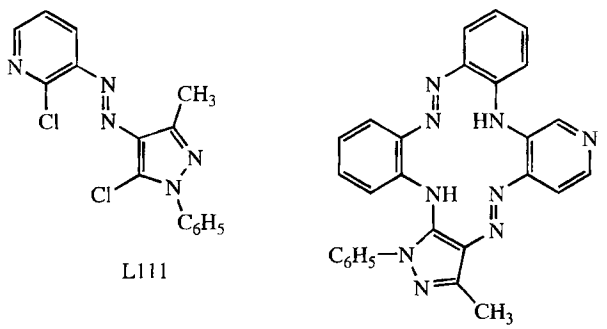
When nickel(II) is used as the template then, in addition to [Ni(L109)], the chelate [Ni(L110)] which yields a non-cyclised ligand product is also formed. The latter is easily demetallated by mineral acids yielding H_2L110 (Eq. 2.64) [144].



H_2L110 (2.64)

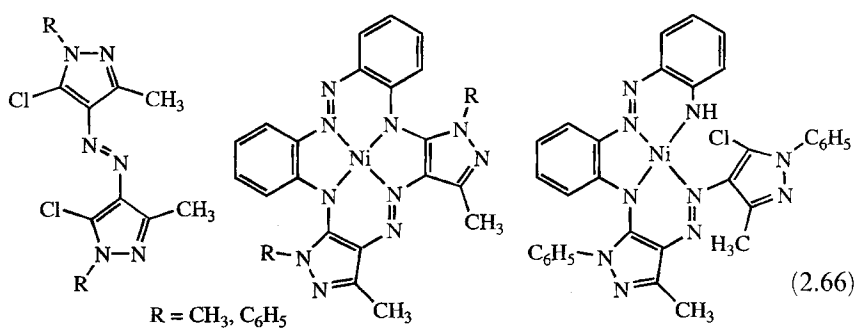
The course of template interaction can be greatly affected by solvent. In the present system, when the reaction is carried out in hexamethylphosphoramide (HMPA = hexametapol) the macrocyclic product [Ni(L109)] and the open-chain chelate [Ni(L110)] appear from the very beginning, the latter in rather greater amount. Subsequently, the content of [Ni(L110)] in the reaction mixture decreases. In dimethylformamide the amount of both products increases with time, but now the proportion of [Ni(L110)] does not decrease as the reaction proceeds. When H_2L110 is heated in HMPA in the presence of nickel(II) acetate and potassium carbonate, [Ni(L109)] is isolated. However, attempts to realise such transformations in DMF failed. We conclude that consecutive substitution of chlorine and bromine and the process of synchronous nucleophilic substitution of both halogens proceed in parallel. In addition, in HMPA both paths lead to the formation of [Ni(L109)], and in DMF the only source for building the latter is simultaneous interaction of the two ligsons (L107 and L108) together with the synchronous sub-

stitution of halogens [144]. If L111 is taken as the *o,o'*-dihalogenazo compound, instead of L108, then, as a result of the template reaction, only the H_2L112 macrocyclic system, in the form of its nickel(II) complex, is formed (Eq. 2.65) [146].



L111 H_2L112 (2.65)

Reaction of L113 with L107 in DMF or in HMPA in the presence of nickel(II) results in the macrocyclic product [Ni(L114)] and a small amount of the chelate [Ni(L115)] for R = C_6H_5 (Eq. 2.66) [147, 148].



$R = CH_3, C_6H_5$

L113 [Ni(L114)] [Ni(L115)] (2.66)

An X-ray crystal structure analysis for [Ni(L114)] (R = CH_3) showed [148] that the crystal consists of two independent molecules (Figure 2-18), one of which has azo groups disordered over two positions, the molecule being a superposition of the two 5566 isomers, with *cis*-located azo groups, whereas the second is the 5656 isomer, with an alternation of five- and six-membered chelate rings and *trans*-located azo groups. Slightly distorted square-planar coordination of the ligand to the nickel ion is observed in both isomers. Nevertheless, both molecules are characterised by significant non-planarity. They have the same symmetrical saddle conformation. Molecular mechanics calculations reveal that both isomers are markedly strained.

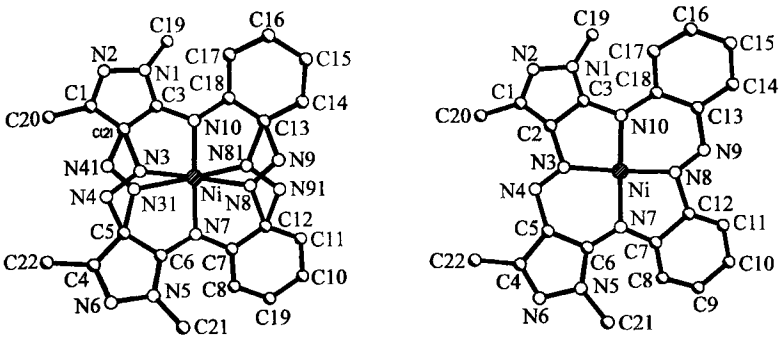


Figure 2-18. The structure of the two independent molecules in [Ni(L114)] (R = CH_3); superposition of the two 5566 isomers (left), and the 5656 isomer (right).

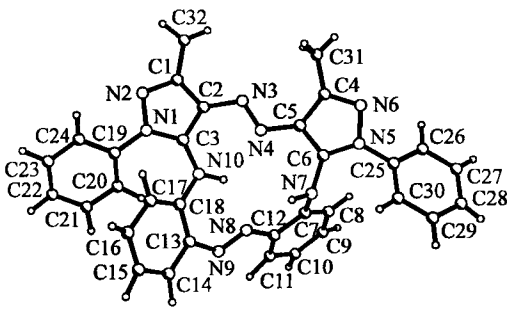
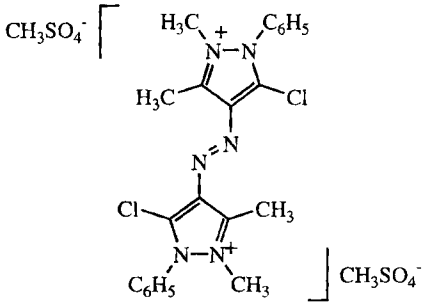


Figure 2-19. Molecular structure of H_2L114.

This is reflected in a difference between the conformational and geometrical parameters of the real isomers compared with the optimised ones. Other evidence comes from the structure of the related metal-free ligand H_2L114 for R = C_6H_5 (Figure 2-19), which, as can be seen, is not optimally prearranged for square-planar coordination to the metal ion [149].

Compound [Ni(L115)], like [Ni(L110)], is easily demetallated leaving the metal-free H_2L115 [147]. On refluxing in DMF in the presence of K_2CO_3, [Ni(L115)] is converted into [Ni(L114)].

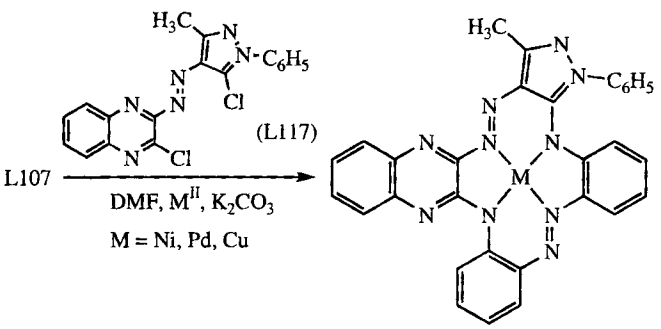
It should be noted that H_2L114 cannot be obtained by demetallation of [Ni(L114)]. It can be synthesised, however, if the reactivity of the halogen atom in the pyrazole nucleus towards nucleophilic substitution is increased by quaternisation, i.e. by treatment of L113 with dimethylsulphate. The bis-quaternised derivative L116 (Eq. 2.67) reacts with 2,2′-diaminoazobezene in DMF in the presence of potassium carbonate to give H_2L114 [147] as well as H_2L115 [149]. The H_2L114 structure was established from its mass-spectrum and was later confirmed by X-ray diffraction (Figure 2-19) [150].



L116 (2.67)

The macroheterocycle H_2L114 is highly non-planar. The hydrogen atom attached to N10 is nearly coplanar with the mean plane of the ring, deviating by 1.0 nm, whereas the hydrogen connected to N7 is considerably displaced (by 11.0 nm). In the azobispyrazole moiety, both five-membered rings are almost coplanar (the dihedral angle is 9°). In contrast, the benzene rings in the azobisbenzene fragment are far from coplanar (the dihedral angle is 43°).

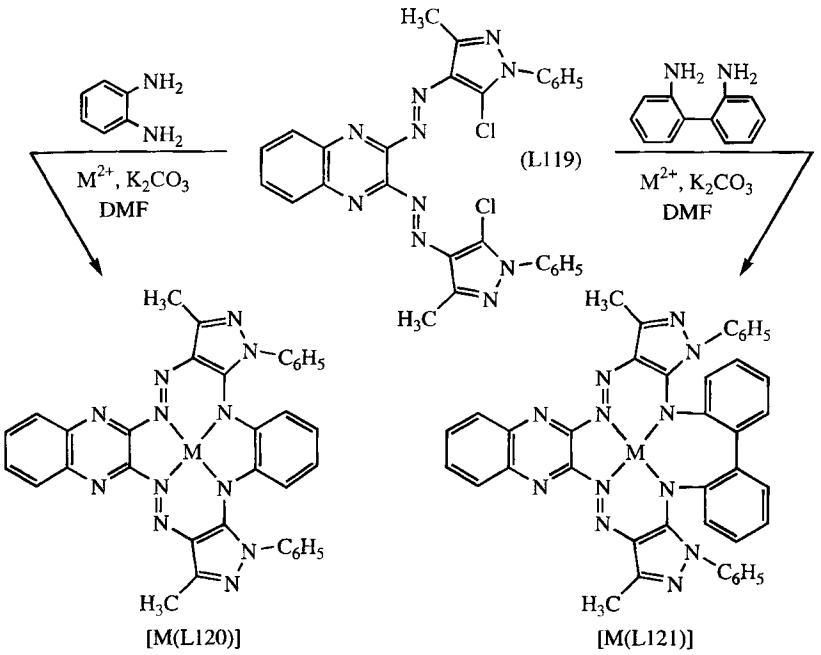
Taking into account the results given above, one can conclude that the template effect of d metal ions in the process of creating hexaazatetradecine systems is largely confined to organisation and activation of the interacting ligsons. The template reaction of the *o,o'*-dihalogen-azo-compound L117 with L107 proceeds in the presence of nickel(II), palladium(II) or copper(II) yielding the macrocyclic system [M(L118)] (Eq. 2.68). This is confirmed by mass spectra, where the peaks for the respective molecular ions are observed [143].



L107 (L117) DMF, M^{II}, K_2CO_3 M = Ni, Pd, Cu [M(L118)] (2.68)

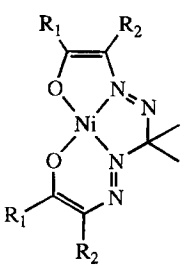
Derivatives of [1, 2, 5, 6, 9, 12]hexaazacyclotetradecine and [1, 2, 5, 6, 9, 14]hexaazacyclohexa-decine can also be synthesised by reaction of the dichloro-bis-(azo) compound L119 with aromatic diamines on a nickel(II) or palladium(II) matrix according to Scheme 2-10 [151]. Molecular ion peaks in the mass spectra of [M(L120)] and [M(L121)] confirm the macrocyclisation processes shown in Scheme 2-10 [151].

By reaction of benzil monohydrazone, 2,3-butanedione or 3,3'-dimethyl-1,2-butanedione monohydrazone with acetone in the presence of nickel(II), complexes [Ni(L122)]–[Ni(L124)] containing quadridentate open-chain ligands were obtained (Eq. 2.69). They consist of two residues of a monohydrazone α-dicarbonyl com-



Scheme 2-10. Synthesis of [M(L120)] and [M(L121)].

pound linked by means of the carbon atom of the acetone molecule [152, 153]. The composition and structure of the chelates and the mode of ligand coordination follow from the IR, mass and ^{1}H NMR spectra [153].



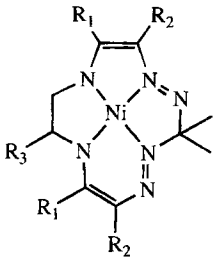
$R_1 = R_2 = C_6H_5$ [Ni(L122)]

$R_1 = R_2 = CH_3$ [Ni(L123)]

$R_1 = C(CH_3)_3$, $R_2 = H$ [Ni(L124)] (2.69)

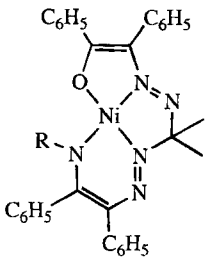
By interaction of [Ni(L122)] with 1,2-diaminoethane (en) or 1,2-diaminopropane, or by interaction of [Ni(L123)] with en, the 13-membered macrocyclic products [Ni(L125)]–[Ni(L127)] were synthesised (Eq. 2.70) [153–155]. The $P^{+\cdot}$ peaks are the most intense in the mass-spectra. Compound [Ni(L124)] does not condense with 1,2-diaminoethane in an analogous manner, even under more forcing conditions [154]. Hence, the reactivity of the coordinated –CO groups in chelates of the [Ni(L122)]–[Ni(L124)] type depends on the nature of the peripheral substituents. The bulky and electron-releasing *t*-butyl group makes the coordinated –CO group

less vulnerable to nucleophilic attack by a diamine in comparison with attack at the –CO group in [Ni(L122)] and [Ni(L123)], which contain methyl and phenyl substituents, respectively.



$R_1 = R_2 = C_6H_5$, $R_3 = H$ [Ni(L125)]
$R_1 = R_2 = C_6H_5$, $R_3 = CH_3$ [Ni(L126)]
$R_1 = R_2 = CH_3$, $R_3 = H$ [Ni(L127)] (2.70)

If 1,3-diaminopropane is used, then as a result of its interaction with [Ni(L122)], the nickel(II) complex with the potentially pentadentate ligand H_2L128 is isolated (Eq. 2.71) [153].



$R = (CH_2)_3NH_2$ [Ni(L128)]
$R = C_2H_5$ [Ni(L129)] (2.71)

Thus here the condensation reaction proceeds at only one coordinated –CO group, as evidenced by the IR spectrum data for [Ni(L128)]. No bands are observed in the 3100 and 1630 cm^{-1} regions corresponding to $\nu(NH_2)$ and $\delta(NH_2)$ vibrations in [Ni(L125)] and [Ni(L126)]. Confirmation is provided by the presence in the mass-spectrum of [Ni(L128)] of the peak with the maximum m/z corresponding to the product with molecular mass 18 amu greater than for the expected macrocyclic compound. Attempts to obtain the cyclised product by prolonged heating of [Ni(L128)] in vacuum over P_4O_{10} or in various solvents were unsuccessful.

A kinetics study of the template reaction of [Ni(L122)] with en showed [156] that formation of [Ni(L125)] is a two-step process. Moreover, both steps proceed at comparable rates. This is consistent with the existence in the reaction mixture of a certain amount of an intermediate in which only one –CO group of [Ni(L122)] is condensed with one of the 1,2-diaminoethane end groups. The existence of an intermediate similar to [Ni(L128)] is supported by adding benzoyl chloride to the reaction mixture; the mass-spectrum of the isolated product confirmed the presence of the monobenzoyl derivative intermediate.

In accordance with the above observations it should be noted that, on interaction of [Ni(L4)] (see p. 6) with 1,2-bis(bromomethyl)benzene, it is impossible to detect an intermediate compound [157]. In this case a two-step mechanism for the gener-

ation of the macrocyclic product [Ni(L5)Br_2] was also proposed, with the first slow step consisting of 1,2-bis(bromomethyl)benzene attack on the coordinated thiol group followed by the second very fast cyclisation step. The latter results from the pronounced kinetic coordination template effect of the nickel ion holding spatially reactive groups in close proximity and thus facilitating their interaction.

Unlike the reaction for [Ni(L4)] [157], the slow second step of the reaction of [Ni(L122)] with en is probably the result of the relative mobility of the second $-NH_2$ group after the condensation of [Ni(L122)] with 1,2-diaminoethane by one of the coordinated –CO groups. It means that the coordination kinetic template effect is not as pronounced as in the synthesis of [Ni(L5)Br_2] described above. Another reason is possibly the different reactivity of –CO groups in the five- and six-membered cycles. This assumption is confirmed by the fact that from the reaction of [Ni(L122)] with ethylamine in a sealed tube at 110°C, only the chelate [Ni(L129)] was isolated; the disubstituted product cannot be obtained even if prolonged reaction times and higher temperatures are used.

A multistep mechanism was proposed for formation of [Ni(L128)] by the reaction of [Ni(L122)] with 1,3-diaminopropane in the presence of base [158]. In the first step, 1,3-diaminopropane coordinates to the nickel ion in the axial position; in the second step, deprotonation of the polarised diamine takes place with subsequent nucleophilic attack on the carbon atom of the –CO group and removal of the second 1,3-diaminopropane molecule from the complex with the formation of [Ni(L128)]. It was claimed that the kinetic template effect is operative in the formation of the latter. In our opinion, following the discussion given in Chapter 1 about the place of template reactions among other related transformations, this reaction cannot strictly be considered as a template reaction, because it does not result in formation of a new chelate ring. It should be noted, however, that in certain conditions the free amino group of a pendant arm can coordinate to the metal ion. Nevertheless we assign the above reaction to those of coordinated ligands.

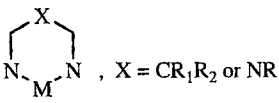
2.5 Saturated polyazamacrocyclic compounds

Completely saturated tetraazamacrocyclic compounds and their complexes with metals are usually obtained by non-template procedures [159]. Nevertheless, there are two often-used template strategies which show the effectiveness of using reactions on matrices for assembling such systems:

- interaction of bis(diamine) or tetramine 3d metal complexes with formaldehyde and a nucleophilic locking fragment;
- template assembly of unsaturated macrocycles with consequent reduction of the azomethine bonds produced.

The first is exemplified by the formaldehyde/nitroethane method of macrocyclisation of *cis*-disposed coordinated primary amines by reaction with HCHO and

a potential nucleophile ($C_2H_5NO_2$) capable of attacking the C=N bonds formed and activated via coordination to the metal ion. During the 1990s this approach has rapidly been developed. Besides nitroethane a range of other suitable nucleophilic-locking agents have been discovered. These include a number of nitro-containing –C–H acids, usually nitroalkanes (mono- and di-), ammonia, primary amines (mono- and di-), carboxamides, sulphonamides and heterocyclic nucleophiles. The ring-closure steps are directed by metal ions preferring a square-planar arrangement of ligsons around them, such as Ni^{II}, Cu^{II}, Pd^{II} and Au^{III} and end with formation of one or two six-membered chelate rings (Eq. 2.72).

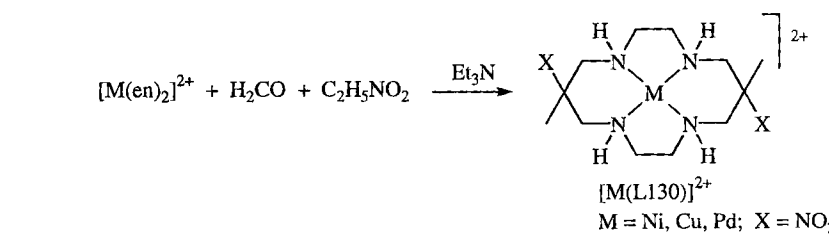


, X = CR_1R_2 or NR (2.72)

It is an attractive and efficient route to introduce functional groups attached at the macrocycle backbone via carbon atoms (*C*-functions), which can be easily and broadly modified by chemical transformations, permitting the production of species which can be isolated in the metal-free state and involved in direct metal–ligand complexation reactions with metal ions of other than square-planar stereochemistry. Sometimes template macrocyclisation can be achieved with a high degree of selectivity in the absence of locking agents through the formation of NH–CH_2–NH linkages. Examples of such processes are presented in the following discussion.

The second route will be considered mainly in the following sections that deal with unsaturated polyazamacrocycles. At the end of this section is illustrated the applicability of this strategy with the particular example of exclusively and efficiently building up small-ring saturated macrocycles.

The discussion commences with examples illustrating the effectiveness of the first synthetic approach, where the manifestation of the coordination template effect of the metal template is evident. Thus, for instance, interaction of $[M(en)_2]^{2+}$, where M = Ni, Cu or Pd, with an excess of formaldehyde and carbon acid nitroethane in basic solution gives the cyclam-substituted derivatives $[M(L130)]^{2+}$ in high yield (Eq. 2.73) [160–162].

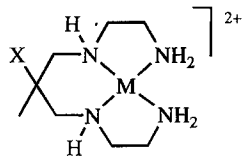


$[M(L130)]^{2+}$

M = Ni, Cu, Pd; X = NO_2 (2.73)

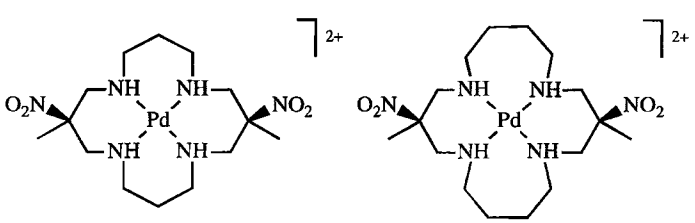
Two geometric isomers are potentially possible: *cis* (or *syn*), with nitro groups located on the same side of the macrocycle mean plane; *trans* (or *anti*), with nitro groups arranged on opposite sides of the macrocycle. In the case of palladium(II) and copper(II) the above reaction is stereoselective in that the *anti* isomer is preferentially formed.

For copper(II) and palladium(II), in addition to $[M(L130)]^{2+}$, the intermediate half-capped $[M(L131)]^{2+}$ may also be isolated, and can be chromatographically separated from competing species (including the macrocycle; Eq. 2.74).



$[M(L131)]^{2+}$, X = NO_2, M = Cu, Pd (2.74)

The relative yields of macrocyclic and open-chain chelates can be varied by controlling the amounts of ligsons employed. It should be noted that condensation reactions around copper(II), nickel(II) and palladium(II) can only be carried out successfully at relatively high pH. This permits the generation of sufficient concentrations of carbanion and negatively charged coordinated amido ligand necessary for the condensation reaction with formaldehyde to proceed at an acceptable rate. Using the gold(III) complex of 1,2-diaminoethane, $[Au(en)_2]^{3+}$, the above condensation reactions with formaldehyde and nitroethane occur at pH = 7.5 to yield both a macrocyclic $[Au(L130\text{-}H)]^{2+}$ and an open-chain chelate $[Au(L131\text{-}H)]^{2+}$, containing the corresponding ligand products in monodeprotonated form [163]. This is not surprising, taking into account the higher oxidation state of the metal ion, which facilitates the deprotonation of the coordinated 1,2-diaminoethane and relatively high acidity of nitroethane ($pK_{a1} = 8.6$). It is evident that the construction of both the macrocyclic and half-capped intermediates can be realised in the presence of metal ions which form relatively stable square-planar complexes. Another obligatory requisite to control the condensation chemistry around the metal ion is sufficient thermodynamic stability of the starting bis(diamine)metal salt. 1,3-Diaminopropane and 1,4-diaminobutane nickel(II) and copper(II) bis(chelates) of significantly lower thermodynamic stability, due to formation of six- and seven-membered rather than five-membered rings, cannot be used for the synthesis of macrocyclic and open-chain complexes under the conditions employed [162]. Palladium(II), however, forms bis(chelates) with 1,3-diaminopropane and 1,4-diaminobutane of greater thermodynamic and kinetic stability sufficient to perform controlled condensation reactions with formaldehyde and nitroethane in close proximity of the metal ion. They result in formation of 16- and 18-membered macrocyclic complexes $[Pd(L132)]^{2+}$ and $[Pd(L133)]^{2+}$, predominantly as *syn* isomers (Eq. 2.75) [162].



$[Pd(L132)]^{2+}$ $[Pd(L133)]^{2+}$ (2.75)

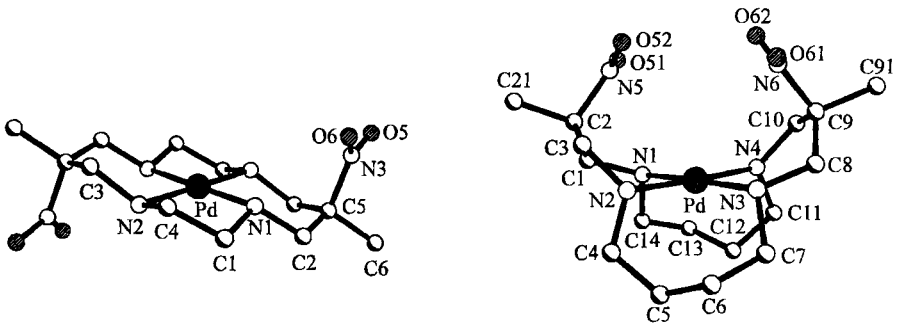
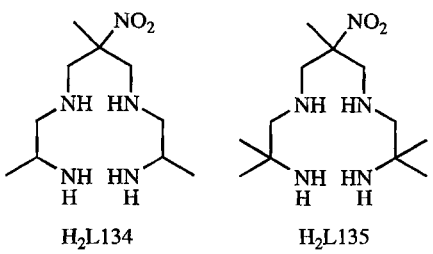


Figure 2-20. The structures of $[Pd(L130)]^{2+}$ (left) and $[Pd(L133)]^{2+}$ (right).

X-ray crystal structures of the 14- and 18-membered macrocyclic palladium(II) complexes are shown in Figure 2-20.

The influence of the consecutive introduction of one and then two methyl groups at one 1,2-diaminoethane carbon atom on copper(II)-conducted carbon acid–formaldehyde condensation reactions has been studied [164]. It was shown that these reactions occur predominantly distant from the site of *C*-methylation, leading mainly to the half-capped intermediates H_2L134 and H_2L135 (Eq. 2.76).

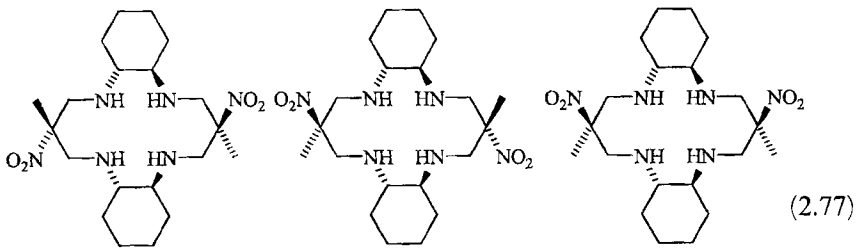


H_2L134 H_2L135 (2.76)

The formation of macrocyclic species decreases dramatically on going from ethane-1,2-diamine to propane-1,2-diamine and further to 2-methylpropane-1,2-diamine.

Sterically more demanding copper(II) chelates based on *trans*-cyclohexane-1,2-diamine reveal similar condensation chemistry [165]. The yield of macrocyclic products, however, decreases compared to the reaction with ethane-1,2-diamine-containing chelates. The formation of copper(II) complexes of half-capped ligands is favoured compared to capped species for steric reasons. The presence of two asymmetric carbon atoms in the starting ligson allows synthesis of new chiral macrocycles. The most suitable for macrocyclisation has proved to be the *R,R*:*S,S* bis(cyclohexane-1,2-diamine)copper(II). The three isomers of H_2L136 possible

from combinations of an *R,R*-cyclohexane and an *S,S*-cyclohexane fragment are shown in Equation (2.77).



(2.77)

In addition to the four asymmetric centres carried into the macrocyclic backbone by the initial cyclohexane ligsons, two pseudo-asymmetric centres located on the tertiary carbon atoms carrying the pendant nitro groups are present in the structure of H_2L136.

Nitro groups in coordinated L130 and L131 undergo reduction by Zn/HCl or Sn/HCl. However, the initial complexes are partially decomposed. This can be avoided if reduction of the corresponding nitro derivatives is performed by catalytic hydrogenation; $[Cu(L130)]^{2+}$ ($X = NH_2$) and $[Cu(L131)]^{2+}$ ($X = NH_2$) can be obtained.

Coordinated ligands of the L130 type ($X = NO_2$, NH_2) and their diethyl-substituted analogues [167] in copper(II) complexes exist in *meso* or *rac* form, depending on the mode of arrangement of the X substituents, namely, on both sides or one side with respect to the macrocycle plane. For certain amino derivatives separation of diastereomers was achieved. It was also shown that the ratio between *meso*-$[Cu(L130)]^{2+}$ ($X = NH_2$) and *rac*-$[Cu(L130)]^{2+}$ ($X = NH_2$) is 3:1. For *meso*-$[Cu(L130)](ClO_4)_4 \cdot 6H_2O$, an X-ray diffraction study [161] showed square-planar coordination of copper(II) in the complex, with the pendant primary amine groups uncoordinated. Apparently the Jahn-Teller tetragonal elongation, common with this ion, makes solids with primary amine groups coordinated energetically disfavoured relative to arrangements in which these groups engage in other types of lattice interactions [160, 161].

A different situation is realised in the case of $[Ni(L130)](ClO_4)_2 \cdot H_2O$ and $[Co(L130)]Cl_2(ClO_4)$ [160]. In both these complexes the crystal structure analysis defines hexacoordination. The structures of the Ni^{II} and Co^{III} compounds are similar, with four nitrogen atoms of the macrocycle planar-coordinated, as in the case of the copper(II) product [161]. The six-membered chelate rings are folded back into boat conformations which permit pendant amino groups to coordinate axially. The structure of the $[Co(L130)]^{3+}$ cation is given in Figure 2-21. It is notable that

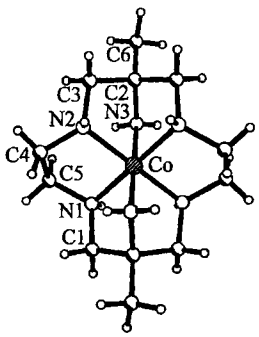
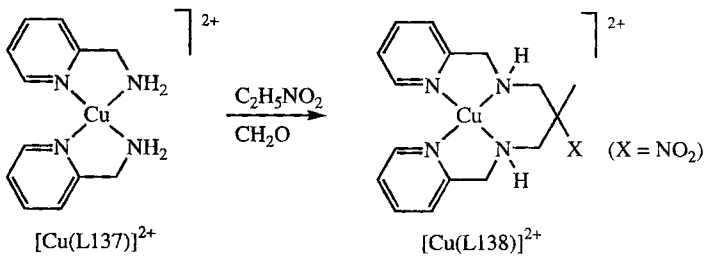


Figure 2-21. The structure of the $[Co(L130)]^{3+}$ cation.

for $[Co(L130)]^{3+}$ the Co–N distances are similar for the equatorial (macrocycle) and axial (pendant) nitrogens at 19.38(1) and 19.46(2) nm, respectively. The $[Ni(L130)]^{2+}$ cation shows a greater tetragonal distortion with mean Ni–N distances of 20.70(3) (equatorial) and 21.26(3) nm (axial).

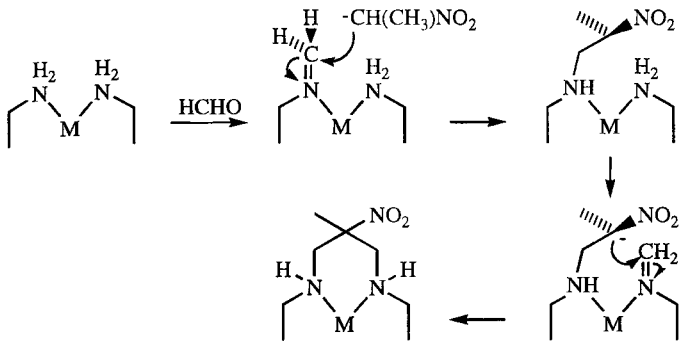
On interaction of $[Cu(L137)](ClO_4)_2$ with nitroethane and formaldehyde, condensation occurs only at the terminal coordinated aminogroups, with isolation of $[Cu(L138)](ClO_4)_2$, as product. The structure of the latter has been proved by X-ray diffraction (Eq. 2.78) [166].



$[Cu(L137)]^{2+}$ $[Cu(L138)]^{2+}$ (2.78)

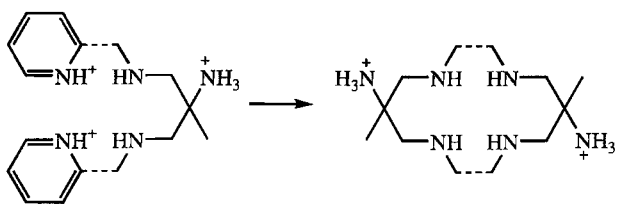
The condensation reaction of coordinated amines with formaldehyde and nitroalkanes is believed [166] to proceed through an imine (or aminol) intermediate sensitive to attack of the carbon acid conjugate base on the imine carbon atom (Scheme 2-11). The intramolecular path shown in this diagram is entropically favourable, so construction of the six-membered chelate cycle becomes possible and its formation proceeds in high yield. It should also be pointed out that the first condensation step involves nucleophilic attack on an HCHO molecule by a coordinated amido ligand arising from deprotonation of the metal-bound primary amine.

Attempts to reduce the nitro group in $[Cu(L138)](ClO_4)_2$ with zinc in aqueous hydrochloric acid unexpectedly led to the isolation of $[Cu(L130)](ClO_4)_2 \cdot H_2O$ in 90% yield [168]. To explain such a course of reaction, it was supposed that the for-



Scheme 2-11. Template assembly of a new chelate ring *via* formaldehyde/nitroethane chemistry.

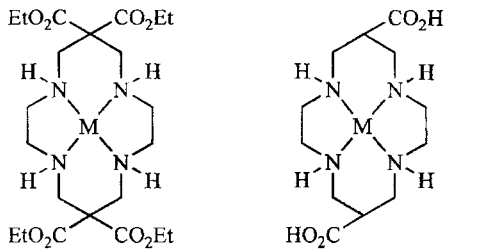
mation of the final product resulted from combining two fragments appearing in the reduction process. These fragments were derived from breaking off both pyridine residues from the quadridentate ligand L138 (X = NH_2) (Eq. 2.79).



$[H_3L138]^{3+}$ $[H_2L130]^{2+}$ (2.79)

Cleavage of the C–C bond becomes possible under these reaction conditions because the protonated aromatic radical is quite a stable group. The subsequent fast recombination of the saturated biradicals into a 14-membered macrocycle must be entropically more favourable than seven-membered ring formation by each of them individually. The high yield of the macrocycle L130 indicates the template role of the metal ion.

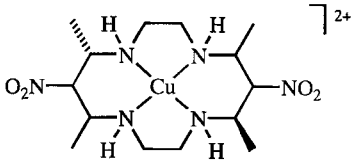
Metal-promoted condensations of coordinated primary amines with HCHO and nitroalkanes are the most often used and most inexpensive routes toward *C*-functionalised macrocyclic amines. Both ligsons, however, can sometimes be replaced by other suitable locking reagents. For instance, the use of diethylmalonate, $C_2H_5OOCCH_2COOC_2H_5$, which is a weaker –C–H acid (pK_{a1} = 13.3) compared to nitroalkanes, makes it possible to isolate in a diminished yield nickel(II) and copper(II) complexes of 6,6,13,13-tetraester-substituted cyclams $[M(L139)]^{2+}$ [169]. The tetraester complexes in their turn hydrolyse in the presence of base to tetracarboxy-substituted derivatives, which decarboxylate in acid to yield the 6,13-dicarboxysubstituted derivatives $[M(L140)]^{2+}$ (M = Ni, Cu; Eq. 2.80).



$[M(L139)]^{2+}$, M = Ni, Cu $[M(L140)]^{2+}$, M = Ni, Cu (2.80)

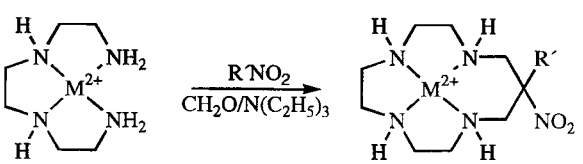
The structures of the two isomers of $[Cu(L140)]^{2+}$ arising from the different orientations of carboxy groups (axial and equatorial) have been reported [169]. The copper(II) 6,13-dicarboxy-substituted complex has been demetallated in boiling HCl to yield the metal-free ligand as tetrahydrochloride L140·4HCl. The latter has been used in direct complexation reaction with iron(III) [170], which proved to be non-effective for template assembly of this macrocycle.

Replacing HCHO by acetaldehyde permits analogous condensation with $[Cu(en)_2]^{2+}$ and nitromethane in methanol in the presence of triethylamine to give the complex $[Cu(L141)]^{2+}$ in 23% yield (Eq. 2.81) [171]. According to X-ray crystal structure analysis the *SSRR* isomer has been formed exclusively.



$[Cu(L141)]^{2+}$ (2.81)

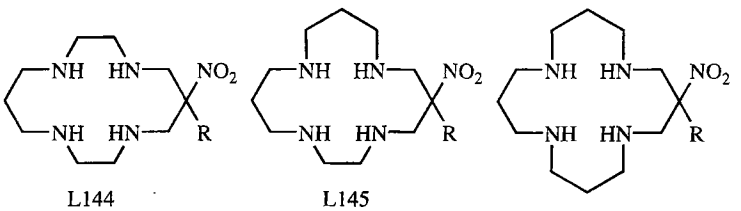
The undoubted fact is that the use of linear tetramine ligsons instead of 1,2-diaminoethane essentially simplifies construction of macrocyclic products. The latter are isolated as a rule as sole products in high yield. For example, by reaction of $[Cu(L142)]^{2+}$ or $[Ni(L142)]^{2+}$ with formaldehyde and RNO_2 (R = C_2H_5 or *n*-C_3H_7) in methanol in the presence of triethylamine, the complexes of the corresponding metals with the 13-membered macrocyclic ligand $[M(L143)](ClO_4)_2$, where M = Cu or Ni, were obtained in good yield (Eq. 2.82) [172].



$[M(L142)]^{2+}$ M = Cu, Ni $[M(L143)]^{2+}$ R´ = CH_3, C_2H_5 (2.82)

X-Ray diffraction examination of $[Cu(L143)](ClO_4)_2$ (R′ = CH_3), for example, showed that square-planar coordination of L143 to the central ion is achieved in the complex through the four nitrogen atoms [172].

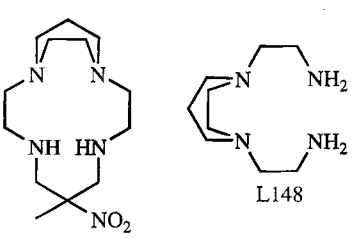
Analogously, starting from corresponding acyclic tetramines, high-yielding template condensation reactions produced 14-membered [173], 15-membered [174] and 16-membered [175] macrocyclic tetramines L144–L146 (Eq. 2.83).



L144 R = CH_3 L145 R = CH_3 L146 R = CH_3 (2.83)

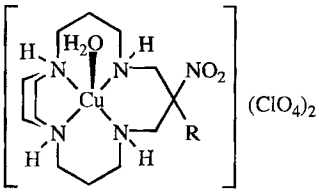
X-Ray diffraction studies of $[Cu(L145)](ClO_4)_2$ and $[Cu(L146)](ClO_4)_2$ established that both complexes contain the copper(II) in a distorted square plane of the macrocycle amine donors, with the pendant nitro group occupying one axial site (Cu–O = 24.43 and 27.03 nm in the L131 and L134 complexes, respectively) and a perchlorate oxygen in the other (Cu–O ca. 25.8 nm in each case). Notably, the Cu–N bond length increases on going from L143 to L144, with no marked difference from L145 to L146 in the respective complexes. The effects of ring size for the series on solution structures, analysed by electronic and ESR spectroscopy, on copper(II) reduction potentials, and on rate constants for acid hydrolysis have been reported; the L144 cavity appears most appropriate for accommodation of copper(II) [175].

The copper(II) complexes $[Cu(L147)(H_2O)](ClO_4)_2$ and $[Cu(L147)(NO_3)]ClO_4$ were also synthesised using the nitroethane/formaldehyde route to effect ring closure of the copper(II) compound with L148 (Eq. 2.84) [176]. The two products have different colours: $[Cu(L147)(H_2O)](ClO_4)_2$ is red, $[Cu(L147)(NO_3)]ClO_4$ is blue. However, both compounds have identical electronic spectra in aqueous solution. Crystallographic studies show the bond lengths to the copper(II) to be rather different in the two complexes. Thus, the axial Cu–O (nitrate) bond length in the blue complex (22.0 nm) is considerably shorter than Cu–O (H_2O) in the red complex (23.4 nm), and the mean Cu–N bond lengths in the red compound are slightly shorter than those in the blue complex. In addition, the Cu atom in the blue product is 3.4 nm out of the mean plane of the nitrogen donors, whereas in the red complex it is only 2.5 nm out of this plane. The crystallographic study suggests that the difference in colour in the solid state arises from these differences in coordination geometry [176].



L147 L148 (2.84)

By interaction of copper(II) nitrate with bis(3-aminopropyl)piperazine in methanol and subsequent addition of triethylamine, nitroethane and formaldehyde, the compound $[Cu(L149)(H_2O)](ClO_4)_2$ was obtained (Eq. 2.85) [177].



$[Cu(L149)(H_2O)](ClO_4)_2$ (2.85)

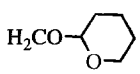
X-Ray diffraction of $[Cu(L149)(H_2O)](ClO_4)_2$ revealed the copper ion to Be in a square-pyramidal environment of four nitrogen donors and a water molecule. The Cu–secondary N and Cu–tertiary N distances are 20.44(8), 20.56(8) and 20.53(8), 20.72(8) nm, respectively, with the Cu–O distance being 22.59(8) nm. Reduction of $[Cu(L149)(H_2O)](ClO_4)_2$ with Zn/HCl yields the 7-methyl-1,5,9,13-tetraazabicyclo[11.2.2]heptadecane-7-amine analogue, characterised as copper(II) and cobalt(III) complexes [177].

As has been noted [175], the nitroalkane/formaldehyde approach to the template synthesis of macrocyclic tetramine ligands has two notable advantages compared with conventional synthesis of comparable ligands:

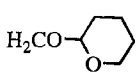
- the syntheses are virtually one-step reactions and usually lead to high yields of one main product;
- the resulting nitro-substituted macrocycle is a useful starting material for various derivatisations by diverse reactions of the nitro group, by altering the nitroalkanes, and by modifying the macrocycle itself.

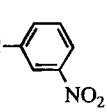
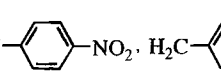
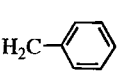
The generality of the formaldehyde/nitroethane approach for macrocyclisation of linear tetramines has further been extended [178, 179]. By replacing nitroethane by a variety of other –C–H acids, such as 1-nitrododecane, 12-nitrododecanoic acid, 3-nitropropanoic acid, tetrahydro-2-(2′-nitroethoxy)-2H-pyran, 1-nitro-3-(2-nitroethylbenzene), 1-nitro-4-(2-nitroethylbenzene) and 2-phenylnitroethane, several macrocyclic tetramine complexes of the types $[M(L143)]^{2+}$ and $[M(L145)]^{2+}$ have been prepared (Eq. 2.86).

$[M(L143)]^{2+}$ with M = Ni, Cu; R = $(CH_2)_{10}CH_3$, $(CH_2)_{10}COOH$, CH_2COOH,

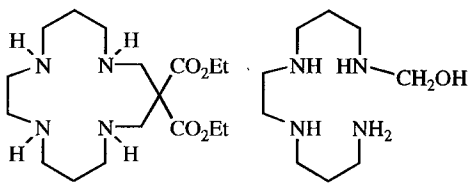


$[M(L145)]^{2+}$; M = Ni, Cu; R = $(CH_2)_{10}CH_3$, $(CH_2)_{10}COOH$, CH_2COOH, (2.86)



$[M(L145)]^{2+}$ with M = Cu; R =  ,  , 

The possibility of using carbon acids other than nitro-containing derivatives has also been exploited [174]. Substitution of diethylmalonate for nitroethane led to two main products which could be separated chromatographically. After purification the macrocyclic compound L150 can be crystallised as its copper(II) perchlorate complex in approximately 2% yield. The copper(II) complex with the open-chain ligand L151 was obtained in much higher yield (Eq. 2.87).

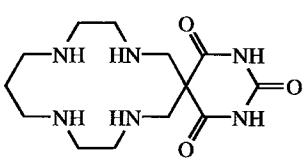


L150 L151 (2.87)

Ligand L151 is supposed [174] to appear as a consequence of hydroxide ion attack on an imine intermediate, as shown in Scheme 2-11. The existence of these hydroxide ions in the reaction mixture is caused by the presence of water. It should also be taken into account that the pK_a of the $(C_2H_5OOC)_2CH^-$ anion is comparable with that for OH^- in the conditions of reaction.

Thus, nitroalkanes are more effective agents than diethylmalonate in effecting the macrocyclisation given above. It is quite possible that carbon acids with higher pK_a values than $C_2H_5NO_2$, for example $(C_2H_5OOC)_2CH_2$, in non-aqueous conditions would be more effective.

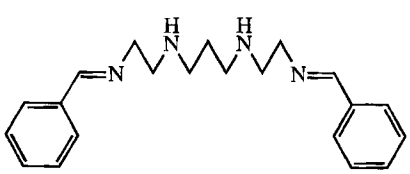
Barbituric acid has also proved to be an efficient locking fragment. The reaction of the copper(II) complex of 3,7-diazanonane-1,9-diamine with formaldehyde and barbituric acid in aqueous methanol results in an efficient building up (41% yield) of the macrocyclic compound $[Cu(L152)(H_2O)(ClO_4)]ClO_4 \cdot H_2O$, bearing the barbituric acid fragment as a spirosubstituent and determined as octahedral on the basis of X-ray structure analysis (Eq. 2.88) [180].



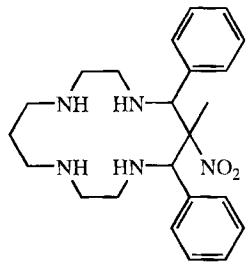
L152 (2.88)

Substitution of bulkier benzaldehyde for commonly used formaldehyde permitted the elucidation of some mechanistic peculiarities of the copper(II)-promoted macrocyclisation of acyclic tetramines [181]. For this particular example, it has been established that the overall process proceeds with more difficulty than reactions involving formaldehyde as the ring-closure ligson. In contrast to the generally accepted pathway of condensation chemistry using the formaldehyde/nitroalkane approach involving in the first step generation of the nucleophilic amido ligand from the coordinated primary tetramine, it has been convincingly shown that the Schiff base condensation of the metal-free open-chain tetramine takes place first. Only after this initial step does the copper(II) ion act as a template, organising the

Schiff base (L153) via coordination for nucleophilic attack by the deprotonated nitroethane fragment. This results in ring-closure and generation of the macrocyclic product $[Cu(L154)]^{2+}$ (Eq. 2.89) [181].



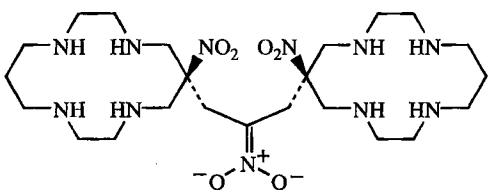
L153 (*EE* conformation)



L154 (2.89)

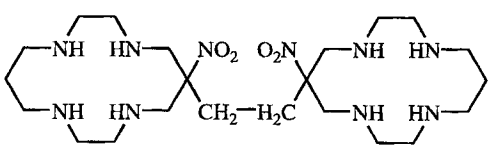
It is worth noting that the bulky nature of benzaldehyde permitted isolation of the intermediate species $[Cu(L153)]^{2+}$, which has been characterised by X-ray diffraction.

A rather unexpected reaction has been discovered, when dipotassium nitroacetate $K_2(O_2CCHNO_2)$ was employed as locking agent in a condensation with a linear tetramine copper(II) complex and formaldehyde [182]. It yielded, according to an X-ray crystal structure determination, a dimeric tetranuclear complex (a dimer of dimers) $[Cu_2(L155)]_2(ClO_4)_3Cl_3$ (Eq. 2.90).

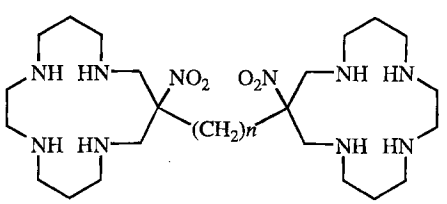


L155 (2.90)

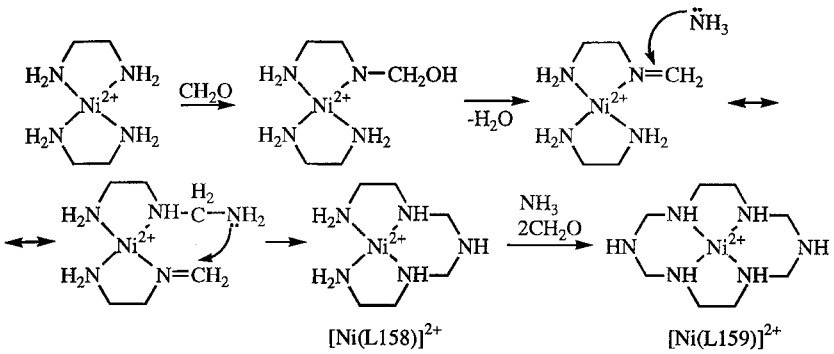
This result clearly shows that bifunctional locking groups can be successfully employed to generate related dinuclear species. The formaldehyde/dinitroalkane route proved to be very simple and efficient for the directed synthesis of bis(macrocyclic) octamine dicopper(II) complexes $[Cu_2(L156)]^{4+}$ and $[Cu_2(L157)]^{4+}$, based on 14- and 15-membered saturated macrorings connected by alkyl bridging chains of different lengths (Eq. 2.91) [183].



L156



L157 (n = 2-4) (2.91)

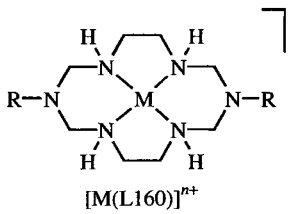


Scheme 2-12. The proposed route of template construction of the diazacyclam complex $[Ni(L159)]^{2+}$.

The nitro derivatives can be reduced with Zn/HCl and the metal-free octaazamacrocyclic compounds, bearing two pendant amino groups, isolated in reasonable yield.

The range of nucleophilic locking agents has been extended even more to include ammonia and primary amines. For instance, synthesis of $[Ni(L159)]X_2$, where X = ClO_4 or I, appears [184] to follow the route given in Scheme 2-12.

The reaction is proton-catalysed and the precursor $[Ni(L158)]X_2$ is formed initially. The cyclic complex $[Ni(L159)]X_2$ is obtained when $[Ni(L158)]X_2$ is refluxed in aqueous solution for about 100 h with formaldehyde and ammonia in the mole ratio 1:2:1. Analogously, hexaazamacrocyclic complexes $[M(L160)]^{n+}$ are isolated by interaction of $[M(en)_2]^{n+}$ (M = Ni, Cu, n = 2; M = Au, n = 3) with formaldehyde and RNH_2 (R = CH_3, C_2H_5, $CH_2C_6H_5$, CH_2CH_2OH) (Eq. 2.92) [185–189].



$[M(L160)]^{n+}$

M = Ni, Cu; R = CH_3, C_2H_5;
M = Ni; R = $CH_2C_6H_5$, CH_2CH_2OH;
M = Au; R = CH_2CH_2OH (2.92)

Template tailoring of acyclic tetramines can also be carried out using formaldehyde and primary amines, amides and sulphonamides [190–195]. From the general reaction (2.93) pentaazamacrocyclic species $[M(L161)]^{2+}$, where M = Ni or Cu have been prepared. Details concerning the yield of each particular reaction and designation of substituent R are given in Tables 2-1 and 2-2, for nickel(II) and copper(II) complexes, respectively.

Table 2-1. The dependence of yields of nickel(II) azacyclam macrocyclic complexes on the locking agents used.

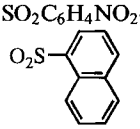
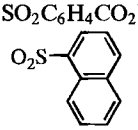
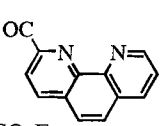
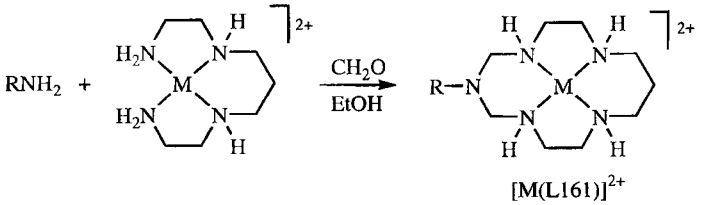
Complex	Substituent R	Yield (%)	Reference
$Ni(L161)(ClO_4)_2$	CH_3	32	190
$Ni(L161)Cl_2$	$C_{16}H_{33}$	29	191
$Ni(L161)(ClO_4)_2$	$COCH_3$	14	191
$Ni(L161)(ClO_4)_2$	COPh	13	191
$Ni(L161)Cl_2$	$COC_6H_4NO_2$-*o*	82	191
$Ni(L161)Cl_2$	$COC_6H_4NO_2$-*p*	52	191
$Ni(L161)(ClO_4)_2 \cdot HClO_4$	COPy-*m*	33	192
$Ni(L161)(ClO_4)_2 \cdot HClO_4$	COPy-*p*	30	192
$Ni(L161)Cl_2$	SO_2CH_3	42	191,193
$Ni(L161)Cl_2$	$SO_2C_{16}H_{33}$	21	191,193
$Ni(L161)Cl_2$	$SO_2C_6H_5$	27	191,193
$Ni(L161)Cl_2$	$SO_2C_6H_4Me$-*p*	24	191,193
$Ni(L161)(ClO_4)_2$	$SO_2C_6H_4Cl$-*p*	14	191
$Ni(L161)Cl_2$	$SO_2C_6H_4NO_2$-*o*	17	191
$Ni(L161)Cl_2$	$SO_2C_6H_4NO_2$-*p*	61	191
$Ni(L161)Cl_2$		62	191
$Ni(L161)(ClO_4)_2$	SO_2Fc	27	194

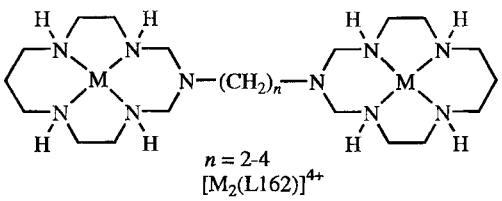
Table 2-2. The dependence of yields of copper(II) azacyclam macrocyclic complexes on the locking agents used.

Complex	Substituent R	Yield (%)	Reference
$Cu(L161)(ClO_4)_2$	$COCH_3$	28	193
$Cu(L161)(NO_3)_2$	COPh	45	193
$Cu(L161)(NO_3)_2$	SO_2CH_3	53	193
$Cu(L161)(NO_3)_2$	SO_2Ph	43	193
$Cu(L161)(NO_3)_2$	$SO_2C_6H_4Me$-*p*	45	193
$Cu(L161)(NO_3)_2$	$SO_2C_6H_4CO_2H$-*p*	33	193
$Cu(L161)(NO_3)_2$		30	193
$Cu(L161)(NO_3)_2 \cdot H_2O$		49	195
$Cu(L161)(NO_3)_2$	SO_2Fc	43	194



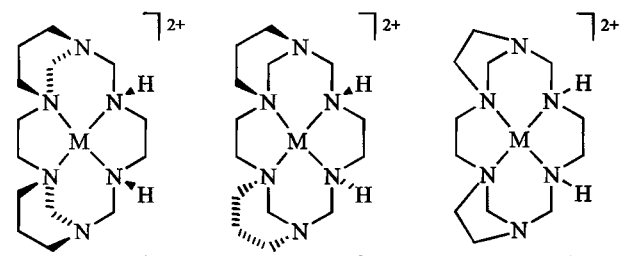
(2.93)

Utilisation of primary diamines instead of monoamines in such reactions opens the way to the preparation of bis(macrocyclic) complexes. Thus, the reactions of stoichiometric amounts of $[Ni(2,3,2\text{-tet})](ClO_4)_2$ with CH_2O and $H_2N\text{-}(CH_2)_n\text{-}NH_2$ (n = 2-4) in boiling methanol–water (4:1) led to formation of $[Ni_2(L162)]^{4+}$ (Eq. 2.94) [196].



(2.94)

In contrast, the condensation of $[M(3,2,3\text{-tet})]^{2+}$ and $[M(2,2,2\text{-tet})]^{2+}$ (M = Ni, Cu) with formaldehyde and en does not give the metal(II) bis(macrocyclic) compounds. Instead, complexes of two isomeric tricyclic ligands $[M(L163)]^{2+}$ and $[M(L164)]^{2+}$ have been prepared in high yield [197, 198]. The structures of both isomers of $[Cu(L163)]^{2+}$ and $[Ni(L163)]^{2+}$, and $[Ni(L164)]^{2+}$ have been proved by X-ray crystal structure analyses (Eq. 2.95) [197, 198].

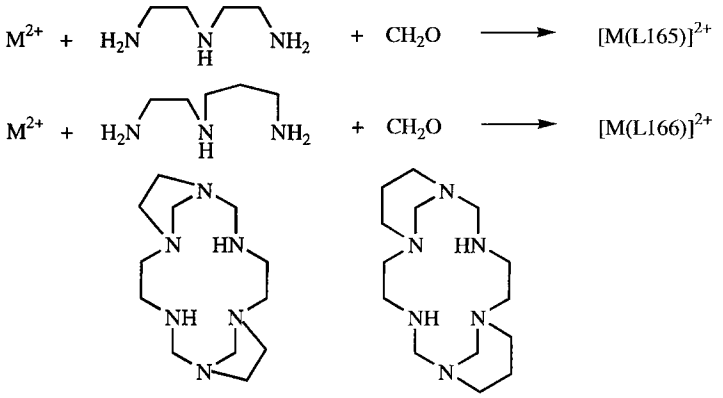


(2.95)

The nickel(II) complex $[Ni(anti\text{-}L163)]^{2+}$ was reduced with sodium amalgam in acetonitrile under an inert atmosphere to give two nickel(I) products: square-planar $[Ni(anti\text{-}L163)]^{+}$ and the square-pyramidal configurational isomer $[Ni(syn\text{-}L163)(NHC(OH)CH_3)]^{+}$ [199]. According to X-ray crystal structure analyses, reduction induces a small distortion of the coordination geometry without expansion of the macrocycle cavity for $[Ni(anti\text{-}L163)]^{+}$ [197, 199] and more dramatic changes resulting in configurational isomerisation of the starting ligand with its square-

planar coordination to the nickel(I), the fifth apical position being occupied by an acetamide in iminol form [200].

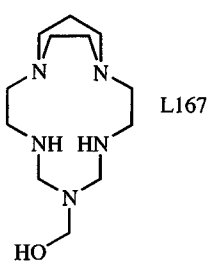
By using the approach described [201], template synthesis of nickel(II) [202] and copper(II) [203] complexes of L165 and L166, which are isomeric with those of L163 and L164, was carried out according to reactions (Eq. 2.96).



(2.96)

These macrocyclic compounds contain rarely occurring 1,3-diazacyclopentane or 1,3-diazacyclohexane small-ring moieties. These confer high rigidity on coordination. As a result, both L164 and L165 act in complexes as quadridentate ligands.

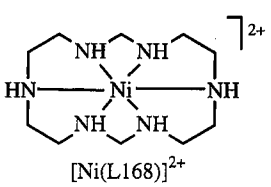
Nickel chloride hexahydrate interacts with L148, ammonia, and excess of formaldehyde to give the heterocyclic compound L167, isolated as its nickel complex (Eq. 2.97) [204]. When building up the latter, formaldehyde is not only involved in the ring closure reaction, as in the other cases given in this section, but also replaces the remaining hydrogen atom of ammonia by CH_2OH.



L167

(2.97)

Starting from nickel(II) complexes of diethylenetriamine (dien) and formaldehyde two types of macrocyclic products can be obtained. If the mole ratio of interacting species is 1:2, then the complex $[Ni(L168)]^{2+}$ is obtained (Eq. 2.98) [205].



$[Ni(L168)]^{2+}$

(2.98)

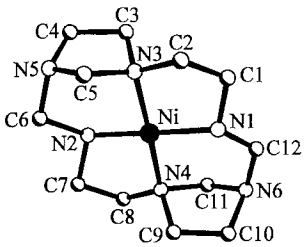
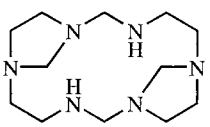


Figure 2-22. The structure of the cation $[Ni(L169)]^{2+}$.

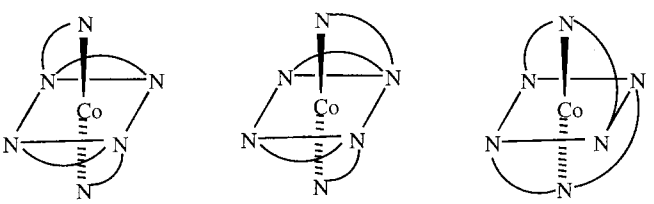
When an excess of formaldehyde (ratio 1:4) is used, complexes of the tricyclic ligand L169 were isolated (Eq. 2.99) [206]. Copper(II)-directed condensation was performed in a similar manner [207].



L169 (2.99)

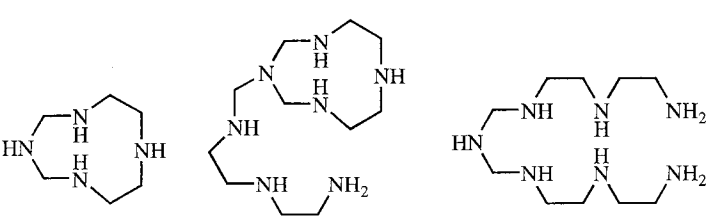
X-Ray diffraction analysis of $[Ni(L169)](ClO_4)_2$ showed square-planar coordination of L169 to the metal ion through four nitrogen atoms. The ligand diazacyclopentane rings are non-planar (Figure 2-22).

Details of the condensation reactions of three isomers of $[Co(dien)_2]^{3+}$ with formaldehyde and ammonia have been reported (Eq. 2.100) [208]. They illustrate the influence of the topology of the starting template on the final product.



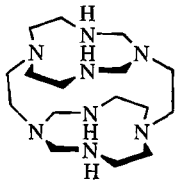
s-*cis* s-*fac* u-*cis* u-*fac* *trans* *mer* (2.100)

The s-*fac* isomer gave ligand product L170, isolated as $[Co(L170)]^{2+}$. From the u-*fac* isomer $[Co(L171)]^{2+}$ was synthesised, whereas the *mer* isomer gave the complex $[Co(L172)]^{3+}$ along with $[Co(L171)]^{2+}$ (Eq. 2.101).



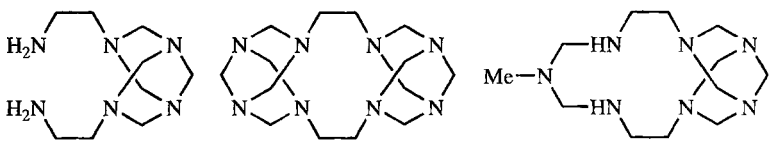
L170 L171 L172 (2.101)

By the reaction of tris(aminoethyl)amine and formaldehyde in the presence of nickel(II) a mononuclear complex $[Ni(L173)]^{2+}$ has been obtained (Eq. 2.102) [209]. It is worth noting that the ligand product consists of two fully saturated 10-membered tetraazamacrocyclic species L170 that are linked together by two $-CH_2CH_2-$ chains in an antiparallel face-to-face arrangement. It is also extremely interesting that this complex molecular architecture is achieved in a one-pot template reaction.



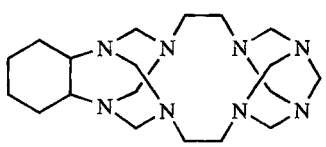
L173 (2.102)

Condensation of ethane-1,2-diamine with formaldehyde and ammonia in the presence of nickel(II) in methanol–water (1:1) results in the open-chain half-capped complex $[Ni(L174)]^{2+}$ [209]. Attempts to prepare the macrocyclic capped complex $[Ni(L175)]^{2+}$ failed. However, an asymmetrically locked macrocyclic product $[Ni(L176)]^{2+}$ has been synthesised by reaction of $[Ni(L174)]^{2+}$ with formaldehyde and methylamine in methanol (Eq. 2.103) [210].



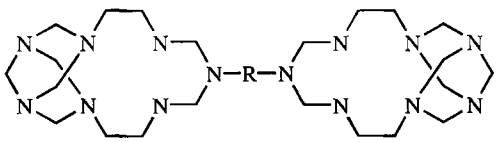
L174 L175 L176 (2.103)

Starting from the same half-capped precursor $[Ni(L174)]^{2+}$, reaction with formaldehyde and *trans*-cyclohexane-1,2-diamine in methanol results in formation of the octaazamacrohexacyclic complex $[Ni(L177)]^{2+}$ (Eq. 2.104) [211]. The X-ray crystal structure has also been reported.



L177 (2.104)

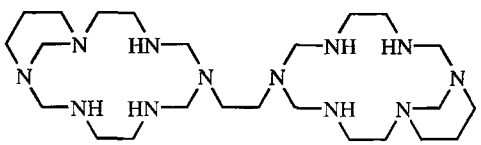
Template condensation of L174 with formaldehyde and a primary diamine (ethane-1,2-diamine, butane-1,4-diamine and/or 1,4-bis(aminomethyl)-benzene affords bis(macrocyclic) nickel(II) complexes $[Ni_2(L178)]^{4+}$ (Eq. 2.105), which can be reduced to corresponding dinickel(I) species, which are extremely sensitive to oxygen and moisture [212].



L178 (2.105)

R = $-(CH_2)_2-$
R = $-(CH_2)_4-$
R = $-CH_2-p-C_6H_4-CH_2-$

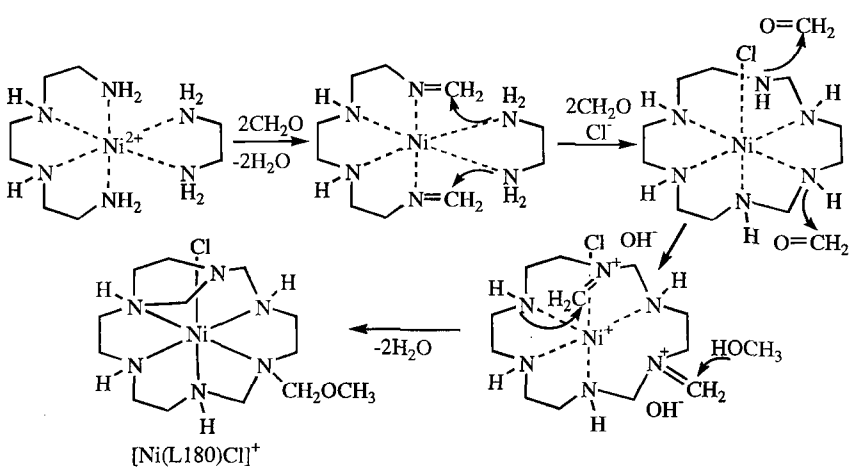
Dinuclear nickel(II) complexes $[Ni_2(L179)]^{4+}$ have been assembled from dipropylenetriamine, formaldehyde and ethane-1,2-diamine in the presence of nickel(II) in a mole ratio 2:8:3:2 in methanol (Eq. 2.106) [213].



L179 (2.106)

The template condensation of triethylenetetramine, en and CH_2O in the presence of $NiCl_2 \cdot 6H_2O$ in a mole ratio of 2:1:4:2 in methanol produced the six-coordinate $[Ni(L180)Cl]^+$ cation. A possible route for the formation of this complex is presented in Scheme 2-13 [201].

An X-ray diffraction study of $[Ni(L180)Cl]ClO_4$ showed that this complex has a distorted octahedral geometry (Figure 2-23). The hexaazamacrobicyclic ligand serves as a pentadentate ligand upon coordination to the nickel(II) ion through the two tertiary (N1, N4) and three secondary (N3, N5, N6) nitrogen atoms. It is of special interest that the complex contains, besides the usual five- and six-membered metallocycles, a rarely observed four-membered chelate ring.



Scheme 2-13. A possible route for template building $[Ni(L180)Cl]^+$.

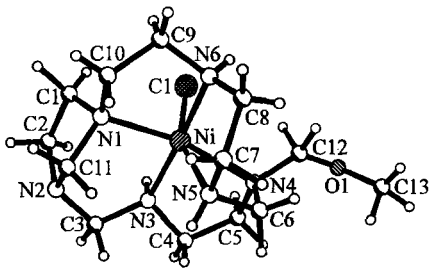
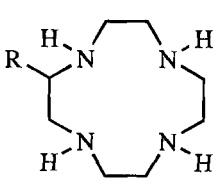


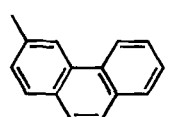
Figure 2-23. The structure of the cation $[Ni(L180)Cl]^+$.

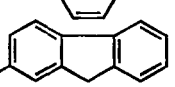
Quite recently [214] an efficient metal-templated route to *C*-functionalised 12-membered saturated macrocyclic tetramines has been discovered. A 12-membered macrocycle is too small to form square-planar N_4 complexes. For this reason a convenient template method to assemble this kind of macrocycle has not been found earlier. Triethylenetetramine has been shown to form well-defined *cis*-$[MLCl_2]$ complexes with some first row transition metal chlorides. These undergo cyclo cocondensation reactions with 1,2-dicarbonyl ligsons with formation of unsaturated intermediates, which can be reduced to give the desired ligand products. The most suitable as template appeared to be iron(III). By reaction of phenylglyoxal with *cis*-$[Fe(L142)Cl_2]Cl$ prepared *in situ* in dry methanol with subsequent reduction of the diimine intermediate by $NaBH_4$ the cyclic 12-membered tetramine L181 was obtained in 60% yield (Eq. 2.107). Effective demetallation takes place under these conditions. Analogously, a number of substituted phenyl, 3-phenanthryl and 2-fluorenyl derivatives have been synthesised.



L181

R = Ph
= *m*-C_6H_4CN
= *m*-$C_6H_4NO_2$





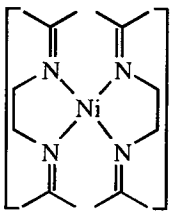
(2.107)

2.6 Tetra- and hexaazamacrocyclic complexes derived from diamines and bifunctional carbonyl compounds

Numerous and various macrocyclic compounds can be synthesised by template condensation of ethane-1,2-diamine or related blocks with corresponding ligsons containing C=O functional groups in a position suitable for chelation. In this

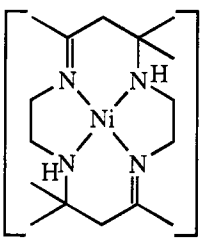
context, reactive centres in the molecule existing in a disguised form, such as a C=C double bond, may be also looked upon as the second functional group.

The first investigations in this direction were made before the introduction of template synthesis [215–218], during a study of the interaction products between tris(ethane-1,2-diamine)metal(II) salts and acetone. The tetra-*N*-isopropylidene structure was initially assigned to the product obtained by reacting $[Ni(en)_3](ClO_4)_2$ with acetone (Eq. 2.108) [215].



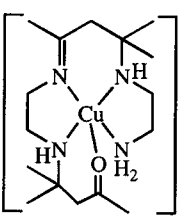
$(ClO_4)_2$ (2.108)

However, this was soon replaced by a 14-membered macrocyclic structure for $[Ni(L15)](ClO_4)_2$ (Eq. 2.109) [216].



$(ClO_4)_2$ $[Ni(L15)](ClO_4)_2$ (2.109)

This was subsequently proved [219] by the template reaction of $[Cu(en)_3](ClO_4)_2$ with acetone, in which $[Cu(L182)](ClO_4)_2$ is accumulated in sufficient concentration, to permit its isolation from the reaction mixture (Eq. 2.110).

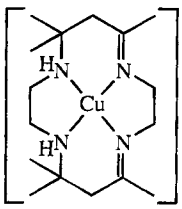


$(ClO_4)_2$ $[Cu(L182)](ClO_4)_2$ (2.110)

The product is kinetically rather stable, due to the lack of (or reduced) nucleophilic properties of the coordinated primary amine group. However, in basic media, it easily turns into $[Cu(L15)](ClO_4)_2$. The kinetic coordination template effect is presumably manifested at this key step of macrocyclisation if one assumes that, in the presence of base, the nucleophilic amido ligand is generated in sufficient concentration to allow the ring-closure reaction to proceed at a reasonable rate.

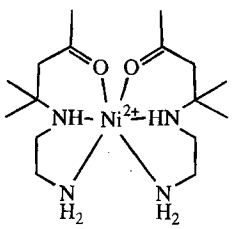
Interaction of $[Cu(en)_2](ClO_4)_2$ with acetone at room temperature in the presence

of en results in the formation of a mixture of $[Cu(L15)](ClO_4)_2$ and its *cis* isomer $[Cu(L183)](ClO_4)_2$ (Eq. 2.111) [220, 221].



$(ClO_4)_2$ $[Cu(L183)](ClO_4)_2$ (2.111)

When using $[Ni(en)_3](ClO_4)_2$, a *cis* product $[Ni(L183)](ClO_4)_2$ is formed together with the *trans* isomer [220, 216]. On starting from $[Ni(en)_2](ClO_4)_2$, the chelate $[Ni(L184)_2](ClO_4)_2$ is formed (Eq. 2.112) [219]. This is decomposed by aqueous solutions of acids or bases, but in pyridine it turns into $[Ni(L15)](ClO_4)_2$.



$[Ni(L184)_2]^{2+}$ (2.112)

As for $[Cu(L182)](ClO_4)_2$, the lone pair of the primary amino group in L184 is involved in coordination to the nickel(II) ion, preventing its interaction with the carbonyl function. The self-condensation of coordinated ligand L184 requires dissociation of the coordinated NH_2 group from the metal ion. In addition, water should be excluded from the reaction mixture. Note that for a labile metal ion like Ni^{2+} the generation of nucleophilic amino groups via dissociation of metal-ligand bonds is probable.

The product $[Cu(L15)](ClO_4)_2$, free from the isomeric *cis* compound, can be obtained by boiling $[Cu(en)_2](ClO_4)_2$ in acetone with one equivalent of en [222].

Using cobalt(II) as template, the *trans* compound $[Co(L15)](ClO_4)_2$ can be obtained [220, 223]. Cobalt(III) appeared to be non-effective in syntheses of this type, presumably because of formation of non-labile diamine complexes. The effectiveness of platinum(II) and palladium(II) as templates is reduced markedly compared to nickel(II) and copper(II) for the same reason [220]. Tris(ethylenediamine) iron(II) interacts with acetone in the presence of atmospheric oxygen according to Equation (2.113).

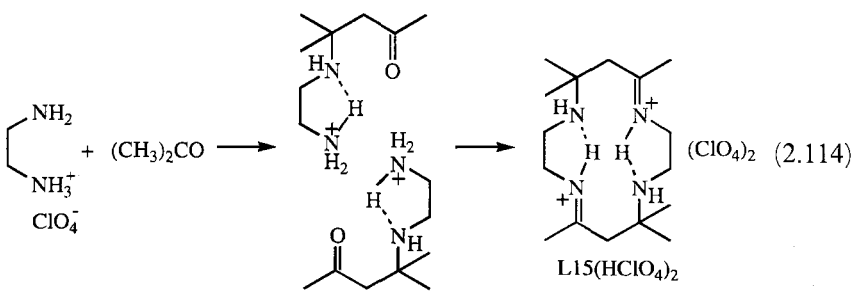
$$[Fe(en)_3](ClO_4)_2 \xrightarrow[O_2]{(CH_3)_2CO} L15(HClO_4)_2 + nH_2O + \text{iron(III)oxide} \quad (2.113)$$

In this case the ligand product is isolated as its perchlorate salt [223]. On adding

the stoichiometric amount of 1,2-diaminoethane to dry magnesium perchlorate in acetone, a fast exothermic reaction takes place and, as in the previous example, $L15(HClO_4)_2$ (in admixture with MgO) precipitates [220].

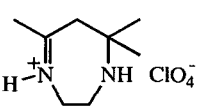
The building up of L183 in the presence of metal ions is believed [220] to be a template process. The template nature of L15 synthesis under analogous conditions may be questioned [220], because L15 can also be prepared from the same starting materials in the absence of metal ions. However, it has been stated that both macrocyclic products L15 and L183 are formed by the thermodynamic template pathway [159]. This is caused by their removal from the reaction media by the corresponding metal ions owing to their pronounced coordinating ability. Such a statement is not indisputable [225] because, in this situation, ions of various transition metals are expected to show much the same effect as they all form rather stable tetraazamacrocyclic compounds. At the same time ions of different transition metals have different influences on the course of this process [215–219, 221–224]. It may be concluded that in this case both kinetic and thermodynamic coordination effects operate. This is confirmed by the fact that various products are formed as intermediates depending on the metal ion. For instance, when using $[Cu(en)_2](ClO_4)_2$, reaction proceeds through the formation of L182 as its complex [219], whereas $[Ni(en)_2](ClO_4)_2$ gives $[Ni(L184)_2](ClO_4)_2$ as an intermediate.

The synthesis of $H_2L15(ClO_4)_2$ can be performed in the absence of metal ions by reaction of $[enH]ClO_4$ with acetone (Eq. 2.114) [220, 226].



(2.114)

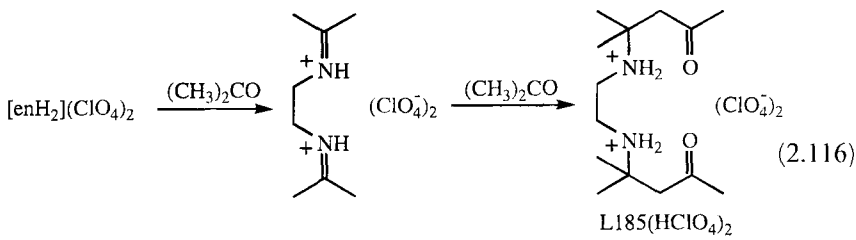
In addition to the main product, a small amount of diazepine monohydroperchlorate L19·$HClO_4$ is formed (Eq. 2.115).



(L19·$HClO_4$) (2.115)

Ligand L19 is a (1 + 1) cyclisation product of en with mesityl oxide, resulting from aldol dimerisation of acetone molecules. This is distinct from L15, which may be considered as a product of (2 + 2) condensation.

Reaction of $[enH_2](ClO_4)_2$ with acetone proceeds as (1 + 2) addition, giving the *cis* dione L185 as its perchlorate salt (Eq. 2.116) [227, 228].



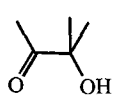
$$L185(HClO_4)_2 \qquad (2.116)$$

Attempts to synthesise L183 in the absence of metal ions were unsuccessful. This may be due to low stability of the azomethine bonds of the *cis* diene macrocyclic compound to acid hydrolysis. This assumption is proved by the conversion of L183 into L185 under the action of perchloric acid [227, 228].

There are different interpretations of the mechanism of formation of $L15(HClO_4)_2$ from $[enH]ClO_4$ and acetone. Thus, for example, a template role for H^+ has been proposed [229] and denied [225]. In our opinion, the topological role of H^+ in the synthesis of $L15(HClO_4)_2$, as of $L19 \cdot HClO_4$ and $L185(HClO_4)_2$, from the initial ligsons is clear.

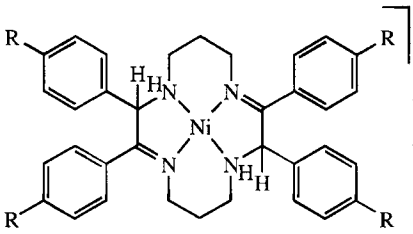
Reactions of the type shown in ref. [220], used for building up macrocyclic systems, can also be carried out with other starting ligsons. For example, varying the nitrogen-containing partner by lengthening the aliphatic chain or by introducing extra donor atoms permits the synthesis of compounds with different macroring sizes, containing different numbers of double bonds and functional groups. Employment of such carbonyl reagents as α,β-unsaturated ketones and diacetone alcohol results in building up diene macrocyclic systems with different numbers of peripheral substituents [220, 225, 230–233]. Use of such ligsons in the presence of metal ion templates allows the assembly of macrocycles with 14- to 18-membered rings.

Replacement of diacetone alcohol (or mesityl oxide) by the aliphatic α-hydroxyketones L186 or L187 (Eq. 2.117) does not permit the synthesis of 14-membered



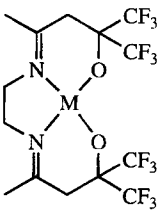
R = H L186
R = CH_3 L187 (2.117)

macrocyclic systems through template interaction with 1,3-diaminopropane [234, 235]. However the prolonged heating of $[Ni(pn)_3](ClO_4)_2 \cdot \frac{1}{2}H_2O$ with benzoin in absolute methanol in the presence of anhydrous $CaSO_4$, or with anisoin in the absence of solvent, gives macrocyclic products $[Ni(L188)](ClO_4)_2 \cdot \frac{1}{2}H_2O$ and $[Ni(L189)](ClO_4)_2$, respectively (Eq. 2.118) [235].



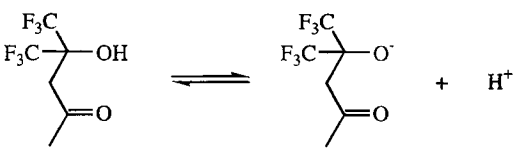
R = H [Ni(L188)]$^{2+}$ or isomer
R = OCH_3 [Ni(L189)]$^{2+}$ or isomer (2.118)

It is impossible to synthesise macrocyclic products by template interaction of hexafluorodiacetone alcohol with 1,2-diaminoethane or related compounds. Thus, for example, en reacts with this alcohol on nickel(II) and copper(II) matrices to form chelates [M(L190)] (Eq. 2.119) [236, 237].



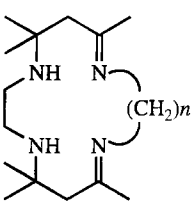
[M(L190)]
M = Ni, Cu (2.119)

This must be due to significant dissociation of the hexafluorodiacetone alcohol, because of the electron-accepting properties of CF_3 substituents (Eq. 2.120). As a consequence the hydroxide group loses its ability to condense with an amine.

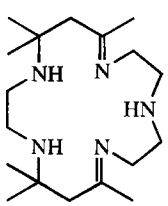


(2.120)

The *cis* dione L185 appeares to be a suitable ligson for metal-directed condensation with various diamines [238], as well as with diethylenetriamine [239], to give the macrocyclic compounds L191–L196 as corresponding complexes (Eq. 2.121).



n = 2 L191
n = 3 L192
n = 4 L193
n = 5 L194
n = 6 L195

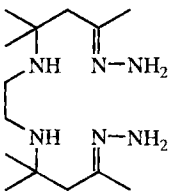


L196 (2.121)

It is worth noting that nickel(II) and copper(II) complexes of L193–L195 with seven- to nine-membered chelate rings undergo transamination processes when

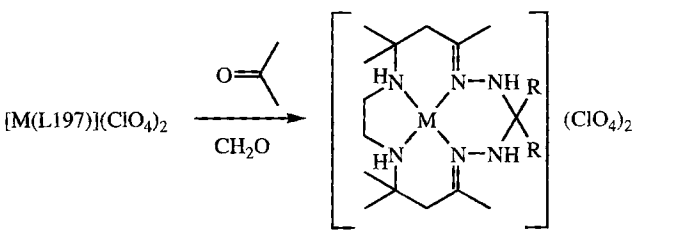
reacting with ethane-1,2-diamine. Complexes $[M(L191)]^{2+}$, containing thermodynamically more stable five-membered chelate rings, result from these substitution reactions [238].

When $L185(HClO_4)_2$ interacts with hydrazine, $L197(HClO_4)_2$ is formed. The appropriate dihydrazone complexes are isolated in the presence of nickel(II) and copper(II) perchlorates (Eq. 2.122) [227, 240].



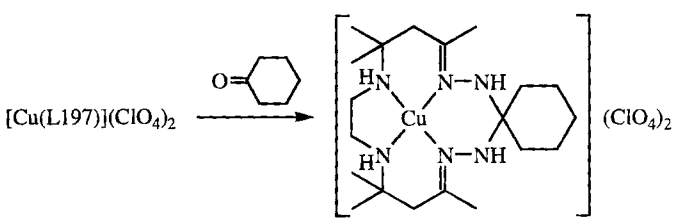
L197 (2.122)

Nickel(II) and copper(II) perchlorate complexes of L197 react with aliphatic monocarbonyl compounds leading to 16-membered hexaazamacrocyclic compounds (Eq. 2.123a,b) [241, 242]. X-Ray confirmation of the structure of $[Cu(L199)](ClO_4)_2$ is available [230].



$[M(L198)](ClO_4)_2$

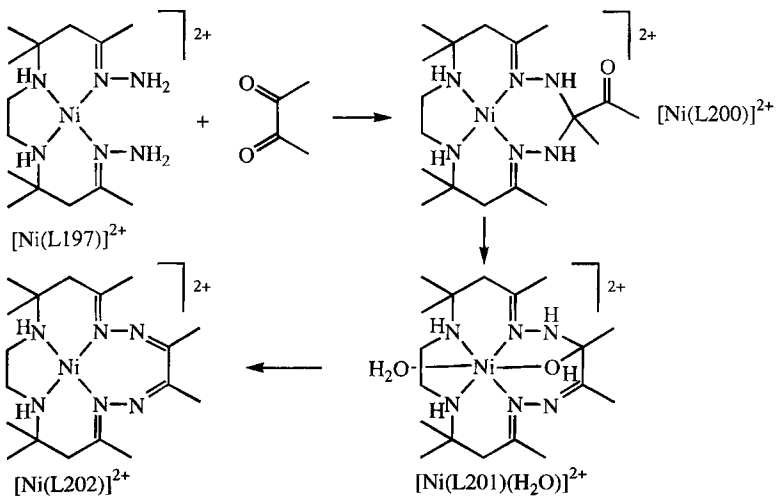
M = Ni, R = CH_3, H; M = Cu, R = H (2.123a)



$[Cu(L199)](ClO_4)_2$ (2.123b)

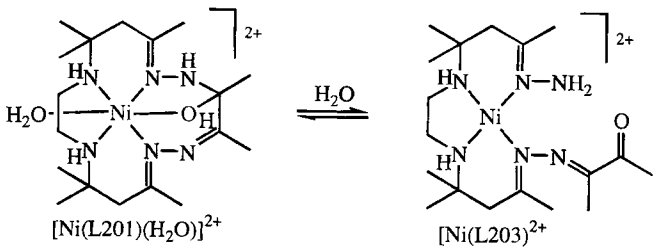
To carry out template macrocyclisation of L197, butane-2,3-dione is also suitable as ring-closing agent [243, 244]. By reaction of butane-2,3-dione with $[Ni(L197)](ClO_4)_2$ the macrocyclic product $[Ni(L202)](ClO_4)_2$ is obtained. Interestingly, this template reaction proceeds by formation of two other intermediate macrocyclic species, $[Ni(L200)]^{2+}$ and $[Ni(L201)]^{2+}$, as shown in Scheme 2-14.

The macrocyclic carbinolamine cation $[Ni(L201)(H_2O)]^{2+}$ in water forms an



Scheme 2-14. Template reaction of $[Ni(L197)]^{2+}$ with butane-2,3-dione.

equilibrium with the tautomeric cation $[Ni(L203)]^{2+}$, containing non-reacted carbonyl and hydrazine functions (Eq. 2.124).



(2.124)

An X-ray diffraction study confirmed the structure of the carbinolamine intermediate $[Ni(L201)(H_2O)]^{2+}$ and the formation of a seven-membered chelate ring in $[Ni(L202)]^{2+}$ as the result of template condensation [243, 244]. Nickel(II) is in a tetrahedrally distorted square-planar coordination in the $[Ni(L202)]^{2+}$ cation (Figure 2-24).

Complexes $[Ni(L200)]^{2+}$, $[Ni(L201)(H_2O)]^{2+}$ and $[Ni(L203)]^{2+}$ demetallate rapidly even in the presence of dilute acetic acid, whereas the cation $[Ni(L202)]^{2+}$ releases the metal ion slowly [245]. By transmetallation of $[Ni(L203)]^{2+}$ the copper(II) complex $[Cu(L203)]^{2+}$ has been prepared, which can easily be converted into the macrocyclic species $[Cu(L202)]^{2+}$ [245].

Reaction of $[Ni(L197)](ClO_4)_2$ with pentane-2,4-dione proceeds in an unexpected manner, its course being influenced by the reaction conditions. Thus, $[Ni(L204)(H_2O)](ClO_4)_2$ is formed in 60% yield in methanol/water (3:1) medium (Scheme 2-15) [241]. (Note that Ni(acacen) is also isolated in this preparation).

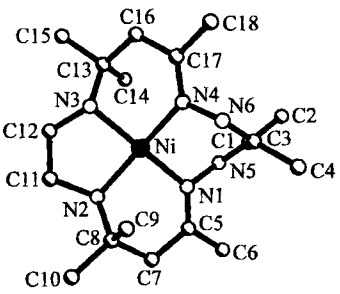
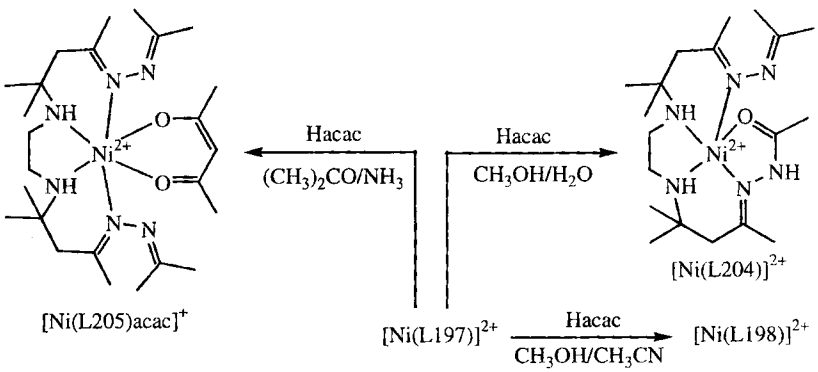


Figure 2-24. The structure of the cation $[Ni(L202)]^{2+}$.



Scheme 2-15. Synthesis of macrocyclic species $[Ni(L198)]^{2+}$.

The compound $[Ni(L198)](ClO_4)_2$ is prepared in methanol/acetonitrile (3:1) mixture in the absence of water. Acetone undoubtedly plays a role in this synthesis of L198; the pentane-2,4-dione may be its source. It should be noted, however, that $[Ni(L198)](ClO_4)_2$ can be obtained also as a product of the reaction of $[Ni(L197)](ClO_4)_2$ with benzaldehyde. This can be understood if the way to build up the final product consists of the following steps:

- benzaldehyde interacts with the initial complex, splitting off a hydrazine molecule;
- the resultant is hydrolysed, releasing acetone by a reverse Michael reaction.

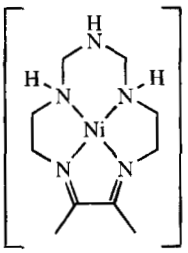
This acetone locks the end $-NH_2$ groups of the undecomposed part of the $[Ni(L197)](ClO_4)_2$ molecules. In the reaction of $[Ni(L197)]^{2+}$ with pentane-2,4-dione in methanol/acetonitrile (3:1), the acetone necessary for $[Ni(L198)]^{2+}$ formation can be supplied at the expense of L197 hydrolysis.

Reaction of $[Ni(L197)](ClO_4)_2$ with a mixture of pentane-2,4-dione and acetone in the presence of triethylamine or aqueous ammonia yields the product $[Ni(L205)(acac)]ClO_4$ (see Scheme 2-15).

The copper(II) complex $[Cu(L204)(ClO_4)]ClO_4$ is formed, in low yield, in a way

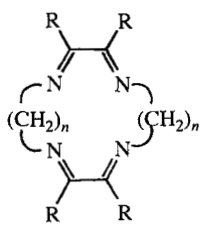
similar to that shown in Scheme 2-15 for the nickel(II) analogue. It can also be synthesised by transmetallation, by boiling $[Ni(L203)](ClO_4)_2$ with a small excess of copper(II) perchlorate in methanol/water (1:1) mixture [241].

Complexes $[Ni(L206)]X_2$ (X = ClO_4, I) were obtained by reaction of $[Ni(L158)]X_2$ with glyoxal or butane-2,3-dione (Eq. 2.125) [246].



X_2 $[Ni(L206)]X_2$, R = H, CH_3 (2.125)

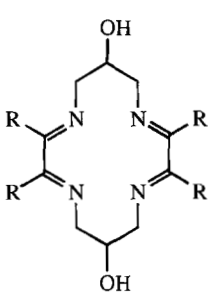
Cadmium(II) complexes with L207 have been synthesised by the reaction of butane-2,3-dione or benzil with the corresponding aliphatic diamines in the presence of Cd^{II} as the template (Eq. 2.126) [247].



L207

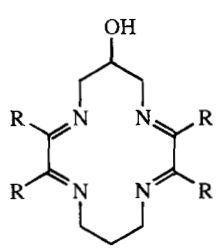
R = CH_3 or C_6H_5
n = 2–4, 6, 8, 12 (2.126)

The syntheses of $[Co(L207)Cl_2]PF_6$ (R = CH_3, n = 3) [248], $[Co(L207)Br_2]Br \cdot CH_3OH$ (R = C_6H_5, n = 3) [249], $[Fe(L207)(CH_3CN)_2](PF_6)_2$ [250], $[Co(L208)Br_2]Br$ (R = CH_3, C_6H_5), and $[Co(L209)Br_2]Br$ (R = CH_3, C_6H_5) [249] have been described. The complexes were obtained by interaction of the corresponding ligsons in the presence of the respective metal ions as templates (Eq. 2.127).



L208

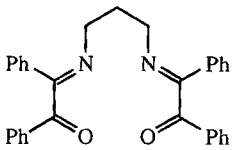
R = CH_3, C_6H_5



L209

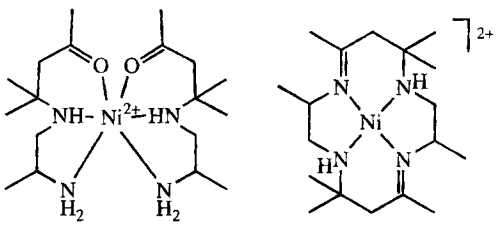
(2.127)

The precursor L210 of macrocycle L207 (R = C_6H_5) was also described (Eq. 2.128) [249]. This precursor can subsequently react with a second 1,3-propanediamine ligson only when cobalt(II) is present in solution, demonstrating the template nature of this macrocycle synthesis [247–254].



L210 (2.128)

Bis(1,2-diaminopropane)nickel(II) perchlorate, taken as the racemate, reacts with acetone over a period of days to yield $[Ni(L211)_2](ClO_4)_2$. This forms a violet solution in pyridine which slowly changes to orange, giving the *C-meso*-$[Ni(L212)](ClO_4)_2$ isomer (Eq. 2.129) [251].



$[Ni(L211)_2]^{2+}$ $[Ni(L212)]^{2+}$ (2.129)

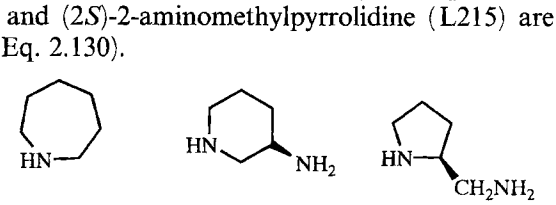
The conversion of $[Ni(L211)_2]^{2+}$ into $[Ni(L212)]^{2+}$ indicates that the coordinated β-amino-ketone has the structure $H_2NCH(CH_3)CH_2NHC(CH_3)_2CH_2COCH_3$. The exclusive formation of the *C-meso* form of $[Ni(L212)]^{2+}$ suggests that the precursor also has the *C-meso* configuration and that the cyclisation is intramolecular.

Analogously, bis(*R*-1,2-diaminopropane)nickel(II) perchlorate reacts with acetone to give the *RR*-$[Ni(L211)_2]^{2+}$ isomer, which is converted in pyridine exclusively into the *RR*-$[Ni(L212)]^{2+}$ isomer [251]. Reaction of tris(propane-1,2-diamine) nickel(II) perchlorate prepared from racemic diamine with acetone affords *C-rac* and *C-meso* isomers of $[Ni(L212)]^{2+}$ in approximately equal amounts [218, 251].

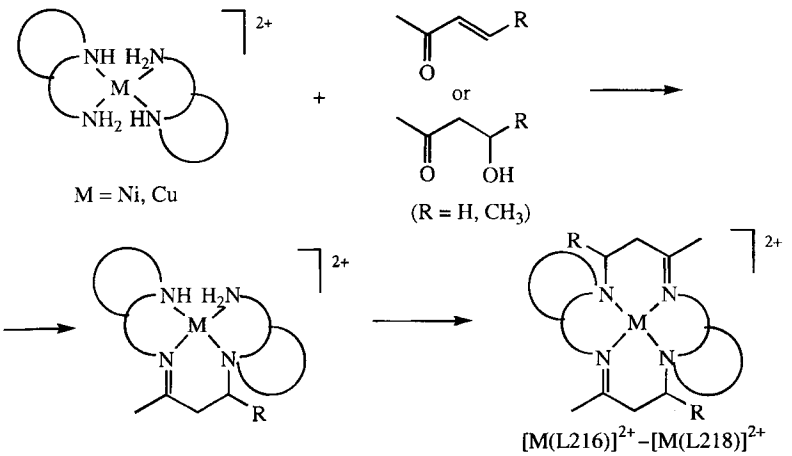
The tris(propane-1,2-diamine)copper(II) perchlorate containing racemic diamine reacts with acetone to yield a mixture of two species – $[Cu(L212)](ClO_4)_2$ in its *meso* form and, presumably, the C-*rac* isomer [251].

Template synthesis of other chiral tetraazamacrocyclic complexes can also be achieved [252–254]. The corresponding complexes are obtained according to Scheme 2-16.

The compounds (3*S*)-3-aminohexahydroazepine (L213), (3*S*)-3-aminopiperidine (L214) and (2*S*)-2-aminomethylpyrrolidine (L215) are employed as starting diamines (Eq. 2.130).

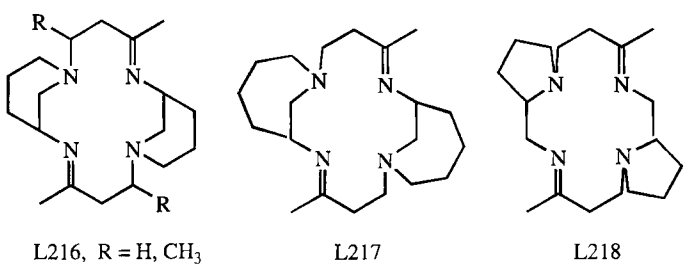


L213 L214 L215 (2.130)



Scheme 2-16. Template synthesis of $[M(L216)]^{2+}$–$[M(L218]^{2+}$

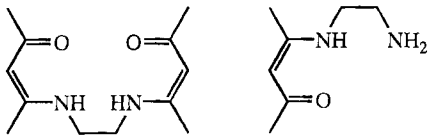
As a result, the copper(II) complexes of L216–L218 and the nickel(II) complex of L218 were obtained (Eq. 2.131).



(2.131)

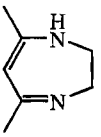
2.7 Macrocyclic complexes with ligands based on 1,3-dicarbonyl compounds and 1,2- or 1,3-diamines

Pentane-2,4-dione (Hacac) and ethane-1,2-diamine (en) can give various products depending on the reaction conditions. The most stable compound isolated, even when using a 1:1 ratio of reagents, is bis-(pentane-2,4-dione)-1,2-diaminoethane (H_2L219) [255]. If, however, carbon tetrachloride or chloroform is used as the solvent, and the pentane-2,4-dione is added to ethane-1,2-diamine under conditions of high dilution, then it is possible to isolate the (1 + 1) product of condensation (HL220) (Eq. 2.132) [256, 257].



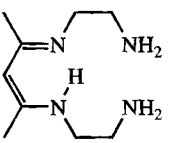
H_2L219 HL220 (2.132)

Product HL220 is also formed by reaction of freshly distilled Hacac with a threefold excess of ethane-1,2-diamine if the temperature of the reaction medium is no greater than 20°C [258]. In strongly acidic media pentane-2,4-dione interacts with ethane-1,2-diamine giving the cyclic product diazepin L221 (Eq. 2.133) [259].



L221 (2.133)

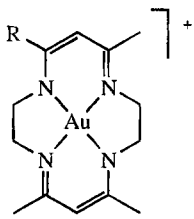
This product was also isolated as a salt in good yield when NH_4Cl was added to an ethanol solution of HL220 [260]. If an aqueous solution containing 1 equivalent of ethane-1,2-diamine and 1 equivalent of acetic acid be added to an aqueous solution of HL220, followed after prolonged mixing by an aqueous solution of sodium carbonate, then a small amount of Schiff base HL222 is formed (Eq. 2.134) [260].



HL222 (2.134)

Complexes of the bivalent 3d metals with H_2L219 can be obtained both by direct interaction of the corresponding metal salt with the presynthesised ligand [261] and *in situ*. For example, [Ni(L219)] is isolated from the reaction of $Ni(en)_2Cl_2$ with pentane-2,4-dione in the presence of a catalytic quantity of pyridine [262], as well as on addition of nickel(II) acetate to an equimolar mixture of ethane-1,2-diamine and pentane-2,4-dione, or by interaction of bis[4-amino-3-penten-2-onato(2-)]nickel(II) with en [260, 263].

It should also be noted that $NiCl_2 \cdot 6H_2O$ on reaction with an Hacac/en mixture in the presence of acetic acid gives [Ni(L222)] [264], which can also be obtained by condensation of $Ni(en)_2Cl_2$ with pentane-2,4-dione [265]. The thermodynamic coordination template effect is likely to be operative in these syntheses. If gold(III) is used as a matrix, then the reaction results in the formation of $[Au(L222)]^{2+}$, and of the macrocyclic complex $[Au(L223)]^{2+}$ (Eq. 2.135) [266–268].



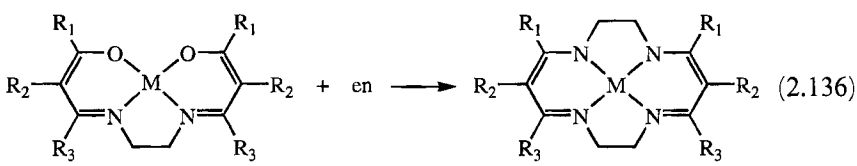
R = CH_3,	$[Au(L223)]^+$
R = C_6H_5,	$[Au(L224)]^+$
R = *iso*-C_3H_7,	$[Au(L225)]^+$
R = *tert*-C_4H_9,	$[Au(L226)]^+$
R = CF_3,	$[Au(L227)]^+$

(2.135)

The species $[Au(L222)]^{2+}$ seems to be the intermediate product of the macrocyclisation, a hypothesis supported by the isolation of $[Au(L223)]^+$ on treating $[Au(L222)]^{2+}$ with acetylacetone at pH 12. Starting from the chelate $[Au(L222)]^{2+}$ and using different β-dicarbonyl compounds, a range of asymmetric macrocyclic systems can be created, isolable as gold(III) complexes of the $[Au(L224)]^+$-$[Au(L227)]^+$ type [267]. Macrocyclisation on gold(III) is obviously controlled by the formation of the nucleophilic cation $Au(en)(en\text{-}H)^{2+}$ from $Au(en)_2{}^{3+}$, when the pH = 8 or above.

Macrocycle H_2L223 can also be obtained in a non-template way by reaction of en with 4-amino-3-penten-2-one [269] or β-aminothiones [270, 271] resulting from activation of ketone or thioketone groups by triethyloxonium tetrafluoroborate.

Attempts to carry out ring closure reactions of H_2L219 and H_2L222 with ethane-1,2-diamine and pentane-2,4-dione, respectively, in the presence of nickel(II) failed [260, 269]. However, introduction of electron-withdrawing substituents into the γ position of the β-diketonate residue gives nickel(II) and copper(II) N_2O_2 chelates of H_2L6 and H_2L228. These react easily with en to give isolable macrocyclic products [M(L7)] and [M(L229)], even in the absence of solvent (Eq. 2.136) [272–275].



(2.136)

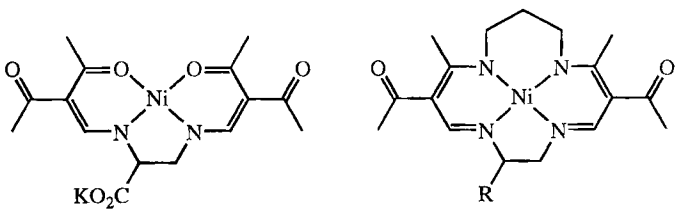
$R_1 = CH_3$, $R_3 = H$	
$R_2 = COCH_3$	[M(L6)]
$R_2 = COOC_2H_5$	[M(L228)]

$R_1 = CH_3$, $R_3 = H$	
$R_2 = COCH_3$	[M(L7)]
$R_2 = COOC_2H_5$	[M(L229)]

Related complexes of other metals, such as [M(L7)] where M = Fe, Co and Pd, have been prepared by the same method [276]. Both the reactions of precursor [Pd(L6)] and final formation of [Pd(L7)] proceed easily. Palladium(II) seems to favour the template process in the same way as nickel(II) and copper(II). In contrast to palladium(II), platinum(II) is oxidised during construction of H_2L6, and the resulting product in this case is $[Pt^{IV}(L6)Cl_2]^{2+}$. All attempts to produce the macrocyclic complex of platinum(II) were unsuccessful because, after the reaction with en, $[Pt(L6)Cl_2]^{2+}$ decomposed. The template reaction probably fails to take place due to the octahedral coordination of the metal, as the postulated mechanism for the ring closure reaction involves ethane-1,2-diamine taking up axial positions [277].

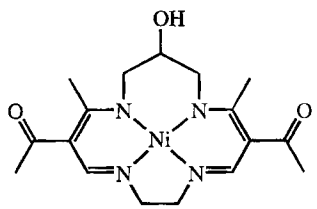
Iron complexes of the non-cyclic ligand H_2L6 could not be isolated; the condensation reaction to obtain [Fe(L7)] was realised *in situ* [276].

Starting from (*S*)-2,3-diaminopropanoic acid and 3-ethoxymethylene-pentane-2,4-dione the open chain chiral chelate [Ni(L230)] has been prepared [278]. The latter, taken as the racemate, reacts with propane-1,3-diamine leading to the unsymmetrically substituted macrocyclic complex [Ni(L231)] (R = CO_2K). This product is oxidatively decarboxylated in the presence of acid to give the hydroxy-substituted macrocycle [Ni(L231)] (R = OH) presumably by a disproportionation reaction (Eq. 2.137). The structure of this compound is also available [278]. Note that using a large excess of the diamine and forcing ring-closure reaction conditions should be avoided. The transamination processes leading to replacement of *S*-2,3-diaminopropanoic acid by the corresponding ethane-1,2-diamine or propane-1,3-diamine have been observed.



[Ni(L230)] [Ni(L231)], R = KO_2C, OH (2.137)

The template ring closure of [Ni(L6)] with 1,3-diaminopropan-2-ol occurs on heating the reagents at 150°C for 1 h to yield [Ni(L232)] (Eq. 2.138) [279].



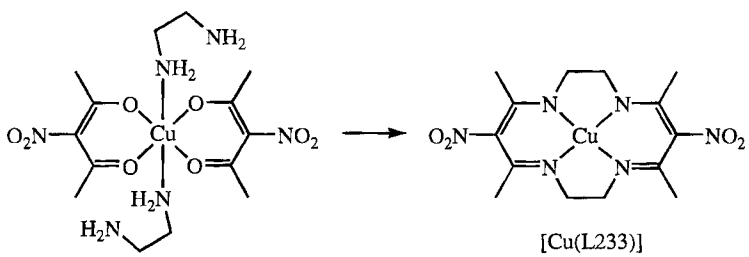
[Ni(L232)] (2.138)

If chemical shifts of the coordinated CO groups in ^{13}C NMR spectra of [Ni(L219)], [Ni(L6)] and [Ni(L229)] are compared (Table 2-3), it is not difficult to see that the CO groups in [Ni(L219)] are considerably less activated than in [Ni(L6)] and [Ni(L229)]. As discussed in Chapter 1, investigation of the kinetics of the reaction of [Ni(L6)] with en showed [277] that in the first step a six-coordinate paramagnetic adduct [Ni(L6)$(en)_2$] is formed, where the ethane-1,2-diamine molecules are axially arranged. As a result of polarisation of the coordinated CO and $-NH_2$ groups, the subsequent course of the macrocyclisation process is considerably facilitated. [Ni(L219)] remains diamagnetic in the solution in the presence of pyridine [260], probably due to the greater electron density at the central ion in [Ni(L219)] in comparison with [Ni(L6)] and [Ni(L229)], as indicated by the $E_{1/2}$ half-wave potentials for these chelates (Table 2-3). The formation of an unstable adduct is likely to be an essential step in this macrocyclisation process.

Table 2-3. Chemical shifts of the coordinated CO groups in ^{13}C NMR spectra [281, 282] and the $E_{1/2}$ values of the reduction process $NiL + e^- \rightarrow (NiL)^-$ in CH_3CN at 20°C versus SCE for a series of nickel(II) complexes [280].

Compound	Chemical shift (ppm)	$E_{1/2}$(V)
[Ni(L219)]	176.8	−2.04
[Ni(L6)]	188.0	−1.68
[Ni(L229)]	187.1	−1.71

The solid-state macrocyclisation reaction of bis[3-nitro-2,4-pentanedionato(2-)] copper(II) with ethane-1,2-diamine favours the above [283]. The adduct Cu $(3\text{-}NO_2acac)_2 \cdot 2en$, isolated from ethanol, converts into the macrocyclic product [Cu(L233)] on heating in the solid state (Eq. 2.139).



$Cu(3\text{-}NO_2acac)_2 \cdot 2en$ [Cu(L233)] (2.139)

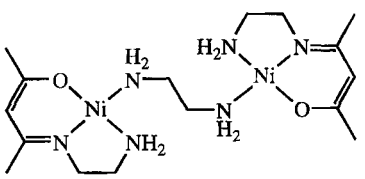
The IR spectrum of [Cu(L233)] coincides with that for the compound synthesised by heating $Cu(3\text{-}NO_2acac)_2 \cdot 2en$ with en in xylene [284]. On treatment of the chloroform solution of [Cu(L233)] with hydrogen sulphide, demetallation takes place, and metal-free H_2L233 is isolated in good yield [284].

Thus, introduction of electron-withdrawing groups into the γ position of β-diketonate residues results in considerable activation of the coordinated CO groups and creates conditions favourable for the kinetic coordination template effect to operate. Chelates [M(L6)] and [M(L228)], where M = Ni or Cu, also interact with 1,3-diaminopropane forming 15-membered macrocyclic systems [273, 285].

During the self-condensation of the tridentate Schiff base HL220 in the presence of sodium methoxide and $NiPy_2Cl_2$ (as the template ion source), [Ni(L223)] is assembled in 30% yield [260]. It can be also obtained by interaction of $[Ni(L220)Py]^+$ with HL220, but in smaller yield. Unlike [Ni(L219], compound $[Ni(L220)Py]^+$ readily gives six-coordinate adducts, for instance $[Ni(L220)Py_3]^+$. In the absence of base, reaction of HL220 with Ni^{2+} ions gives rise to [Ni(L219)] [260]. In the presence of $(NEt_4)_2Co^{II}Br_4$ and a base the self-cyclisation of HL220 does not proceed, but the octahedral cobalt(III) complex $[Co^{III}(L220)_2]Br$ is formed [256]. (It is supposed that an intermediate including two orthogonally disposed monodeprotonated ligands $(L220)^-$ is obtained on self-condensation of HL220 in the presence of nickel(II), succeeded by formation of [Ni(L223)]).

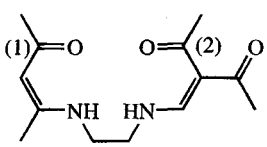
In the case of copper(II), the trinuclear complex $[Cu_3(L220)_3OH](ClO_4)_2$ is isolated from the reaction mixture [286]. Thus, macrocyclisation does not occur in the presence of copper(II). This is not surprising in that during the interaction of H_2L223 with copper(II) salts, the concentration of the macrocyclic complex passes through a maximum and then decreases as a consequence of its decomposition in solution [284].

Depending on the experimental conditions in the system HL220/Ni^{2+}/en, either the binuclear complex $[Ni_2(L220)_2en]^{2+}$ or the mononuclear species $[Ni(L222)]^+$ can be formed [260]. The binuclear complex is isolated when HL220 is treated with sodium methoxide in methanol and then with $Ni(ClO_4)_2 \cdot 6H_2O$ and en, whereas [Ni(L222)] results from interaction of $[Ni(HL220)Py]^+$ with en and NaOH in water on heating. In the first case en acts as a bridge and links two nickel ions, whereas in the second case one of the $-NH_2$ groups of the ethane-1,2-diamine reacts with the carbonyl group of HL220. If en is used in the stoichiometric amount at room temperature, then a condensation reaction does not occur and the binuclear species $[Ni_2(L220)_2en]^{2+}$ is isolated (Eq. 2.140).



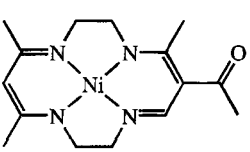
$[Ni_2(L220)_2en]^{2+}$ (2.140)

From tridentate HL220 it is possible to synthesise various asymmetric tetradentate Schiff bases. Some can then be used as ligsons for template condensation with diamines. For example, upon interaction of HL220 with 3-ethoxymethylenepentane-2,4-dione, H_2L234 is formed (Eq. 2.141) [281, 287].



H_2L234 (2.141)

On comparing the chemical shifts of the carbon atoms of the CO groups in H_2L234 ($C_{(1)}$ 194.8, $C_{(2)}$ 196.1 ppm) and [Ni(L234)] ($C_{(1)}$ 177.3, $C_{(2)}$ 188.7 ppm), it is apparent that the polarising effect of the Ni^{2+} ion on the $C_{(2)}$=O bond is significantly greater than on $C_{(1)}$=O. According to the chemical shift of $C_{(1)}$ in [Ni(L234)], the reactivity of the CO group distant from the electron-withdrawing substituent CH_3CO must be quite low, as in the case of [Ni(L219)] (Table 2-3). Reaction of [Ni(L234)] with en, however, still gives rise to [Ni(L235)] (Eq. 2.142) [281, 288].



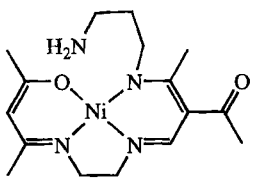
[Ni(L235)] (2.142)

The following mechanism of macrocyclisation was proposed [281]:

- in the first step, the six-coordinate complex is formed;
- in the second step, deprotonation of the coordinated ethane-1,2-diamine amino-group and attack of the $C_{(2)}O$ group by nucleophilic $^{-}NH-CH_2-CH_2-NH_2$ takes place;
- in the final step, taking into account the low reactivity of the $C_{(1)}O$ group, the kinetic coordination template effect seems to be non-pronounced.

Note that [Ni(L235)] formation is thermodynamically preferable to isolation of the unclosed product.

By interaction of [Ni(L234)] with propane-1,3-diamine, the non-cyclised complex [Ni(L236)] is obtained (Eq. 2.143).

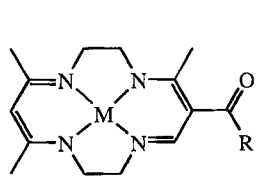


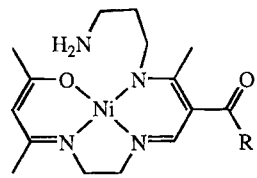
[Ni(L236)] (2.143)

This result can be explained by the fact that nickel(II) complexes with 14-membered macrocyclic ligands with alternating 6-5-6-5 metallocycles are more stable than their 15-membered 6-5-6-6 analogues [289]. However, if there are two CH_3CO- groups at the γ positions of the acetylacetone residues, building up of the 15-membered macrocycles proceeds easily in the presence of nickel(II) or copper(II) [273, 285].

So, when assessing the possibility of achieving either template process, the reactivity of the interacting groups, the conditions for displaying kinetic (the possibility of coordination and activation of the ligsons participating in the reaction, by $E_{1/2}$ data) and thermodynamic coordination template effects, as well as the factors enumerated earlier in Chapter 1, must all be taken into account.

The products [Cu(L235)] and [Cu(L236)], [M(L237)] and [M(L238)] where M = Ni or Cu, [Ni(L239)] and [Ni(L240)] have been obtained similarly (Eq. 2.144) [288].





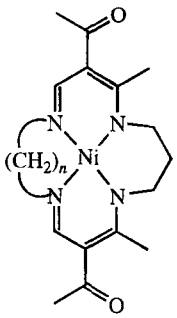
(2.144)

R = C_6H_5, [M(L237)]
R = OC_2H_5, [M(L238)]
M = Ni, Cu

R = C_6H_5, [M(L239)]
R = OC_2H_5, [M(L240)]
M = Ni, Cu

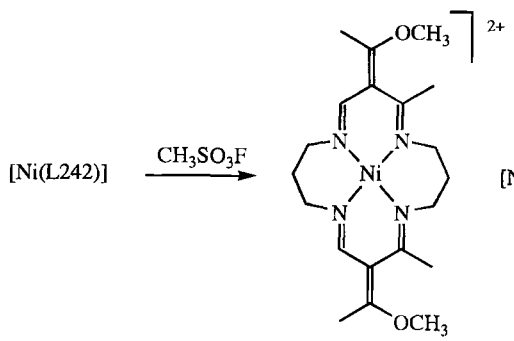
Building up the [Ni(L7)], [Ni(L241)] and [Ni(L242)] systems (Eq. 2.145) by template methods [285] illustrates the general strategy for creating lacunar macro-

cyclic complexes of the $[Ni(L14)]^{2+}$ and $[Ni(L244)]^{2+}$ type, so-called to denote the presence of the cavity [225].



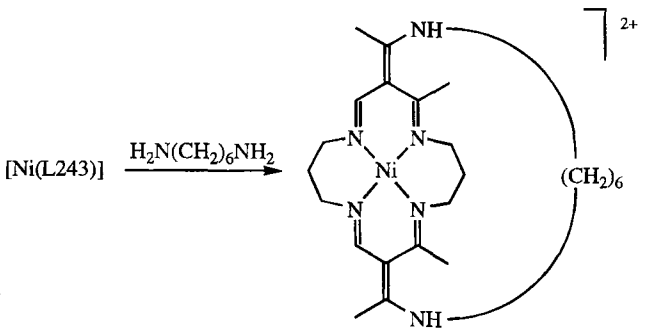
$n = 2$, [Ni(L241)]
$n = 3$, [Ni(L242)] (2.145)

Substances containing methoxyethylidene groups have been obtained by treatment of [Ni(L7)], [Ni(L241)] or [Ni(L242)] in CH_2Cl_2 with strong methylating agents, such as methyl fluorosulphonate (Eq. 2.146) [290].



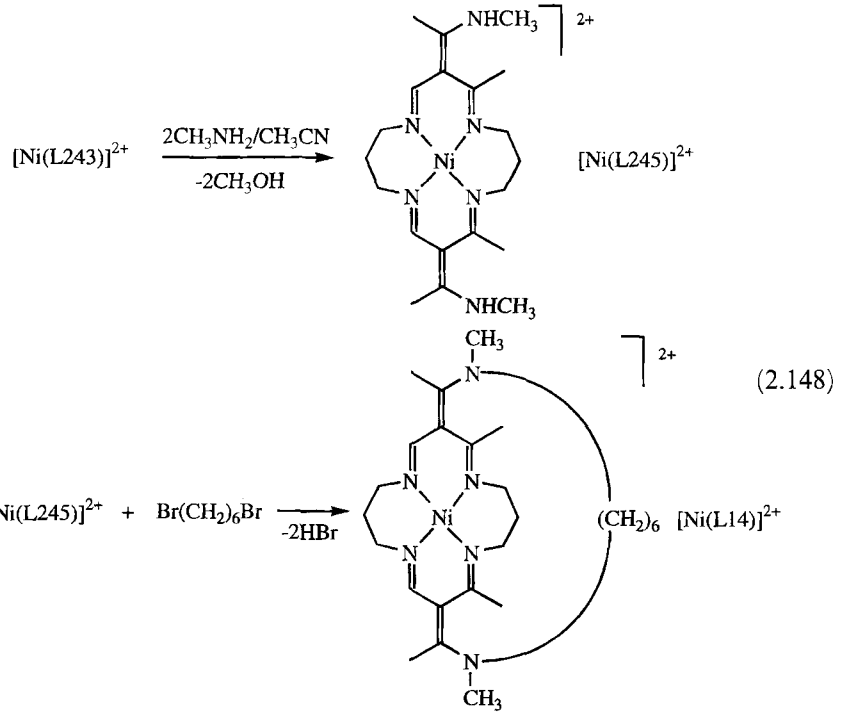
(2.146)

The species $[Ni(L243)]^{2+}$ readily enters into nucleophilic substitution reactions with diamines. In this way lacunar macrobicyclic complexes such as [Ni(L244)] are formed (Eq. 2.147) [291, 292].



(2.147)

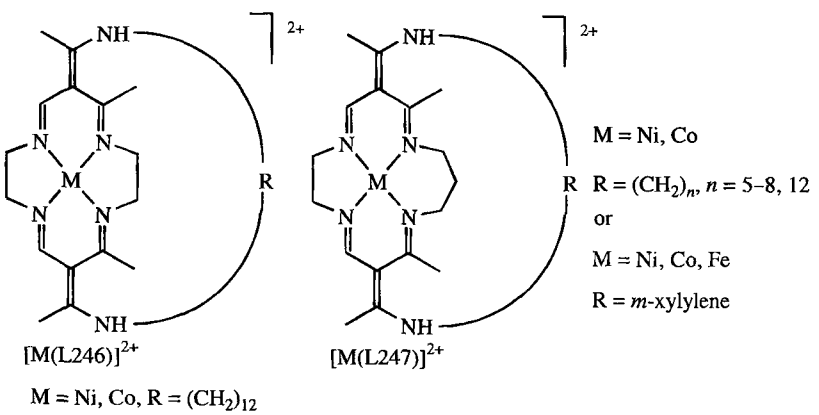
To create superstructures with three-dimensional cavities, nitrogen-containing derivatives such as $[Ni(L245)]^{2+}$ are also suitable. They can be obtained by reaction of $[Ni(L243)]^{2+}$ with amines (Eq. 2.148) [292–294].



(2.148)

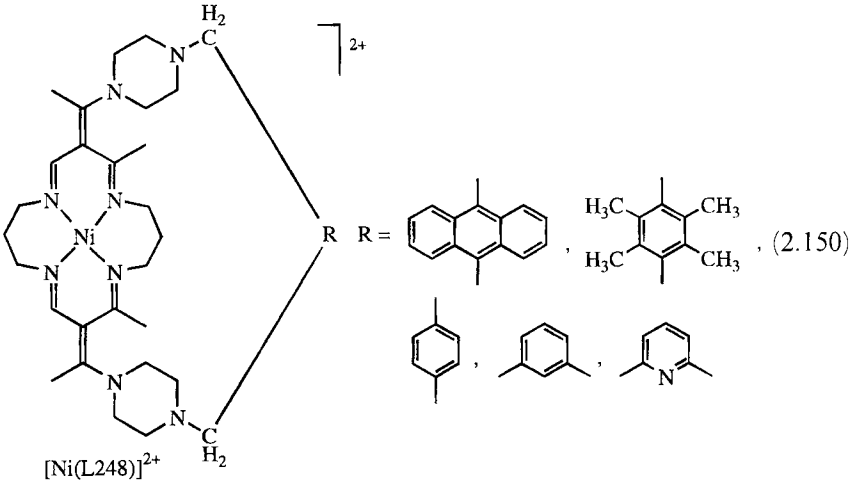
The main achievements in the field of macrocyclic coordination compounds with lacunar superstructure ligands have been discussed in detail [225].

Lacunar nickel(II) complexes of 14- and 15-membered cyclidene ligands $[Ni(L246)](PF_6)_2$, having $(CH_2)_{12}$, and $[Ni(L247)](PF_6)_2$, having $(CH_2)_n$ (n = 5–8, 12) or *m*-xylylene bridging units, have also been synthesised using the template approach in the early stages (Eq. 2.149). Ligand salts have been produced by demetallation of the nickel(II) complexes with gaseous HBr and HCl. Corresponding cobalt(II) and iron(II) complexes have been prepared by direct interaction between metal salts and ligands [295, 296].



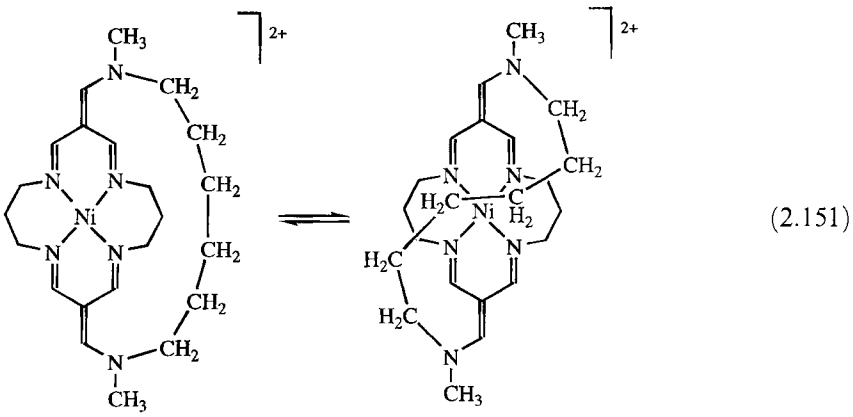
(2.149)

The synthesis of lacunar compounds, such as the series $[Ni(L248)](PF_6)_2$, has been described in detail (Eq. 2.150) [297, 298]



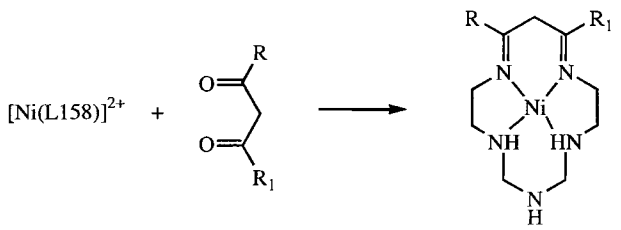
$[Ni(L248)]^{2+}$ (2.150)

Starting from triformylmethane and propane-1,3-diamine and using nickel(II) ion as template at key ring closure steps, macrocyclic products containing only formyl groups as peripheral substituents have been prepared [299]. Following the usual synthetic transformations in cyclidene chemistry the latter have been converted into a new kind of lacunar 16-membered nickel(II) and cobalt(II) complexes, which exhibit *cis-trans* bridge isomerism as shown in Equation (2.151) for $[Ni(L249)]^{2+}$ [299, 300].



$[Ni(L249)]^{2+}$ (2.151)

Reaction of $[Ni(L158)](ClO_4)_2$ with acetylacetone or benzoylacetone in the presence of H^+ leads to the formation of $[Ni(L250)](ClO_4)_2$ and $[Ni(L251)](ClO_4)_2$ (Eq. 2.152) [184].

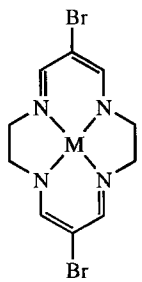


(2.152)

$R = R_1 = CH_3$ $[Ni(L250)]^{2+}$

$R = CH_3$, $R_1 = C_6H_5$ $[Ni(L251)]^{2+}$

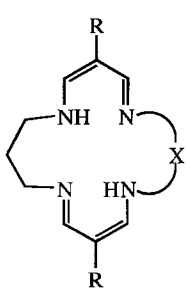
Interaction of ethane-1,2-diamine with bromomalondialdehyde in the presence of nickel(II), copper(II) or cobalt(II) acetates results in formation of complexes [M(L252)] (Eq. 2.153) [301].



[M(L252)]
M = Ni, Cu, Co

(2.153)

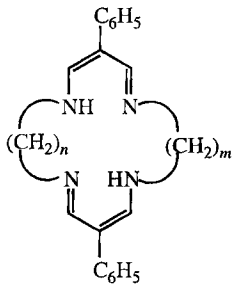
By condensation of 1,2- or 1,3-aliphatic diamines with phenylazomalondialdehydes on nickel(II) or copper(II) matrices, tetraazamacrocyclic compounds H_2L253-H_2L256 were obtained, as the respective complexes (Eq. 2.154) [302]. (Note that H_2L256 is assembled on the nickel(II) matrix only).



$X = C_3H_6$,	$R = -N{=}N-C_6H_5$	H_2L253
$X = C_3H_6$,	$R = -N{=}N-(2-Cl)-C_6H_4$	H_2L254
$X = C_2H_4$,	$R = -N{=}N-C_6H_5$	H_2L255
$X = o\text{-}C_6H_4$,	$R = -N{=}N-C_6H_5$	H_2L256

(2.154)

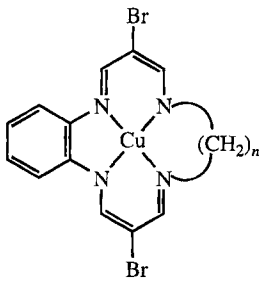
Interaction of 1,2-dithiolium cations or vinylogous β-aminothiones with diamines provides a non-template synthesis of tetraazamacrocycles H_2L257–H_2L259 (Eq. 2.155) [303, 304].



$n = m = 2$, H_2L257
$n = 2, m = 3$, H_2L258
$n = m = 2$, H_2L259 (2.155)

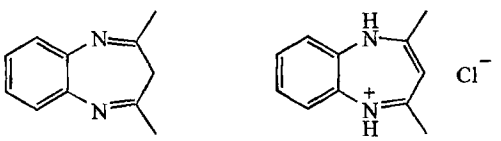
This process is possible due to the high electrophilic reactivity of 1,2-dithiolium cations and β-aminothiones in their reactions with primary amines.

By reaction of $[Cu(en)(o\text{-phda})]^{2+}$ or $[Cu(1,3\text{-pn})(o\text{-phda})]^{2+}$ (*o*-phda = *o*-phenylenediamine) with bromomalondialdehyde, macrocyclic systems [Cu(L260)] and [Cu(L261)], combining aliphatic and aromatic diamine residues in the cyclic backbone, were synthesised (Eq. 2.156) [301, 305].



$n = 2$ [Cu(L260)]
$n = 3$ [Cu(L261)] (2.156)

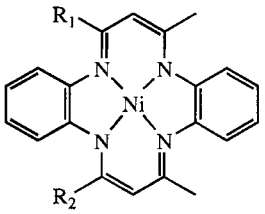
Upon interaction of acetylacetone with 1,2-diaminobenzene, 2,4-dimethyl-1,5-benzdiazepine L262 is obtained; its monohydrochloride [HL262]Cl is obtained in the presence of hydrochloric acid (Eq. 2.157) [306, 307].



L262 [HL262]Cl (2.157)

The species L262 is stable in moderately acid or alkaline media, but on heating in acid it decomposes to 2-methylbenzimidazole and acetone [306, 307].

Template reaction of bis(acetylacetone)nickel(II) with molten *o*-phenylenediamine results in formation of the dibenzotetraaza[14]annulene complex [Ni(L263)] in low yield (Eq. 2.158) [308].



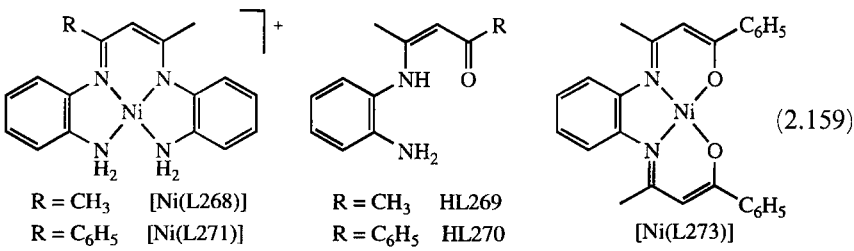
$R_1 = R_2 = CH_3$	[Ni(L263)]
$R_1 = C_2H_5$, $R_2 = CH_3$	[Ni(L264)]
$R_1 = C_2H_4OH$, $R_2 = CH_3$	[Ni(L265)]
$R_1 = C_7H_{15}$, $R_2 = CH_3$	[Ni(L266)]
$R_1 = C_{13}H_{27}$, $R_2 = CH_3$	[Ni(L267)]
$R_1 = R_2 = C_6H_5$	[Ni(L272)]

(2.158)

A higher yield of [Ni(L263)] is obtained by reaction of acetylacetone with 1,2-diaminobenzene in methanol or in absolute ethanol in the presence of nickel(II) acetate [302, 309–311]. Aqueous ethanol leads to a decrease in yield of [Ni(L263)] [312]. Increasing dilution leads to a sharp decrease in the yield of [Ni(L263)]. An analogous reaction between $[HL262]^+$ and nickel(II) salts gives the nickel(II) complex with 2-methylbenzimidazole [312]. A number of other substituted derivatives [Ni(L264)]–[Ni(L267)] are available by treatment of [Ni(L263)] with one equivalent of *n*-butyl Li followed by the corresponding alkylation reagent [313, 314].

On boiling L262 and $Ni(CH_3COO)_2 \cdot 4H_2O$ (molar ratio 2:1) in aqueous ethanol, [Ni(L263)] and the nickel complex of 2-methylbenzimidazole are formed [312].

The tricyclic chelate $[Ni(L268)]PF_6$ (Eq. 2.159) was obtained by interaction of *o*-phenylenediamine with nickel acetate and pentane-2,4-dione (molar ratio 1:2:1), or by interaction of 2,4-dimethyl-1,5-benzdiazepinium hexafluorophosphate with *o*-phenylenediamine and nickel acetate (molar ratio 1:1:1) [315]. On reaction with pentane-2,4-dione in methanol, $[Ni(L268)]PF_6$ yields [Ni(L263)] [316].



$R = CH_3$	[Ni(L268)]	$R = CH_3$	HL269
$R = C_6H_5$	[Ni(L271)]	$R = C_6H_5$	HL270

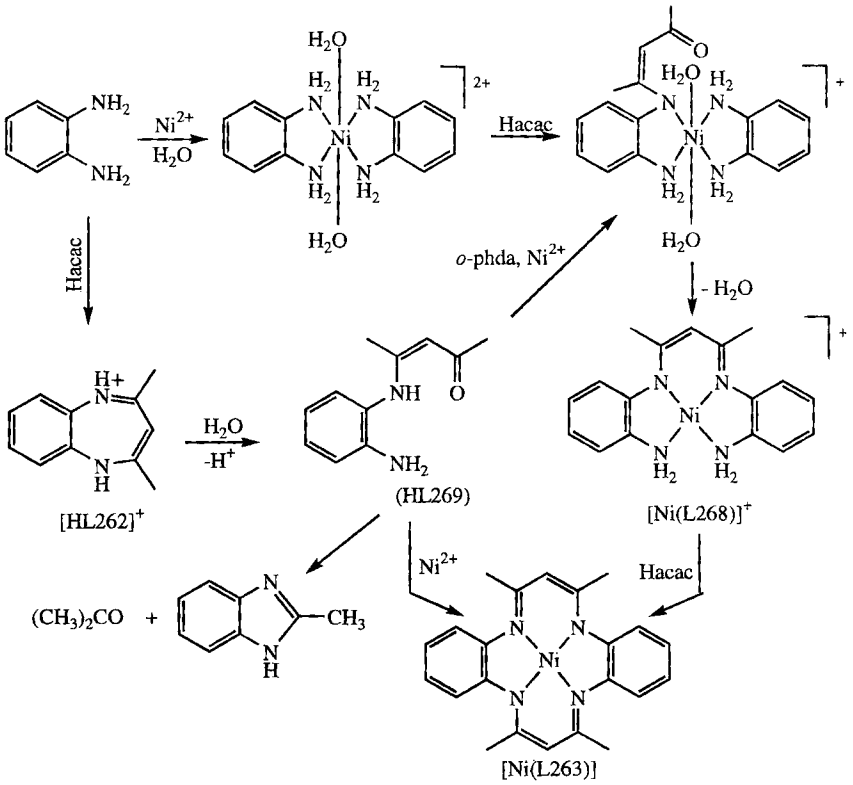
[Ni(L273)]

(2.159)

In aqueous solution the benzdiazepinium salt can enter into reactions characteristic of a mixture of *o*-phenylenediamine and pentane-2,4-dione [317]. Hydrolytic dissociation of the 2,4-dimethylbenzdiazepinium salt proceeds through deprotonation followed by azomethine bond breaking and formation of HL269 [307, 317].

These observations suggest that HL269 is one of the intermediate compounds in the template synthesis of [Ni(L263)]. The benzdiazepinium cation, in turn, represents an intermediate in the synthesis of [Ni(L263)] from *o*-phenylenediamine and acetylacetone in the presence of Ni^{2+} [311].

Attempts to isolate HL269 with the object of obtaining [Ni(L263)] or [Ni(L268)] were unsuccessful because of the instability of monoanil products [315]. Nevertheless, upon interaction of *o*-phenylenediamine and benzoylacetone, the stable monoanil HL270 is formed [315]. Prolonged heating of a mixture of HL270 and



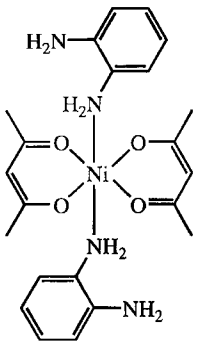
Scheme 2-17. Possible routes for assembling [Ni(L263)].

nickel(II) acetate in aqueous methanol or aqueous dimethylformamide results in a green solution, whose electronic absorption spectrum is identical to that for $[Ni(L271)]^+$. In addition, the macrocyclic product [Ni(L272)] is isolated in low yield. The species $[Ni(L271)]^+$ is also obtained from 2-methyl-4-phenyl-1,5-diazepinium, *o*-phenylenediamine, and nickel acetate [315], whereas [Ni(L272)] is obtained by prolonged heating of a mixture of *o*-phenylenediamine, $Ni(CH_3COO)_2 \cdot 4H_2O$ and benzoylacetone (2:1:2), in anhydrous butanol in an inert atmosphere [318]. Compound [Ni(L273)] is obtained by reaction of $Ni(o\text{-phda})_2Cl_2$ with an excess of benzoylacetone in alcohol at room temperature [318].

Taking all the evidence into account, it is suggested that the building up of [Ni(L263)] from the corresponding ligsons in the presence of nickel(II) follows Scheme 2-17 [312, 315].

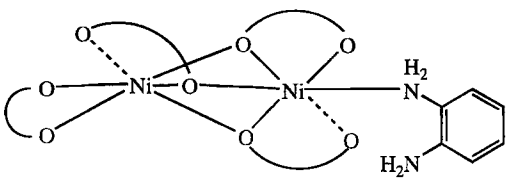
o-Phenylenediamine gives the complex $[Ni(o\text{-phda})_2(H_2O)_2]^{2+}$ at room temperature. If the temperature is increased, then the reaction proceeds in several directions (see Scheme 2-17). Controlled synthesis of [Ni(L263)] is observed as soon as nickel ion is introduced into the system at the appropriate step.

$Ni(acac)_2 \cdot 2o$-phda (Eq. 2.160) can also be formed in the system Hacac/o-phda/Ni^{2+} [319].



$Ni(acac)_2 \cdot 2o$-phda (2.160)

After prolonged heating of this adduct in dry ethanol, (1,2-diaminobenzene)-tetrakis(pentane-2,4-dionato)dinickel(II) may be isolated (Eq. 2.161).



$Ni_2(acac)_4(o$-phda) (2.161)

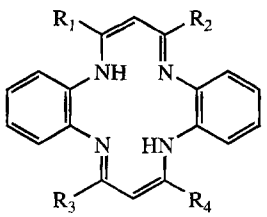
On boiling a mixture of $Ni(acac)_2 \cdot 2o$-phda and nickel(II) acetate in equimolar ratio in dry ethanol, a considerable amount of $[Ni(L268)]^+$ and a very small quantity (1.2%) of [Ni(L263)] are formed as well as $Ni_2(acac)_4(o$-phda). Compound [Ni(L263)] is also obtained in low yield on heating the adduct in n-butanol without adding nickel acetate; addition of Ni^{2+} to the n-butanol system results in a considerable improvement in the yield of [Ni(L263)] (up to 6.9%).

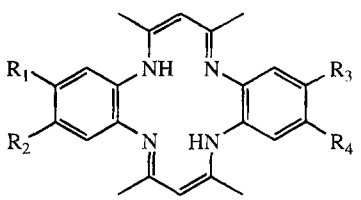
The opinion has been expressed [319] that $Ni(acac)_2 \cdot 2o$-phda is not an intermediate but merely a competing product of reaction in the macrocyclisation process. However, it should be recalled that during template interactions of β-diketones with ethane-1,2-diamine, formation of such adducts is one of the main conditions of macrocycle assemblage [277, 260, 283]. It is not excluded that solid-state template macrocyclisation process can take place, as in the case of $Cu(3\text{-}NO_2\text{-acac})_2 \cdot 2en$ [283]. In this connection it should be noted that $Ni(acac)_2 \cdot 2H_2O$ reacts with molten o-phda to give [Ni(L263)] [308].

The comparison of the ligson systems Hacac/en and Hacac/o-phda shows that, in the latter case, the chelate $[Ni(L268)]^+$ could be successfully used as a precursor for template synthesis of the macrocyclic product [Ni(L263)] [312, 315], whereas it was impossible to carry out the corresponding process for $[Ni(L225)]^+$ [260]. Taking this into account, it is difficult to support the supposition [260] that the non-occurence of the reaction $[Ni(L222)]^+ + Hacac \rightarrow [Ni(L223)]$ is due to the inability of $[Ni(L222)]^+$ to form unstable penta- or hexacoordinate intermediates. Most probably, for both

$[Ni(L268)]^+$ and $[Ni(L222)]^+$, formation of such intermediates takes place on adding acetylacetone to their solutions. Nevertheless, the stability of these open-chain precursor complexes is presumably a decisive factor in performing macrocyclisation. It is obvious that the presence of aromatic rings in the system $(L268)^-$ decreases the basicity of $-NH_2$ groups over those in $(L225)^-$. As a result, more labile complexes of HL268 should be expected. The topological factor, if necessary in both cases, is not sufficient for constructing macrocyclic products, operating only when electronic factors are appropriate.

In addition to the above-mentioned macrocyclic systems, the compounds [Ni(L274)]-[Ni(L281)] were obtained in good yield by reaction of aromatic 1,2-diamines and β-diketones in the presence of nickel(II) (Eq. 2.162) [302, 309]. For [Ni(L276)], [Ni(L280)] and [Ni(L281)], *cis* and *trans* isomers are possible, as shown by ^1H NMR for [Ni(L280)] and [Ni(L281)] [309]. The action of gaseous hydrogen chloride on [Ni(L263)], [Ni(L277)] or [Ni(L281)] results in demetallation; the macrocyclic Schiff bases H_2L263, H_2L277 and H_2L281 can be isolated. In mineral acids [Ni(L263)] is destroyed, giving the benzdiazepinium salt [HL262]X, where X is the anion of the acid used [302].

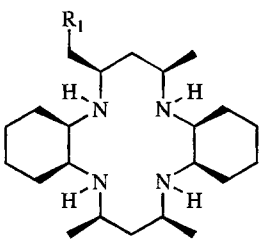




(2.162)

$R_1 = R_2 = R_3 = R_4 = C_2H_5$	H_2L274	$R_1 = R_2 = R_3 = R_4 = CH_3$	H_2L277
$R_1 = R_2 = R_3 = R_4 = n\text{-}C_3H_7$	H_2L275	$R_1 = R_4 = Cl, R_2 = R_3 = H$	H_2L278
$R_1 = R_4 = CH_2C_6H_5$,		$R_1 = R_2 = R_3 = R_4 = Cl$	H_2L279
$R_2 = R_3 = CH_3$	H_2L276	$R_1 = R_4 = COC_6H_5$,	
		$R_2 = R_3 = H$	H_2L280
		$R_1 = R_4 = CH_3, R_2 = R_3 = H$	H_2L281

Raney-nickel stereospecific hydrogenation of nickel(II) complexes [Ni(L263)]–[Ni(L267)] results in their demetallation and liberation of fully saturated substituted cyclams H_4L282–H_4L286 of exclusively *cis(R,S,R,S)* configuration with all hydrogen atoms at one side of the macrocycle (Eq. 2.163) [313, 314].



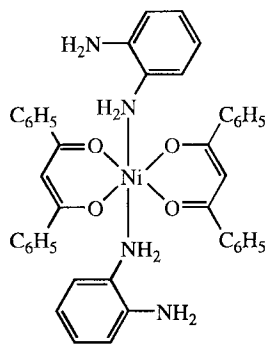
$R_1 = H$	H_4L282
$R_1 = CH_3$	H_4L283
$R_1 = CH_2OH$	H_4L284
$R_1 = C_6H_{13}$	H_4L285
$R_1 = C_{12}H_{25}$	H_4L286

(2.163)

Metal complexes of these ligands with $Ni(CH_3COO)_2$, $FeSO_4$, $Cu(CH_3COO)_2$,

$Zn(ClO_4)_2$, $La(CH_3COO)_3$ and SmI_2 have been obtained by direct complexation reactions. The structures of metal-free $H_4L282 \cdot 2CHCl_3$ and metal complexes $[Ni(H_4L282)](CH_3COO)_2$, $[Zn(H_4L282)(CH_3OH)](ClO_4)_2$ and $[Cu(H_4L282)](CH_3COO)_2 \cdot 2H_2O \cdot 2C_6H_5CH_3$ are available [313, 314].

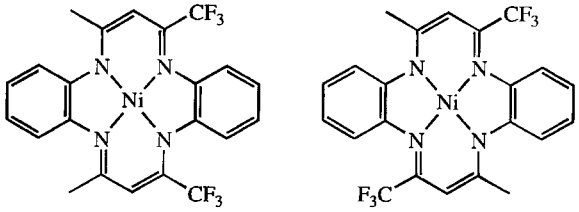
Condensation reactions on nickel(II) matrices are sensitive to steric effects. X-Ray structural analysis showed [310, 320–328] that H_2L263 and its metal complexes are saddle-like, rather than planar. The sources of structural nonplanarity are steric repulsions between methyl groups $R_{1,4}$ and *ortho*-aromatic protons of the Schiff bases. The increase in the bulk of the groups in these positions hinders macrocyclisation. For example, 3,5-heptanedione, 4,6-nonanedione and 1-phenyl-2,4-pentanedione form cyclic products [Ni(L274)]–[Ni(L276)], whereas dibenzoylmethane, 2,6-dimethyl-3,5-heptanedione and 2,2,6,6-tetramethyl-2,5-heptanedione do not give macrocyclic compounds in the presence of nickel(II) and *o*-phda [300, 320]. In the case of dibenzoylmethane, the nickel(II) *β*-diketonate bis-diamine adduct is isolated (Eq. 2.164) [319].



(2.164)

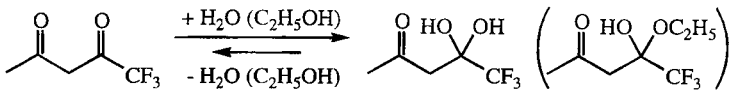
The analogous product is also obtained in the presence of iron(III) [329], although the conclusion that macrocycle formation occurs on the Fe^{III} as matrix [330] is wrong. Macrocyclic systems are also not formed in the case of 1,2-diamines which contain substituents sterically interacting with acetylacetone methyl groups. Thus, 3,4,5-trichloro-*o*-phenylenediamine and 9,10-diaminophenanthrene do not give cyclic products of template condensation with acetylacetone. Nevertheless, all diamines with substituents in positions 4 and 5 of the aromatic ring give nickel(II) macrocyclic complexes. The reaction of 4-nitro-*o*-phenylenediamine with acetylacetone in the presence of nickel(II) does not result in macrocycle construction. As the nitro group in the 4-position should not alter the steric requirements of unsubstituted *o*-phda, the difference in their behaviour must be of an electronic nature [309].

A mixture of the *cis*- and *trans*-bis(trifluoromethyl) substituted macrocyclic complexes [Ni(L287)] results in a very low yield from the reaction of 1,1,1-trifluoropentane-2,4-dione, 1,2-diaminobenzene and nickel(II) acetate in ethanol (Eq. 2.165) [331]. The isomers have easily been separated, but not identified. Supposedly, the formation of the *trans* isomer is favoured by the need to minimise steric interactions with the hydrogen atoms of the aromatic rings.



cis-[Ni(L287)] *trans*-[Ni(L287)] (2.165)

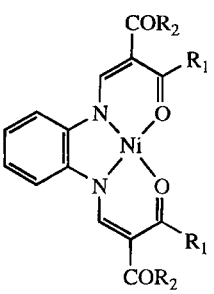
The low yield has been attributed to the ability of trifluoromethyl ketones easily to form hydrates or hemi-acetals (Eq. 2.166).



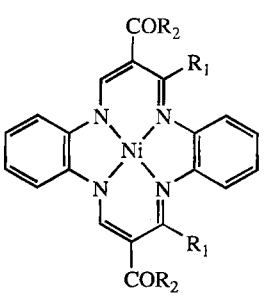
(2.166)

Overall it seems that template macrocyclisation reactions with the participation of *o*-phda proceed more easily than those with 1,2-diaminoethane.

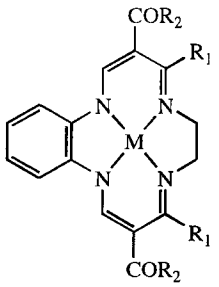
By interaction of *β*-ketoiminate complexes [Ni(L288)]–[Ni(L291)] (Eq. 2.167) with 1,2-diaminobenzene the products [Ni(L292)]-[Ni(L295)] were obtained (Eq. 2.168), whereas by reaction of [M(L291)] and ethane-1,2-diamine the complexes [M(L296)] (M = Ni, Cu) and [Cu(L297)] were synthesised (Eq. 2.169) [272, 332, 333].



$R_1 = CH_3$, $R_2 = CH_3$ [Ni(L288)]
$R_1 = CH_3$, $R_2 = C_6H_5$ [Ni(L289)]
$R_1 = CH_3$, $R_2 = OC_2H_5$ [Ni(L290)]
$R_1 = C_6H_5$, $R_2 = OC_2H_5$ [Ni(L291)] (2.167)



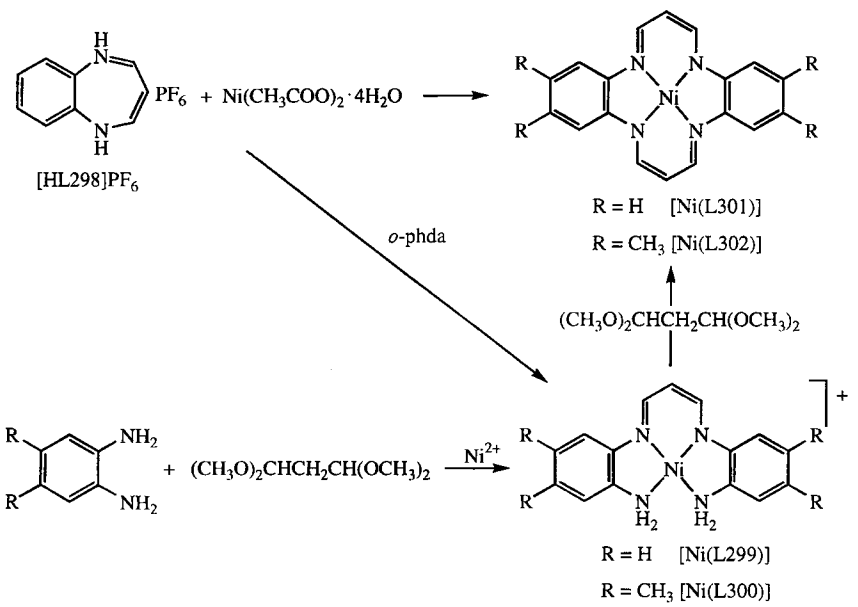
$R_1 = CH_3$, $R_2 = CH_3$ [Ni(L292)]
$R_1 = CH_3$, $R_2 = C_6H_5$ [Ni(L293)]
$R_1 = CH_3$, $R_2 = OC_2H_5$ [Ni(L294)]
$R_1 = C_6H_5$, $R_2 = OC_2H_5$ [Ni(L295)] (2.168)



$R_1 = CH_3$, $R_2 = CH_3$ [M(L296)]
$R_1 = CH_3$, $R_2 = C_6H_5$ [M(L297)]
M = Ni, Cu (2.169)

Note that if H is in the *meso* position, template condensation of the β-ketoiminate complex with *o*-phda also takes place [308, 334].

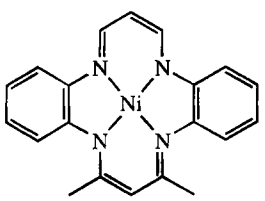
For the template synthesis of dibenzotetraaza[14]annulene systems, not only β-diketonates, but also β-dialdehydes, 3-chloroacroleins, propargyl aldehyde, acetals, and a number of other compounds are all suitable. For example, [Ni(L301)] can be obtained according to Scheme 2-18 in two ways. The first involves using the 1,5-benzdiazepinium salt $(HL298)PF_6$, which in the presence of nickel(II) acetate in boiling aqueous methanol or dimethylformamide gives [Ni(L301)] in 20% yield [335]. The second is considered to be more effective as, on heating an aqueous solution of *o*-phda, 1,1,3,3-tetramethoxypropane and nickel(II) acetate (2:2:1), the analytically pure macrocyclic product is isolated in a more than 85% yield [335]. In the absence of the nickel ions, a sediment of undefined composition not containing



Scheme 2-18. Synthetic pathways to [Ni(L301)] and [Ni(L302)].

H_2L301 is formed [335]. Malondialdehyde, produced from hydrolysis of 1,1,3,3-tetramethoxypropane, reacts with *o*-phda giving a polymeric product [307].

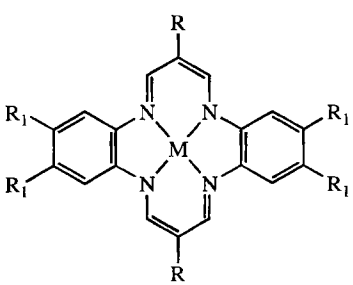
By reacting *o*-phda or 4,5-dimethyl-*ortho*-phenylenediamine with 1,1,3,3-tetramethoxypropane, or [HL298]PF_6 with *o*-phda, on a nickel(II) matrix, it is possible to synthesise chelates [Ni(L299)] or [Ni(L300)] (see Scheme 2-18). These are in turn suitable intermediates for building up symmetric ([Ni(L301)] and [Ni(L302)]), and asymmetric ([Ni(L303)]) dibenzotetraaza[14]annulene systems. For example, on heating [Ni(L299)]PF_6 in aqueous dimethylformamide with 1,1,3,3-tetramethoxypropane, [Ni(L301)] has been obtained in quantitative yield, whereas by interaction of [Ni(L299)]PF_6 with acetylacetone in ethanol, containing NaOH, the asymmetric macrocyclic complex [Ni(L303)] may be synthesised (Eq. 2.170) [335].



[Ni(L303)] (2.170)

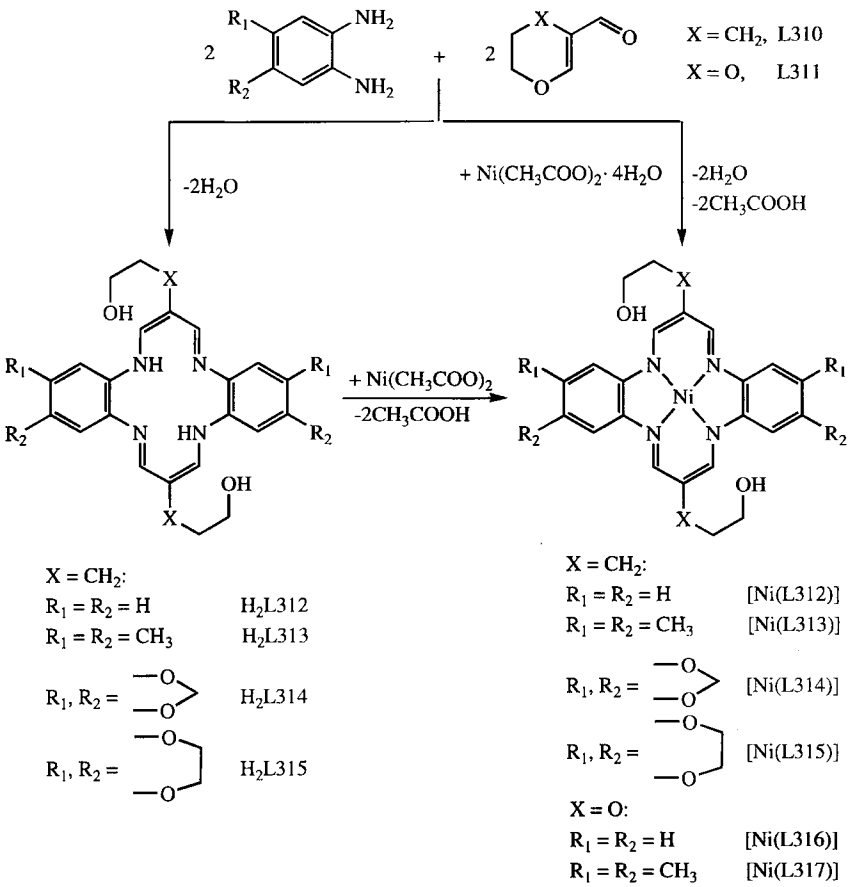
By heating a mixture of solutions of *o*-phda in dimethylformamide and propargyl aldehyde in methanol the Schiff base H_2L301 was obtained in 27% yield [336]. In the presence of Cu^{2+}, Co^{2+} or Ni^{2+} ions, macrocyclic complexes are produced in about 70% yield, thanks mainly to the thermodynamic coordination template effect.

Bromomalondialdehyde reacts with M(*o*-phda)$_2$(CH_3COO)$_2$ (M = Co, Ni, Cu) in ethanol at room temperature giving neutral macrocyclic complexes [M(L304)], in 60% yield in the case of cobalt(II), and almost 100% in the case of copper(II) [301]. The reaction of the corresponding acrolein and diamine ligsons with vanadyl acetate in refluxing DMF affords complexes [VO(L305)]-[VO(L308] in 51–68% yield [337]. Prolonged heating of Ni(*o*-phda)$_2$$Cl_2$ with 2-(*p*-tolyl)malondialdehyde in DMF gives [Ni(L306)] [338]. Compounds H_2L304–H_2L307 are also formed in the absence of the above-mentioned metal ions [339–341], but in lower yield, emphasising the template role of cobalt(II), nickel(II), copper(II) and oxovanadium(IV) ions in these reactions. This role consists of sequestering the macrocyclic compounds H_2L304-H_2L308 as generated as the respective metal complex (Eq. 2.171).



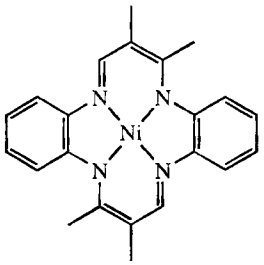
R_1 = H, R = Br	[M(L304)] M = Co, Ni, Cu
R_1 = H, R = CH_3, M = VO	[VO(L305)]
R_1 = H, R = *p*-tolyl	[M(L306)] M = Ni, VO
R_1 = R = CH_3, M = VO	[VO(L307)]
R_1 = CH_3, R = *p*-tolyl, M = VO	[VO(L308)]

(2.171)



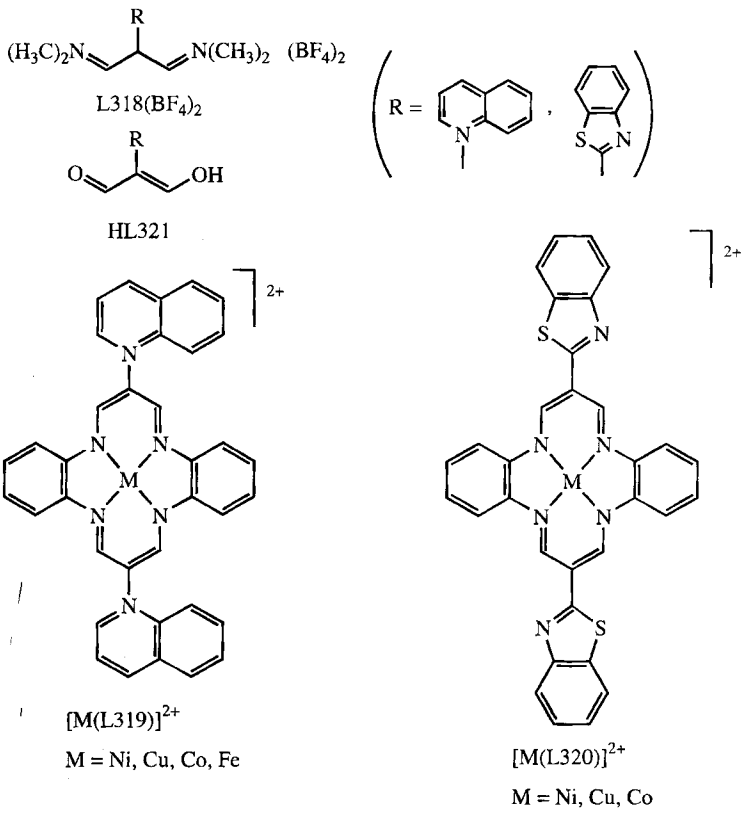
Scheme 2-19. Template and non-template routes to substituted tetraazamacrocycles H_2L312–H_2L317.

The compound [Ni(L309)] (Eq. 2.172) is obtained by reaction of *o*-phda with 2,3-dimethyl-3-chloroacrolein in the presence of nickel(II) acetate, in the ratio 2:2:1, in hot alcohol in an inert atmosphere, with subsequent extraction of the final product with toluene [342]. In the absence of the Ni^{2+}, at least 12 compounds are formed (according to thin-layer chromatography data). For synthesising macrocyclic systems containing peripheral hydroxypropyl groups, the heterocycle L310 is used [343]. Its reaction with substituted aromatic 1,2-diamines gives the metal-free macrocyclic compounds H_2L312–H_2L315 in yields from 12% to 32% (Scheme 2-19). These substances can be isolated as nickel(II) complexes in considerably greater yield (40–85%) on Ni^{2+} as matrix. Complexes [Ni(L316)] and [Ni(L317)] are assembled from the appropriate diamines and the acrolein derivative L311.



[Ni(L309)] (2.172)

By reaction of $L318(BF_4)_2$ with *o*-phda in the presence of metal acetates, macrocyclic compounds $[M(L319)](BF_4)_2$ [344] and $[M(L320)](BF_4)_2$ [345] were prepared (Eq. 2.173). Similarly HL321, an analogue of $(L318)^{2+}$, serves as ligson for constructing H_2L319 and H_2L320.



$L318(BF_4)_2$

HL321

$[M(L319)]^{2+}$

M = Ni, Cu, Co, Fe

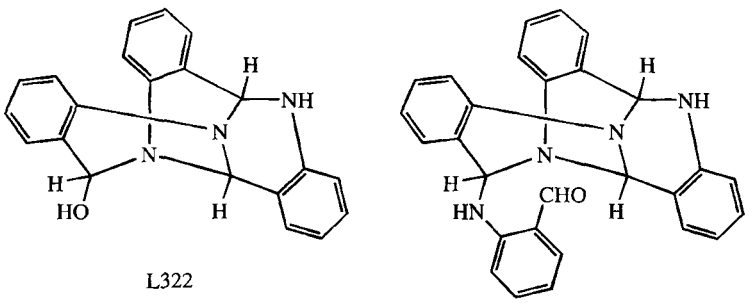
$[M(L320)]^{2+}$

M = Ni, Cu, Co

(2.173)

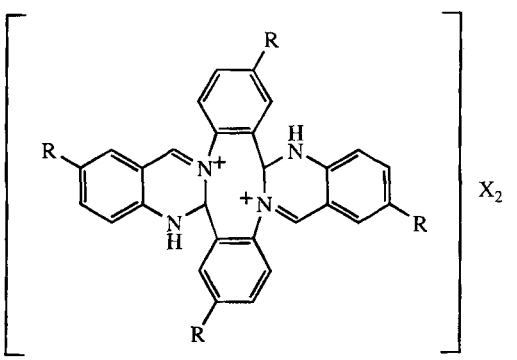
2.8 Macrocyclic systems based on aromatic *o*-aminocarbonyl compounds and their derivatives

The simplest block for the template building of macrocyclic derivatives of aromatic *o*-aminocarbonyl compounds is *o*-aminobenzaldehyde. Owing to its structural peculiarities it easily forms cyclic products on self-condensation. Thus, for instance, on long standing it transforms [346] into various polycyclic structures, particularly the *bis*-anhydrotrimer L322 and the *tris*-anhydrotetramer L323 (Eq. 2.174).



(2.174)

Formation of the trimer L322 is accelerated under the influence of weak or dilute acids [347]. The twice-protonated salt $H_2(L11)X_2$ is isolated (Eq. 2.175) from strongly acidic media to give, as a result of hydrolysis, the tris-anhydrotetramer L323 [347, 348].



(2.175)

R = H $H_2(L11)X_2$ (= $H_2(TAAB)X_2$)

R = Me $H_2(L324)X_2$ (= $H_2(Me_4TAAB)X_2$)

The course of this self-condensation is markedly controlled by transition metal ions in the reaction mixture. Depending on their nature, two kinds of closely related macrocyclic azomethine systems, TAAB (*o*-aminobenzaldehyde based tetramer) and TRI (*o*-aminobenzaldehyde based trimer), are isolated in the form of com-

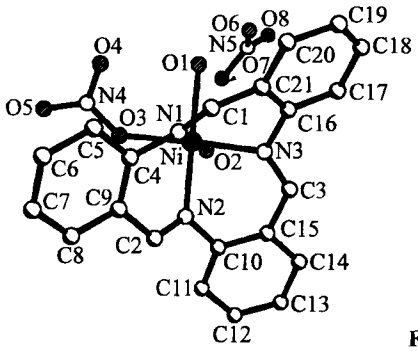


Figure 2-25. The structure of $[Ni(TRI)NO_3(H_2O)_2]NO_3$.

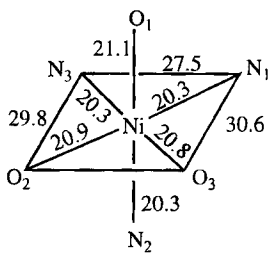


Figure 2-26. The octahedral configuration around the nickel ion in $[Ni(TRI)NO_3(H_2O)_2]NO_3$.

plexes. In the presence of copper(II), cobalt(II), zinc(II), iron(II), palladium(II) or platinum(II), *o*-aminobenzaldehyde cyclises exclusively to TAAB [346, 349–353]. (In the case of Co^{II} this synthesis is carried out in an inert atmosphere). However, in the presence of oxovanadium(IV) ions, self-condensation results in the formation of complexed TRI [354]. An identical product is obtained by reaction of vanadyl chloride with the bis-anhydrotrimer L322 or with $H_2(TAAB)(ClO_4)_2$ in dry ethanol.

Template reactions using nickel(II) or cobalt(II) ions give mixtures of complexes $Ni(TAAB)^{2+}$ and $Ni(TRI)(H_2O)^{2+}$, or $Co(TAAB)^{3+}$ and $Co(TRI)_2{}^{3+}$ (the cobalt products are obtained in the presence of an oxidant) [349, 355, 356]. Heating equimolar quantities of bis-anhydrotrimer L322 and nickel(II) nitrate in absolute ethanol gives only $Ni(TRI)(NO_3)_2 \cdot H_2O$. On starting with 2 mol of L322 and 1 mol of nickel(II) nitrate, $Ni(TRI)_2(NO_3)_2 \cdot H_2O$ separates from the methanol solution during heating. This salt can also be obtained by interaction of $Ni(TRI)(NO_3)_2 \cdot H_2O$ with 1 mol of L322 [357].

The structures of TAAB and TRI have been confirmed by X-ray diffraction studies of $[Ni(TAAB)](BF_4)_2$ and $[Ni(TAAB)I(H_2O)]I$ [358], $Ni(TRI)(NO_3)_2 \cdot 2H_2O$ [359] and $[Co(TRI)_2](ClO_4)_3 \cdot 3H_2O$ [360]. Structural data for $Ni(TRI)(NO_3)_2 \cdot 2H_2O$ are given in Figures 2-25–2-27, and for $Ni(TAAB)I_2 \cdot H_2O$ in Figures 2-28 and 2-29.

In both these high-spin complexes the central atom is in an octahedral configuration. In the case of $Ni(TRI)(NO_3)_2 \cdot 2H_2O$ the macrocyclic ligand occupies a face of the octahedron. Two water molecules and a nitrate ion fill the remainder of the

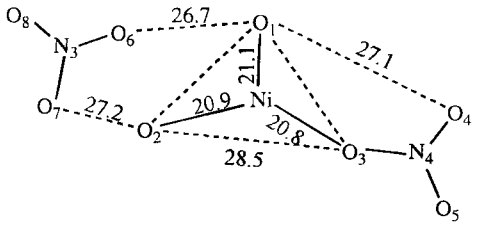


Figure 2-27. The nickel, water and nitrate configuration in $[Ni(TRI)NO_3(H_2O)_2]NO_3$.

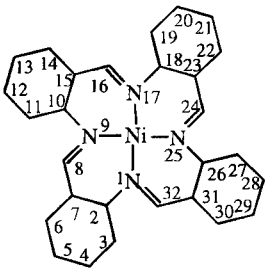


Figure 2-28. The numbering system for the TAAB ligand; the two sets of 16 atoms are related by a twofold rotation in $Ni(TAAB)I_2 \cdot H_2O$.

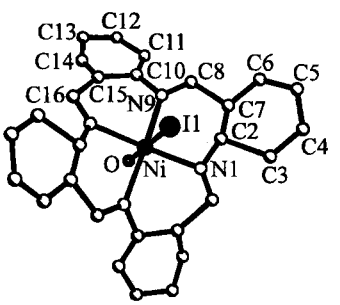
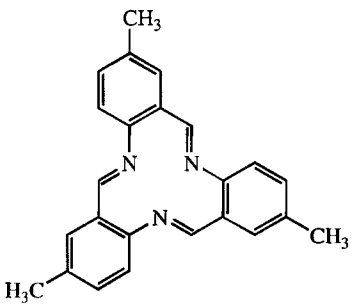


Figure 2-29. The structure of the cation $[Ni(TAAB)(H_2O)I]^+$.

positions. The second nitrate is not bound to the nickel. In $Ni(TAAB)I_2 \cdot H_2O$ the central ion has a distorted octahedral configuration, the TAAB being disposed equatorially. The apical positions are occupied by an iodide ion and by a water molecule. In general the bond distances in the two complexes are quite similar, but there are significant differences in the angles involving the bridging carbon and benzene ring, and nitrogen atom and benzene ring. In TRI the $C-C_{benzene}-C_{benzene}$ angle is 124° and the $C_{benzene}-C_{benzene}-N$ angle is 118°, not greatly different from the expected angle of 120°. However, in TAAB, the corresponding angles are 130 and 113°, which may reflect the additional strain introduced into the tetradentate ligand over that in the tridentate ligand.

It has proved impossible to obtain metal-free TAAB and TRI by the action of bases on $H_2(TAAB)X_2$, of dehydrating agents on L323 and dehydrogenating agents on H_4TAAB or H_8TAAB, by treatment of nickel(II) or copper(II) complexes of TAAB with sulphides, cyanides or with sodium amalgam [159], or by the action of

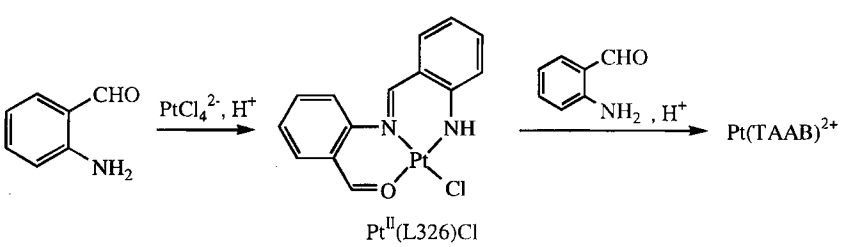
concentrated mineral acids on the nickel(II) complex of TRI [355]. Attempts to obtain copper(II) coordination compounds of TRI were unsuccessful [349, 357]. Here the Jahn–Teller effect may require the nitrogen atoms of the symmetrical TRI to be in unfavourable positions. On this basis, isolation of the complex $[Cu\{(CH_3)_3TRI\}_2](BF_4)_2$ (Eq. 2.176), formed together with $[Cu\{(CH_3)_4TAAB\}](BF_4)_2$ from the reaction of copper(II) acetate with $H_2[\{(CH_3)_4TAAB\}](BF_4)_2$ [361] is unexpected. X-Ray structural analysis of $[Cu\{(CH_3)_3TRI\}_2](BF_4)_2$, carried out both at 298K and 105K revealed high symmetry for the complex, with all six nitrogen atoms equidistant from the central ion. Although no phase transition was detected at low temperature, the coordinated nitrogen atoms show a large temperature anisotropy caused by dynamic Jahn-Teller distortion. Reaction of a copper(II) salt with $H_2(TAAB)X_2$, or even with the bis-anhydrotrimer L322, gave only $Cu(TAAB)^{2+}$ [357].



$(CH_3)_3TRI$ (L325) (2.176)

5-Chloro-2-aminobenzaldehyde does not self-condense in the presence of nickel(II) to form macrocyclic products. This may be connected with the decreasing reactivity of the carbonyl and amine groups under the influence of the chlorine atom [362]. In the absence of nickel ions, the corresponding bis-anhydrotrimer was isolated, which is converted into $Ni(Cl_3TRI)(NO_3)_2 \cdot C_2H_5OH$ on interaction with a nickel(II) salt in ethanol.

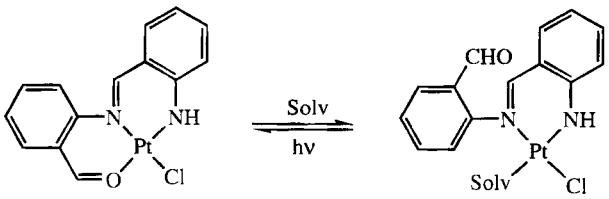
It is unlikely that the template syntheses of TRI, TAAB or their methyl derivatives are one-step processes. At least in the case of platinum(II) macrocyclisation of *o*-aminobenzaldehyde has been shown to proceed step by step [363]. This was proved by the isolation of Pt(L326)Cl, which gives the macrocyclic product $Pt(TAAB)^{2+}$ on subsequent interaction with *o*-aminobenzaldehyde (Scheme 2-20).



$Pt^{II}(L326)Cl$

Scheme 2-20. The synthesis of $Pt(TAAB)^{2+}$ *via* the intermediate $Pt^{II}(L326)Cl$.

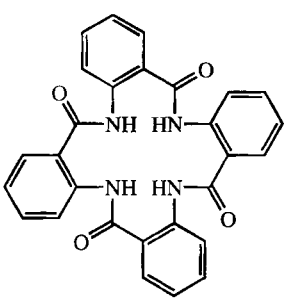
The compound Pt^{II}(L326)Cl, whose structure has been established by X-ray diffraction, can be isolated by interaction of K_2PtCl_4 with H_2(TAAB)X_2 [363]. The chemistry of Pt^{II}(L326)Cl gives additional information about the *o*-aminobenzaldehyde template self-condensation mechanism. Thus an equilibrium is set up in dimethylsulphoxide (DMSO) or acetonitrile (Eq. 2.177) [364].



(2.177)

Thus Pt^{II}(L326)(Solv)Cl is a probable intermediate in *o*-aminobenzaldehyde condensation, in which this ligand is tridentate. The influence of the kinetic and thermodynamic template effects has been examined for Pt^{II}(L326)Cl and Pt^{II}(L326)(Solv)Cl reacting with 1,2-diaminobenzene, 1,2-diaminoethane, 1,3-diaminopropane, *o*-aminobenzylamine, *o*-toluidine, *o*-methylbenzylamine, methylamine and *n*-propylamine [365]. It was established that Pt^{II}(L326)Cl reacts with all these amines. As a result of these studies, the major role of the metal ion was found to be as a Lewis acid in stabilising the carbinolamine intermediate via a thermodynamic template effect. Metal control in this manner is critical to the reaction, because the reaction does not appear to occur to an appreciable extent in the case of Pt^{II}(L326)(Solv)Cl, in which the aldehyde is not coordinated to the metal. The kinetic template effect is, therefore, not nearly as crucial in this sequence as in reactions that proceed to fully closed macrocyclic rings.

Template synthesis of the related polyamide macrocycle H_4L327, by self-condensation of *o*-aminobenzoic acid on nickel(II), cobalt(II), zinc(II) and copper(II) matrices, has been claimed [366] (Eq. 2.178).

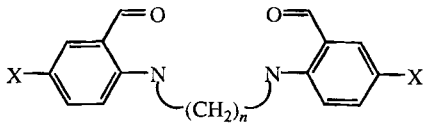


H_4L327

(2.178)

However, there is no X-ray structural or mass-spectral evidence for its formation available.

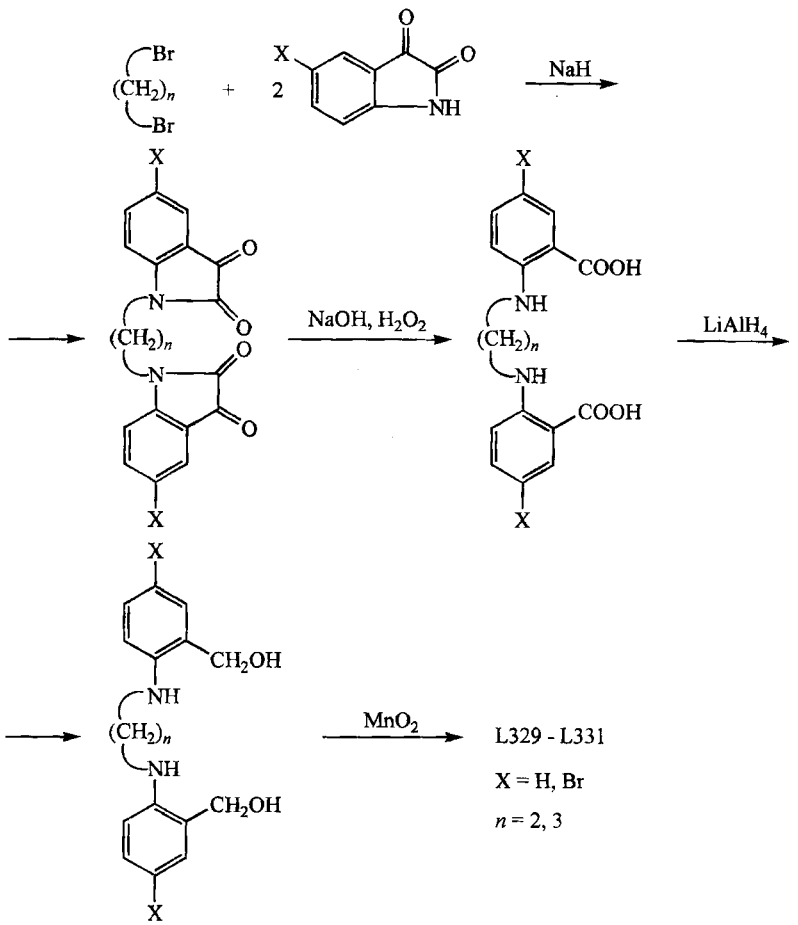
Of the derivatives of the aromatic *o*-aminocarbonyl compounds, the diaminodialdehydes L328–L334 are quite suitable for the template assembling of cyclic products (Eq. 2.179).



X = H:		X = Br:	
$n = 2$	L328	$n = 2$	L330
$n = 3$	L329	$n = 3$	L331
$X = NO_2$:		$X = CH_3$:	
$n = 2$	L332	$n = 2$	L334
$n = 3$	L333		

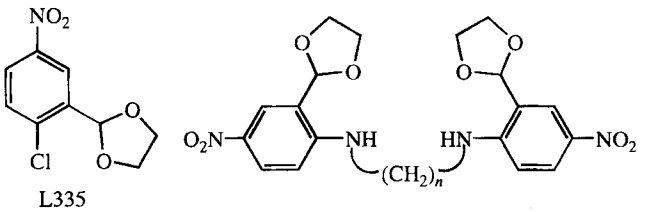
(2.179)

Of the several different routes documented [229, 367–370], the most successful variants are noted here. Thus L328 is synthesised in good yield by acylating methyl anthranilate with oxalyl chloride, followed by reduction of the resulting diformyloxanilide with $LiAlH_4$ to the bis-alcohol, and its oxidation with freshly activated manganese dioxide [229, 367]. Compounds L329–L331 are successfully synthesised according to Scheme 2-21 [367, 370, 371].



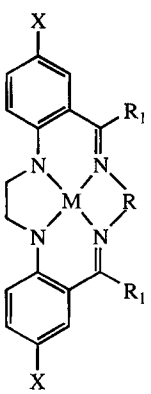
Scheme 2-21. Synthesis of dialdehydes L329–L331.

Dialdehydes L332 and L333 are obtained by interaction of L335 with ethane-1,2-diamine or propane-1,3-diamine in DMSO at 100°C, followed by hydrolysis of the products L336 and L337 in dilute acid (Eq. 2.180) [368, 369].



(2.180)

Compounds L328 and L334 react with diamines $H_2N–R–NH_2$, where R = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$ and o-$C_6H_2(R_1R_2)$, in the presence of nickel(II), cobalt(II) or copper(II), yielding the corresponding complexes with macrocyclic ligands L338–L346 (Eq. 2.181) [229, 372–375].



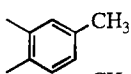
R_1 = X = H:

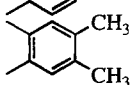
R = $(CH_2)_2$ [M(L338)] (M = Ni, Co, Cu)

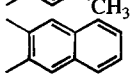
R = $(CH_2)_3$ [M(L339)] (M = Ni, Co, Cu)

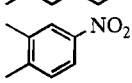
R = $(CH_2)_4$ [M(L340)] (M = Ni, Co, Cu)

R = o-C_6H_4 [M(L341)] (M = Ni, Co, Cu)

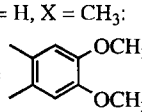
R =  [M(L342)] (M = Ni, Cu)

R =  [M(L343)] (M = Ni, Co, Cu)

R =  [M(L344)] (M = Ni, Co, Cu)

R =  [M(L345)] (M = Ni, Cu)

R_1 = H, X = CH_3:

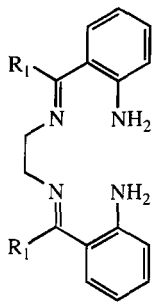
R =  [M(L346)] (M = Ni, Co)

R = $(CH_2)_2$, R_1 = CH_3 [Ni(L347)]

R = $(CH_2)_2$, R_1 = C_6H_5 [Ni(L348)]

(2.181)

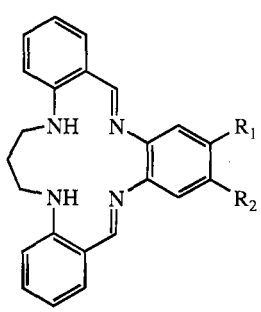
X-Ray diffraction studies of [Ni(L338)] and [Cu(L340)] have been reported [374, 376]. It should be noted that [Ni(L338)] and macrocyclic complexes [Ni(L347)], [Ni(L348)], which have similar structural formulae, are synthesised differently, by alkylating the corresponding nickel(II) chelates of H_2L349, H_2L350 and H_2L351 with 1,2-dibromoethane (Eq. 2.182) [230].



$R_1 = H$ H_2L349
$R_1 = CH_3$ H_2L350
$R_1 = C_6H_5$ H_2L351 (2.182)

The 15-membered macrocyclic systems are also built up in the presence of the metal ions enumerated above by reaction of L329 with *o*-phenylenediamine and its derivatives [370, 373].

In the absence of a template, L328 and en give polymeric products. In the presence of iron(II), zinc(II) or cadmium(II) both cyclic H_2L338 and polymeric products are isolated. Under conditions of high dilution, L328 and en give metal-free H_2L338 in 50% yield. Unlike en, 1,3-diaminopropane and 1,4-diaminobutane react with L328 forming H_2L339 and H_2L340 at normal concentrations. The low basicity of the aromatic diamines in comparison with aliphatic analogues precludes macrocyclisation without using metal ions. In the presence of zinc(II), metal-free H_2L341, H_2L352 and H_2L353 were isolated (Eq. 2.183) [367, 373].

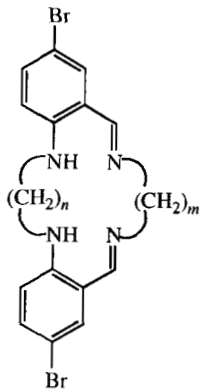


$R_1 = R_2 = H$ H_2L352
$R_1 = R_2 = CH_3$ H_2L353 (2.183)

Synthesis of cyclic products H_2L338–H_2L340 can probably be carried out successfully in the absence of metal ions, due to the stabilising and orienting effects of intramolecular hydrogen-bonding acting as template in this case.

Complexes [M(L354)]–[M(L356)] (M = Ni, Co, Cu) and [Ni(L357)] were obtained [370] by template synthesis (Eq. 2.184).

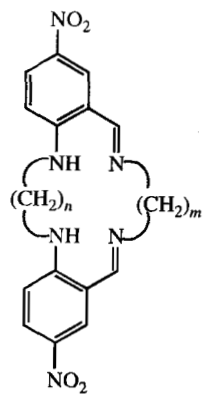
By reaction of L332 and L333 with a twofold excess of en, propane-1,3-diamine, 2-methyl-propane-1,2-diamine, cyclohexane-1,2-diamine, 1,2-diaminobenzene or its derivatives, or of 1,8-diaminonaphthalene, in the presence of the corresponding metal ions in boiling dimethylformamide, neutral nickel(II), cobalt(II) and

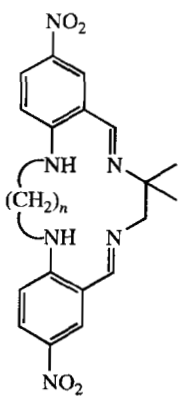


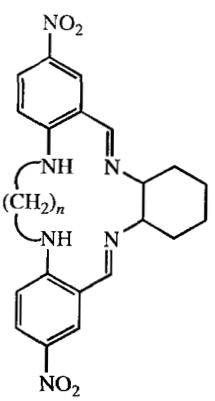
$n = 2, m = 2$, H_2L354
$n = 2, m = 3$, H_2L355
$n = 3, m = 2$, H_2L356
$n = 3, m = 3$, H_2L357

(2.184)

copper(II) complexes with macrocyclic ligands H_2L358–H_2L379 were synthesised (Eqs 2.185 and 2.186) [368, 369, 373].







$n = 2, m = 2$ H_2L358
$n = 2, m = 3$ H_2L359
$n = 3, m = 2$ H_2L360
$n = 3, m = 3$ H_2L361

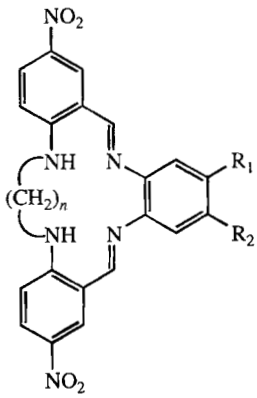
$n = 2$ H_2L362
$n = 3$ H_2L363

$n = 2$ H_2L364
$n = 3$ H_2L365

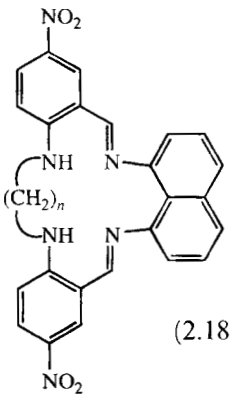
(2.185)

In the mass spectra of the nickel(II) compounds of H_2L358–H_2L366, H_2L378 and H_2L379, as well as some copper(II) complexes, peaks of molecular ions were detected, corroborating L332 and L333 diformyl ligsons closing by the diamines enumerated.

The presence of electron-withdrawing substituents in the dialdehydes and aromatic diamines strongly affects the solubility of the initial ligsons and the final template products in organic solvents. For this reason, and sometimes also for reasons of low stability, they cannot always be isolated in an analytically pure form



$n = 2, R_1 = R_2 = H$	H_2L366
$n = 2, R_1 = CH_3, R_2 = H$	H_2L367
$n = 2, R_1 = R_2 = CH_3$	H_2L368
$n = 2, R_1, R_2 = -C_4H_4-$	H_2L369
$n = 2, R_1 = Cl, R_2 = H$	H_2L370
$n = 2, R_1 = NO_2, R_2 = H$	H_2L371
$n = 3, R_1 = R_2 = H$	H_2L372
$n = 3, R_1 = CH_3, R_2 = H$	H_2L373
$n = 3, R_1 = R_2 = CH_3$	H_2L374
$n = 3, R_1 = R_2 = -C_4H_4-$	H_2L375
$n = 3, R_1 = Cl, R_2 = H$	H_2L376
$n = 3, R_1 = NO_2, R_2 = H$	H_2L377

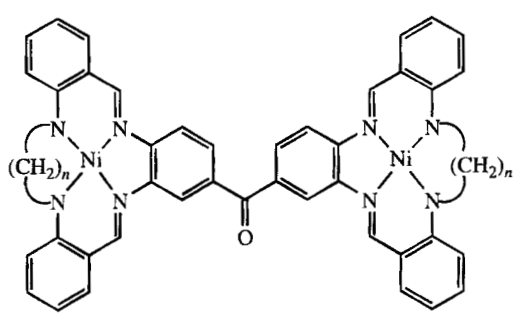


$n = 2$ H_2L378
$n = 3$ H_2L379

(2.186)

[369]. In addition, electron-withdrawing groups presumably encourage hydrolytic attack on the imine bonds, especially in the case of nitro derivatives. For example, [Ni(L370)] and [Ni(L371)] are probably formed in dimethylformamide solution, but are destroyed on addition of methanol to give the initial dialdehydes L332 and L333; there is no evidence for even the transient formation of [Ni(L376)] and [Ni(L377)].

In the absence of Ni^{2+}, Co^{2+} or Cu^{2+}, or in the presence of Mn^{2+}, Mg^{2+} or Zn^{2+}, condensation of L332 and L333 with diamines gives polymeric materials which do not form complexes with metals [369]. By condensation of L328 and L329 with 3,3′,4,4′-tetraminobenzophenone in the presence of nickel(II), binuclear [Ni_2(L380)] and [Ni_2(L381)] are synthesised (Eq. 2.187) [373].

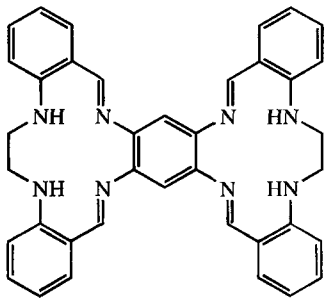


$n = 2$ [Ni_2(L380)]
$n = 3$ [Ni_2(L381)]

(2.187)

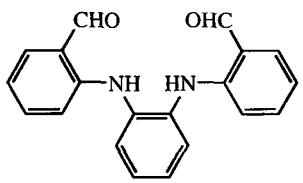
Similarly the binucleating system H_4L382 was obtained from L328 and 1,2,4,5-tetraminobenzene in methanol in an inert atmosphere [377]. In this process intramolecular hydrogen bonding plays the role of template. The conformationally rigid tetramine ligson and L328 are probably reactive enough to interact without addi-

tional activation (for example, by coordination of L328 to a metal ion). Complementarity of the reacting ligsons ensures formation of the macrocyclic product. Formation of H_4L382 was confirmed by the presence of the molecular ion peak in its mass spectrum (Eq. 2.188) [377].



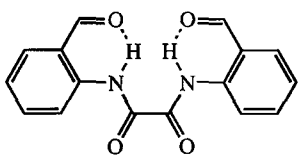
H_4L382 (2.188)

Numerous attempts to carry out template condensations with the diaminodialdehyde H_2L383 (Eq. 2.189), in which a diaminoalkane chain is replaced by 1,2-diaminobenzene, with 1,2-diamines failed [378]. A decrease in reactivity of the aldehyde groups due to formation of strong intramolecular hydrogen bonds may be the reason for this [378].



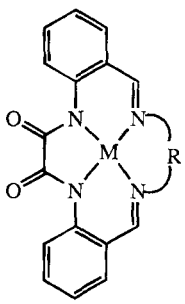
H_2L383 (2.189)

Compound H_2L384 is an effective ligson (Eq. 2.190). On heating with a wide range of suitable diamines in the presence of nickel(II), cobalt(II) and copper(II) and organic bases it gives complexes of the corresponding metals with H_2L385–H_2L397 (Eq. 2.191) [379, 380].



H_2L384 (2.190)

Metal-free H_2L389 and H_2L394 were obtained by continuous heating of the



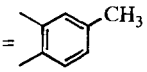
R = $(CH_2)_2$ [M(L385)] (M = Ni, Cu)

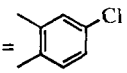
R = $(CH_2)_3$ [M(L386)] (M = Ni, Cu)

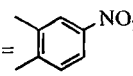
R = $-CH_2(CHOH)CH_2-$ [M(L387)] (M = Ni, Cu)

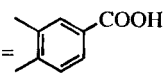
R = $-C_2(CN)_2-$ [M(L388)] (M = Ni)

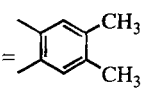
R = o-C_6H_4 [M(L389)] (M = Ni, Co, Cu)

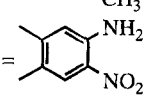

[M(L390)] (M = Ni, Co, Cu)

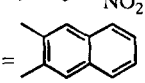

[M(L391)] (M = Ni)

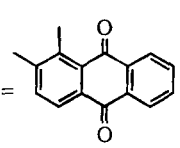

[M(L392)] (M = Ni) (2.191)


[M(L393)] (M = Ni)


[M(L394)] (M = Ni, Cu)

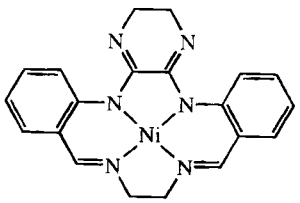

[M(L395)] (M = Ni, Co, Cu)


[M(L396)] (M = Ni, Cu)


[M(L397)] (M = Ni, Cu)

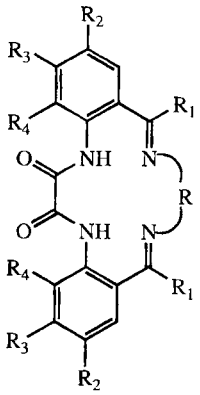
dialdehyde H_2L384, stabilised by intramolecular hydrogen bonds in the conformation suitable for macrocyclisation with the complementary rigid diamines of the 1,2-diaminobenzene type. These reactions were carried out in dioxane, in the presence of triethylammonium hydrochloride and triethylamine, and in an inert atmosphere [381]. In this case a template role for the triethylammonium cation in the construction of the macrocyclic systems H_2L389 and H_2L394 has been suggested [382].

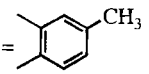
The compound [Cu(L389)] is isolated after oxidation of [Cu(L340)] by prolonged heating in dimethylformamide [383]. The compound [Ni(L398)] can be isolated as a byproduct from the synthesis of [Ni(L337)] (its composition and structure have been proved by X-ray diffraction (Eq. 2.192) [376]). It is presumably formed by oxidation of [Ni(L337)] to the oxamide, and subsequent condensation of the latter with an excess of en added to the reaction mixture.



[Ni(L398)] (2.192)

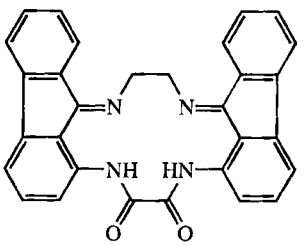
The macrocyclic complexes [Ni(L399)]–[Ni(L405)] have been prepared by template condensation of a number of H_2L384 derivatives with diamines in the presence of nickel(II) (Eq. 2.193) [380]. The macrocycle H_2L400 may also be constructed in the presence of copper(II) ions and isolated as the corresponding complex.



$R_1 = H, R_2,R_3 = -OCH_2O-, R_4 = H, R = o\text{-}C_6H_4$	H_2L399
$R_1 = R_2 = R_3 = H, R_4 = CH_3, R = o\text{-}C_6H_4$	H_2L400
$R_1 = CH_3, R_2 = R_3 = R_4 = H, R = -CH_2CHOHCH_2-$	H_2L401
$R_1 = CH_3, R_2 = R_3 = R_4 = H, R = o\text{-}C_6H_4$	H_2L402
$R_1 = C_6H_5, R_2 = R_3 = R_4 = H, R = o\text{-}C_6H_4$	H_2L403
$R_1 = C_6H_5, R_2 = Cl, R_3 = R_4 = H, R = o\text{-}C_6H_4$	H_2L404
$R_1 = C_6H_5, R_2 = Cl, R_3 = R_4 = H, R =$ 	H_2L405

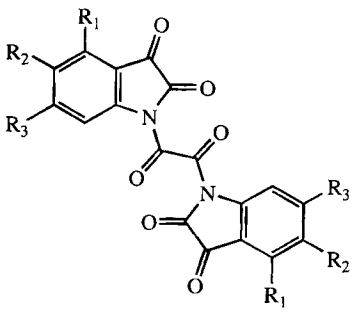
(2.193)

For the series of compounds H_2L399–H_2L406 (Eq. 2.194) more prolonged interaction of ligsons is needed to accomplish macrocyclisation of diaminodiketones with the diamines than in the case of diaminodialdehydes.



H_2L406 (2.194)

Treatment of oxalylbisisatins L407–L417 with alcohols yielded the bis-glyoxylate esters by direct ring opening of the acyl isatins (Eq. 2.195) [382, 384].

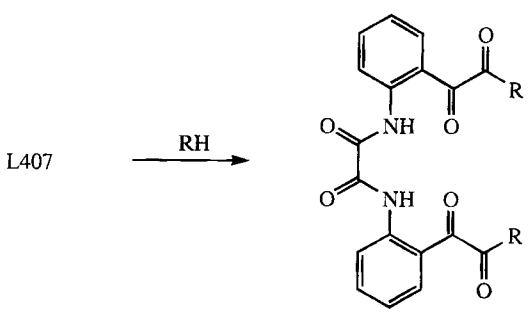


$R_1 = R_2 = R_3 = H$	L407
$R_1 = R_3 = H, R_2 = CH_3$	L408
$R_1 = R_3 = H, R_2 = OCH_3$	L409
$R_1 = R_3 = H, R_2 = NO_2$	L410
$R_1 = R_3 = H, R_2 = F$	L411
$R_1 = R_3 = H, R_2 = Cl$	L412
$R_1 = R_3 = H, R_2 = Br$	L413
$R_1 = R_3 = H, R_2 = C_6H_5$	L414
$R_1 = R_3 = CH_3, R_2 = H$	L415
$R_1 = R_3 = OCH_3, R_2 = H$	L416
$R_1 = R_2 = o\text{-}C_6H_4, R_3 = H$	L417

(2.195)

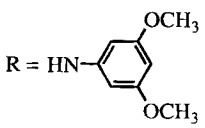
For example, L418–L421 were obtained from L407. The yield depends on the nucleophilic strength of the respective alcohol and its steric characteristics [382].

The analogous transformations involving cleavage of an *N*-acylisatin ring take place when L407–L417 are treated with ammonia or with aliphatic or aromatic amines (primary or secondary). Amide derivatives L422–L436 were obtained, for example, again from L407 (Eq. 2.196) [382].



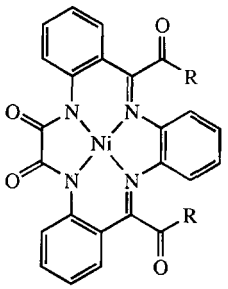
(2.196)

$R = OCH_3$	H_2L418
$R = OC_2H_5$	H_2L419
$R = OCH(CH_3)_2$	H_2L420
$R = OC(CH_3)_3$	H_2L421
$R = NH_2$	H_2L422
$R = NH(CH_2)_3CH_3$	H_2L423
$R = NH(CH_2)_{11}CH_3$	H_2L424
$R = NHCH_2C_6H_5$	H_2L425
$R = NHCH_2COOC_2H_5$	H_2L426
$R = NHOCH_3$	H_2L427

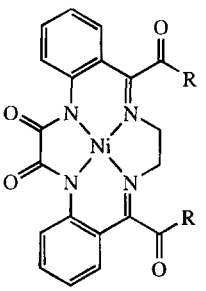
$R = NHC_6H_5$	H_2L428
$R = NHC_6H_4N(CH_3)_2\text{-}p$	H_2L429
$R = NHC_6H_4NO_2\text{-}p$	H_2L430
$R = NHC_6H_4OCH_3\text{-}p$	H_2L431
	H_2L432
$R = NHC_6H_5N{=}NC_6H_4\text{-}p$	H_2L433
$R = N(CH_3)_2$	H_2L434
R = pyrrolidin-1-yl	H_2L435
R = morpholin-4-yl	H_2L436

By heating stoichiometric quantities of H_2L418–H_2L421, *o*-phda, en or propane-1,3-diamine with nickel(II) acetate in the presence of triethylamine in alcohol under reflux, nickel(II) complexes containing ester terminal groups ([Ni(L437)]–[Ni(L445)]) were obtained in good yield. In an analogous manner, using di-

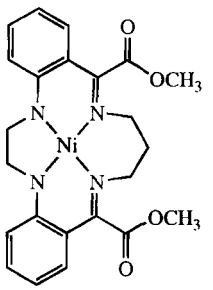
methylformamide [382] instead of an alcohol as solvent, [Ni(L446)]–[Ni(L460)], [Cu(L447)] and [Cu(L454)] were synthesised (Eq. 2.197).



R = OCH_3	[Ni(L437)]
R = OC_2H_5	[Ni(L438)]
R = $OCH(CH_3)_2$	[Ni(L439)]
R = $OC(CH_3)_3$	[Ni(L440)]



R = OCH_3	[Ni(L441)]
R = OC_2H_5	[Ni(L442)]
R = $OCH(CH_3)_2$	[Ni(L443)]
R = $OC(CH_3)_3$	[Ni(L444)]



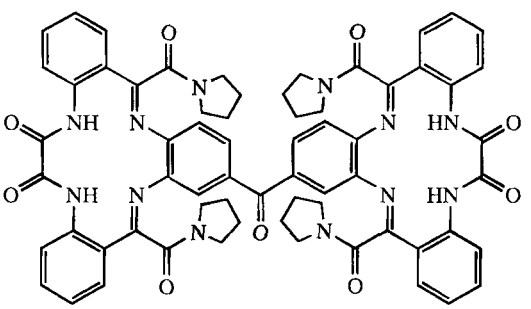
[Ni(L445)]

(2.197)

R = NH_2	[Ni(L446)]
R = $NH(CH_2)_3CH_3$	[Ni(L447)]
R = NHC_6H_5	[Ni(L448)]
R = $NHC_6H_4N(CH_3)_2$-*p*	[Ni(L449)]
R = $NHC_6H_4NO_2$-*p*	[Ni(L450)]
R = $NHC_6H_4N{=}NC_6H_4$-*p*	[Ni(L451)]
R = pyrrolidin-1-yl	[Ni(L452)]

R = NH_2	[Ni(L453)]
R = $NH(CH_2)_3CH_3$	[Ni(L454)]
R = NHC_6H_5	[Ni(L455)]
R = $NHC_6H_4N(CH_3)_2$-*p*	[Ni(L456)]
R = $NHC_6H_4NO_2$-*p*	[Ni(L457)]
R = $N(CH_3)_2$	[Ni(L458)]
R = pyrrolidin-1-yl	[Ni(L459)]
R = morpholin-4-yl	[Ni(L460)]

The binucleating system H_4L461, isolated as $[Ni_2(L461)]$, was obtained by interaction of the appropriate ligsons on a nickel(II) template (Eq. 2.198) [382].



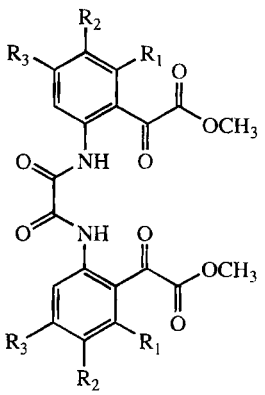
H_4L461 (2.198)

Attempts to condense H_2L418–H_2L436 with diamines in the presence of metal ions other than Ni^{2+} and Cu^{2+} failed. For example, Fe^{2+}, Zn^{2+}, Mn^{2+}, Mg^{2+}, Cd^{2+} or Hg^{2+} were ineffective for template assembly of macrocyclic systems from

H_2L435 and diamines. Attempts to carry out non-template macrocyclisation under conditions of high dilution were also unsuccessful; only starting materials and small amounts of insoluble polymeric materials were isolated from the reaction mixture. It proved to be impossible to demetallate the oxamide macrocyclic nickel(II) complexes using cyanide because of the high stability of the metal–amide bonds [382].

Derivatives H_2L418–H_2L436 enter into metal-template condensation with diamines much more readily even than the dialdehyde H_2L384. The high reactivity of bis-α-ketoesters and α-ketoamides containing electron-withdrawing substituents R is due to their making the α-ketogroups more electrophilic.

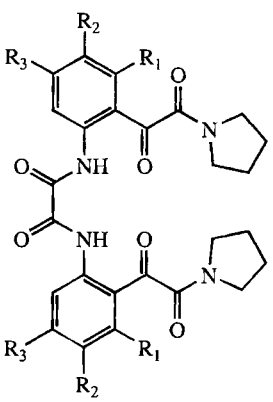
It has been claimed, citing H_2L418 and H_2L462–H_2L471 as examples, that the bis-esters having a substituent at C6 (i.e. R_1) are thermally less stable than their analogues substituted at C5 (i.e. R_2) (Eq. 2.199) [384].



$R_1 = R_2 = R_3 = H$	H_2L418
$R_1 = R_3 = H, R_2 = CH_3$	H_2L462
$R_1 = R_3 = H, R_2 = OCH_3$	H_2L463
$R_1 = R_3 = H, R_2 = NO_2$	H_2L464
$R_1 = R_3 = H, R_2 = F$	H_2L465
$R_1 = R_3 = H, R_2 = Cl$	H_2L466
$R_1 = R_3 = H, R_2 = Br$	H_2L467
$R_1 = R_3 = H, R_2 = C_6H_5$	H_2L468
$R_1 = R_3 = CH_3, R_2 = H$	H_2L469
$R_1 = R_3 = OCH_3, R_2 = H$	H_2L470
$R_1 = R_2 = o\text{-}C_6H_4, R_3 = H$	H_2L471

(2.199)

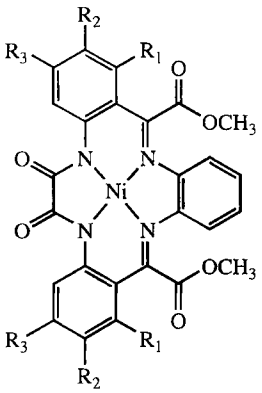
Thus, for example, 4,6-dimethylisatin is isolated even from a cold dimethylformamide solution of H_2L469. A similar picture is observed for the series of ketopyrrolidinylamides H_2L435 and H_2L472–H_2L481 (Eq. 2.200), although, generally, they are more stable than H_2L418 and H_2L462–H_2L471.



$R_1 = R_2 = R_3 = H$	H_2L435
$R_1 = R_3 = H, R_2 = CH_3$	H_2L472
$R_1 = R_3 = H, R_2 = OCH_3$	H_2L473
$R_1 = R_3 = H, R_2 = NO_2$	H_2L474
$R_1 = R_3 = H, R_2 = F$	H_2L475
$R_1 = R_3 = H, R_2 = Cl$	H_2L476
$R_1 = R_3 = H, R_2 = Br$	H_2L477
$R_1 = R_3 = H, R_2 = C_6H_5$	H_2L478
$R_1 = R_3 = CH_3, R_2 = H$	H_2L479
$R_1 = R_3 = OCH_3, R_2 = H$	H_2L480
$R_1 = R_2 = o\text{-}C_6H_4, R_3 = H$	H_2L481

(2.200)

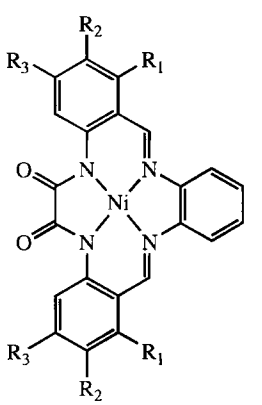
Complexes [Ni(L482)]–[Ni(L488)], together with [Ni(L437)]–[Ni(L440)], can readily be obtained by interaction of the appropriate ligson from the series H_2L418 and H_2L462–H_2L468 with *o*-phda and alcohol (Eq. 2.201). In the more polar solvent dimethylformamide, macrocyclisation proceeds faster, although small amounts of decomposition products are also found.



$R_1 = R_2 = R_3 = H$	[Ni(L437)]
$R_1 = R_3 = H, R_2 = CH_3$	[Ni(L482)]
$R_1 = R_3 = H, R_2 = OCH_3$	[Ni(L483)]
$R_1 = R_3 = H, R_2 = NO_2$	[Ni(L484)]
$R_1 = R_3 = H, R_2 = F$	[Ni(L485)]
$R_1 = R_3 = H, R_2 = Cl$	[Ni(L486)]
$R_1 = R_3 = H, R_2 = Br$	[Ni(L487)]
$R_1 = R_3 = H, R_2 = C_6H_5$	[Ni(L488)]

(2.201)

Thus, for instance, when reacting H_2L465 with *o*-phda and nickel(II) acetate in dimethylformamide, the macrocyclic ester complex [Ni(L485)] is formed. After extended heating of the reaction mixture at 110°C, however, [Ni(L491)] is isolated (Eq. 2.202), whose formation involves hydrolysis and decarboxylation of [Ni(L485)] [384].



$R_1 = R_2 = R_3 = H$	[Ni(L389)]
$R_1 = R_3 = H, R_2 = CH_3$	[Ni(L489)]
$R_1 = R_3 = H, R_2 = OCH_3$	[Ni(L490)]
$R_1 = R_3 = H, R_2 = F$	[Ni(L491)]
$R_1 = R_3 = H, R_2 = Cl$	[Ni(L492)]
$R_1 = R_3 = H, R_2 = Br$	[Ni(L493)]
$R_1 = R_3 = H, R_2 = C_6H_5$	[Ni(L494)]

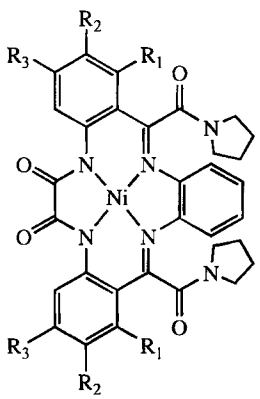
(2.202)

In a similar way, the methyl ester H_2L418 was converted through the appropriate macrocyclic ester complex [Ni(L437)] into a substance whose spectral data coincide with those for [Ni(L389)] as prepared by nickel(II)-directed condensation of bis-*o*-formyloxanilide with *o*-phenylenediamine [379, 380, 384]. Such ester compounds as,

for example, [Ni(L437)], [Ni(L482)], [Ni(L483)], [Ni(L485)] and [Ni(L488)] are decarboxylated under similar conditions giving [Ni(L389)], [Ni(L489)]–[Ni(L491)] and [Ni(L494)], respectively. However to achieve the same result in the case of [Ni(L486)] or [Ni(L487)], hexamethylphosphoramide must be used as solvent. Compounds [Ni(L389)] and [Ni(L489)]–[Ni(L494)], obtained as a result of decarboxylation, are stable in cold concentrated sulphuric acid. Attempts to synthesise the corresponding macrocyclic systems from the bis-esters H_2L469–H_2L471 failed. Even cold solutions of H_2L469 in dimethylformamide are unstable, the H_2L469 gradually turning into 4,6-dimethylisatin. In the case of H_2L471, naphthisatin was isolated from the reaction mixture. The low thermal stability of H_2L469–H_2L471 and their inability to react with diamines by metal–template condensation to form macrocyclic systems is probably explained by unfavourable interaction of the benzene ring C6 substituent with the terminal ester carbonyl group. This interaction firstly facilitates oxamide hydrolysis and subsequent cyclisation of the ester into the appropriate isatin and, secondly, leads to displacement of the reactive α-carbonyl group from the plane which is most suitable for efficient template reaction.

In the case of the substituted pyrrolidinylamide complexes, template macrocyclisation with the diamines was achieved only for the derivatives containing substituents attached to C5 (i.e. R_2).

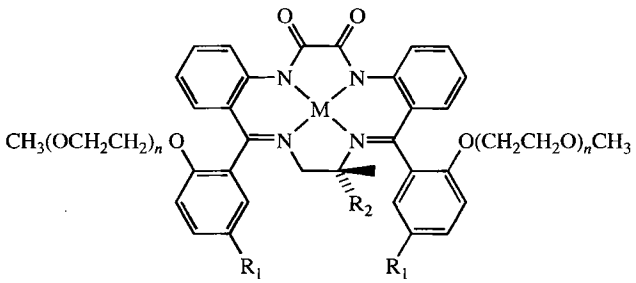
Although [Ni(L452)] and [Ni(L495)]–[Ni(L501)] (Eq. 2.203) are more stable than their ester analogues, extended heating of [Ni(L495)] results in the formation of [Ni(L389)] in low yield.



$R_1 = R_2 = R_3 = H$	[Ni(L452)]
$R_1 = R_3 = H, R_2 = CH_3$	[Ni(L495)]
$R_1 = R_3 = H, R_2 = OCH_3$	[Ni(L496)]
$R_1 = R_3 = H, R_2 = NO_2$	[Ni(L497)]
$R_1 = R_3 = H, R_2 = F$	[Ni(L498)]
$R_1 = R_3 = H, R_2 = Cl$	[Ni(L499)]
$R_1 = R_3 = H, R_2 = Br$	[Ni(L500)]
$R_1 = R_3 = H, R_2 = C_6H_5$	[Ni(L501)]

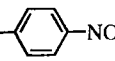
(2.203)

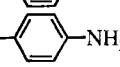
Atropoisomeric chiral macrocyclic systems [Ni(L502)]–[Ni(L505)] with significant peripheral architecture were prepared by the condensation of derivatives of *N*,*N*′-bis(benzoylphenyl)oxamide and ethane-1,2-diamine in the presence of Ni(II) as template (Eq. 2.204) [385].

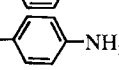


(2.204)

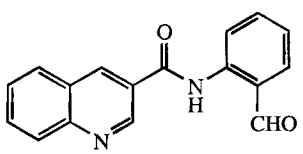
$R_1 = CH_3$, $R_2 = H$, $n = 1$, [Ni(L502)]

$R_1 = CH_3$, $R_2 =$  $n = 1$, [Ni(L503)]

$R_1 = CH_3$, $R_2 =$  $n = 1$, [M(L504)] (M = Ni, Cu)

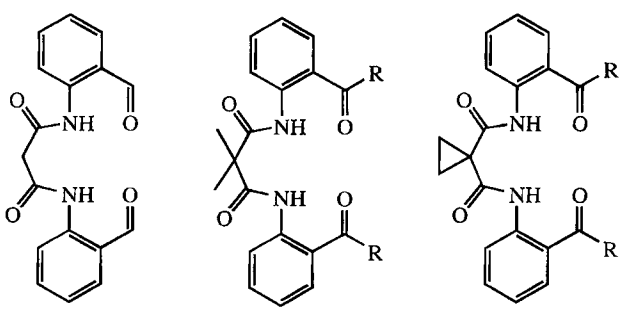
$R_1 = CH_3$, $R_2 =$  $n = 3$, [Ni(L505)]

Reaction of *o*-aminobenzaldehyde with malonyl dichloride gave the product HL506 instead of the expected diformylmalonamide (Eq. 2.205).



HL506 (2.205)

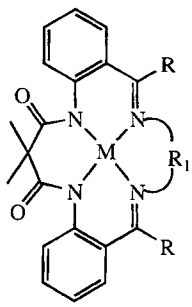
This presumably arose from the intermediate H_2L507 formed by intramolecular condensation of the active methylene and aldehyde groups [386]. To avoid such a reaction dimethylmalonyl dichloride may be used instead of malonyl dichloride as the acylating agent [386] but, in the more vigorous conditions needed, *o*-aminobenzaldehyde more easily underwent self-condensation than interaction with dimethylmalonyl dichloride. In turn, 2-aminoacetophenone and 2′-aminophenylglyoxylamide, which are less sensitive to self-condensation, react smoothly with dimethylmalonyl dichloride to give H_2L508 and H_2L509, respectively. Similarly, using appropriate building blocks, H_2L510 and H_2L511 were obtained (Eq. 2.206) [384].



(2.206)

H_2L507 $R = CH_3$ H_2L508 $R = CONH_2$ H_2L509 $R = CH_3$ H_2L510 $R = C_6H_5$ H_2L511

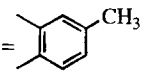
When heating ligsons with H_2L508 and H_2L509 and the appropriate aliphatic or aromatic diamines in the presence of a template, macrocyclic products [Ni(L512)]–[Ni(L515)] and [Cu(L515)] were synthesised (Eq. 2.207) [386, 387].



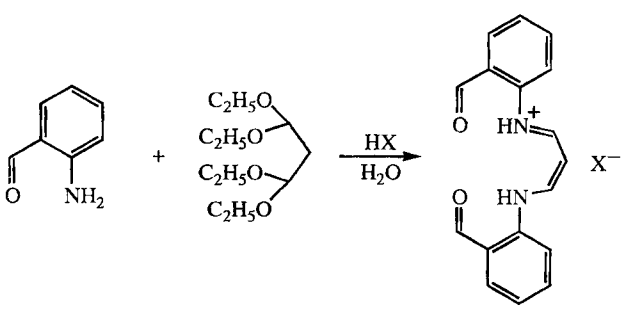
$R = CH_3$, $R_1 = CH_2CH(CH_3)$, M = Ni [Ni(L512)]

$R = CH_3$, $R_1 = (CH_2)_3$, M = Ni [Ni(L513)]

$R = CONH_2$, $R_1 = o\text{-}C_6H_4$, M = Ni [Ni(L514)] (2.207)

$R = CH_3$, $R_1 =$  [M(L515)] (M = Ni, Cu)

The compounds H_2L510 and H_2L511 presumably decompose during the metal–template condensation with diamines, as a result of cyclopropane ring cleavage under the influence of the amine and the high temperature. As a consequence, synthesis of appropriate macrocyclic products was unsuccessful. A suitable block for template macrocyclisation can be obtained from *o*-aminobenzaldehyde and malonaldehyde. Thus, for example, $[H_2L516]X$, where $X = ClO_4$, I, Br or Cl, can be isolated in good yield as a result of acid hydrolysis of acetal and subsequent addition of a methanolic solution of *o*-aminobenzaldehyde (Eq. 2.208).

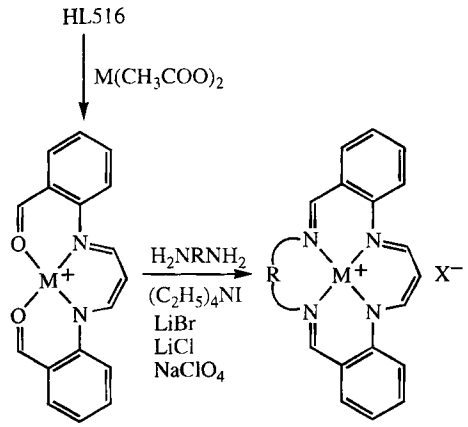


$[H_2L516]^+X^-$

$X^- = ClO_4^-, I^-, Br^-, Cl^-$ (2.208)

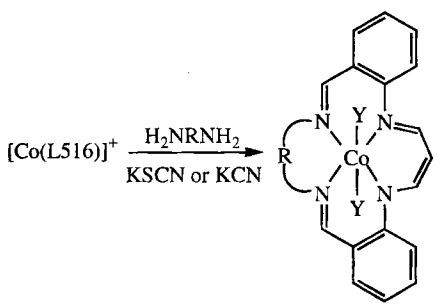
By neutralisation of $[H_2L516]X$ with triethylamine in dichloromethane, the Schiff base HL516 has been obtained. Its nickel(II), copper(II) and cobalt(II) complexes were synthesised from the latter (Schemes 2-22 and 2-23) [388, 389].

The final products in Scheme 2-23 are cobalt(III) complexes but some $[Co^{II}(L517)]^+$ is present in solution. On addition of sodium borohydride to such a solution, the cobalt(II) is reduced to cobalt(I). It is remarkable that, when



M = Ni, X = I:
R = $(CH_2)_2$ [Ni(L517)]I
R = $(CH_3)CHCH_2$ [Ni(L518)]I
R = $(CH_2)_3$ [Ni(L519)]I
R = o-C_6H_4 [Ni(L520)]I
M = Ni, X = Br,
R = $(CH_2)_2$ [Ni(L517)]Br
M = Ni, X = Cl,
R = $(CH_2)_2$ [Ni(L517)]Cl
M = Cu, X = ClO_4,
R = $(CH_2)_2$, [Ni(L517)]ClO_4

Scheme 2-22. Template synthesis of L517.



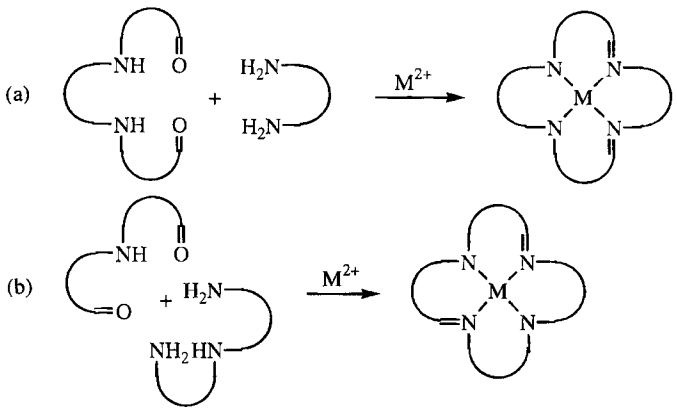
R = $(CH_2)_2$, Y = SCN [Co(L517)$(SCN)_2$]
R = $(CH_2)_2$, Y = CN [Co(L517)$(CN)_2$]
R = $(CH_2)_3$, Y = SCN [Co(L519)$(SCN)_2$]

Scheme 2-23. Template synthesis of L517 and L519.

[Co(L517)] or $[Co(L517)]^+$ solutions react with methyl or ethyl iodide, coordination of CH_3 or C_2H_5 groups to the metal atom with simultaneous conversion to the cobalt(III) species [Co(L513)(R′)X] (R′ = CH_3, C_2H_5; X = anion) takes place [390]. Three different oxidation states of cobalt can be stabilised in these systems.

The order in which reagents are added in the general procedure of template synthesis is important. For example, interaction of en with HL516 in dry methanol and subsequent addition of $Ni(CH_3COO)_2$ leads to the isolation of [Ni(L349)]. The malondialdehyde fragment is presumably displaced as a result of nucleophilic attack of added en or water from the condensation of amine with aromatic aldehyde. Hydrolysis is avoided by the introduction of Ni^{2+}, Cu^{2+} or Co^{2+} ions into the reaction mixture. They bind the initial ligson HL516 into the appropriate complex and thus stabilise it.

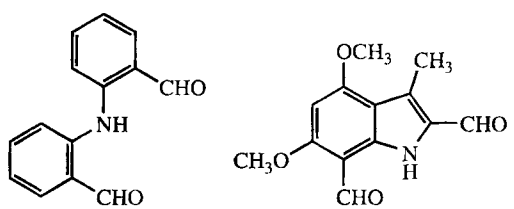
Zinc(II) also displays template activity in conditions analogous to those given in Schemes 2-22 and 2-23. In addition, however, the metal-free macrocyclic product



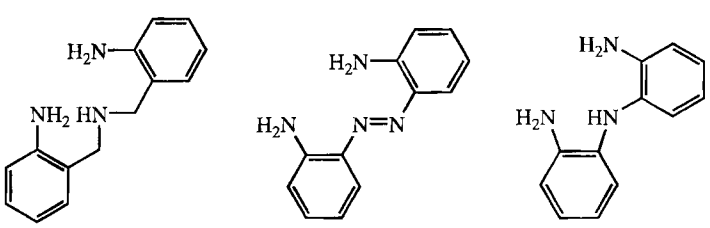
Scheme 2-24. General routes to macrocycles based on *o*-aminobenzaldehyde.

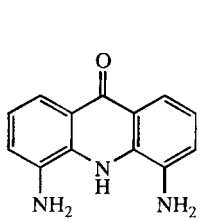
can be isolated in pure form. Obviously, this is connected with the fact that zinc(II) gives less stable complexes than nickel(II), copper(II) or cobalt(II), so the intermediate complex $[Zn(L516)]^+$ does not form as easily. It should be noted that, on addition of the corresponding diamine to a mixture of a zinc salt and HL516, competing reactions proceed concurrently with the desired reaction. As a result, the main macrocyclic compound is contaminated with byproducts [389].

Tetradentate and pentadentate macrocyclic systems based on *o*-aminobenzaldehyde and its derivatives can be obtained by metal–template reactions of diaminodicarbonyl compounds with diamines (Scheme 2-24(a)), and also by interaction of monoaminodicarbonyl compounds with primary diamines containing additional supporting nitrogen atoms in the chain (see Scheme 2-24(b)) [391].

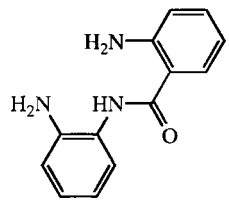


(2.209a)

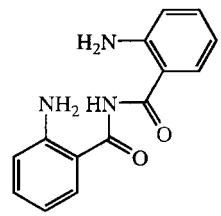




L526

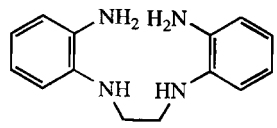


L527



HL528

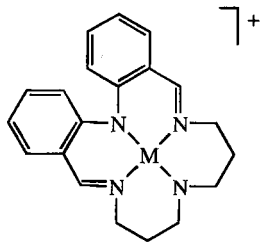
(2.209b)



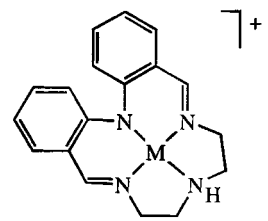
HL529

The synthesis of the ligsons HL521–HL529 has been described [378, 391, 392]. Their end groups provide sites for building more complex substances, including macrocycles (Eqs. 2.209a and 2.209b).

Thus, for instance, perchlorate salts of monocationic products $[M(L530)]ClO_4$, where M = Ni, Cu or Co, were obtained by heating stoichiometric quantities of metal(II) chloride, HL521, and dipropylenetriamine in ethanol–water (3:1) mixture with subsequent partial removal of solvent and addition of sodium perchlorate (Eq. 2.210) [378].



$[M(L530)]^+$ (M = Ni, Co, Cu)

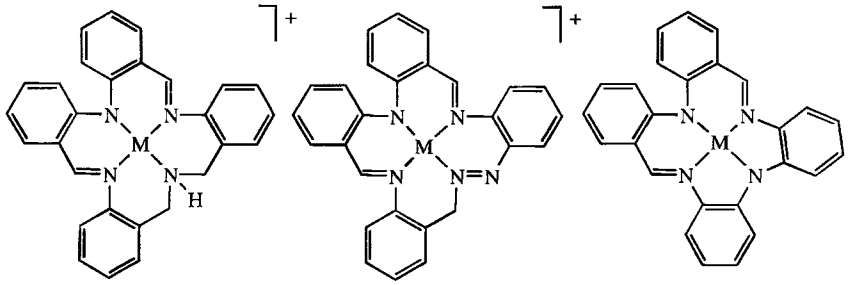


$[M(L531)]^+$ (M = Ni, Co, Cu)

(2.210)

In the case of diethylenetriamine, synthesis of macrocyclic compounds such as $[M(L531)]ClO_4$ proceeds better if the appropriate perchlorate salt is employed as the source of the metal ions and pure ethanol is used as solvent. It is impossible to carry out macrocyclisation in the presence of zinc(II), probably because of the formation of $Zn(OH)_2$ in the presence of the basic triamine [378].

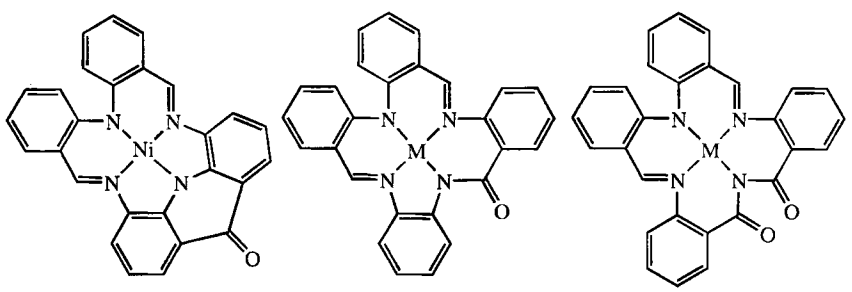
On reaction of HL521 with L523, L524 or HL525 in the presence of nickel(II), copper(II) or cobalt(II), monocations $[M(L532)]ClO_4$ and $[M(L533)]ClO_4$ and neutral complexes [M(L534)] were isolated (Eq. 2.211) [378].



$[M(L532)]^+$ (M = Ni, Co, Cu) $[M(L533)]^+$ (M = Ni, Co, Cu) [M(L534)] (M = Ni, Co, Cu)

(2.211)

From the diaminoacridone HL526, and from HL521, template reactions gave only the complex [Ni(L535)], in reasonable purity. In contrast, reaction of HL521 with HL527 or HL528 on nickel(II), copper(II) or cobalt(II) matrices yielded the neutral products [M(L536)] and [M(L537)], where M = Ni, Cu or Co (Eq. 2.212).

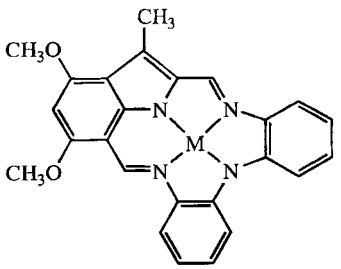


[Ni(L535)] [M(L536)] (M = Ni, Co, Cu) [M(L537)] (M = Ni, Co, Cu)

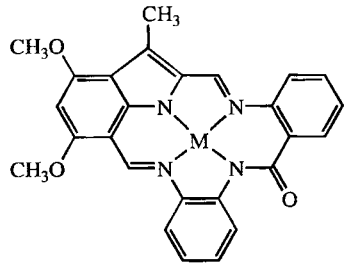
(2.212)

The macrocyclic nature of the templately assembled ligand products is confirmed by mass spectra of [M(L534)] (M = Ni, Cu), [M(L536)] (M = Ni, Cu) and [Ni(L537)], in which the $[P]^{+\cdot}$ peaks were clearly present.

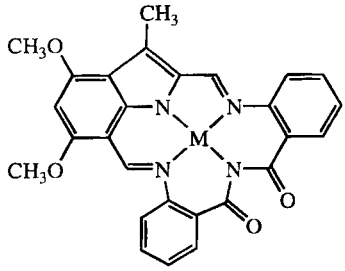
Macrocyclic complexes [M(L538)]–[M(L540)], where M = Ni or Cu, were obtained in the presence of metal ions from the ligsons HL522 and HL525–HL527, respectively (Eq. 2.213) [392].



[M(L538)]



[M(L539)]



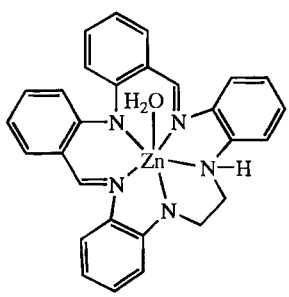
[M(L540)]

M = Ni, Co, Cu

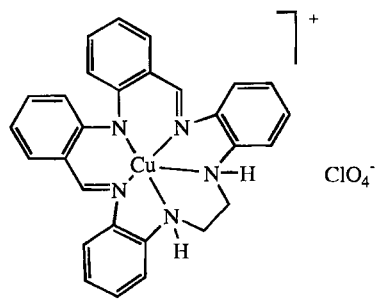
(2.213)

By treatment of HL521 with the primary diamine HL529, which contains two extra nitrogen atoms, pentaazamacrocyclic compounds [Zn(L541)(H_2O)] and [Cu(HL541)]ClO_4 were obtained in the presence of zinc(II) and copper(II) salts (Eq. 2.214) [378].

Attempts to carry out metal-template dimerisation of the aminodialdehydes L542–L545 failed. Either there was no reaction, or stable diazepins and polymeric products were formed (Eq. 2.215) [393, 394].

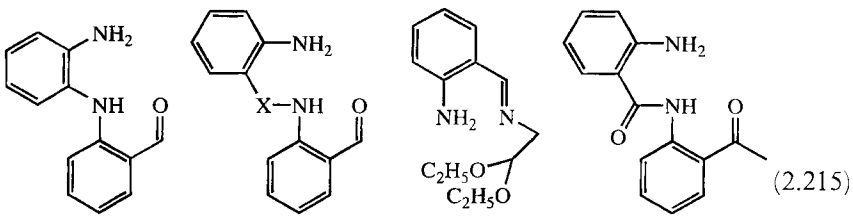


[Zn(L541)(H_2O)]



[Cu(HL541)]ClO_4

(2.214)



(2.215)

L542 X = CH_2 L543 X = CO L544 L545 L546

Compound L546 does not self-condense even in the presence of metal salts. This may be explained [393] by the existence of strong hydrogen bonds in this aminoketone.

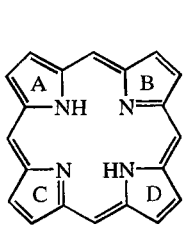
The strategy of Scheme 2-24 for the synthesis of macrocyclic metal complexes by template condensation of monoaminodicarbonyl compounds with polyfunctional diamines is not limited to examples drawn from the chemistry of *o*-aminobenzaldehyde derivatives. In Section 3.1, in particular, various macrocyclic products built up by using 2,6-diformylpyridine and related compounds as ligsons are considered.

2.9 The role of transition metal ions in the construction of model systems

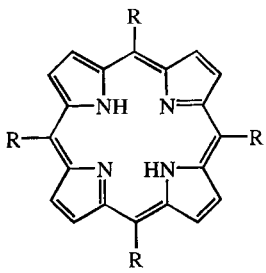
Template synthesis is widely used for obtaining series of natural macrocycles and of synthetic analogues modelling them (porphyrins, corrins, phthalocyanines and related compounds). Synthesis of such systems is rather complex and, as a rule, a multistep process. At the final ring-closing stage, metal ions are used as matrices, to give pure or only slightly contaminated macrocycles. They are isolated either as complexes of the corresponding metals or in the metal-free state. If the metal ion is absent, macrocyclic systems are also built up in many cases, but in low yield, and isolation and purification become difficult. Indeed, macrocyclisation is often completely unrealisable in the absence of a suitable template.

2.9.1 Porphyrins and related compounds

Porphyrins are the most widespread macrocyclic compounds in nature. Synthetic porphyrins, which can be obtained in good yields from quite cheap raw materials by simple technology, are also of interest. Substances containing the porphin nucleus as a cyclic backbone are usually referred to as porphyrins (Eq. 2.216) [231].



(Porphin nucleus)

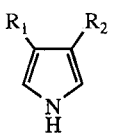


$R = CH_3$ H_2L547
$R = H$ H_2L548
$R = C_6H_5$ H_2L549

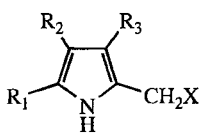
(2.216)

Template synthesis of porphyrins is carried out by:

- interaction of pyrroles, HL550 (Eq. 2.217), having free α-positions with reagents able to form the methyne bridges of the porphin ring;
- pyrrole tetramerisation with the methylene grouping in one of the α-positions (HL551);
- coupling two fragments containing two pyrrole rings (2 + 2 method);
- ring closure of linear tetrapyrrole chains.



HL550

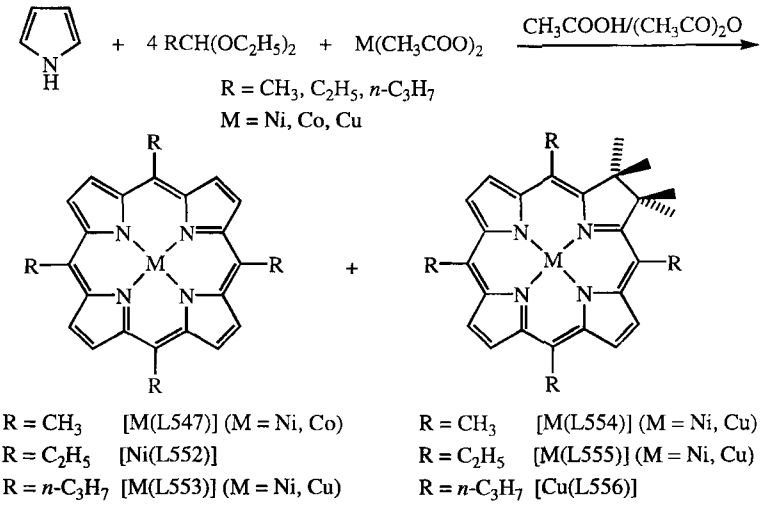


HL551

(2.217)

Reactions of pyrroles with aldehydes in the presence of pyridine [395] give the respective *meso*-tetrasubstituted porphyrins, for example, *meso*-tetramethylporphyrin H_2L547 or porphyrin H_2L548, in extremely low yield (0.03%) [396]. Carrying out the pyrrole condensation with benzaldehyde under forcing conditions (in a sealed tube at high temperature) leads to the *meso*-tetraphenylporphyrin H_2L549 in quite good yield [397, 398]. The yield can be improved by approximately 10%, if the reaction is carried out in the presence of zinc(II) acetate [399]. The corresponding complex is then formed, from which the metal can be removed with mineral acid.

Acetals can also be used for tailoring the porphyrin products [400–402]. In the case of acetals of aliphatic aldehydes, porphyrin systems can be assembled only by the template way. Thus, reaction of acetal itself with pyrrole in the presence of nickel(II) acetate and 2% acetic anhydride in acetic acid (Scheme 2-25; M = Ni, $R = CH_3$) gives a mixture of [Ni(L547)] and [Ni(L554)] in the ratio 1:4. This can easily be separated chromatographically. When M = Cu and $R = CH_3$, [Cu(L554)] is the only product of template synthesis. In the presence of cobalt(II) acetate, [Co(L547)] is formed [401, 402]. If the content of acetic anhydride in the reaction mixture is increased 2.5 times, then [Ni(L547)] may be isolated in pure form. The ratio of chlorin/porphyrin is thus mainly influenced by the nature of the metal and the quantity of anhydride added. The process shown in Scheme 2-25 is also sensitive to the nature of the alkyl substituent R. When $R = C_2H_5$ and the anhydride content

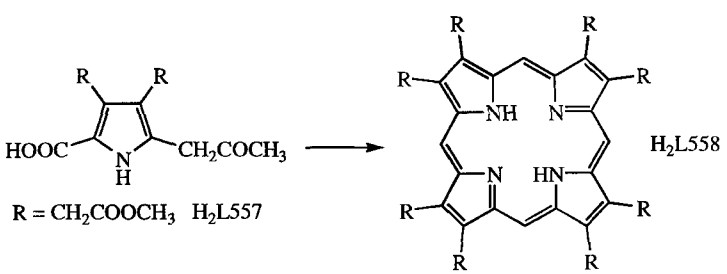


Scheme 2-25. Template synthesis of chlorin/porphyrin species.

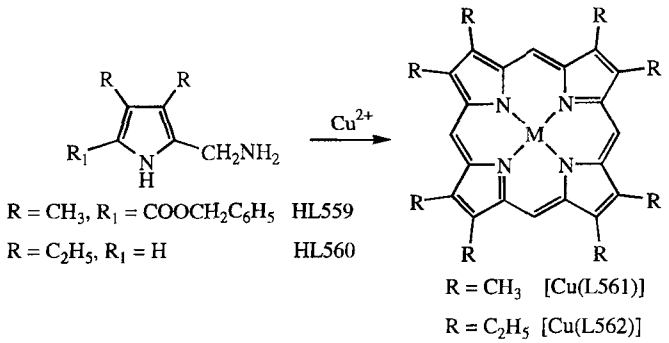
is 2%, [Ni(L552)] and traces of [Ni(L555)] are formed. In the case of copper, some *meso*-tetrapropylporphyrin is assembled and little *meso*-tetraethylporphyrin formed; tetraalkylchlorines ([Cu(L555)] and [Cu(L556)]) are the main products of reaction on matrices [401, 402].

By tetramerisation of pyrroles having a methylene unit in one of the α positions, e.g. H_2L557, it is possible to prepare coproporphyrin tetramethylene ester H_2L558 in 29% yield [403]. In the presence of cobalt(II) chloride, H_2L558 is assembled in the form of the corresponding complex, in considerably greater yield (52%) (Eq. 2.218) [403].

Copper(II) octamethylporphynate and octaethylporphynate ([Cu(L561)] and [Cu(L562)] respectively) are obtained in an analogous way from aminomethylpyrroles HL559 and HL560 on copper(II) matrices in 20% yield (Eq. 2.219) [404]. Ions of other metals (nickel, magnesium, iron) are either not effective or give only a low yield of the product (zinc, cobalt).

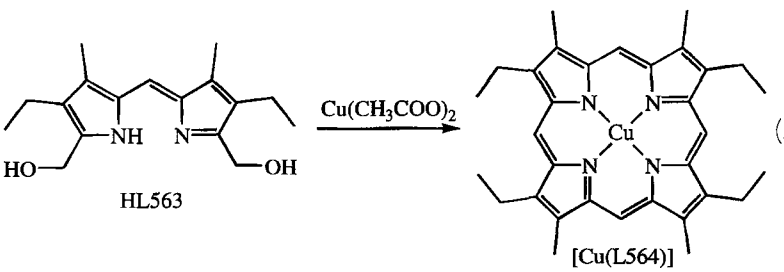


(2.218)



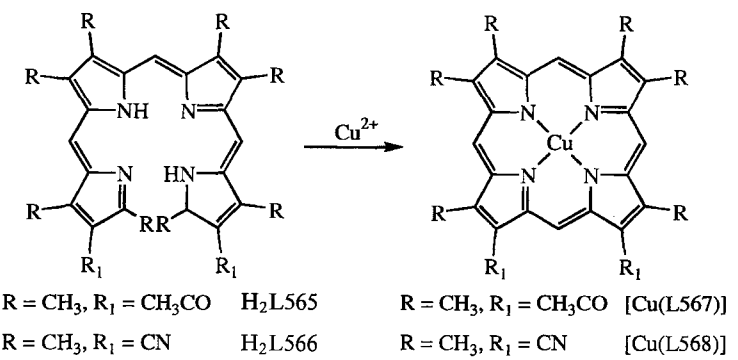
(2.219)

By reaction of the dihydroxymethyl derivative HL563 with copper(II) acetate, [Cu(L564)] is formed in 21% yield (Eq. 2.220) [405].



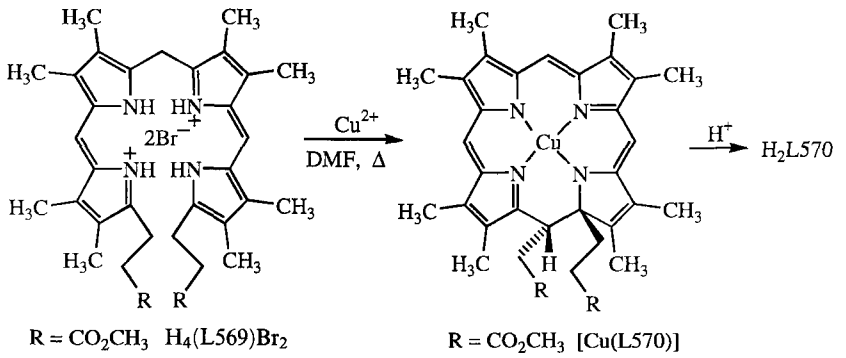
(2.220)

By intramolecular coupling tetrapyrrole systems H_2L565 and H_2L566, complexes [Cu(L567)] and [Cu(L568)] were synthesised in the presence of copper(II) (Eq. 2.221) [406].

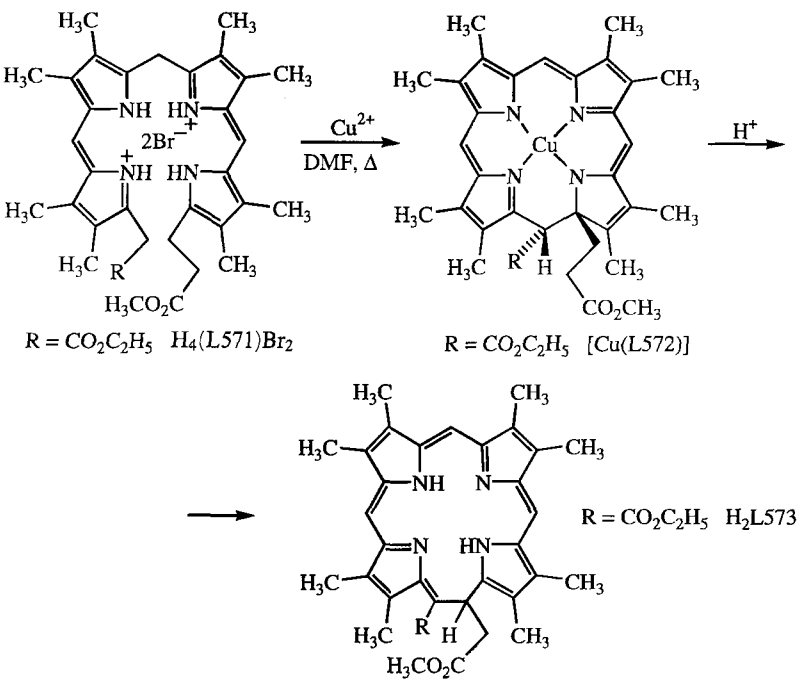


(2.221)

The methodology for constructing porphyrins employing copper(II) salts as templates for cyclisation of tetrapyrrole ligsons [405] has been generalised [407–411]



Scheme 2-26. Template synthesis of unsymmetrical porphyrins [Cu(L570)].

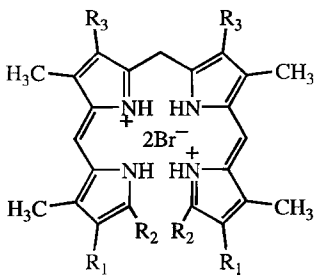


Scheme 2-27. Synthesis of metal-free unsymmetrical porphyrin H_2L573.

to include the preparation of unsymmetrical porphyrins. For example H_2L570 and H_2L573 can be obtained from $H_4(L569)Br_2$ and $H_4(L571)Br_2$, respectively [412] (Schemes 2-26 and 2-27). In both cases, copper(II) was employed as the acetate. Demetallation of [Cu(L570)] occurs with release of the metal-free macro-

cycle (54% yield), whose structure remains intact, but attempts to remove copper(II) with acid from [Cu(L572)] resulted in ring expansion to give H_2L573. This reaction probably [412] proceeds by way of initial ring opening followed by closure in a different sense; ring opening is favoured in the case of [Cu(L572)] (compared with [Cu(L570)]) by the presence of the enolisable proton at the macrocyclic carbon.

The Cu^{II}, Cr^{III}, Ru^{III} and Rh^{III} salts have been used in the cyclisation of several 1,19-dialkyl[*a,c*]biladienes $H_4(L574)Br_2$–$H_4(L576)Br_2$ [413]. The succesive cyclisation of [*a,c*]biladienes has been carried out in the presence of air dioxygen. When copper(II) is used, the products H_2L577–H_2L579 are isolated as coordination compounds (Eq. 2.222). Chromium(III) and rhodium(III) permit the isolation of the corresponding metal-free H_2L577–H_2L579 [413].

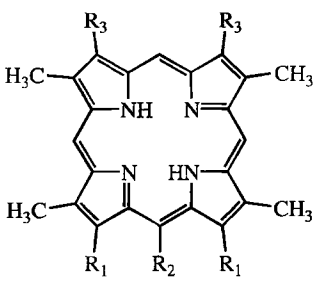


$R_1 = R_2 = R_3 = CH_3$ $H_4(L574)Br_2$

$R_1 = R_2 = CH_3, R_3 = C_2H_5$ $H_4(L575)Br_2$

$R_1 = CH_3, R_2 = R_3 = C_2H_5$ $H_4(L576)Br_2$

(2.222)

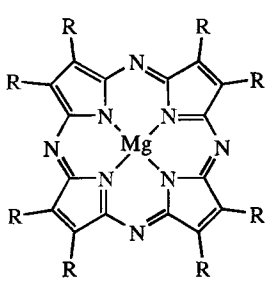


$R_1 = R_2 = CH_3, R_3 = H$ H_2L577

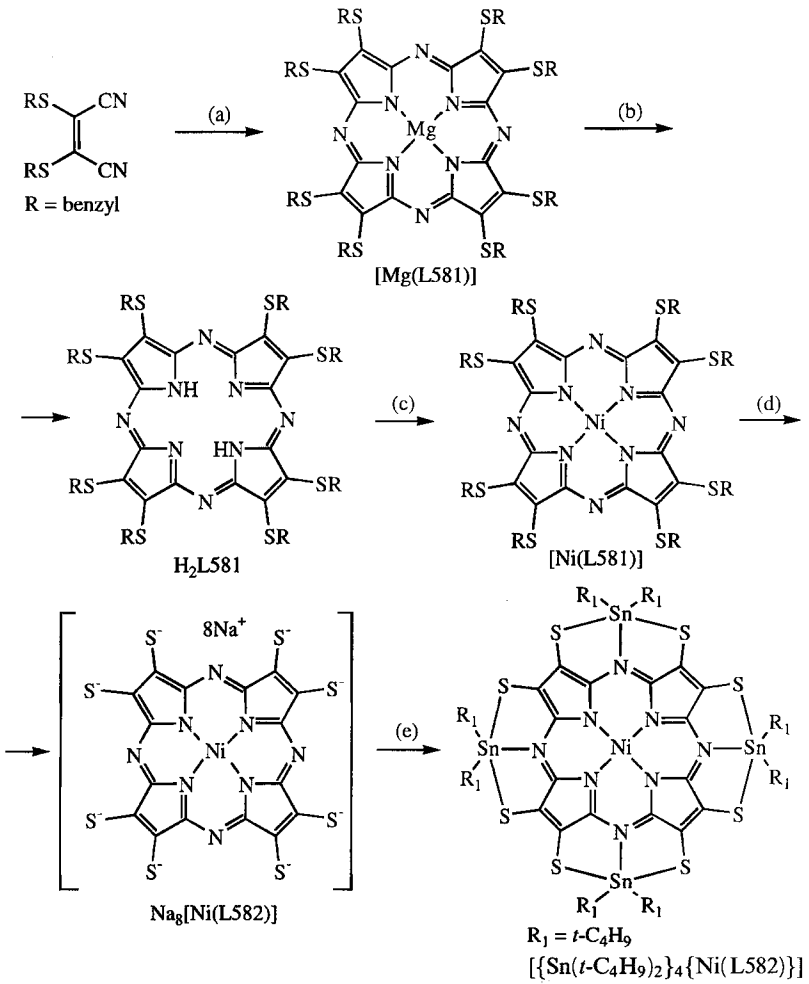
$R_1 = CH_3, R_2 = H, R_3 = C_2H_5$ H_2L578

$R_1 = R_3 = C_2H_5, R_2 = H$ H_2L579

Template condensation of 1,2-dicyano-1,2-bis(methylthio)ethylene in the presence of magnesium propylate results in the magnesium complex of the octa-substituted tetraaza porphyrin [Mg(L580)] (Eq. 2.223) [414].



$R = CH_3S$ [Mg(L580)] (2.223)



(a) $Mg(OC_3H_7)_2$, C_3H_7OH, 100°C, 12 h (b) CF_3COOH, 25°C, 16 h

(c) $Ni(CH_3COO)_2$, C_6H_5Cl, 4 h (d) Na (24 equiv.), NH_3, THF, -33°C, not isolated

(e) $(t\text{-}C_4H_9)_2Sn(NO_3)_2$, CH_3OH, H_2O, 25°C, 1 h

Scheme 2-28. Synthesis of $[\{Sn(t\text{-}C_4H_9)_2\}_4\{Ni(L582)\}]$.

By treating this with sulphuric acid, the metal-free compound H_2L580 was isolated. This was then used to synthesise the nickel(II) and copper(II) complexes [414]. Attempts to obtain [Ni(L580)] and [Cu(L580)] by transmetallation of the magnesium complex were unsuccessful.

The macrocyclic compound [Mg(L581)] was synthesised by template condensation according to the first step in Scheme 2-28 [415].

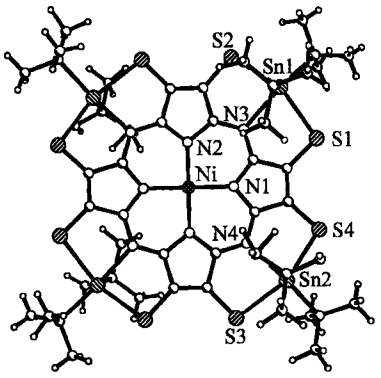


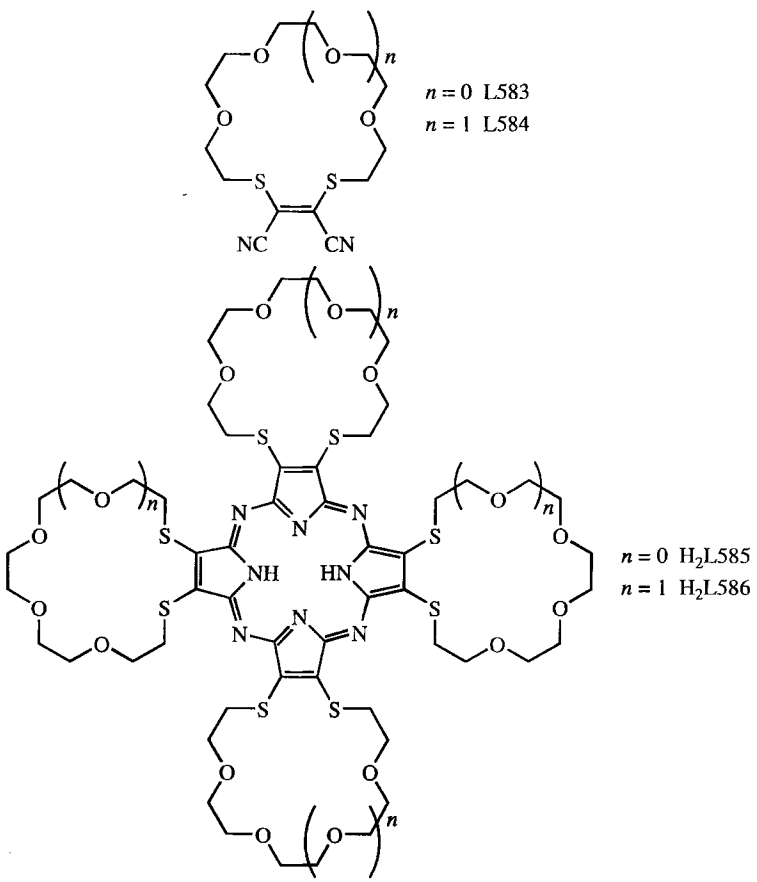
Figure 2-30. The structure of [{Sn(*t*-C_4H_9)$_2$}$_4${Ni(L582)}].

After demetallation of [Mg(L581)], [Ni(L581)] could be obtained. This was debenzylated to give the highly air sensitive Na_8[Ni(L582)], which was converted into [{Sn(*t*-C_4H_9)$_2$}$_4${Ni(L582)}] by reacting with di-*tert*-butyltin dinitrate. The X-ray crystal structure of [{Sn(*t*-C_4H_9)$_2$}$_4${Ni(L582)}] was established [415]. Figure 2-30 depicts the structure of this unprecedent metal-encapsulated porphyrazine complex.

The peculiarities of that part of the structure which involves the tin atoms have been emphasised [415]. The tin atoms have square-pyramidal geometry with one *tert*-butyl group at the apex. The coordination of two thiolate groups of different pyrrole rings is unexpected, because in known dialkyltin dithiolene complexes containing pyrrole units, the tin atom is chelated to the two adjacent sulphur atoms of a single pyrrole ring [416]. The two sulphur atoms on a given pyrrole ring are unusually far apart as a result of their coordination to different tin atoms. Typical sulphur–sulphur distances in metal-dithiolene complexes [417–419] are 31–33 nm, whereas in [{Sn(*t*-C_4H_9)$_2$}$_4${Ni(L582)}] the distance between two sulphurs on a pyrrole is 37.3 nm. Likewise the C=C–S bond angle has increased from about 120° in normal metal–dithiolene complexes to 133° in [{Sn(*t*-C_4H_9)$_2$}$_4${Ni(L582)}]. This structure provides the first example of a metal ion coordination by the *meso* nitrogen of a porphyrazine.

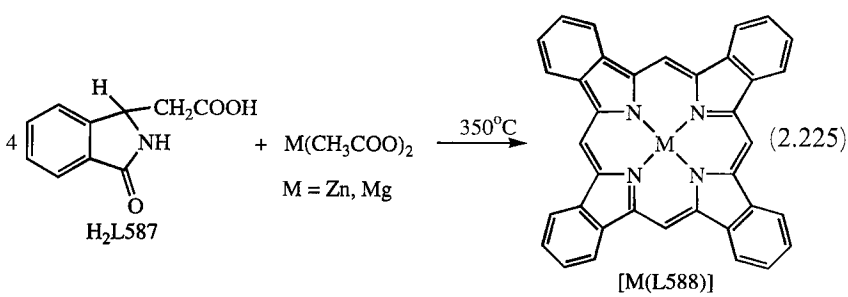
Related crowned porphyrazines H_2L585 and H_2L586, in the form of their magnesium(II) complexes, have been assembled from the appropriate crown derivatives of dithiomaleonitriles H_2L583 and H_2L584 in the presence of Mg(II) as the template in refluxing butanol or propanol (Eq. 2.224) [420–423]. Magnesium(II) complexes are easily demetallated by treatment with trifluoroacetic acid. The metal-free porphyrazines react with an excess of nickel(II) or copper(II) acetate to give the corresponding complexes in nearly quantitative yield.

Template synthesis has become a classic technique for the synthesis of tetrabenzoporphyrin metal complexes which, like [Mg(L580)] and [Mg(L581)], occupy an intermediate position between porphyrins and phthalocyanines. Thus complexes [M(L588)], where M = Zn or Mg are obtained by condensation of 3-carboxy-



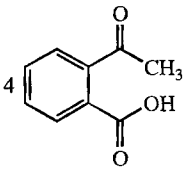
(2.224)

methylphthalimidine H_2L587 with zinc or magnesium acetates under nitrogen at 345°C (Eq. 2.225) [424, 425].



(2.225)

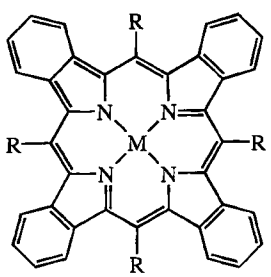
Template synthesis of [Zn(L588)] has been carried out by heating *o*-acetylbenzoic acid with zinc(II) acetate to 400°C in the presence of alkali, concentrated ammonia and molecular sieve (40 nm) (Eq. 2.226) [426].



$$+ \quad [Zn(NH_3)_4]^{2+} \xrightarrow[-\,12\,H_2O]{+\,2e^-} [Zn(L588)] \qquad (2.226)$$

Reaction on a zero oxidation state iron matrix (iron powder) proceeds analogously, with formation of [Fe(L588)] [427]. Zinc(II) tetrabenzoporphinate [Zn(L588)] can also be obtained by interaction of potassium phthalimide with malonic acid or sodium acetate in the presence of zinc(II) acetate [428], as well as by template condensation of isoindolene with a carbonyl component, such as mesoxalic acid hydrate, paraform, diphenylformamide, or *N*-methylformanilide at 300–360°C and in the presence of alkali [429]. On treatment of [Zn(L588)] with mineral acid, demetallation takes place with the release of metal-free porphin. This may be then used for synthesis of tetrabenzoporphynates of those metals which are not effective as template agents [427].

By reaction of phthalimide or potassium phthalimide with corresponding arylacetic acids or their sodium or potassium salts in the presence of zinc(II) or cadmium(II) acetates at 340–380°C in a flow of inert gas, zinc(II) and cadmium(II) *meso*-tetraaryltetrabenzoporphinates [M(L589)] (M = Zn, Cd) and [Zn(L590)]–[Zn(L592)] (Eq. 2.227) were obtained [430].

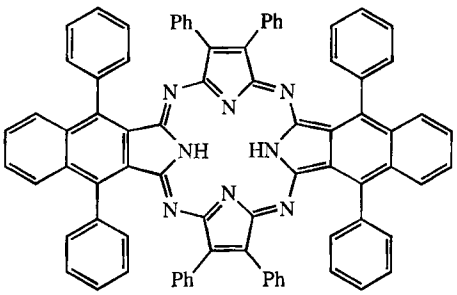


R = C_6H_5	[M(L589)] (M = Zn, Cd)
R = *p*-$CH_3C_6H_4$	[Zn(L590)]
R = *p*-$CH_3OC_6H_4$	[Zn(L591)]
R = 1-$C_{10}H_7$	[Zn(L592)]

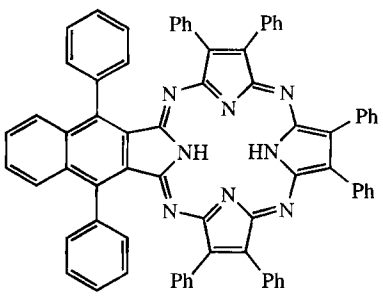
(2.227)

Zinc(II) tetrabenzoporphynates with substituents in positions 3, 4 and 5 of the benzene rings were synthesised by template tetramerisation of substituted 3-carboxymethylphthalimidines or phthalimides with malonic or phenylacetic acid in the presence of zinc(II) acetate [431].

Tetraazaporphyrin H_2L593, containing two fused naphthalene units at the opposite pyrrole rings, has been prepared in a very low yield by the condensation of 2,3-dicyano-1,4-diphenylnaphthalene and diphenylmaleonitrile taken in a 3:1 ratio in the presence of $Zn(CH_3COO)_2$ or $CoCl_2$ at 250–260°C under an inert atmosphere [432]. The product has been isolated in the form of its corresponding zinc(II) or cobalt(II) complex and purified chromatographically. The expected parent peaks of m/z = 1186 ($P^{+\cdot}$) for [Zn(L593)] and m/z = 1180 ($P + 1^+$) for [Co(L593)] have been found in the FAB mass spectra. The synthesis of the related asymmetric zinc(II) complex [Zn(L594)], containing only one fused naphthalene ring, has also been reported (Eq. 2.228) [433].



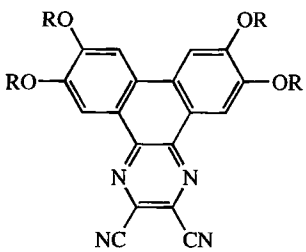
H_2L593



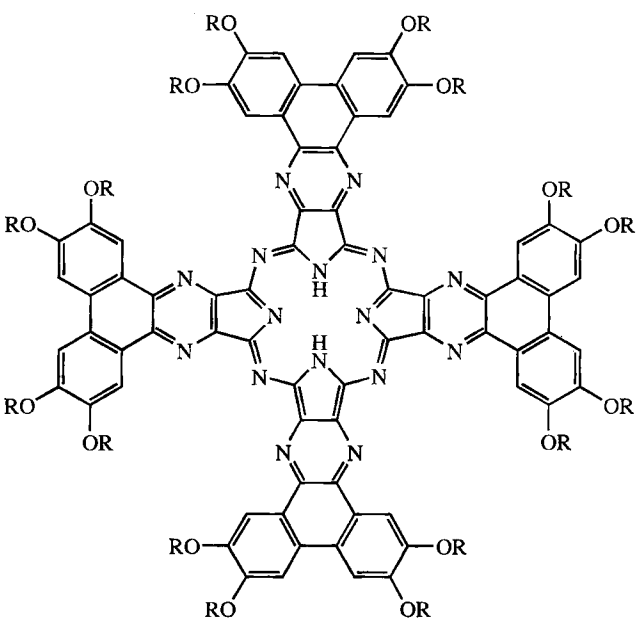
H_2L594

(2.228)

By prolonged refluxing of 6,7,10,11-tetrakis(decyloxy)-1,4-diazatriphenylene-2,3-dinitrile (L595) with either $CuCl_2$ or $NiCl_2$ as the template salt and 1,8-diazabicyclo [5.4.0]undec-7-ene as the catalyst in 2-methylbutan-2-ol, mesogenic porphyrazine complexes [M(L596)], where M = Cu or Ni, bearing decyloxy side-chains have been synthesised (Eq. 2.229) [434].



L595

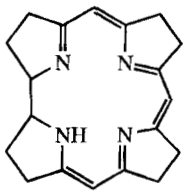


$R = C_{10}H_{21}$ H_2L596

(2.229)

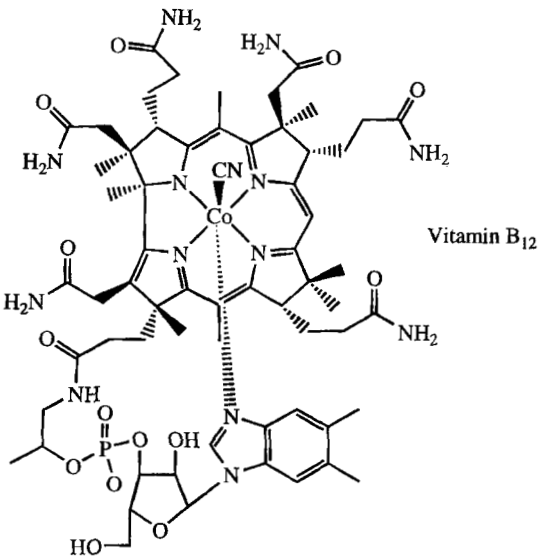
2.9.2 Corrins

In contrast to porphyrins, corrins are characterised by complete saturation of the peripheral part of the molecule. They also have a smaller macroring, because two of the four five-membered rings are directly linked (Eq. 2.230).



(2.230)

Biological compounds with the corrin structure are of particular interest, with cobyric acid and vitamin B_{12} occupying a special place [435–442]. The latter was first isolated in 1948 [435] and structurally characterised in 1955 (Eq. 2.231) [443].

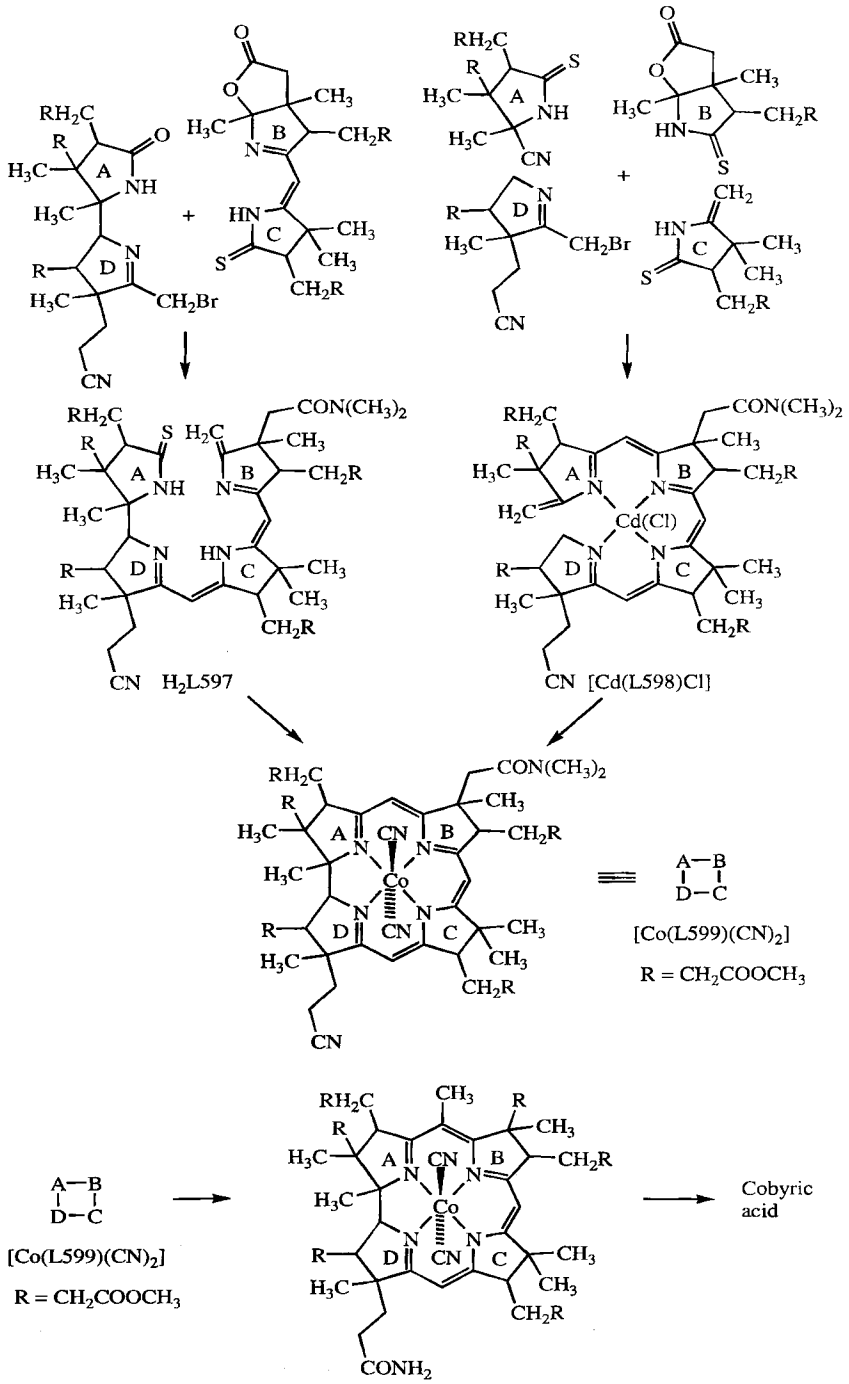


(2.231)

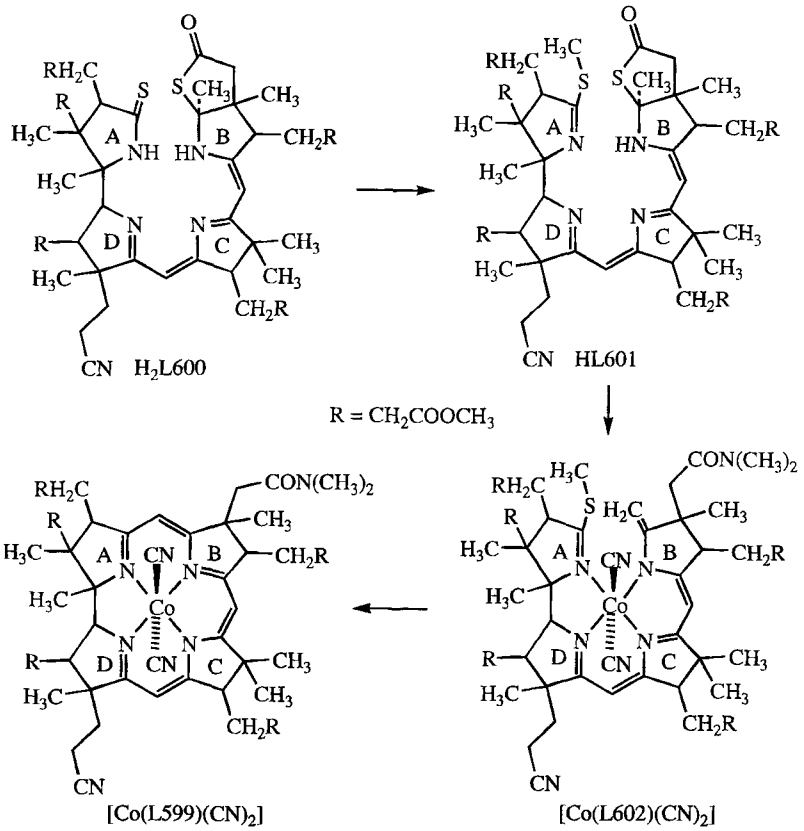
Two very elegant variants (A/B and A/D) of the cobyric acid multistep synthesis have so far been realised, which are shown in Scheme 2-29 [441, 444].

The synthesis of cobyric acid is the culminating achievement in corrin chemistry. The key step in cobyric acid synthesis is transformation of the open-chain organic system into the corresponding macrocyclic corrin by means of chemically joining cycles A and B (the A/B route) as well as by secocorrin/corrin cyclisation between rings A and D (the A/D route).

Macrocyclisation by the A/B route may be achieved in two ways [439]. One of these, designed by Woodward's group in Cambridge, consists in joining cycles A



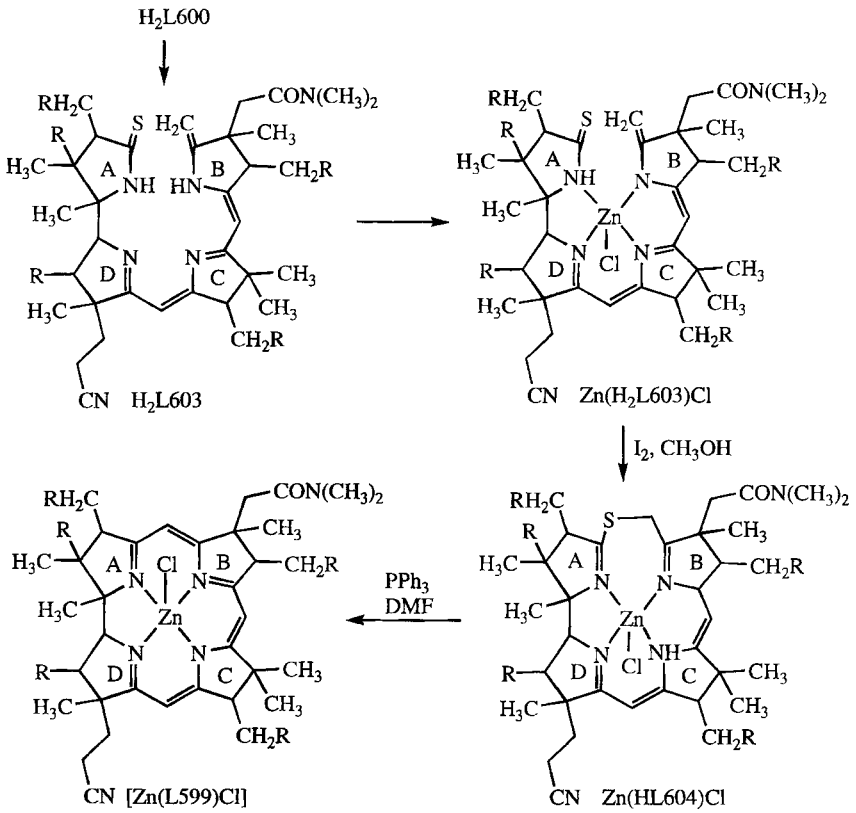
Scheme 2-29. The A/B and A/D pathways of the cobyric acid multistep synthesis.



Scheme 2-30. Woodward's approach of macrocyclisation by the A/B route.

and B by means of the reactions given in Scheme 2-30. Thiolactam H_2L600 is converted into its S-methyl derivative (HL601) by treating it with trimethyloxonium tetrafluoroborate. Then treatment with dimethylamine at room temperature results in thiolactone ring opening, forming a dimethylamide compound with concurrent loss of the sulphur atom. In addition, a methyl group is transformed into the exocyclic methylene group. This product is rather labile (the exocyclic double bond is not stable), so it is immediately converted into the appropriate cobalt(III) complex $[Co(L602)(CN)_2]$. Heating the latter with diazacyclononane in dimethylacetamide at 60°C leads to smooth cyclisation with C–C bond formation accompanying loss of the thiomethyl group.

The second method, designed by Eschenmoser in Zurich, consists in the smooth opening of the thiolactone ring in H_2L600 under the influence of dimethylamine to form H_2L603, containing dimethylamide and exocyclic methylene groupings. This is converted into its zinc(II) complex, which undergoes iodine oxidation to give Zn(L604)Cl. The sulphur atom is displaced with triphenylphosphine in the presence



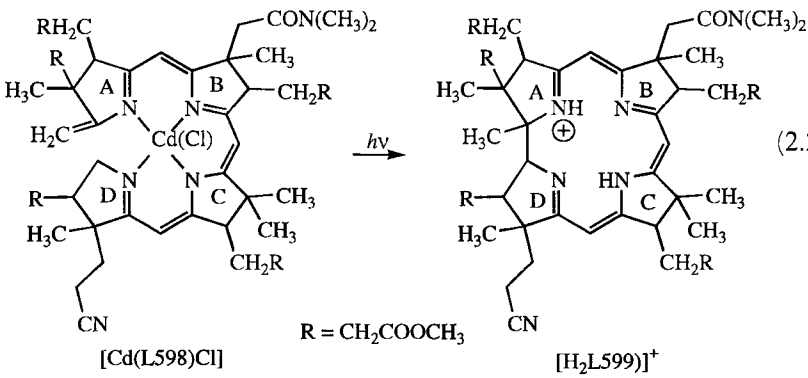
Scheme 2-31. Eschenmoser's method of macrocyclisation by the A/B route.

of trifluoroacetic acid in dimethylformamide (Scheme 2-31), forming the required C–C bond to give the corrin system.

Despite the differences between the various macrocyclisation schemes, the different approaches share the common feature of using transition metal ions in the very important ring-closure step of assembling the macrocycle. Cobalt(III) and zinc(II) ions stabilise labile compounds with exocyclic methylene groups, as well as holding reacting fragments in close proximity and correct orientation to facilitate formation of the corrin ring system.

The A/D route, for which the complete scheme has been given [444], became possible due to the pioneering investigations on the synthesis of tetradehydrocorrins and aromatic corroles [445, 446], and to the development of the Woodward–Hoffman rules [447, 448]. Thermal cycloisomerisation of a secocorrin metal complex into a corrin complex is forbidden, although photochemical cyclisation is allowed [442]. When the cadmium(II) secocorrin complex is exposed to visible light, the

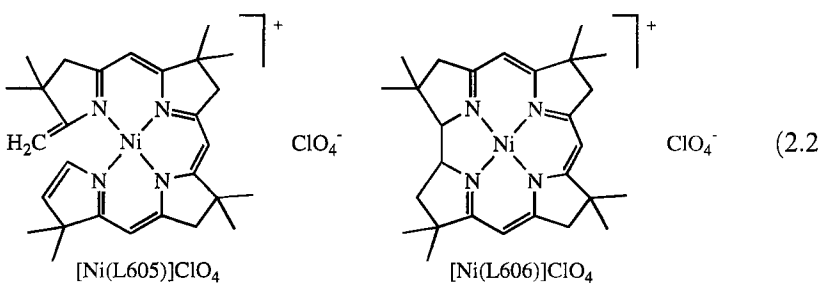
cycloisomerisation A/D (secocorrin/corrin) takes place in one step with high diastereoselectivity (Eq. 2.232) [441, 444, 449].



(2.232)

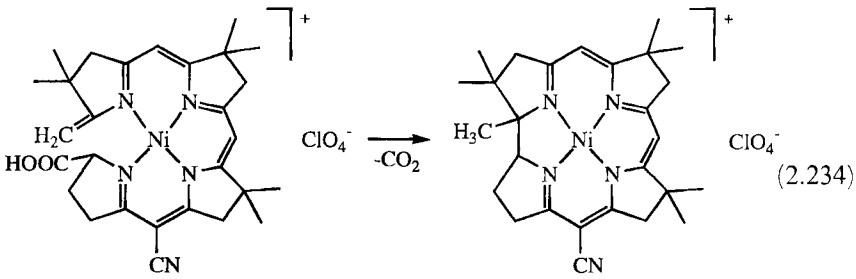
Photoinduced cycloisomerisation can also be carried out in the presence of other metal ions serving as templates. For example, secocorrin coordinated to metal ions such as lithium(I), magnesium(II), zinc(II) or cadmium(II) readily cyclises in the absence of oxygen in almost quantitative yield at room temperature [441, 444]. Platinum(II) and palladium(II) complexes (quantum yield 0.008 in chloroform at 20°C) also cyclise, but more slowly. However, nickel(II), cobalt(III) and copper(II) secocorrinates do not undergo such a transformation [441, 444]. If, however, the nickel(II) 1-methylidene-1,19-secocorrinate is subjected to one-electron electrochemical oxidation, followed by direct reduction of the isomerised cation-radical, then such a transformation is realisable [450].

Another model system, nickel(II) Δ^{18}-dehydro-A/D-secocorrinate $[Ni(L605)]ClO_4$, is cyclised to corrin $[Ni(L606)]ClO_4$ in 50–60% yield by electrochemical reduction (Eq. 2.233) [451].



(2.233)

Thermal decarboxylation of nickel(II) 1-methylidene-2,2,7,7,12,12-hexamethyl-15-cyano-19-carboxy-1,19-secocorrinate $[Ni(L607)]ClO_4$ in a non-polar solvent also leads to formation of a corrin system, $[Ni(L608)]ClO_4$ (Eq. 2.234) [452].



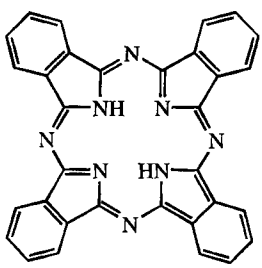
[Ni(L607)]ClO_4 [Ni(L608)]ClO_4 (2.234)

In the presence of transition metal ions it is possible to reconstruct dihydrocorphynole $[M(L609)]^+$ into corrin $[M(L611)]^+$ by contracting the 20-membered macrocycle by one member [453]. The chemical transformations taking place are shown in Scheme 2-32 [436, 453]. (Corphines are the hexahydroporphinoid ligands having a corrin-like chromophore but the macrocyclic skeleton of porphin [436]). These reactions are considered to be a potential biomimetic way for construction of the corrin ring of vitamin B_{12} [436, 454].

Examples of template syntheses of other synthetic corrins, as well as of related synthetic corroles and tetradehydrocorrins, have been considered in detail elsewhere [231].

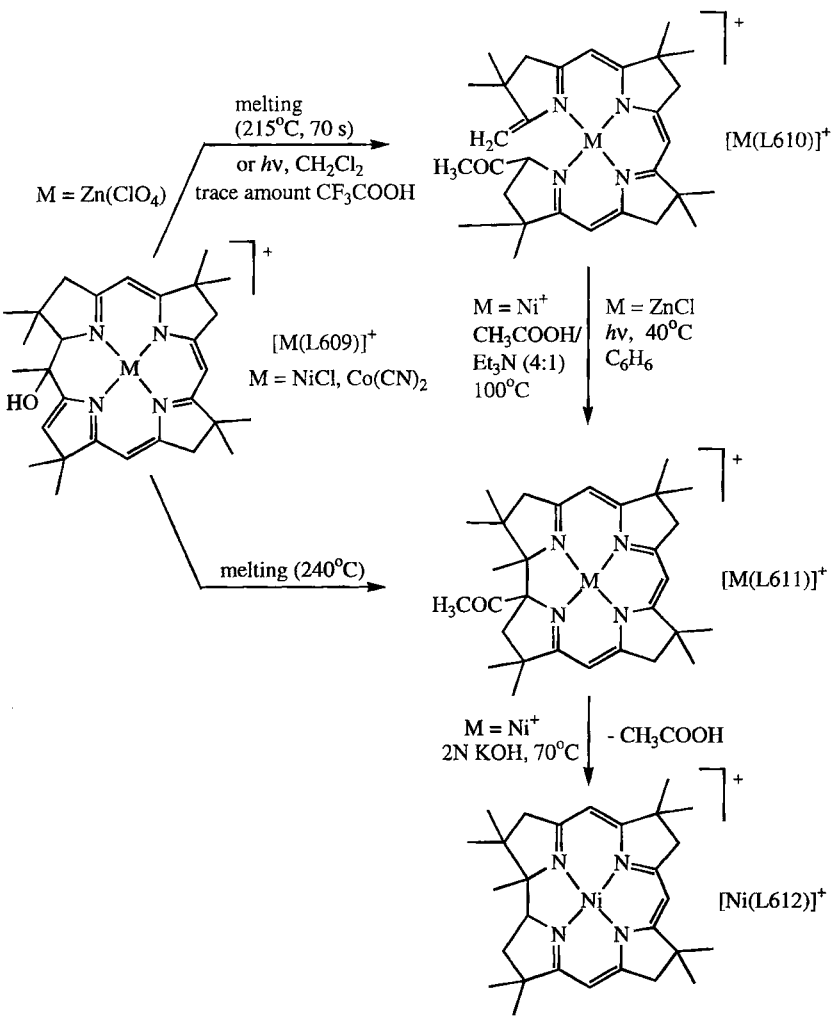
2.9.3 Phthalocyanines

Compounds including the structure given in Equation (2.235) are called phthalocyanines. This name is derived from the Greek words *naphtha* and *cyanide*, i.e. rock oil and dark-blue [455]. The first phthalocyanine was obtained by a template reaction by chance in 1927 in attempting to prepare 1,2-dicyanobenzene from *o*-dibromobenzene and CuCN in pyridine at 200°C [456].



H_2Pc (H_2L613) (2.235)

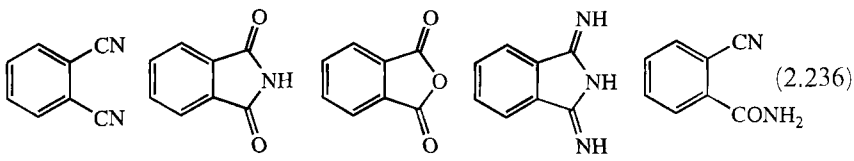
Phthalocyanine complexes are usually assembled by template reactions from appropriate building blocks which comprise fragments of the final macrocycle. The



Scheme 2-32. The synthesis of the corrins [M(L611)].

thermodynamic template effect is often considered to be dominant in these reactions, in which a variety of ligsons are used (Eq. 2.236) [457].

Metal ions or metals in zero oxidation state are used as templates. Template syntheses based on phthalimide and phthalic anhydride require an aminating agent (for instance, urea) and catalysts (ammonium molybdate, boric acid, $ZrCl_4$) [455–457]. In all cases the reaction proceeds either in a molten mixture of the reagents or in an inert high-boiling solvent (nitrobenzene, chloronaphthalene, *o*-dichlorobenzene, trichlorobenzene, ethylene glycol) [456–460].

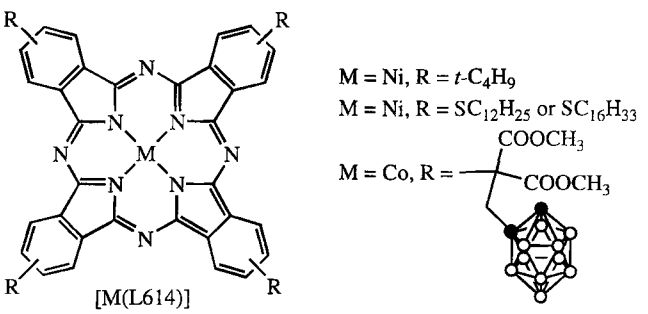


(2.236)

Phthalonitrile Phthalimide Phthalic anhydride Diiminoisoindoline *o*-Cyanobenzamide

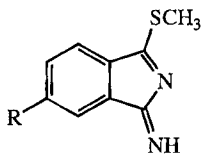
The most convenient and usual starting material for the assembly of phthalocyanine systems is phthalonitrile, from which complexes of almost all known metals were obtained. Silver and mercury are an exception [457]. Metals (Zn, Cd, Co, Sn, Cu, Fe), salts ($NiCl_2$, $CoCl_2$, $ZnCl_2$, $AlCl_3$, $PtCl_2$, $RhCl_3$, $Y(HCOO)_3$, $PbSO_4$, $BaSO_4$), or oxides (CaO, PbO, OsO_4, V_2O_5, MnO_2) [457] have all been used as matrix sources.

A few examples from the numerous syntheses of phthalocyanine systems are given below. Condensation of 4- and 3-substituted phthalonitriles, phthalic anhydrides or other related derivatives in the presence of a metal salt normally give a non-statistical mixture of structural isomers of [M(L614)] (Eq. 2.237) [461–465].

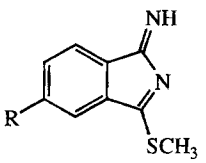


(2.237)

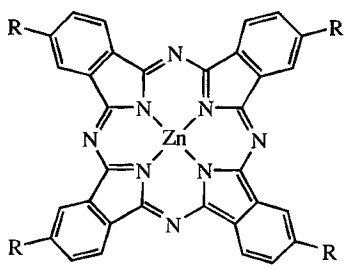
In rare cases (for example, if R = $OCH_2C_6H_5$-*p*-C_4H_9, 3-OCH_3 or $OCH_2C(CH_3)_3$ and M = Zn) the condensation of 3-substituted phthalonitriles or their derivatives proceeds with single isomer formation [466, 467]. Both the steric and electronic natures of the substituent seem to be crucial. Development of low-temperature template syntheses should also be important in this context [467]. Thus the condensation reaction of L615 or L616 at −20°C in DMF using $Zn(CH_3COO)_2$ as a template source gave [Zn(L614)] [468] as single structural isomer, together with a mixture of starting ligsons and byproducts from the linear condensation of two, three or four blocks, L617–L621 (Eq. 2.238).



L615

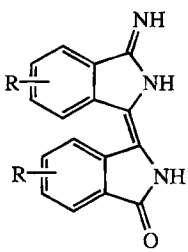


L616

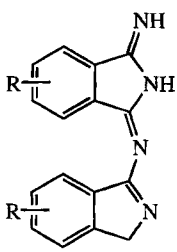


[Zn(L614)]

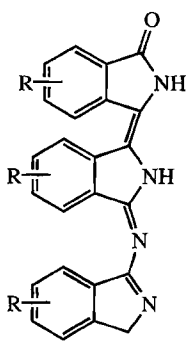
$R = OCH_2C(CH_3)_3$ (2.238)



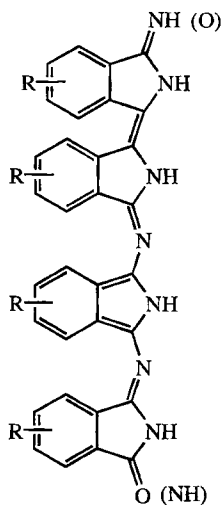
L617



L618

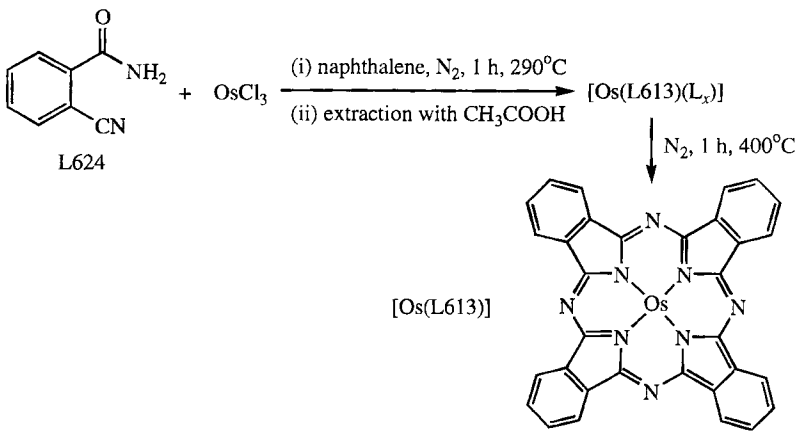


L619

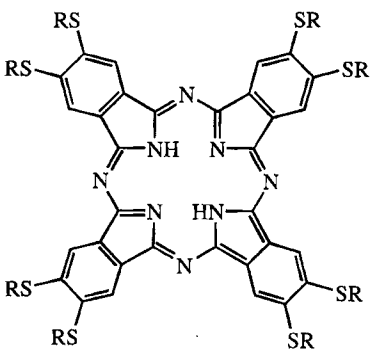


L620 (L621)

Metal-free octasubstituted alkylthiophthalocyanine (H_2L622) and metal phthalocyaninates ([M(L622)], where M = Ni, Cu, Co or Zn, and [Ni(L623)]) have been prepared from 4,5-bis(alkylthio)phthalonitrile and 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) or the corresponding metal salt ($NiCl_2$, CuCl, $CoCl_2$ or $Zn(CH_3COO)_2$) (Eq. 2.239) [469]. The highest yield is achieved in the presence of CuCl (62%) or $Zn(CH_3COO)_2$ (48%) compared with 38% for metal-free H_2L622 synthesised in the absence of template salt. The thermodynamic template effect predominates in these syntheses.



Scheme 2-33. Synthesis of [Os(L613)].



$R = C_6H_{13}$ H_2L622
$R = C_{12}H_{25}$ H_2L623 (2.239)

The complex [Os(L613)] has been obtained according to Scheme 2-33 [470]. The crude product [Os(L613)(L_x)] might actually be a bi-axially coordinated species, with a derivative of phthalic acid or the cyclised *o*-cyanobenzamide (denoted as L_x) axially coordinated. When the crude [Os(L613)(L_x)] is heated slowly up to 400°C the pure macrocyclic complex [Os(L613)] is obtained [470].

Template syntheses of a number of phthalocyanine complexes have been reported [471, 472]. Thus, by heating L624 with $RuCl_3 \cdot xH_2O$ in naphthalene at 290°C, subsequent extraction with CH_3COOH, and recrystallisation of the isolated adduct from DMSO, [Ru(L613)] has been obtained [471]. This procedure, however, has the disadvantages of a tedious purification of the crude [Ru(L613)] by extraction with glacial acetic acid and the relatively high temperature required for thermal decomposition of the DMSO adduct. New routes for the syntheses of [Ru(L613)] have therefore been developed, which are illustrated in Scheme 2-34 [471].

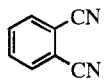
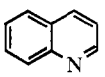
Method A

L624 + $RuCl_3 \cdot xH_2O$ $\xrightarrow{\text{naphthalene, } 290^\circ C}$ '[Ru(L613)]'

'[Ru(L613)]' + 2Py $\longrightarrow$ [Ru(L613)(Py)$_2$]

[Ru(L613)(Py)$_2$] $\xrightarrow[\text{vacuum}]{250^\circ C}$ [Ru(L613)]

Method B

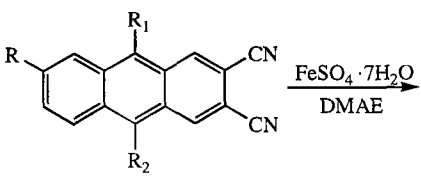
L624 or  + $RuCl_3 \cdot xH_2O$ +  $\xrightarrow{250^\circ C}$ [Ru(L613)(Qn)$_2$]

(Qn)

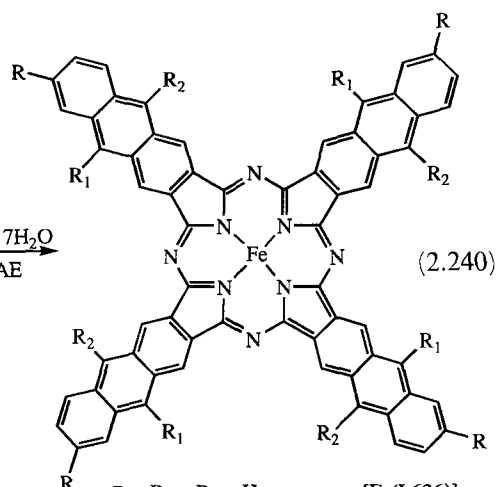
[Ru(L613)(Qn)$_2$] $\xrightarrow[\text{vacuum}]{250^\circ C}$ [Ru(L613)]

Scheme 2-34. Synthetic pathways to [Ru(L613)].

Synthesis of 2,3-anthracenocyaninatoiron(II) derivatives [Fe(L626)]–[Fe(L628)] has been achieved [473] from L625 in the presence of Fe^{II} in *N,N*-dimethylaminoethanol (DMAE) (Eq. 2.240).



L625



(2.240)

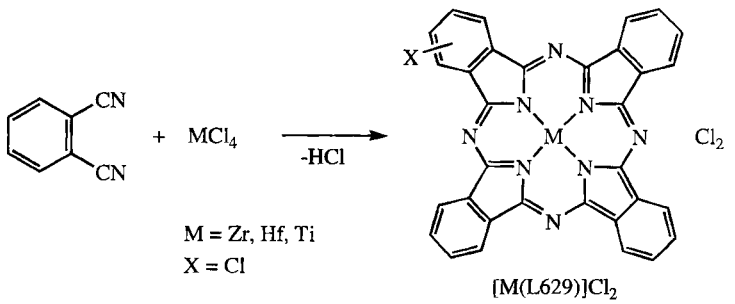
R = R_1 = R_2 = H [Fe(L626)]

R = *t*-C_4H_9, R_1 = R_2 = H [Fe(L627)]

R = H, R_1 = R_2 = C_6H_5 [Fe(L628)]

Metal carbonyls are also suitable for assembling phthalocyanine systems [455, 474]. The use of volatile metal-containing compounds, including carbonyls, as matrix sources is of practical interest because of the possibility of obtaining catalysts with molecularly dispersed heterogeneous phthalocyanine complexes supported on zeolites [475–477].

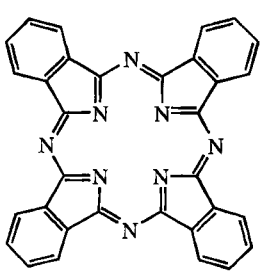
The use of chlorides often results in halogenation of an aromatic nucleus (Eq. 2.241) [478, 479].



(2.241)

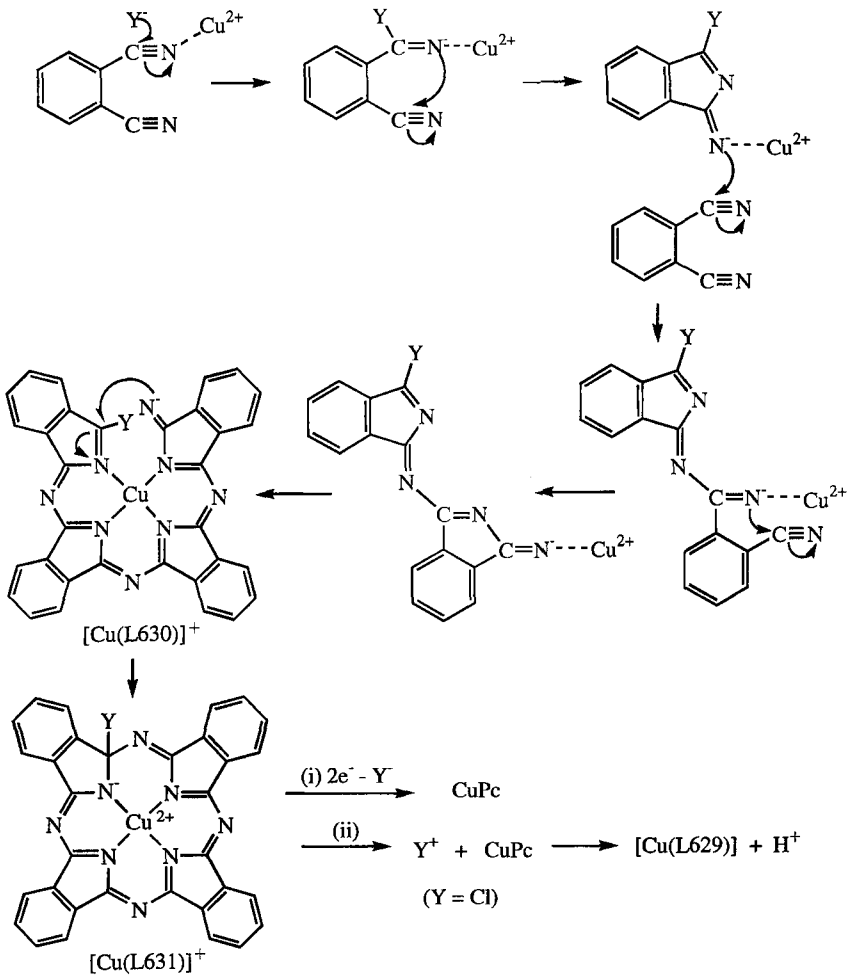
The thermal characteristics of the reaction of phthalonitrile with a range of copper compounds have been investigated by differential scanning calorimetry, with product analysis by IR spectroscopy [480]. It was established that reaction with copper metal to give copper(II) phthalocyanine (CuPc) is exothermic and requires the presence of atmospheric oxygen or a small amount of a copper(II) salt. Reaction with copper(I) chloride is air sensitive and gives a mixture of CuPc and [Cu(L629)]. These results suggest that in all cases it is the Cu^{II} ion that participates in phthalocyanine formation. Scheme 2-35 may serve as a model showing how coordination with the Cu^{II} might play a role in retaining structure [Cu(L630)] in a conformation favourable for ring closure by intramolecular nucleophilic attack to form intermediate [Cu(L631)].

Direct elimination of the original nucleophile Y^- from [Cu(L631)] is not favoured, as this would lead to the dehydrophthalocyanine L632 (Eq. 2.242), which is generally considered as a 16 π-electron system [457] and as such is unstable. Where copper metal is the reactant, two electrons may be transferred from the metal allowing elimination of Y^- to form the stable 18 π-electron copper(II) phthalocyanine CuPc (route i) [480]. Consequently, the copper(0) is oxidised to copper(II) as



L632

(2.242)



Scheme 2-35. Illustration of the kinetic coordination template effect in the synthesis of phthalocyanines.

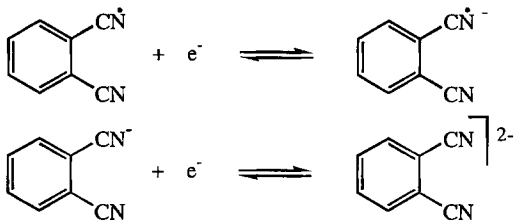
required to participate further in the reaction sequence. When copper(II) chloride is the reactant, so that there is no comparable reducing agent present, it is supposed [480] that Y^+ (in this case the chloronium ion) is eliminated to form CuPc (route ii), the driving force for this elimination being the exceptionally high stability of CuPc. The eventual formation of [Cu(L629)] in this case is explained by a subsequent electrophilic substitution reaction involving CuPc and the released chloronium ion. When copper(I) chloride reacts, it is probable that route (i) is followed initially, the source of the two electrons required being two Cu^+ ions. The result of this first phase of the reaction sequence would be the formation of equimolar amounts of

CuPc and copper(II) chloride, the latter reacting subsequently in the second phase by route (ii) to give [Cu(L629)].

Phthalocyanine complexes with more chlorines in the molecule can be obtained by directed synthesis starting from chloro-containing ligsons [231].

Traditional template synthesis of metal phthalocyanines requires high temperatures to be used. In contrast, electrochemical template methods allow the highly efficient assembly of phthalocyanine–metal complexes in organic solvents under ambient conditions.

Phthalonitrile in dimethylformamide is characterised by two half-wave potentials at −2.12 V and −2.76 V, which correspond to two successive reductions (Eq. 2.243) [481]. Results of phthalonitrile cyclic voltammetry in absolute ethanol confirm that the peak at −1.62 V corresponds to the first wave in the polarographic investigation, i.e. to the formation of the nitrile anion radical [482].

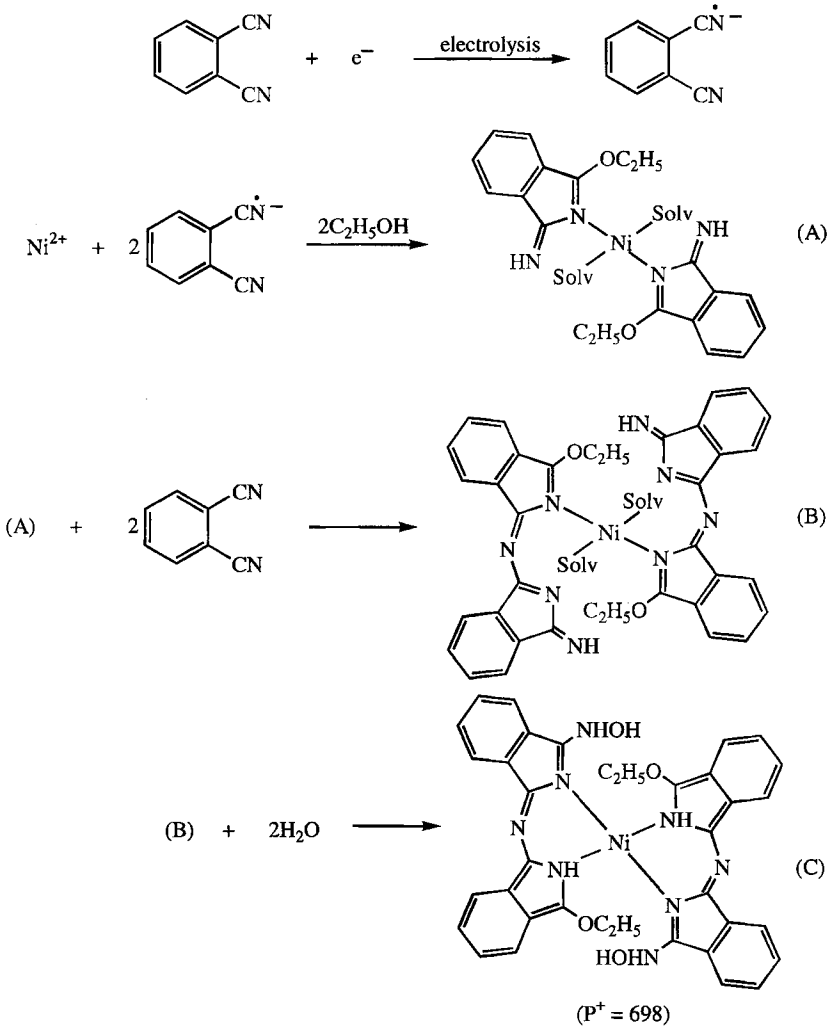


(2.243)

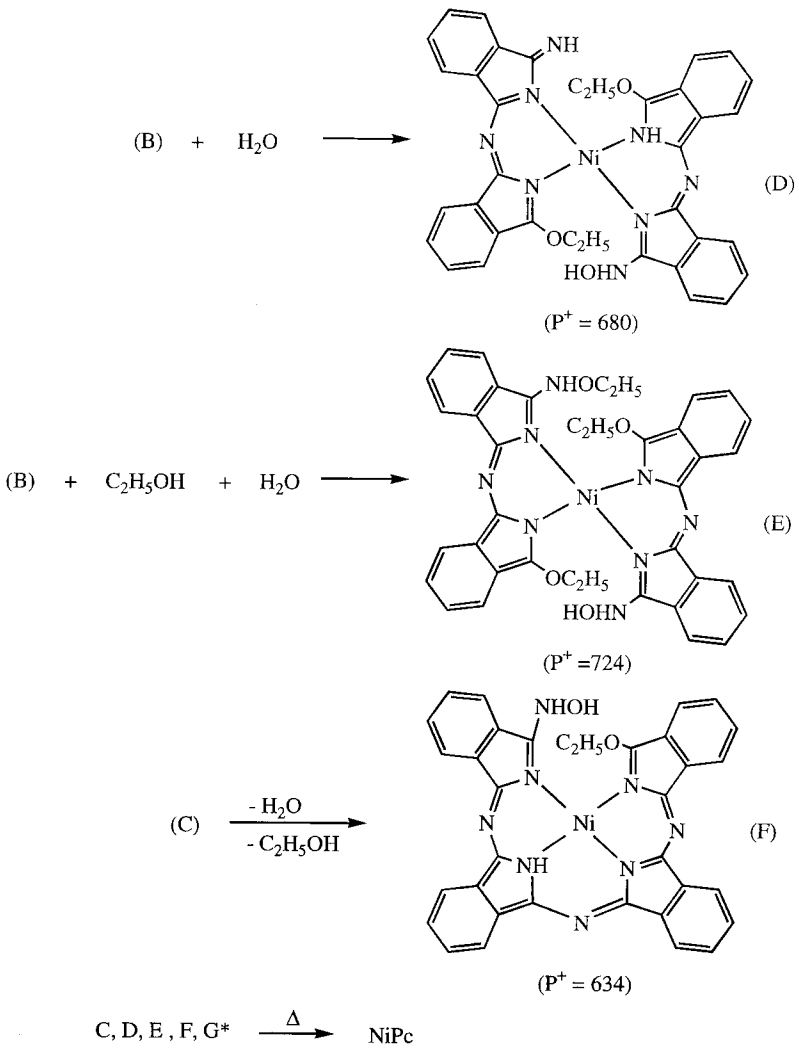
If an ethanol solution of tetrabutylammonium perchlorate and phthalonitrile is put into the cathode compartment of the electrolytic cell, separated from the anode compartment by an ion-exchange diaphragm, and an ethanol solution of nickel(II) sulphate is used as anolyte, then on electrolysis NiPc can be isolated in high yield. CuPc is obtained analogously. The fact that in both cases electrolysis proceeds at −1.6 V (i.e. independently of the nature of the metal ion), confirms the determining role of anion radicals in building up MPc and that metal ions are not involved in the electrochemical reaction [482]. (If both the metal salt and phthalonitrile are placed in the cell cathode section, then NiPc or CuPc are formed in very small yield. The majority of the metal is deposited on the cathode). Moreover, it is supposed that the active participants of the transformations in the electrolytic cell are solvent molecules, because although MPc is formed in dimethylformamide or alcohol solutions, the phthalocyanine-metal complex is not produced in acetonitrile in spite of the generation of anion radicals [483].

The electrochemical template synthesis of MPc is a complicated multistep process. This is confirmed by the isolation and mass-spectrometric identification of a series of intermediate products in NiPc synthesis, which could be formed according to Scheme 2-36.

Nickel ions, as potential templates, migrate from the anode compartment through the ion-exchange diaphragm and react with two anion radicals, appearing near the cathode, and with two ethanol molecules, forming (A), which in its turn forms (B) on interaction with two phthalonitrile molecules. Although (A) and (B) were not isolated, without their existence it is difficult to explain the formation of



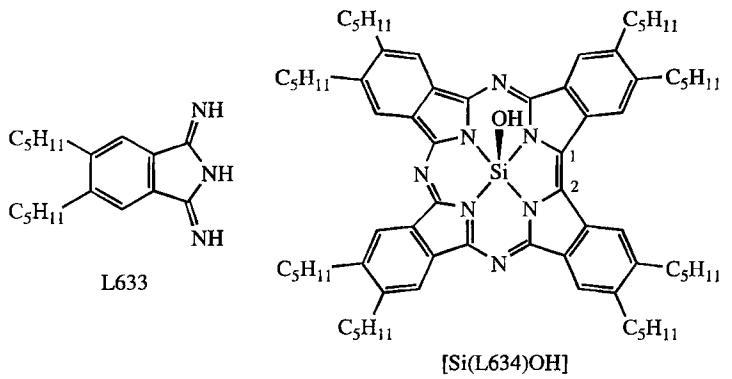
Scheme 2-36. Electrochemical template synthesis of [Ni(Pc)].



Scheme 2-36. (*Continued*)

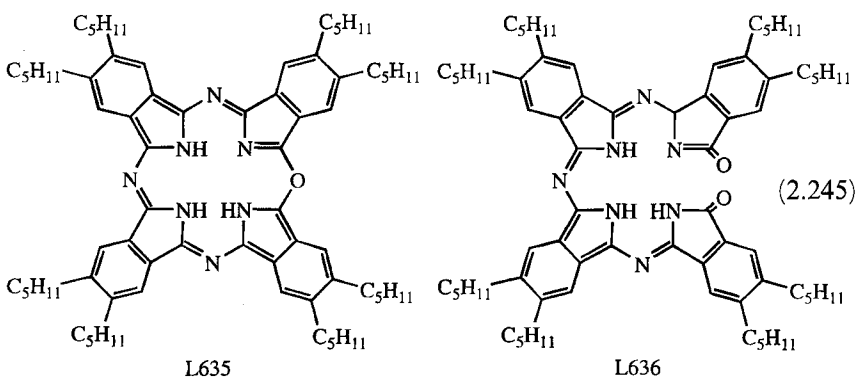
intermediates C, D, E and F, separated chromatographically and identified mass-spectrometrically. (Note that $m/z = 744$ corresponds to product G*, but this substance remained unidentified). The intermediate compounds convert into NiPc stepwise at room temperature, or rapidly on heating, by splitting off the alkoxy groups and by bond redistribution [483].

As previously mentioned, most of the metal-ion templates involved in the condensation of phthalonitriles, phthalic anhydrides, phthalimides, diiminoisoindolines and related derivatives give the traditional tetradentate phthalocyanines. The use of silicon, lanthanide, boron or uranyl compounds as templates permits the building up other interesting molecular macrocyclic architectures. Thus reaction of 4,5-dipentyldiiminoisoindoline (L633) with Si_2Cl_6 in quinoline results in the ring-contracted product [Si(L634)OH] in 35% yield (Eq. 2.244) [484].



(2.244)

The latter undergoes photolysis in solution yielding silicon-free compounds L635 and L636 (Eq. 2.245) as cleavage products of the 1,2-double bond.



(2.245)

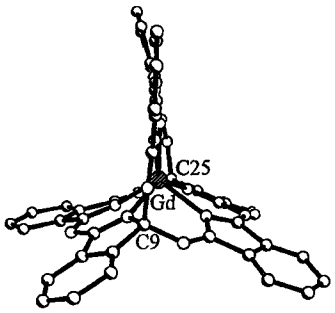
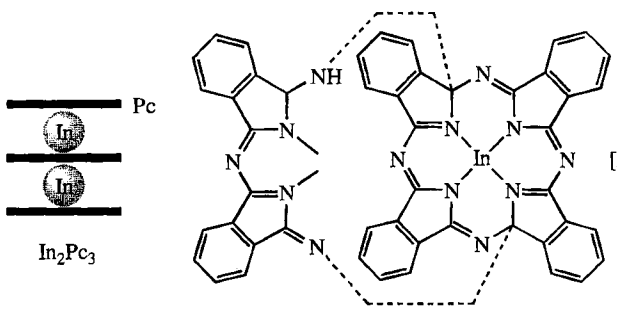


Figure 2-31. Molecular structure of [Gd(L637, A)].

Phthalocyanine complexes of the sandwich type, in which the metal ion is held between two phthalocyanine macrocycles, can be built up on lanthanide and actinide matrices [485–487]. For example, by interaction of MI_4 (M = Th, U) with phthalonitrile at 240°C and subsequent extraction of the crude product with benzene and sublimation in vacuum, the products MPc_2, where M = Th or U, were obtained [486].

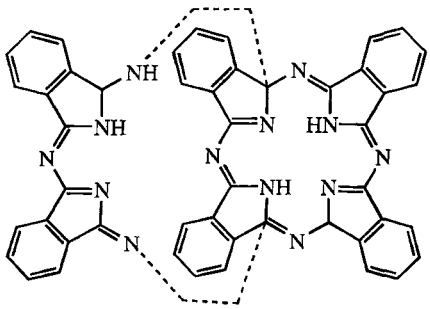
Two other interesting species In_2Pc_3 and [In(L637, A)] have been synthesised from condensation reaction of phthalonitrile under a low nitrogen pressure at about 210°C in the presence of indium in formally zero oxidation state (Eq. 2.246) [488, 489].



(2.246)

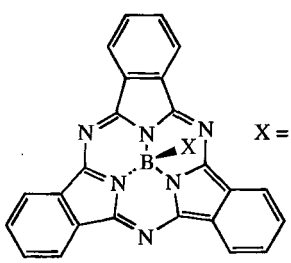
The structures of In_2Pc_3 and [In(L637, A)] have been proved by X-ray crystallographic data. An analogous gadolinium(III) bicyclic phthalocyaninate has also been reported [490]. The structure of [Gd(L637, A)] is shown in Figure 2-31. The ligand acts as a trianion and has a three-dimensional bicyclic structure. The nonplanarity of the Pc moiety is explained by the interruption of the conjugation of the π-electron system at the two sp^3-hybridised bridging atoms C9 and C25. The hexadentate ligand is coordinated to the gadolinium by six nitrogen atoms, forming a distorted trigonal prism. It is believed that thallium and cerium control the formation of the same ligand product [490].

An isomeric bicyclic phthalocyanine (L637, B) is assembled in the presence of niobium(0), as confirmed by an X-ray diffraction study of [Nb(L637, B)Cl] [491]. The main difference between the ligands is in the bridging C atoms. In the H_3(L637, A) the bridging C atoms belong to the two opposite isoindole rings of the Pc, whereas in H_3(L637, B) they belong to two neighbouring isoindole rings (Eq. 2.247).



H_3(L637, B) (2.247)

The subphthalocyanines (SubPcs; the trimeric homologues of tetrameric Pcs) have been prepared in the presence of boron(III) as template. No other metal ions controlling the formation of SubPc have been found so far. Originally, the unsubstituted SubPcs would have been synthesised by the reaction of phthalonitrile with BF_3 or BCl_3 at 240°C in 1-chloronaphthalene as solvent in 20–40% yield (Eq. 2.248) [492]. The products are normally contaminated by halogen-substituted subphthalocyanines and their separation is tedious. The structure of the chloro derivative is available [493].



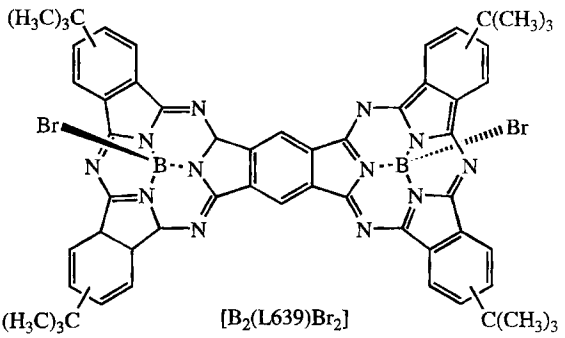
X = F, Cl, C_6H_5 (2.248)

[B(L638)X] or [B(SubPc)X]

The self-condensation of phthalonitrile in the presence of BPh_3 as a matrix source and 1,8-diazabicyclo[5, 4, 0]undec-7-ene (DBU) as a base in naphthalene at 218°C for 15 min affords highly pure [(SubPc)BPh] in 10% yield [494]. The tetrahedral coordination of the boron atom and the bowl-shaped conformation of the coordinated macrocycle has been revealed by X-ray diffraction.

The synthesis and spectroscopic properties of non-substituted and substituted subphthalocyanines and related subnaphthalocyanines have been reviewed [495].

Only one example of a dimeric SubPc, $[B_2(L639)Br_2]$, has been documented (Eq. 2.249) [496].

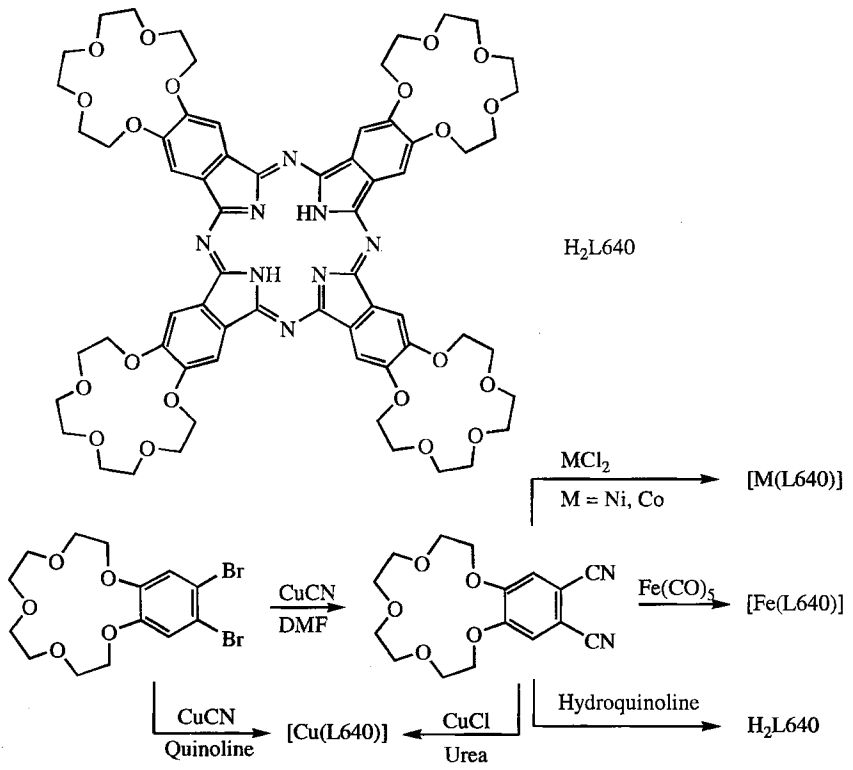


$[B_2(L639)Br_2]$ (2.249)

Metal-free SubPcs are unstable species, which convert into the common tetramers through a ring-enlargement reaction. This peculiarity of SubPc chemistry has been explored to prepare unsymmetrically substituted tetrameric phthalocyanines [497, 498]. Thus a mixture of monoamino-substituted H_2L629, where X = NH_2, (60%) and unsubstituted Pc was obtained by heating [B(SubPc)Cl] with 5-amino-1,3-diiminoisoindoline in 1:4 ratio in *N,N*-dimethylaminoethanol [498]. In the presence of metal ions (Ni^{2+}, Zn^{2+}, Fe^{2+}) the yield of unsymmetric tetramer (Pc) and statistically distributed substituted phthalocyanines increases to some extent [495, 498].

The higher, pentameric analogue of Pc (superphthalocyanine; SupPc) (L29), can be prepared in the presence of UO_2^{2+} as template [499]. On transmetallation the pentameric species undergoes rearrangement to the typical tetrameric Pc.

Attempts to use Pb(II) as template in methanol resulted in isolation of metal-free phthalocyanine [482]. This can also be obtained by heating phthalonitrile at high temperature [500] or by demetallation of labile metal phthalocyanines in the presence of the concentrated sulphuric acid [454, 457]. Metal-free Pc is formed in high yield on boiling a phthalonitrile solution in 2-dimethylaminoethanol or 1-dimethylaminopropan-2-ol under an atmosphere of ammonia [501]. The solubilities of phthalocyanines, as well as other physical and chemical properties, can be influenced by introducing appropriate substituents into the aromatic rings, such as *t*-C_4H_9, NR_2, OR, COOH, CF_3, SO_3H, *n*-C_4H_9, or *n*-$C_{12}H_{25}$ [474, 502–504]. High solubilities of sodium and potassium phthalocyaninates in organic solvents can be achieved, for instance, by complexation of their cations with crown ethers [505]. In the light of this, results [506, 507] on template building of metal-phthalocyanines containing four 15-crown-5 fragments in the molecule are of special interest. Com-

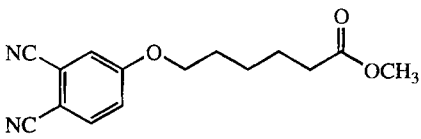


Scheme 2-37. Synthetic pathways to H_2L640.

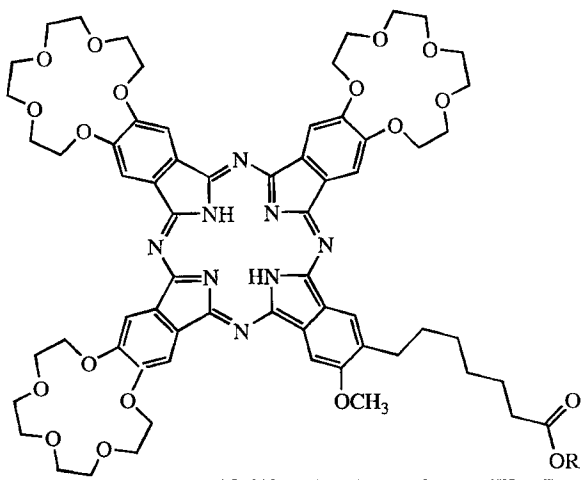
plexes [M(L640)], where M = Cu, Co, Ni or Fe, were obtained either by template reaction of dibromobenzo-15-crown-5 with CuCN in quinoline or from the dicyanoderivative and appropriate metal salts or carbonyl compounds in a high-boiling solvent (Scheme 2-37). By heating a mixture of dicyanobenzo-15-crown-5 with hydroquinone in a sealed tube, the metal-free product H_2L640 was obtained [507].

The structure expected for [M(L640)] is confirmed by FAB mass spectra, in which the peaks corresponding to $[M(L640)]^+$ (M = Ni, Co, Cu, Fe) were observed. On dissolving [M(L640)] in chloroform/ethanol mixture and adding NaSCN, KSCN or NH_4NCS in excess, complexes of the composition [M(L640)]·4NaSCN, [M(L640)]·2KSCN and [M(L640)]·2NH_4SCN, where M = Cu, Co, Ni or Fe, are formed.

Unsymmetrically substituted crown ether phthalocyanines H_2L642 have been assembled from *o*-dicyanobenzo-15-crown-5 and L641 in the presence of Zn^{II} and a strong organic base, or from the corresponding diiminoisoindoline derivatives on Pt^{II} as template in hexan-1-ol or pentan-1-ol and isolated as [M(L642)] (Eqs 2.250 and 2.251) [508]. Hexyl or pentyl ester derivatives are formed by the transesterification reaction that accompanies the process of template synthesis. The products have been purified by preparative TLC and identified by FAB mass spectrometry. Hydrolysis of metal(II) monoester phthalocyaninate leads to the acid derivative, which can be converted into its methyl ester by reaction with methanol.

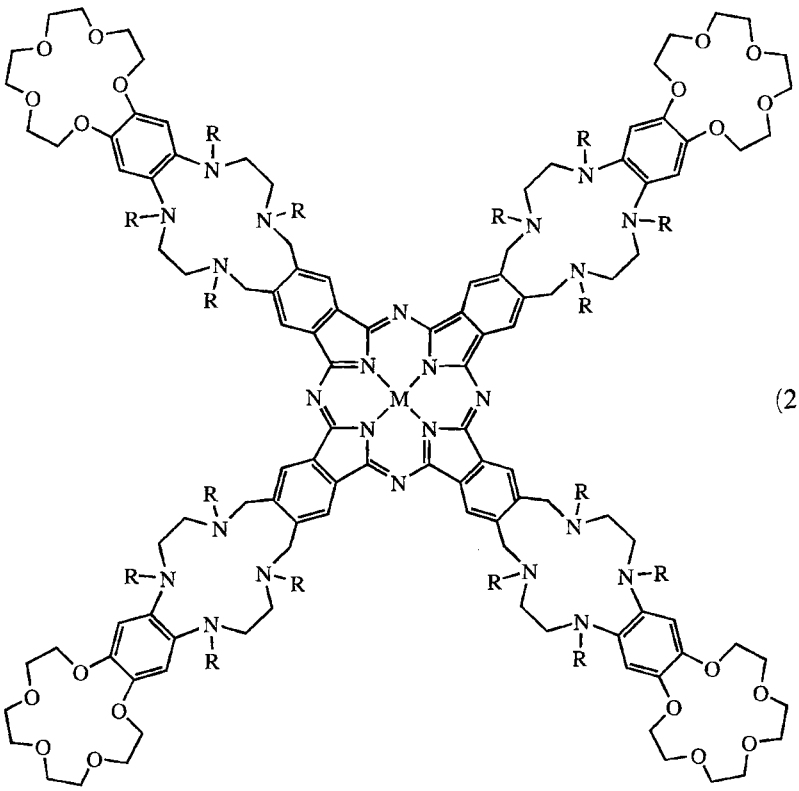


L641 (2.250)



H_2L642 (R = C_6H_{13}, C_5H_{11}, CH_3, H) (2.251)

The synthesis of metallophthalocyanines [M(L643)], where M = Cu or Ni, with even more developed peripheries consisting of four 14-membered tetraaza macrocycles, each fused with a 15-membered crown ether, has been reported (Eq. 2.252) [509]. The copper(II) complex containing four N_4 binding sites is capable of binding in addition four 3d metal ions, as has been shown by reaction with $NiCl_2$ in absolute methanol to give the product $[CuNi_4(L643)]Cl_8$. The latter is soluble in water, due to its highly ionic character. At the same time it should be noted that there is no unambiguous spectroscopic or structural evidence for the formation of such complex architecture as that of H_2L643 and the corresponding metal complexes.



(2.252)

[M(L643)] (M = Cu, Ni; R = Ts, H)

2.10 References

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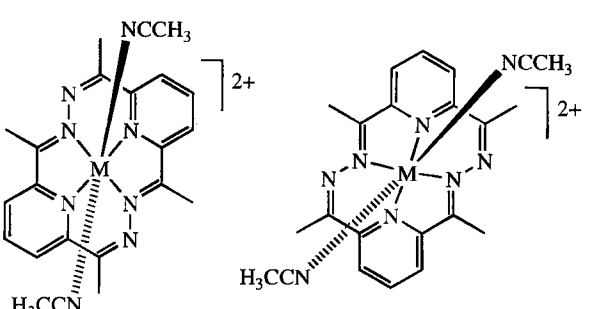
Chapter 3

Template synthesis of macrocyclic systems based on di- and polyamines and polyfunctional dicarbonyl compounds

Polyamines and 2,6-dicarbonylpyridines, as well as related ligsons, are suitable building blocks for various macrocyclic systems. Hydrazine, 1,2-diaminoethane (en) and its homologues, other polyfunctional linear organic compounds containing terminal $-NH_2$ groups, *o*-phenylenediamine (*o*-phda; 1,2-diaminobenzene) and its derivatives are the simplest nitrogen-containing components that may be condensed with heterocyclic dicarbonyl compounds. Depending on the nature of the amine-containing ligson, ions of 3d, alkaline earth and rare earth elements, as well as of some other metals, can be used as patterns. Condensations of (1 + 1), (1 + 2), (2 + 1), (2 + 2), (2 + 3), (3 + 3) and (4 + 4) stoichiometries take place.

3.1 Macrocycles based on 2,6-dicarbonylpyridines, 2,5-diformylpyrrole and the simplest diamines

Template interaction of 2,6-diacetylpyridine (dap) with hydrazine in the presence of iron(II) or cobalt(II) in acetonitrile results in formation of a completely conjugated system, which can be represented by structural formulae I or II (Eq. 3.1) [1].



(I) $[M(L644)(CH_3CN)_2]^{2+}$ (II)

M = Fe, Co

(3.1)

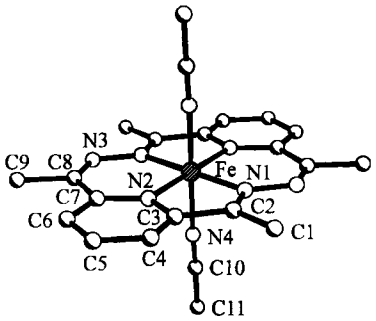


Figure 3-1. The structure of $[Fe(L644)(CH_3CN)_2]^{2+}$.

Results from ^1H NMR and IR spectral analysis do not enable a choice to be made between these formulae. It is clear that variant (I), with the alternation of metallocycles 5,6,5,6, should be more favourable due to its lesser strain with respect to variant (II) (5,5,6,6 metallocycle sequence). For the iron(II) chelate with the ligand product of (1 + 2) stoichiometry, however, the 5,5-combination of the chelate cycles is realised [2], and so formula (II) cannot always be rejected.

An X-ray diffraction study of $[Fe(L644)(CH_3CN)_2](ClO_4)_2$ showed that the structure of the compounds under consideration can be expressed by formula I (Figure 3-1). The structure consists of a six-coordinate iron(II) ion surrounded by four nitrogen atoms of the planar macrocyclic ligand and two molecules of acetonitrile occupying the axial sites in the complex.

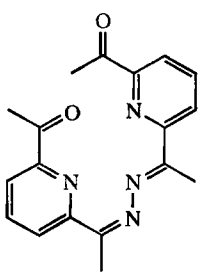
The perchlorate ions are not coordinated and are located in the crystal in voids between complex cations $[Fe(L644)(CH_3CN)_2]^{2+}$ [1]. The 14-membered fully conjugated macrocycle creates a strong ligand field, and the central metal atom in $[Fe(L644)(CH_3CN)_2](ClO_4)_2$ is in the low-spin state. The cobalt(II) complex has an effective magnetic moment of 1.83 BM at room temperature.

The iron(II) compound in solution is easily destroyed by the action of a series of nucleophilic agents (pyridine, hydrazine, imidazole, halide ions, etc.). It is thought [1] that this is connected with the behaviour of C=N bonds, as well as with the presence of the non-coordinated azomethine bonds (the coordination of azomethine nitrogen to metal ion in the majority of complexes stabilises the azomethine bond), raising the sensitivity of coordinated L644 to nucleophiles. The latter reason was suggested as to why the analogous nickel(II) complex could not be isolated. The proposed explanation of nickel(II) non-effectiveness as template for L644 synthesis is confirmed by the fact that in a series of compounds of this metal the C=N groups are preferentially exposed to nucleophilic attack [3]. Later, however, it was shown [4, 5] that synthesis of L644 can be performed on a nickel(II) matrix – reaction of dap with hydrazine in the presence of nickel(II) and cobalt(II) perchlorates in ethanol allows the isolation of products $[M(L644)(H_2O)](ClO_4)_2 \cdot 4H_2O$ in 83% and 89% yield, respectively (the other authors [1] used acetonitrile as solvent). Formation of L644 was confirmed by mass spectra, in which the peak with the maximum m/z of 318, corresponding to the molecular mass of the metal-free macrocycle, was present.

Zinc(II) and magnesium(II) ions [6] have also proved to be effective patterns for 2 + 2 macrocycle construction from dap and hydrazine. In this case $[M(L644)(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (M = Zn, Mg) and $[Mg(L644)(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ in 63, 72 and 61% yield, respectively, were isolated. (An attempt to synthesise L644 by direct interaction of ligsons without dilution in the presence of acid results in formation of polymeric products. The reaction performed under high dilution conditions in benzene in the absence of acid leads to bis(diacetylpyridine)azine [6].) The analogous alkaline earth metal compounds, including that of magnesium(II), were obtained [7] by using 2,6-diformylpyridine (dfp) and hydrazine.

On reaction of dap with hydrazine in the presence of $Sc(ClO_4)_3 \cdot 6H_2O$, $[Sc(L644)(H_2O)_2](ClO_4)_3 \cdot 4H_2O$ is formed [8], for which an octahedral structure with axial disposition of the two molecules of water was proposed. The same ligand product isolated as $[Y(L644)(NO_3)_3] \cdot 2H_2O$ results from condensation of dap with hydrazine in the presence of $Y(NO_3)_3 \cdot 6H_2O$ in the ratio of reactants 1:1:2 [9]. The yttrium ion in this complex is presumably 10-coordinate. Non-stoichiometric amounts of dap and hydrazine are required to prevent the formation of the 1 + 2 ligand product 2,6-diacetylpyridine dihydrazone. Macrocycle formation is confirmed by the presence of a peak for an ion with $m/z = 318$, corresponding to the molecular weight of L644, in the mass spectrum of $[Y(L644)(NO_3)_3] \cdot 2H_2O$. The decisive role in the stabilisation of a macrocyclic product seems to be played by the interaction between the metal ion and the nitrate anions. Note that using yttrium(III) chloride or perchlorate as the template source yields salts of the complex with the open-chain ligand L645, i.e. $[Y(L645)(H_2O)_2]Cl_3 \cdot 2H_2O$ and $[Y(L645)(H_2O)_2](ClO_4)_3 \cdot 2H_2O$ (Eq. 3.2) [9].

The template condensation of dap with hydrazine in the presence of lanthanide perchlorates in ethanol gives the complexes: $[Ln(L644)(H_2O)_2](ClO_4)_3 \cdot 4H_2O$ (Ln = Tb, Dy, Ho, Er, Tm, Yb, Lu), $[Ln(L645)_2](ClO_4)_3 \cdot 2H_2O$ (Ln = La, Pr, Nd, Sm) and $[Ln(L645)(H_2O)](ClO_4)_3 \cdot 2H_2O$ (Ln = Eu, Gd) [10].



L645 (3.2)

Thus for the elements Tb–Lu the reaction results in the synthesis of the macrocyclic complex, whereas for La, Pr, Nd, Sm, Eu and Gd the reaction stops at the azine formation step. Addition of water to solutions of the above-mentioned macrocyclic compounds of Tb–Lu in acetonitrile results in hydrolysis of ligand L644 with the release of one hydrazine block. Thus products containing L645, of composition $[Ln(L645)(H_2O)](ClO_4)_3 \cdot 2H_2O$, are isolated. The Ln^{III} chelates of the acyclic azine do not undergo hydrolysis. In all cases [10] small quantities of Ln^{III}

chelates with dap of the composition $[Ln(dap)_4](ClO_4)_3 \cdot 2H_2O$ (Ln = La, Pr, Nd, Sm), $[Ln(dap)_3(H_2O)](ClO_4)_3 \cdot 2H_2O$ (Ln = Eu, Gd) and $[Ln(dap)_3](ClO_4)_3 \cdot 3H_2O$ (Ln = Tb, Ho, Dy, Er, Tm, Yb, Lu) are isolated together with the main products. It should be noted that when treating the last with hydrazine in acetonitrile, La, Pr, Nd, Sm, Eu, Gd complexes with L645 and Tb, Dy, Ho, Er, Tm, Yb, Lu complexes with L644, were obtained. Hence, chelates of lanthanides with dap can be considered as intermediates in the process of obtaining complexes of L645 and L644. The presence of the pyridine ring between the carbonyl groups probably permits metal ion chelation by means of nitrogen and oxygen atoms of two dap molecules. Such coordination makes the carbonyl groups more vulnerable to nucleophilic attack by hydrazine aminogroups. Synthesis of the metal-free macrocycle L644 is carried out by treating the azine L645 with an excess of hydrazine [6]. Likewise, during $[Ln(L644)(H_2O)_2]^{3+}$ template preparation, interaction of the corresponding $[Ln(L645)(H_2O)_2]^{3+}$ with hydrazine presumably takes place as the last step. This suggests that template formation of rare earth metal compounds with L645 and L644 proceeds stepwise in the sequence

$$M^{III}(dap) \rightarrow M^{III}(L645) \rightarrow M^{III}(L644)$$

and hence is kinetically controlled.

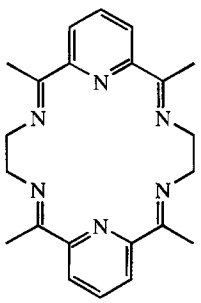
Thus, in the series of rare earth coordination compounds the obvious dependence of their composition on the central ion radius is clearly observed. (The change in coordination number along the series of Ln^{III} complexes with dap is also a result of the lanthanide contraction.) This explains why not all lanthanides are useful as a pattern for obtaining complexes with the macrocycle L644. Indeed, consideration of a molecular model of the 14-membered macrocycle [10] confirms the noneffectiveness of trivalent La, Pr, Nd, Sm, Eu and Gd in the synthesis of L644, because of mismatch between their ion sizes and the macrocycle cavity. In the light of this it becomes clear that the acyclic azine L645 is able to coordinate to ions from Tb^{III} to Lu^{III}, and to the slightly larger Eu^{III} and Gd^{III}, because of its greater conformational flexibility in comparison with L644, forming products of similar structure. Moreover, the acyclic ligand is able to give chelates of the type $[Ln(L645)_2]^{3+}$ with ions of much greater radii. Thus La^{III}, Pr^{III}, Nd^{III} and Sm^{III} are also useful as patterns for synthesis of L645.

For $[Ln(L644)(H_2O)_2]^{3+}$ an octahedral structure was proposed. In this case, four nitrogen atoms of the 14-membered hexaazamacrocycle are disposed in the equatorial plane of the metal ion, and two molecules of water are situated axially.

^1H NMR and IR data for the complexes of La^{III}, Pr^{III}, Nd^{III} and Sm^{III} with L645, in which the ratio M:L645 is 1:2, confirm the presence of uncoordinated C=O. Taking into account the structure of these complexes and the potential denticity of L645, a coordination number of eight for the central atom was proposed [10]. In the compounds of trivalent Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu, where the ratio M:L645 is 1:1, the coordination number of the Ln ions is six, two molecules of water also being coordinated.

1,2-Diaminoethane, its closely related derivatives, and *o*-phenylenediamine, are

the next representatives of ligsons containing two $-NH_2$ groups that are useful for formation of macrocyclic species by condensation with dap. Macrocycle synthesis from dap and 1,2-diaminoethane (L646) is achieved on calcium(II), strontium(II), barium(II) and lead(II) matrices. Ligand L646 is isolated as the complexes with the respective metals (Eq. 3-3) [11–13].



L646 (3.3)

X-Ray diffraction studies of $[Sr(L646)Cl_2]\cdot 2H_2O$ and [Pb(L646)(NCS)(SCN)] showed [12] that the donor atoms of the 18-membered macrocyclic ligand are arranged in the equatorial plane of a hexagonal bipyramid with the anions in the axial positions. In the absence of the above-mentioned metal ions, isolation of L646 fails. Metals such as magnesium(II), manganese(II), iron(II), nickel(II), copper(II), silver(I), cadmium(II) and mercury(II) are ineffective. The fact that Mg^{II} and transition metal ions do not function as patterns in this case seems to be conditioned by mismatch between their ionic radii and the size of the 18-membered macrocycle cavity [12]. As shown in Table 3-1, the yield of the target product obtained on Pb^{II}, Ca^{II}, Sr^{II} and Ba^{II} matrices increases with increase of cation ionic radius. However, this does not explain the unsuitability of cadmium(II), mercury(II) and silver(I)

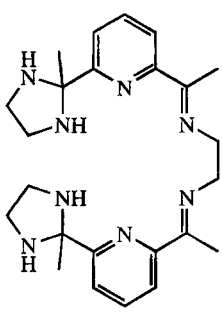
Table 3-1. Ionic radii of metals in an octahedral environment [14].

Ion	Radius (nm)	Yield of the final product (%)
Mg^{II}	7.2	–
Ca^{II}	10.0	55
Sr^{II}	11.8	70
Ba^{II}	13.5	78
Pb^{II}	9.8	42
Mn^{II}	6.7	–
Fe^{II}	6.1	–
Ni^{II}	6.9	–
Cu^{II}	7.3	–
Cd^{II}	9.5	–
Hg^{II}	10.2	–
Ag^{I}	11.5	–

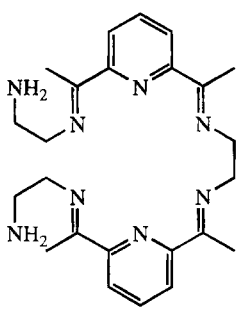
ions, whose radii are close to those of the above-mentioned ions. The reason for the different behaviour of the two groups of ions may be a consequence of differences in the nature of the metal–ligand bonding [12].

Use of $Tl(R)_2ClO_4$ (R = CH_3, C_2H_5, C_6H_5) made it possible to carry out template synthesis of the complex $[Tl(R)_2(L646)]ClO_4$ in acetonitrile [15].

Condensation of dap with en on Ca^{II}, Sr^{II}, Ba^{II} and Pb^{II} matrices occurred as described above when the reagent ratio was 1:1:1. If a five-fold excess of en is used, then in the presence of $Ba(ClO_4)_2$ $[Ba(L647)(ClO_4)_2]\cdot H_2O$ is formed in high yield (90%) [13]. Strontium(II) and calcium(II) give viscous oils of unidentifiable composition under analogous conditions. According to elemental analysis data, ligand L647 is a product of condensation of two molecules of dap with three molecules of en, for which two general formulae L647 and L′647 can be suggested (Eq. 3-4). Both the IR spectra and analysis of molecular models gave preference to formula L647 [13]. If $[Ba(L647)(ClO_4)_2]\cdot H_2O$ is refluxed in dry methanol or ethanol for a short time, then $[Ba(L646)(ClO_4)_2]$ is formed in good yield. This suggests that, in solution, $[Ba(L647)(ClO_4)_2]$ is in equilibrium with $[Ba(L'647)(ClO_4)_2]$, in which L647 assumes the unfolded tetraimine form L′647 (Scheme 3-1). Macrocyclisation proceeds by $[Ba(L'647)(ClO_4)_2]$ $-NH_2$ group intramolecular attack at the neighbouring C=N group, with formation of the intermediate product $Ba(L''647)^{2+}$ and subsequent expulsion of an en molecule. Thus the ring closure process includes a transamination step.

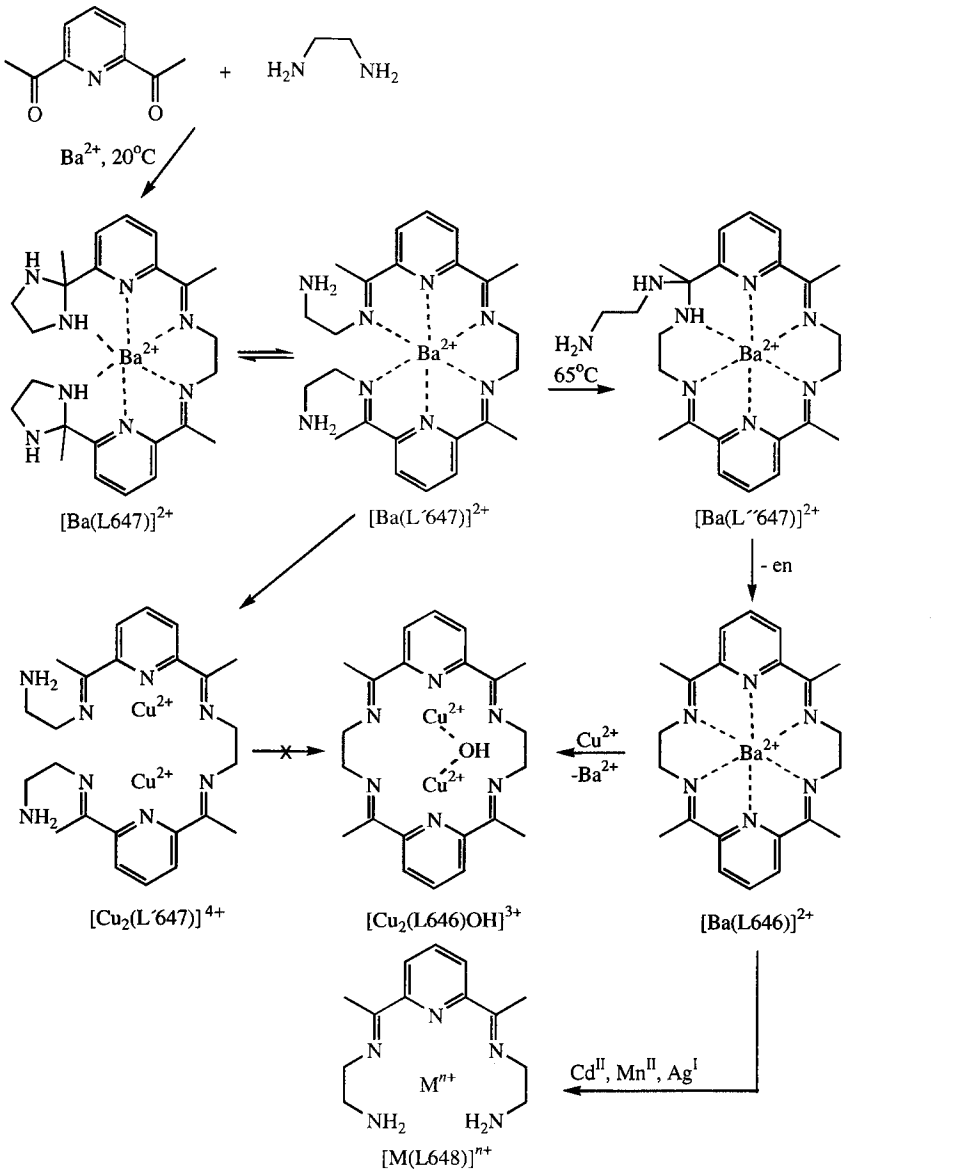


L647



L′647 (3.4)

The complex $[Cu_2(L646)OH](ClO_4)_3\cdot H_2O$ can be synthesised by treatment of $[Ba(L646)(ClO_4)_2]$ with an excess of $Cu(ClO_4)_2\cdot 6H_2O$ in methanol. Upon transmetallation of $[Ba(L647)(ClO_4)_2]$ with copper(II) perchlorate, the binuclear chelate $Cu_2(L'647)(ClO_4)_4\cdot 2H_2O$ was obtained, in which the L′647 form of ligand L647 is stabilised. Unlike the case of the mononuclear barium chelate with the open-chain ligand, it is impossible to convert $Cu_2(L'647)(ClO_4)_4\cdot 2H_2O$ into the appropriate macrocyclic product $[Cu_2(L646)OH](ClO_4)_3\cdot H_2O$. As in Scheme 3-1, transmetallation reactions of $[Ba(L646)(ClO_4)_2]$ with Mn^{II}, Cd^{II} or Ag^{I} salts result in the macrocycle opening as the result of hydrolysis and expulsion of one 2,6-diacetylpyridine ligson, with the formation of complexes containing the acyclic ligand L648. It should be noted that chelate $[Cd(L648)]^{2+}$ has also been obtained by non-template synthesis [13].



Scheme 3-1. Template synthesis of $[Ba(L646)]^{2+}$ and its transmetallation.

The results described above [11–13] reflect the explicit dependence of the template processes on metal nature as well as on stereochemical preferences. It is not difficult to observe that ions of alkaline earth metals, as well as of lead(II), that are able to manifest high coordination numbers form complexes with the macrocyclic and open-chain multidentate ligands. Other ions, characterised by lower coordina-

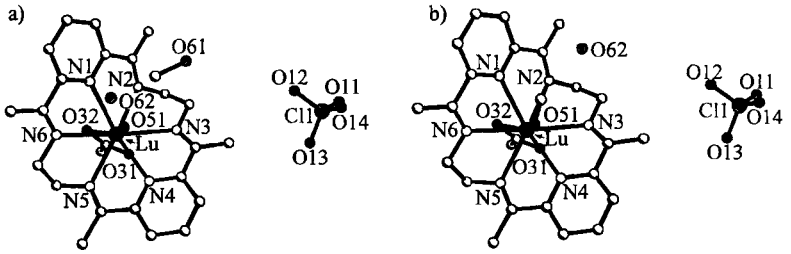


Figure 3-2. The structure of $Lu(L646)(CH_3COO)(OH)(ClO_4)(CH_3OH)\cdot 0.5H_2O$.

tion numbers, are not useful as patterns in these processes. Cadmium(II) is the only exception: template synthesis of the complex with the pentadentate ligand L648 can be performed.

Lanthanide(III) cation radii are close to those for Ca^{II}, Sr^{II} and Ba^{II} [14]. Therefore, lanthanides also display template activity in building up L646 and L646-like macrocyclic systems. Products $[Ln(L646)(NO_3)_3]$ (Ln = La, Ce) and $[Ln(L646)(H_2O)_2](ClO_4)_3$ are synthesised in ethanol by reaction of dap with en on La^{III} and Ce^{III} nitrates or perchlorates in the molar ratio 2:2:1 [16, 17]. The structure of $[Ln(L646)(NO_3)_3]$ was established by X-ray diffraction [16]. The coordination number of the central atom is 12, with donor atoms from hexadentate L646 and bidentate coordinated nitrate groups. The set of lanthanides suitable for obtaining L646 was subsequently extended [18, 19]. It was also stated that the nature of the anion of the Ln^{III} salts used influences the template condensation [18]. This process is favoured by the CH_3COO^- anion to a greater extent than by Cl^- or ClO_4^-. By interaction of dap with en in the presence of lanthanide(III) perchlorates and acetates, products of composition $Ln(L646)(ClO_4)_2(OH)\cdot nH_2O$ ($n = 0, 2$) and $Ln(L646)(CH_3COO)_2Cl\cdot nH_2O$ (n = 3–6), respectively, were obtained for all Ln^{III}, except promethium. The product $Lu(L646)(CH_3COO)(OH)(ClO_4)(CH_3OH)\cdot \frac{1}{2}H_2O$ was also synthesised, for which X-ray analysis was performed (Figure 3-2) [19].

A noteworthy feature of this structure is that the crystals consist of the two species a) and b) of Figure 3-2, present in 1:1 ratio. The species a) has the structural formula $[Lu(L646)(CH_3COO)(H_2O)](ClO_4)(OH)(CH_3OH)$. The macrocycle surrounds the central ion with all nitrogen atoms bound to it, the acetate ion is bidentate and is chelated to the metal ion on one side of the macrocycle, and a water molecule on the opposite side completes the coordination sphere. A hydroxide ion and a distorted perchlorate ion balance the two positive charges of the complex cation, with a methanol molecule clathrated into the structure. The species b) has the structural formula $[Lu(L646)(CH_3COO)(CH_3OH)](ClO_4)(OH)$, and therefore differs from the first species only by having a methanol molecule coordinated to the metal instead of a water molecule. A hydroxide ion, occupying a position different from that of the first species, and a distorted perchlorate ion balance the cationic charges. In both species the coordination number of lutetium(III) is nine [19].

Macrocyclic complexes $Ln(L646)(CH_3COO)_2Cl\cdot nH_2O$ contain practically no hydroxy byproducts and are formed in higher yield than $Ln(L646)(ClO_4)_2OH\cdot$

nH_2O. Attempts to remove the metal from the macrocyclic system by treating solutions of either complex with the most characteristic Ln^{III} precipitating agents (F^-, OH^-, $C_2O_4^{2-}$) were unsuccessful.

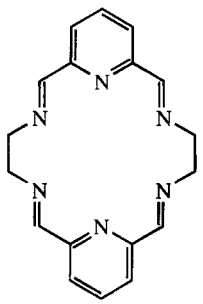
An X-ray diffraction study of $[Ce(L646)(NO_3)_2(H_2O)]NO_3 \cdot H_2O$ and of $[Nd(L646)(NO_3)(H_2O)_2]_2(NO_3)(ClO_4)_3 \cdot 4H_2O$ has been reported [20]. In the former compound the coordination number of the central atom is 11 (six nitrogen atoms of the macrocyclic ligand, oxygen atoms of the two bidentate nitro groups, disposed at opposite sides of the ligand, and an oxygen atom of the water molecule). In the latter compound the metal atom is surrounded by 10 donor atoms (six atoms from the organic ligand, two oxygen atoms from nitrates at one side, and oxygen atoms of the two water molecules at the other side). The macrocyclic ligand is folded along 1,2-diaminoethane segments at an angle of 59.0° in the case of the cerium complex, and of 63.9° for the neodymium compound. (In $[La(L646)(NO_3)_3]$ this angle is 36.7°.)

The isostructural complexes $[Ln(L646)(CH_3COO)_2]Cl \cdot 4H_2O$ (Ln = Nd, Eu) [21] are characterised by the same coordination number, 10. In these complexes the metal ion is linked to the six nitrogen donor atoms of the L646 and to two bidentate chelating acetates, situated on opposite sides of the macrocycle, which adopts the folded-butterfly configuration, common for other lanthanide complexes of L646 [16–18, 20].

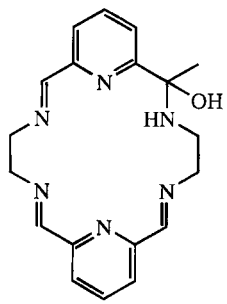
Having ionic radii smaller than barium, lanthanides are not quite as suitable for building up 18-membered, hexadentate, relatively highly conjugated macrocyclic ligands. They do not display stringent geometric demands, but allow the developing ligand to adapt itself to the central atom and to keep its denticity. Hence it is still possible to synthesise L646 on lanthanide ions. (The ability to assemble L646 decreases with diminishing matrix size.) The coordination number decreases in the same order for the respective complexes: 12 for lanthanum, 11 for cerium, 10 for neodymium, 9 for lutetium.

The complexes $Y(L646)(CH_3COO)_2(ClO_4) \cdot \frac{1}{2}H_2O$ and $Y(L649)(CH_3COO)_2Cl \cdot 4H_2O$ were obtained from the metal-templated condensation of dap or 2,6-diformylpyridine (2,6-dfp) with en, employing the corresponding salts of yttrium(III) [22]. Single-crystal X-ray analysis of $Y(L646)(CH_3COO)_2(ClO_4) \cdot \frac{1}{2}H_2O$ revealed that the structure is characterised by the presence of two slightly different coordination entities, $[Y(L646)(CH_3COO)_2]ClO_4$ and $[Y(L646)(H_2O)(CH_3COO)](CH_3COO)ClO_4$, statistically distributed in the crystal lattice in a 1:1 ratio. Both entities contain a nine-coordinate yttrium(III) linked to the six nitrogen-donor atoms of L646. In addition, the central atom is bonded to the two oxygen atoms of a bidentate acetate on the convex side of the macrocycle, and to either a monodentate acetate or a water molecule on the opposite side. Thus Y^{III} and Lu^{III}, with practically the same radii, are characterised by the same coordination numbers in their complexes with L646.

Starting from the nitrates, it proved possible to synthesise 18-membered (2 + 2) macrocyclic compounds from 2,6-dfp and en for all the members of the lanthanide series (except Pm) [23–25]. For trivalent lanthanum, cerium, praseodymium and europium, products containing the tetraimine macrocyclic ligand L649 are formed, for example $Ln(L649)(NO_3)_3$, whereas for the heavier and smaller ions ($Nd^{3+} \rightarrow Lu^{3+}$, besides Eu^{3+}) formation of L650 is preferred (Eq. 3.5).



L649



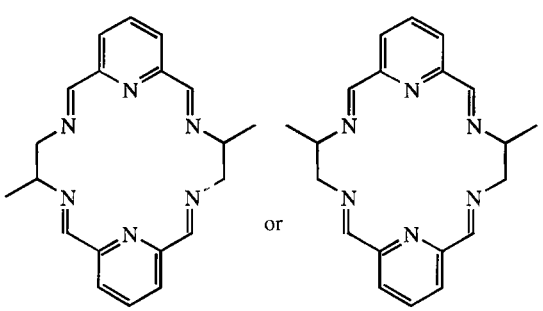
L650

(3.5)

To coordinate the latter cations, the macrocycle must probably have sufficient conformational flexibility, which seems to be achieved in the case of addition of one water molecule across one of the L649 azomethine bonds with the formation of the carbinolamine L650. As a result of preferable coordination of L650 rather than of L649 to small ions, this intermediate form is stabilised as Ln^{III} complexes with L650. This interpretation is confirmed by the fact that during recrystallisation of $Sm(L650)(NO_3)_3$ from water the band at 3210 cm^{-1}, assigned to the secondary amine group, disappears, and a new band at 3560 cm^{-1}, assigned to the Sm–OH group, appears. (Recrystallisation of the complex is carried out at a higher temperature than its synthesis in ethanol.) In addition, $[Sm(L649)(NO_3)(OH)(H_2O)]^+$ is formed, whose structure was established by X-ray diffraction [26]. Thus, during recrystallisation, carbinolamine L650 splits off one molecule of water and converts into L649.

The uranyl ion UO_2^{2+} turns out to be effective in the template synthesis of L646 and L649. Macrocyclic ligands are formed in high yield as products with general formulae $[UO_2(L646)]X_2$ and $[UO_2(L649)]X_2$, where X = NO_3, ClO_4 or I. The template action of the uranyl ion seems to be explained by the suitable size of its ionic radius (10.0 nm), and by its preference to form equatorial-planar coordination bonds with the nitrogen donor atoms [27].

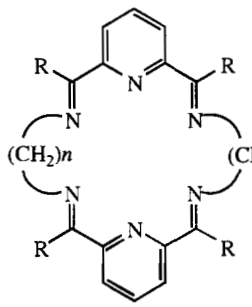
Macrocyclic complexes with ligands derived from 2,6-dfp and 1,2-diaminopropane (L651) have been isolated for all Ln^{III}, except Pm. In these reactions, however, products with the carbinolamine derivatives of ligand L651 were not detected (Eq. 3.6) [23].



L651

(3.6)

Template synthesis of strontium(II) and barium(II) complexes with the 20-membered hexaazamacrocyclic ligand L652, obtained by (2 + 2) condensation of dap with 1,3-diaminopropane, has been reported (Eq. 3.7) [28]. By transmetallation of $[Ba(L652)(ClO_4)_2]$ with copper(II) perchlorate, the binuclear complex $[Cu_2(L652)OH(H_2O)](ClO_4)_3 \cdot H_2O$ was isolated, whose structure was established by X-ray diffraction.

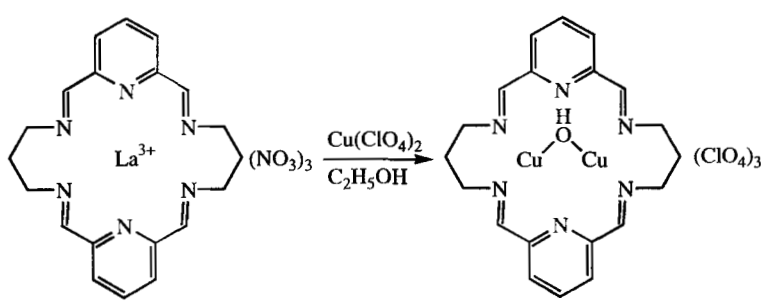


$R = CH_3$:
$n = 3$ L652
$n = 5$ L653
$n = 6$ L654
$R = H$:
$n = 3$ L655
$n = 4$ L656

(3.7)

Lead(II) permitted the synthesis of 24- and 26-membered macrocyclic ligands, isolated as binuclear complexes $[Pb_2(L653)(NCS)_3]NCS$ and $[Pb_2(L654)(NCS)_3]NCS$. The structure of the former was established by X-ray diffraction [29].

Macrocyclic complexes with ligands derived from 2,6-dfp and 1,3-diaminopropane (L655) have been isolated for all Ln^{III}, except Pm [23]. As in the case of L651, products with the carbinolamine derivatives of L655 were not detected. Complexes of La^{III} with L655 undergo transmetallation on heating in ethanol with $Cu(ClO_4)_2 \cdot 6H_2O$ in molar ratio 1:2, forming $Cu_2(L655)(ClO_4)_2(OH)_2 \cdot 3H_2O$. Under the same conditions, but with a reagent ratio of 1:6, it is possible to isolate the binuclear complex $Cu_2(L655)(ClO_4)_3(OH)$ (Eq. 3.8).



$La(L655)(NO_3)_3$ $\xrightarrow[C_2H_5OH]{Cu(ClO_4)_2}$ $Cu_2(L655)(ClO_4)_3OH$

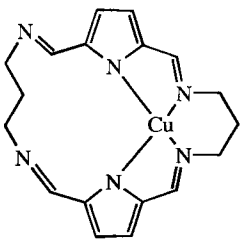
(3.8)

A similar binuclear product can be obtained by transmetallation of the La^{III} compound with L649, but the reaction time must be increased [23]. Thus coordination compounds of the rare earth elements with macrocyclic ligands based on pyridine-2,6-dicarbonyl compounds and lower diaminoalkanes, being

stable to dissociation, are at the same time kinetically labile in transmetallation processes.

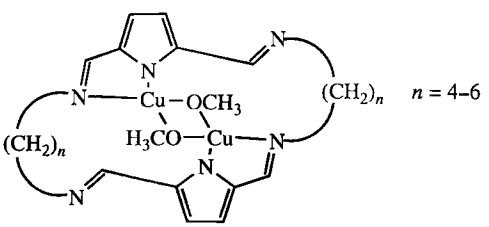
Ligand product L656 was assembled from 2,6-diformylpyridine (2,6-dfp) and butane-1,4-diamine on barium(II) as template [30]. Transmetallation with manganese(II) in the presence of an excess of thiocyanate yielded the tetrathiocyanato derivative $[Mn_2(L656)(NCS)_4]$, which can easily be converted into $[Mn_2(L656)(NCS)_3(OCH_3)]$ on crystallisation from methanol. X-Ray diffraction confirmed the latter complex to be macrocyclic and binuclear [30].

The replacement of 2,5-diformylpyrrole (2,5-dfp) for dap permits condensation with a series of diaminoalkanes on copper(II) as matrix [31]. In addition, the use of en, 1,2-diaminopropane or 1,3-diaminopropane leads to the formation of mononuclear products; an X-ray diffraction study of the complex derived from 1,3-diaminopropane was carried out, the example being [Cu(L657)] (Eq. 3.9).



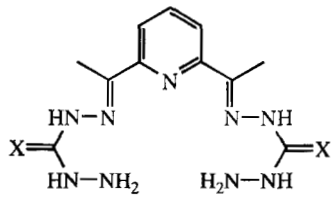
[Cu(L657)] (3.9)

The employment of higher homologues (1,4-diaminobutane, 1,5-diaminopentane and 1,6-diaminohexane) results in the isolation of binuclear complexes with the structure shown in Equation (3.10).

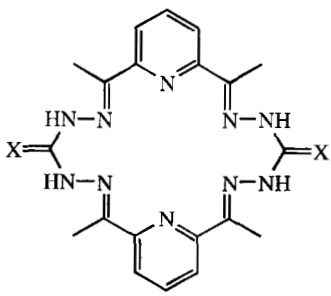


$[Cu_2(L658)(OCH_3)_2]$ (3.10)

Synthesis of mono- and bi-nuclear complexes $[La(L661)X_2]X$, $[La(L662)X_2]X$, $[La_2(L661)X_4]X_2$ and $[La_2(L662)X_4]X_2$, with X = Cl, Br or NO_3, by reaction of L659 and/or L660 with dap and a lanthanum(III) salt, was claimed (Eq. 3.11) [32]. The first product type was isolated when the reagents were used in 1:1:1 molar ratio. Binuclear species result on using an excess of metal salt. Convincing evidence, however, for the formation of macrocyclic ligand products has not been given. The final complexes have been characterised only by elemental analyses and IR spectra.



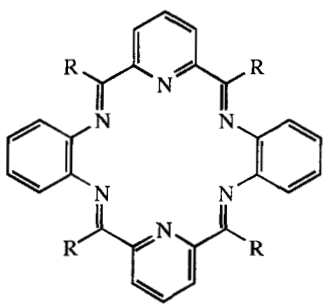
X = O L659
X = S L660



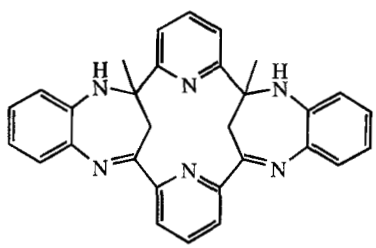
X = O L661
X = S L662

(3.11)

As in the case of en [12], *o*-phenylenediamine (*o*-phda) cannot undergo (2 + 2) condensation with dap or 2,6-dfp to form 18-membered macrocyclic compounds on 3d element matrices. Direct acid-catalysed interaction of *o*-phda with dap under dilution conditions was reported [33] to give the corresponding macrocyclic product L663. The formation of the same ligand product has been claimed when reaction between dap and *o*-phda was carried out in the presence of copper(II). However, it was later shown [34] that the isolated compound was L665 (Eq. 3.12); this was confirmed by an X-ray diffraction study.



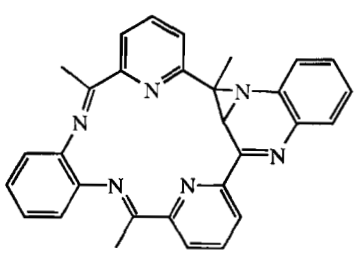
R = CH_3 L663; R = H L664



L665

(3.12)

On reaction with $Cu(ClO_4)_2 \cdot 6H_2O$ in the presence of dioxygen L665 rearranges into L666 (Eq. 3.13), which is able to accommodate the Cu^{II} ion within the 15-membered macrocycle. The structure of the complex formed, $[Cu(L666)(H_2O)](ClO_4)_2 \cdot H_2O$, is available [35].



L666

(3.13)

Theoretical calculations [36] showed that the sides of the hexagon formed by the hypothetical ligand L663 or of its analogue L664, which is formed by six nitrogen atoms, must be approximately equal to 28 nm. Hence, metal–ligand distances in their complexes with metals must be of the same order. It becomes clear that only those ions that have greater radii can occupy the macrocycle cavity without significant distortion of D_{6h} symmetry.

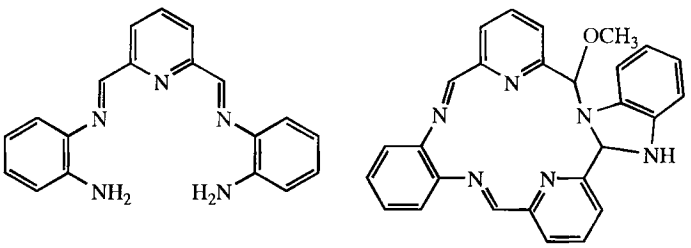
Interaction of 2,6-dfp with *o*-phda in methanol or acetonitrile solution in the presence of calcium(II), strontium(II), barium(II) or lead(II) perchlorates leads to the isolation of L664 as complexes $M(L664)(ClO_4)_2$ (M = Ca, Sr), $Pb(L664)(ClO_4)_2 \cdot 2H_2O$ and $Ba(L664)_2(ClO_4)_2$. In the absence of those ions or in the presence of magnesium(II), cadmium(II), mercury(II), or transition metal ions from manganese(II) to zinc(II), assembly of the macrocyclic system L664 fails [37]. In the electron impact mass spectra of the isolated complexes an intense peak with $m/z = 414$ was observed, which corresponds to $P^{+\cdot}$ of metal-free L664. The X-ray analysis of the lead(II) complex confirmed the formation of the latter and showed that the central atom forms six Pb–N bonds with the organic ligand, of length 26.5–28.5 nm. One molecule of water is coordinated to the central atom in the apical position. Pyridine nitrogen atoms deviate from the mean plane by –4.9 nm and –6.0 nm, and the lead by 3.0 nm. As a result, this complex has the configuration of a distorted hexagonal pyramid. In the calcium and strontium complexes, IR data suggest that the perchlorate ion is coordinated, allowing the assignment of hexagonal-bipyramidal structures to these substances [37]. For $Ba(L664)_2(ClO_4)_2 \cdot 2H_2O$ a sandwich structure has been proposed, in which the coordination number of the central atom is 12, involving all the donor atoms of the two molecules of organic ligand [37].

The template synthesis of $Sr(L664)X_2$ (X = CF_3SO_3, I) has been reported [38]. The X-ray crystal structure of $Sr(L664)(CF_3SO_3)_2 \cdot \frac{1}{2}H_2O$ was determined, showing two molecules (A and B) per asymmetric unit with slightly different coordination spheres. In both molecules the metal atom is bonded to all six nitrogen atoms of L664. In molecule A the central atom is also bonded to two triflate anions, one via two oxygen atoms and the other through just one oxygen. In molecule B, Sr atom is bonded to two triflate ions, both via only one oxygen atom, and to a water molecule. Thus, the Sr atoms are nine-coordinate in both cases [38, 39].

Thus, as in the case of interaction of 2,6-dap or 2,6-dfp with en in the presence of metal ions [11–13, 16–18, 23–25], the dependence on the metal ion used and the complementarity of the template for the final ligand product cavities can be seen. In this connection it should be noted, however, that cadmium(II), whose radius indicates that it should be as effective as calcium(II) as template in the above process, appears to be unsuitable. In the cadmium case the reaction stops at the step of forming the complex $[Cd(L667)(o\text{-phda})](ClO_4)_2$ [13], where L667 is a product of (1 + 2) condensation of 2,6-dfp with *o*-phda. The X-ray diffraction study indicates that pentagonal-pyramidal coordination of the central atom is realised in the complex, and *o*-phda is arranged at the apex and acts as a monodentate ligand. However, when $Ba(L664)_2(ClO_4)_2$ is treated with cadmium(II) ions in ethanol, transmetallation takes place. An X-ray diffraction study showed the product obtained to be $[Cd(L664)(H_2O)(ClO_4)]ClO_4 \cdot CH_3OH$, with the 18-membered macrocycle

remaining intact and the coordination polyhedron approaching the hexagonal bipyramid [37].

If manganese(II), iron(II), cobalt(II) or zinc(II) salts are used as transmetallating agents, their smaller radii induce a complicated process, in which the corresponding coordination compounds with L668 are formed (Eq. 3.14) [40].

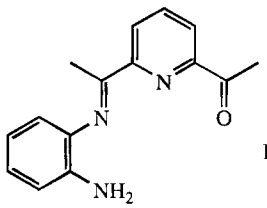


L667 L668 (3.14)

The X-ray diffraction study of $[Co(L668)(H_2O)(CH_3OH)](ClO_4)_2$ established that the central atom has a pentagonal-bipyramidal environment, with nitrogen donors of L668 disposed in the equatorial plane, and molecules of water and methanol occupying the axial coordination sites. In this case the drive to achieve the necessary match between the sizes of the metal ion and of the ligand cavity is resolved by contraction of the initial 18-membered macrocycle to a 15-membered one. This seems to take place in two steps. First, a methanol molecule is added to one of the azomethine bonds in response to strain in the macrocycle which arises from the tendency to form bonds with the small metal ion via all the nitrogen atoms. Flexibility of the macrocyclic system can be achieved by transformation of the C=N double bond into a C–N single bond. As a result, the second step becomes possible. This consists of nucleophilic attack by the secondary amino group at the imino carbon atom of the neighbouring C=N bond, which leads to expulsion of an imidazoline ring and formation of a new pentadentate 15-membered macrocyclic ligand L668, with geometric parameters appropriate to accommodate ions of the given 3d elements [40].

Attempts to use 1,2-diaminobenzene as ligson for condensation with dap and 2,6-dfp in the presence of lanthanide ions are not as successful as in the case of en. Derivatives of L663 with nitrates of the larger lanthanide ions, La^{III} to Nd^{III}, have been reported [41, 42]. However, the characterisation of these complexes, based on elemental analysis, mass spectra, and partial infrared absorption data, still left doubt as to their true structure. Condensation of dap and 1,2-diaminobenzene in the presence of lanthanum(III), praseodymium(III) or neodymium(III), when carried out under conditions described earlier [41, 42], yielded chiefly the metal-free compounds L665 and L669 (Eq. 3.15) [43]. However, small yields of $[M(L663)(NO_3)_3]\cdot nH_2O$ (M = La, Pr, Nd; n = 0.5–3.0) were obtained following a modified procedure in which the reactants were refluxed in methanol in a nitrogen-flushed apparatus for 4 h. The solid formed (L665) was quickly removed from the hot solution. The solution was allowed to stand for 24 h. After this time, a new crop

of L665 (fluffy needles) had crystallised from solution, while a small amount of tiny yellow crystalls (target product) had precipitated on the walls and bottom of the flask permitting their separation from the byproduct. The yellow crystals were washed with methanol and chloroform.



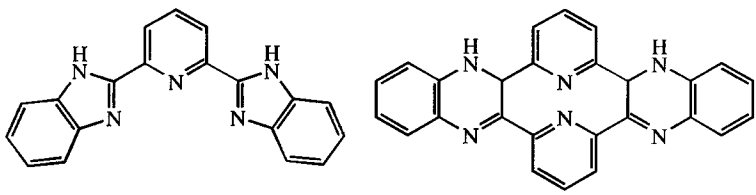
L669 (3.15)

The products $[Pr(L663)(NO_3)_2(CH_3OH)]ClO_4 \cdot \frac{1}{2}CH_3OH \cdot \frac{1}{2}H_2O$ and $Nd(L663)(OH)(NO_3)_{0.5}(ClO_4)_{1.5} \cdot 2H_2O$ have been obtained by addition of an excess of $LiClO_4$ to nitrate complexes of praseodymium(III) and neodymium(III). X-Ray structural investigation of $[Pr(L663)(NO_3)_2(CH_3OH)]ClO_4 \cdot \frac{1}{2}CH_3OH \cdot \frac{1}{2}H_2O$ confirmed the template formation of L663. In this complex the praseodymium(III) ion is 11-coordinate, being linked to the six nitrogen atoms of L663, to a bidentate chelating nitrate, to a methanol molecule on one side of the macrocycle, and to another bidentate nitrate on the other side. The macrocycle itself is folded, with the two pyridine rings directed away from the hemisphere containing the NO_3^- and CH_3OH ligands [43, 44].

The Schiff-base condensation of dap and 1,2-diaminobenzene in the presence of a stoichiometric quantity of uranyl perchlorate produced a mixture of $UO_2(L663)(ClO_4)_2$ and L665, from which the organic side product was removed by repeated extraction with boiling tetrachloroethylene [43].

The role of Ln^{III} ions in the process of dap condensation with 1,2-diaminobenzene remains undefined, despite reliable data about the formation of L663 on a praseodymium(III) matrix.

The macrocycle L664 was also synthesised by a (2 + 2) condensation of 2,6-dfp with 1,2-diaminobenzene using nitrates of all lanthanide(III) ions as templates. The macrocycle was isolated as $M(L664)(NO_3)_3 \cdot nH_2O$, with $n = 0$–4.5 (M = La–Gd) or $M(L664)(NO_3)_{3-x}(OH)_x \cdot nH_2O$, with $n = 0.5$–1.5 (M = Tb–Lu) [39]. For larger La–Nd metal ions the yields were high (80–60%), decreasing for the rest of the members of the series and being only 5% for lutetium. The triflates and acetates can also be used as template salts in some cases, but the yields are smaller compared to the use of nitrates. Note that the transmetallation reaction of $Ba(L664)_2(ClO_4)_2$ with an excess of lanthanide nitrate affords lanthanide(III) complexes of L664 which have identical or similar composition to those obtained by template synthesis [39, 45]. The decreasing yield of macrocyclic complexes from template syntheses along the lanthanide series is complemented by increasing amounts of non-macrocyclic byproducts. 2,6-Bis(2-benzimidazolyl)pyridine (L670) has been isolated and identified as the main product. The same compound is formed but in smaller quantities during the transmetallation process. In the presence of cerium(III) or europium(III) small amounts of another byproduct, L671, are found (Eq. 3.16).

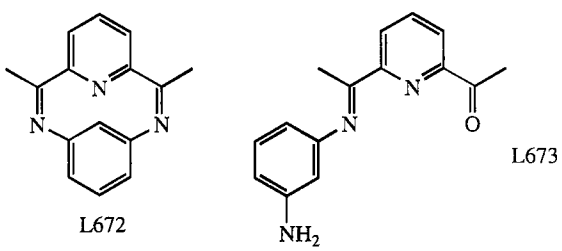


(3.16)

L670 L671

The [La(L664)(CH_3COO)($NCS)_2$] obtained both by template synthesis and metal ion exchange reaction, followed by partial anion metathesis, has been characterised by X-ray diffraction [46]. The La^{III} is bonded to the six nitrogen donors of L664, to a chelating acetate and to the nitrogen atoms of two isothiocyanate groups situated on opposite sides of the macrocycle.

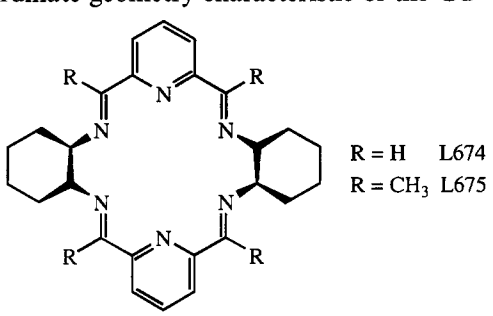
The complex Y(L672)($NO_3)_3 \cdot 3H_2O$ has been prepared [47] by template condensation of dap with 1,3-diaminobenzene in the presence of yttrium nitrate. The same (1 + 1) ligand product has been assembled in the presence of UO_2^{2+} [48]. The formation of the 10-membered triaza macrocycle is confirmed by the presence of an intense peak with $m/z = 235$, corresponding to the metal-free L672 in the mass spectrum of the uranyl complex [UO_2(L672)(NO_3)(H_2O)]$NO_3 \cdot H_2O$. In the absence of the metal ions only the open-chain compound L673 is formed (Eq. 3.17).



(3.17)

L672 L673

The template synthesis of complexes Ln(L674)($NO_3)_3 \cdot n H_2O$ (Ln = Eu, Tb, La, Gd, Dy; n = 0–2), Gd(L674)Cl_3(H_2O) and Y(L674)Cl_3($H_2O)_{5.5}$ was performed in rather high yield (from 33% to 78%) [49–51]. In the liquid secondary ion (LSI) mass spectra the following ions were recorded: [La(L674)($NO_3)_2]^+$, $m/z = 690$ (100); [Gd(L674)$Cl_2]^+$, 654 (12); [Gd(L674)($NO_3)_2]^+$, 707 (80); [Dy(L674)($NO_3)_2]^+$, 714 (100); and [Y(L674)$Cl_2]^+$, 587 (7%) [51]. An X-ray diffraction study of [Gd(L674)($H_2O)_3$]$Cl_3 \cdot 3H_2O$ obtained by recrystallisation of Gd(L674)Cl_3(H_2O) from methanol confirmed the macrocyclic structure of L674 (Eq. 3.18) and showed nine-coordinate geometry characteristic of the Gd^{III} ion.

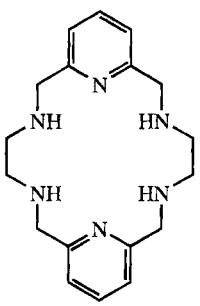


R = H L674
R = CH_3 L675

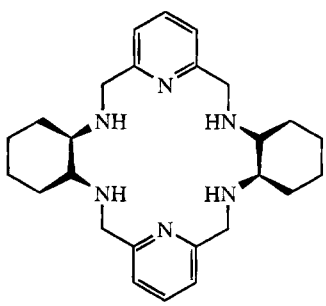
(3.18)

First attempts to prepare the tetramethyl derivative L675 or its complexes failed [49]. The steric repulsion between the methyl group and the hydrogen atom of the cyclohexyl ring was supposed to prevent cyclisation of dap and (±)-*trans*-1,2-diaminocyclohexane. Subsequently, both L674 and L675 have been synthesised non-templately in 68% and 57% yield by dropwise addition of (±)-*trans*-1,2-diaminocyclohexane in methanol to a refluxing solution of dap in methanol in a molar ratio of 1:1. Acetonitrile can also be used as solvent for preparation of L675. The macrocyclic structure of L675 has been proved by X-ray diffraction methods [51].

Reduction of the Ba^{II} complex of L649 prepared *in situ* and the tetraimine metal-free product L674 with $NaBH_4$ affords tetramine macrocyclic ligands L676 and L677 (Eq. 3-19) [51–54], which, by reaction with d metal ions, form assemblies having helical topology [53–56]. The degree of the tetramine macrocycle helicity is controlled by the d metal ion size and its coordination ability.



L676



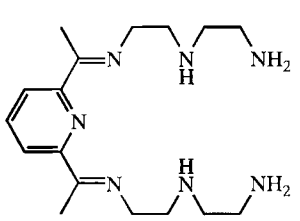
L677

(3.19)

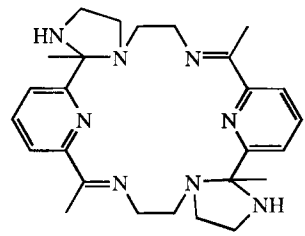
3.2 Macrocycles based on 2,6-dicarbonylpyridines and 1,*n*-diamines containing an additional supporting donor atom

The template condensations considered in this section are to a great extent governed by the relation of metal ion size to the developing macrocycle cavity size. The nature of the template, and the length and rigidity of the amine ligson, determine the stoichiometry of the ligand product formed. The 1 + 1 condensation mode is not characteristic for the simplest ligsons considered here, if the number of atoms separating the terminal NH_2 groups is less than seven. A number of metal-controlled ring-rearrangement reactions (contraction or expansion) are also presented.

The reaction of dap with diethylenetriamine (dien) on barium(II), strontium(II), calcium(II) or magnesium(II) perchlorates or nitrates as template sources, in molar ratio 1:2:1 in methanol at room temperature, results in isolation of chelates $[M(L678)]X_2 \cdot nH_2O$ ($X = ClO_4$, NO_3; $n = 0$, 1) (Eq. 3-20) [57].



L678



L31 (3.20)

Complexes of the above-mentioned metals (except magnesium) with the macrocyclic ligand L31 are formed on adding an equimolar amount of dap to $[M(L678)]X_2 \cdot nH_2O$ in methanol or acetonitrile and subsequent heating for 1 h at 65°C (or upon standing for approximately 15 h at room temperature). The same products can be obtained by refluxing a methanol solution of the reagents employed (molar ratio 1:1:1) for 1–4 h (the excess of amine suppresses the macrocyclisation). Barium(II), strontium(II) and calcium(II) coordination compounds with the macrocyclic ligand L31 are also formed on heating methanol solutions of $[M(L678)]X_2 \cdot nH_2O$ for up to 1 h without adding dap. The X-ray diffraction study of $Ba(L31)(ClO_4)_2$ established that the barium ion is 10-coordinated and is positioned on a centre of symmetry, being bonded to six nitrogen atoms of the L31 and to four oxygen atoms of two perchlorate groups (Figure 3-3). The BaN_6 moiety is approximately planar (maximum deviation 0.6 nm) and as the adjacent N–Ba–N angles are about 60°; the macrocycle can be considered to form a hexagonal girdle around the metal ion [57].

The results show that chelates of the enumerated metals with L678 represent intermediate products in the template condensation of dap with dien by a (2 + 2) mechanism, with subsequent formation of complexes of the macrocyclic ligand L31. The fact that ring closure proceeds, even without adding dap to $[M(L678)]X_2 \cdot nH_2O$, indicates that the process involves a transamination step. This consists of the intermolecular nucleophilic addition of an uncoordinated $-NH_2$ group from one $[M(L678)]^{2+}$ ion to the coordinated C=N group of the neighbouring $[M(L678)]^{2+}$ species, with the subsequent release of a dien molecule. The sequence ends with an analogous intramolecular nucleophilic addition and deamination resulting in

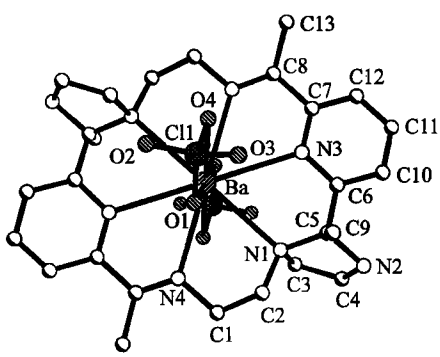
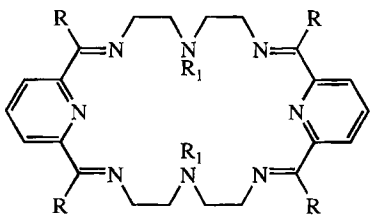


Figure 3-3. The structure of $Ba(L31)(ClO_4)_2$.

macrocycle formation. The most significant result of this template synthesis is the formation not of the 24-membered macrocyclic compound L679 (Eq. 3.21), but of a system with smaller size, containing 18 members (L31).

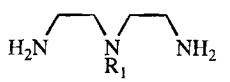


$R = CH_3$, $R_1 = H$	L679
$R = R_1 = H$	L680
$R = CH_3$, $R_1 = CH_2CH_2NH_2$	L681
$R = CH_3$, $R_1 = CH_2CH_2NC(CH_3)_2$	L682
$R = CH_3$, $R_1 = CH_2C_5H_4N$	L683
$R = H$, $R_1 = CH_2CH_2C_6H_5$	L684

(3.21)

The ring contraction from 24 to 18 members must take place as a result of nucleophilic addition of the two secondary amino groups of L679 to the neighbouring azomethine bonds with the expulsion of two five-membered imidazoline rings. The stability of the complexes of the given metals and the thermodynamic driving force for macrocycle contraction are presumably a consequence of mismatch between the cavity size of L679 and the alkaline earth metal ionic radii.

In turn, even the cavity size of L31 appears to be rather large for the particularly small magnesium(II). As a result, ring closure to produce the complex $[Mg(L31)]^{2+}$ from $[Mg(L678)]^{2+}$ fails. On treating $M(L31)(ClO_4)_2$ with silver(I) perchlorate (for M = Ca, Sr) or copper(II) perchlorate (for M = Ba, Sr, Ca) in methanol, transmetallation reaction takes place with formation of $[Ag_2(L679)](ClO_4)_2$ or $[Cu_2(L679)](ClO_4)_4$. Hence, the process has a character inverse to the above-described transformations, and, as a consequence, the 24-membered macrocyclic isomer acts as ligand in the resulting binuclear complexes. Similarly, after refluxing a solution containing stoichiometric amounts of 2,6-dfp, dien and barium(II) perchlorate in absolute methanol, a product was isolated whose IR spectrum is close to that of $[Ba(L31)](ClO_4)_2$ [58]. Reaction with copper(II) perchlorate in methanol led to ring expansion with isolation of the binuclear complex $Cu_2(L680)(ClO_4)_4$ [58]. The 24-membered macrocycle can easily be constructed and isolated by appropriate functionalisation of the starting diethylenetriamine ligson at the supporting nitrogen atom by a direct template procedure. Thus tris(2-aminoethyl)amine (L685; Eq. 3.22) condenses with dap in the presence of Ag(I) as template in 1:1:1 molar ratio in methanol to give $[Ag_2(L681)](BF_4)_2$ [59]. This can readily be converted into $[Ag_2(L682)](BF_4)_2$ by reaction with acetone in methanol. Reaction of $[Ag_2(L681)]^{2+}$ with *o*-hydroxybenzaldehyde gave $[Ag_2(H_2L688)]^{2+}$ (Eq. 3.23) [60]. Transmetallation was then effected with hydrated copper(II) salts in methanol-acetonitrile to give $[Cu_3(OH)(L688)H_2O](ClO_4)_3 \cdot 2H_2O$ [61]. The X-ray structure of the latter (Figure 3-4) shows a tricopper(II) cluster held within the ligand perimeter.



$R_1 = CH_2CH_2NH_2$	L685
$R_1 = CH_2CH_2C_6H_5$	L686
$R_1 = CH_2CH_2C_6H_5$	L687

(3.22)

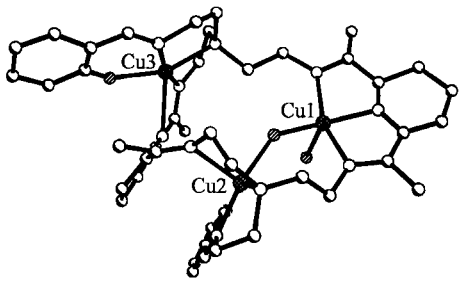
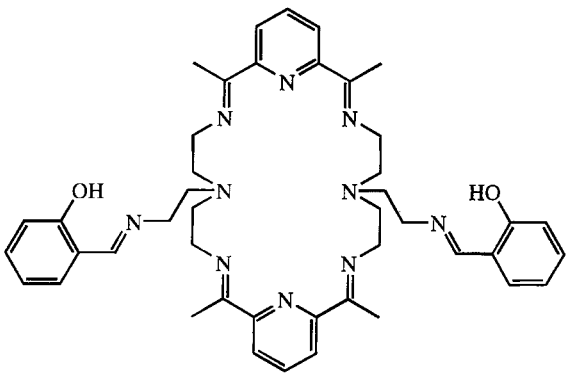


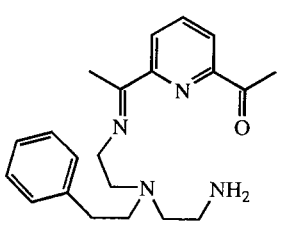
Figure 3-4. The structure of the $[Cu_3(OH)(L688)(H_2O)]^{3+}$ cation.



L688 (3.23)

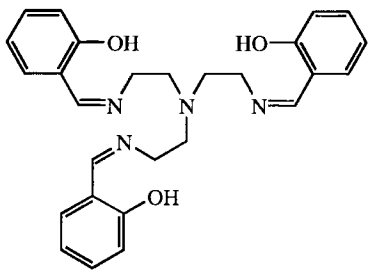
The copper atoms Cu1 and Cu2 are 36 nm apart and bridged by an OH^- group. The third copper atom Cu3 is 49 nm and 59 nm distant from Cu1 and Cu2, respectively. All three copper atoms are found in distorted square pyramidal coordination geometries [61].

The (2 + 2) cyclocondensation reaction between *N,N*-bis(2-aminoethyl)-2-(aminomethyl)pyridine and dap in the presence of Ag(I) as template also affords the non-contracted 24-membered macrocycle L683, isolated as the binuclear metal complex $[Ag_2(L683)](ClO_4)_2$ [60]. (In the absence of a metal template the reaction yields a polymeric gum.) The X-ray crystallographic data for $[Ag_2(L682)](BF_4)_2$ [59] and $[Ag_2(L683)](ClO_4)_2$ [60] showed that both nitrogen-pendant arms, bearing potential donor nitrogen atoms, are involved in coordination to the silver(I) atom. This fact seems to be crucial in stabilisation of the 24-membered macrocycle. In contrast, using *N,N*-bis(2-aminoethyl)-2-phenylethylamine (L687) as starting ligson for silver(I), templated condensation with dap does not lead to the 2 + 2 macrocyclic ligand product. Instead an open-chain 1 + 1 ligand product (L689; Eq. 3.24) arises, which can be isolated in the form of its mononuclear silver(I) complex $[Ag(L689)]ClO_4$ [62].



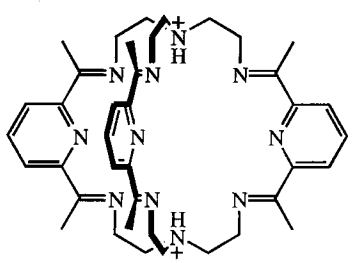
L689 (3.24)

Note that Ba^{II} also proved to be a suitable template with which to assemble L681 and L683 [60, 63]. However, in this case the 2 + 2 condensation products are isolated as mononuclear barium(II) complexes. This can be a consequence of the change in ionic radius from silver(I) (11.3 nm) to barium(II) (14.3 nm). According to X-ray diffraction, all donor atoms are involved in coordination with barium(II) in both complexes [60, 64]. Further functionalisation of the pendant arms in $[Ba(L681)](ClO_4)_2$ using *o*-hydroxybenzaldehyde failed [64]. The reaction led to the formation of the tripodal ligand H_3L690 (Eq. 3.25) and its barium(II) complex $Ba(H_3L690)_2(ClO_4)_2$.



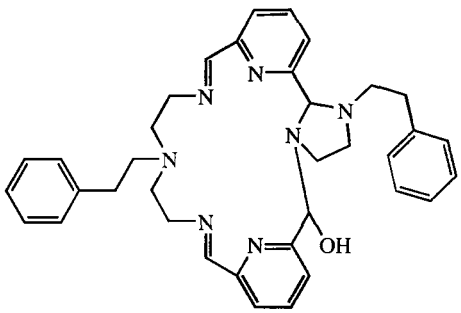
H_3L690 (3.25)

The synthesis of binuclear copper(II) and manganese(II) complexes with L681 has been performed by treating the diprotonated cryptand L691, obtained by (2 + 3) cyclocondensation of dap and L685 in the presence of hydrochloric acid [65], with $Cu(BF_4)_2$ and $Mn(CH_3COO)_2$ in methanol and methanol–acetonitrile, respectively (Eq. 3.26) [66, 67].



$[H_2L691](BF_4)_2$ (3.26)

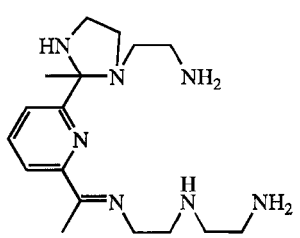
It is noteworthy that barium(II) as template permitted the assembly of the 2 + 2 macrocycle L684 from 2,6-dfp and the dien derivative L687 [68]. In addition the reaction of L687 with 2,6-dfp controlled by Ba(II) in acetonitrile unexpectedly yielded a second product, which has been identified by X-ray diffraction as $[Ba(L692)](ClO_4)_2$, where L692 is an 18-membered ring-contracted macrocycle (Eq. 3.27). The appearance of this product is presumably caused by the presence of *N*-(2-aminoethyl)-2-phenylethylamine as contamination in the starting ligson L687 [68].



L692 (3.27)

Transmetallation of $[M(L678)](ClO_4)_2$ (M = Ba, Sr, Ca) with transition metal perchlorates results in isolation of the products $[M(L678)](ClO_4)_2$, where M = Mn, Fe, Co, Cu or Zn. The X-ray structure determination of the copper(II) complex showed [69] that the chelating ligand remains unchanged and participates in its usual heptadentate role, forming a distorted pentagonal bipyramidal geometry around the central atom. Transformation of these perchlorates into tetraphenylborates and a comparative study of a series of physical parameters and powder diagrams make it possible to conclude that other complexes also have a structure similar to the copper(II) product.

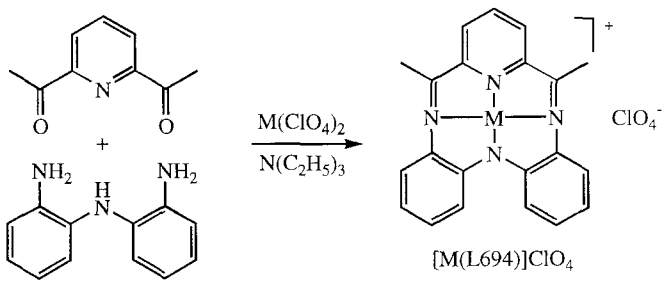
In contrast to the previous 3d elements, the use of nickel(II) as transmetallating agent leads to formation of two products of the same structure, but of different colour, namely brown and green [69, 70]. These were isolated as tetraphenylborates (for the brown form, a perchlorate was also obtained). Boiling a solution of the green $[Ni(L678)](BPh_4)_2$ for an hour or leaving it to stand for 48 h leads to its conversion into the brown isomer. A study of physicochemical properties indicated the green substance to be isostructural with the copper(II) complex. X-Ray diffraction of the brown isomer revealed the product of L678 isomerisation to be hexadentate (L693; Eq. 3.28). The latter is coordinated through a set of six nitrogen donor atoms.



L693 (3.28)

It is not difficult to observe that in this case a transformation analogous to the previous L679 → L31 takes place. The only difference is that the conversion L679 → L693, conditioned by intramolecular metal-directed transformations, involves only one of the amine-containing branches. The thermodynamic driving force for this isomerisation presumably arises from the stereochemical preference of O_h symmetry rather than D_{5h} for nickel(II); steric matching is not the main factor here [70].

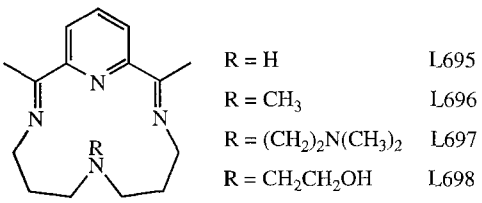
Template condensations of dap with diethylenetriamine proceed mainly as (2 + 2) additions. Formation of (1 + 1) macrocycles is unlikely, as can be seen from the analysis of a macrocycle molecular model, which shows a small cavity size with respect to the radii of the transition metal ions as well as strains which are present even in the metal-free 12-membered macrocyclic ligand [71, 72]. The isolation of $Ag(L689)ClO_4$ provides additional evidence of this feature [62]. Increasing the number of CH_2 units between terminal $-NH_2$ groups in the aliphatic triamine by one still does not permit the (1 + 1) process. Fully conjugated 12-membered macrocyclic complexes $[M(L694)]ClO_4$ can, however, be obtained by heating stoichiometric amounts of dap, 2,2′-imino-bisaniline and triethylamine, and either nickel(II) or copper(II) perchlorate in ethanol (Eq. 3.29) [73].



(3.29)

The essentially planar ligand is probably stabilised by full conjugation, the metal ion being out of the plane of the nitrogen atoms [73].

In the case of aliphatic triamines, (1 + 1) template condensation can be achieved if the number of atoms separating terminal $-NH_2$ groups equals 7. Thus, by interaction of dipropylenetriamine with dap on manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II) matrices, it is possible to synthesise the 14-membered macrocyclic ligand L695 as appropriate complexes (Eq. 3.30) [71, 72, 74–76].

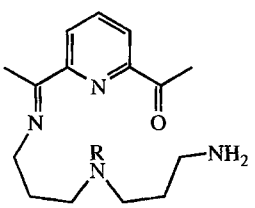


(3.30)

Synthesis is usually carried out in 50% aqueous ethanol by prolonged heating of the reaction mixture. A 50% aqueous solution of dimethylformamide can also be used as the solvent. Reactions proceed smoothly at a higher temperature (105°C), although then byproducts are also produced [72]. In the isolated 3d metal complexes, approximately square-planar coordination of L695 to central atom is achieved [77]. 3,3-Triamines, substituted at the nitrogen atom which is not involved in the condensation reaction, are also useful as ligsons. In this case, L696 formation is similar to the template reaction for obtaining L695 [72]. Note that 2,6-diformyl-

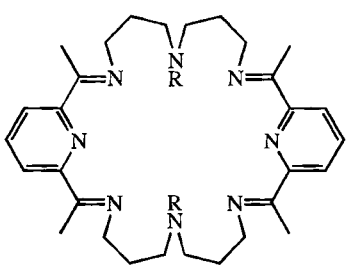
pyridine was also successfully used to build up 14-membered macrocyclic derivatives related to L695 and L696 14-membered macrocyclic derivatives [72].

If 4-(2-dimethylaminoethyl)- or 4-(2-hydroxyethyl)-1,7-diamino-4-aza-heptane are used for condensation, then it is possible to synthesise complexes both with open-chain ligands, L699 and L700 (Eq. 3.31), and with the macrocycles L697 and L698 in the presence of nickel(II) as matrix [78, 79]. Nickel(II) complexes of L699 and L700 are presumably intermediates in template macrocyclisation. They are converted into the fully ring-closed species L697 and L698 under more rigorous conditions (prolonged heating at higher temperature). The nickel(II) macrocyclic complexes of L697 and L698 can exist in solution in two forms depending on the pH of the reaction medium. At low pH values the dimethylamino and hydroxy groups are protonated and square-planar coordination of ligands to the central atom is realised in the complexes. At higher pH, dimethylamino and hydroxy groups (the latter being in the deprotonated form) are coordinated to the nickel in one of the axial positions. The other is occupied by a solvent molecule [79]. This acid-base reaction, accompanied by change of the coordination polyhedron, is the direct consequence of the combination of rigid and kinetically stable structure of macrocycles with flexible and kinetically labile functional groups R.



$R = (CH_2)_2N(CH_3)_2$ L699
$R = CH_2CH_2OH$ L700 (3.31)

Condensation of 3,3′-diaminodipropylamine with dap in the presence of silver(I) perchlorate [11] or lead(II) thiocyanate [80], in the presence of $NaBPh_4$ as precipitating agent, gives binuclear complexes of the (2 + 2) condensation product, of composition $[Ag_2(L701)](BPh_4)_2$ and $Pb_2(L701)(NCS)_4$ (Eq. 3.32).

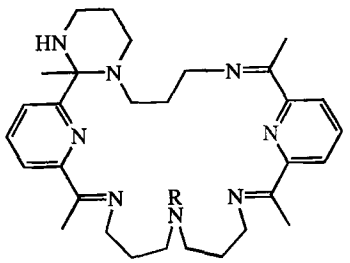


$R = H$ L701
$R = CH_3$ L702
$R = CH_2CH_2C_6H_5$ L703
$R = CH_2C_5H_4N$ L704
$R = CH_2CH_2OCH_3$ L705
$R = CH_2C_6H_4OCH_3$-*o* L706 (3.32)

The macrocycles L702 and L703 are formed in the presence of Ag^I or Pb^{II}, and Ag^I respectively from the appropriate *N*-substituted amine and dap [11, 62]. Other related macrocycles L704–L706, containing *N*-pendant arms bearing potential nitrogen or oxygen donors, have been prepared [60] using silver(I) as template.

Increasing the number of CH_2 groups between nitrogen atoms in the dien derivatives makes it possible to carry out, on a silver(I) matrix, synthesis of the respective 28-membered octadentate 2 + 2 products of interaction with dap. These are isolated as binuclear metal complexes. The structures of $[Ag_2(L701)](BPh_4)_2$, $[Ag_2(L704)](ClO_4)_2 \cdot \frac{1}{2}H_2O$, $[Ag_2(L705)](ClO_4)_2 \cdot \frac{1}{2}H_2O$ and $[Ag_2(L706)](ClO_4)_2$ are available [81, 60].

Using Ca^{II} or Sr^{II} as patterns results in complexes of L707 (Eq. 3.33). This, as judged from ^1H NMR spectra, is a contracted 24-membered macrocycle, formed by intramolecular attack by the secondary NH group on the neighbouring azomethine bond and subsequent expulsion of the tetrahydropyrimidine ring [80].



L707 (3.33)

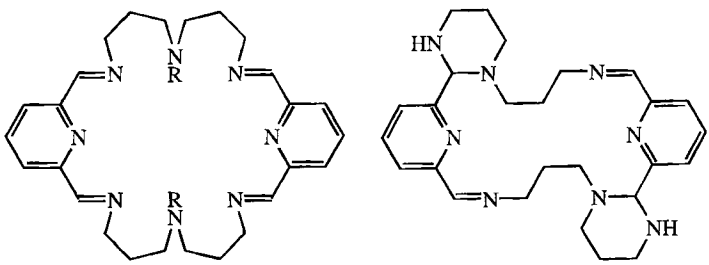
It should be noted that Ca^{II} and Sr^{II} have proved to be ineffective for condensation of dap with *N*-methylated $H_2N(CH_2)_3NH(CH_2)_3NH_2$. This is presumably due to steric impedance of attack by the *N*-methyl group on the azomethine bond in the L702, because of the presence of the CH_3 group. As a result, synthesis of the corresponding L707 analogue cannot be achieved.

Complexes $[Ag_2(L701)](BPh_4)_2$ and $Pb_2(L701)(NCS)_4$, as well as $[Sr(L707)](BPh_4)_2$, undergo transmetallation upon treatment with 3d metal salts in methanol or acetonitrile. As a result, binuclear complexes containing $[M_2(L701)]^{4+}$ are formed independently of the initial compound. Hence, transmetallation is accompanied with the conversion of L707 into L701. It was also possible to obtain a mononuclear product, such as $[Fe(L701)](BPh_4)_2$ for iron(II), when working with stoichiometric amounts of reagents.

Transmetallation reactions of silver(I) and lead(II) binuclear complexes of L702 with Fe^{II}, Co^{II} or Mn^{II} salts give mono- as well as binuclear compounds, with the initial ligand intact.

Macrocycles L701, L702 and L707 must be flexible enough to be able to assume one of several possible conformations, depending on the stereochemical requirements of the metal ion. As a result it is possible to synthesise a range of coordination compounds for these ligands.

In contrast to dap, 2,6-dfp undergoes 2 + 2 cyclocondensation reactions with 3,3-triamines in the absence of metal ions as template. Using bis(3-aminopropyl)-methylamine or *N*,*N*-bis(3-aminopropyl)-*N'*,*N'*-dimethyl-1,2-diaminoethane as ligsons is supposed to give the 28-membered ring-expanded macrocycles L708 and L709, respectively (Eq. 3.34) [82].



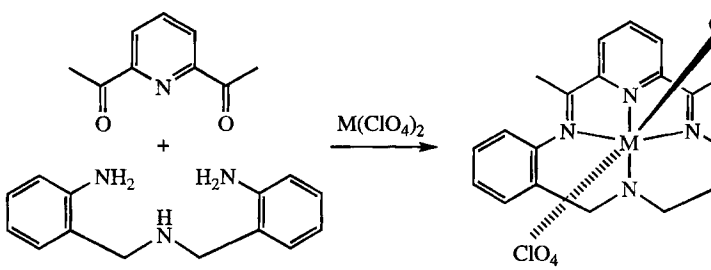
(3.34)

R = CH_3 L708
R = $(CH_3)_2NCH_2CH_2$ L709
R = H L710

L711

In contrast, 3,3-diaminopropylamine, as revealed by X-ray diffraction study, leads to the isolation of a ring-contracted 20-membered macrocyclic species L711 which, according to ^{1}H NMR data, also remains intact in solution [83]. It is supposed that L711 is formed by intramolecular rearrangement of L710.

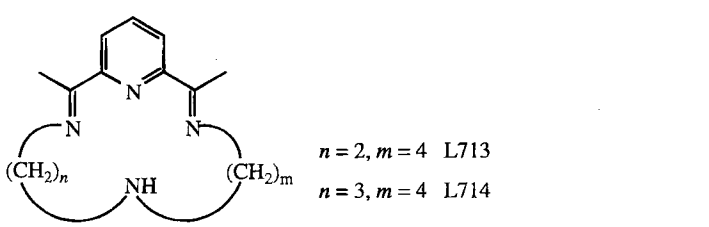
When dap reacts with an aromatic 3,3-triamine in the presence of nickel(II), copper(II) or cobalt(II) perchlorate in ethanol, macrocyclic complexes with tetradentate ligands $[M(L712)](ClO_4)_2$ and having octahedral structures are isolated (Eq. 3.35) [73].



(3.35)

$[M(L712)](ClO_4)_2$
M = Ni, Co, Cu

Unsymmetrical aliphatic triamines containing seven or eight links between the terminal $-NH_2$ groups are also suitable for template condensation with dap. Thus, in the presence of $Cu(ClO_4)_2$, it was possible to perform the reaction of dap with $H_2N(CH_2)_2NH(CH_2)_4NH_2$ in ethanol to give the Cu^{II} complex of L713 (Eq. 3.36) [84].

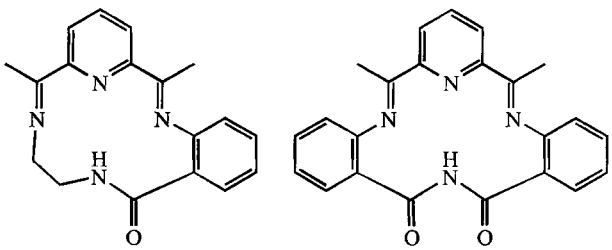


(3.36)

$n = 2, m = 4$ L713
$n = 3, m = 4$ L714

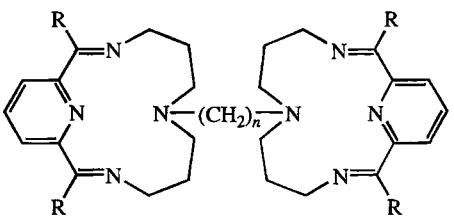
Starting from $H_2N(CH_2)_3NH(CH_2)_4NH_2$ it is possible to synthesise products containing L714 on nickel(II), copper(II) and zinc(II) matrices [72]. Complexes of L713 and L714 with 3d metals are isolated in a lower yield and more easily undergo hydrolysis in aqueous solution in comparison with the respective compounds of L695. This presumably results from the lower stability of seven-membered metallorings compared with six-membered ones.

Condensation of related aromatic diamines containing an amide-supporting nitrogen donor in their chain with dap in the presence of Ni^{II}, Cu^{II} or Co^{II} affords macrocycles L715 and L716, isolated as their complexes with the corresponding metals (Eq. 3.37) [73].



L715 L716 (3.37)

The condensation of dap or 2,6-diformylpyridine with hexamines $(H_2NCH_2CH_2CH_2)_2N(CH_2)_nN(CH_2CH_2CH_2NH_2)_2$ (n = 2–6) was performed templately in low yield under conditions similar to those reported [71] for copper(II) coordination compounds with L695. This was carried out on nickel(II) and copper(II) matrices, L717 and L718 being obtained as the respective metal complexes (Eq. 3.38) [85, 86]. The formation of bis-macrocycles, able to adopt two different conformations in the corresponding metal complexes due to a flexible polymethylene bridge, has been confirmed by a number of X-ray diffraction studies [87–89].

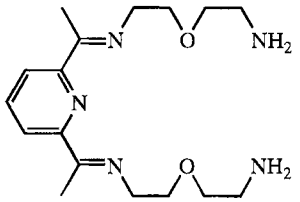


R = CH_3, n = 2–6 L717
R = H, n = 2–6 L718 (3.38)

A low yield of products is probably caused by the sharp decrease of internal entropy of the condensing hexamine upon macrocyclisation, when two macrocycles are assembled into one and the same molecule.

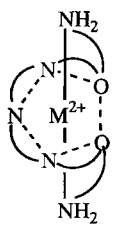
Template condensations of dap and 2,6-dfp with diamines containing oxygen and sulphur atoms have also been successfully carried out. It is not possible to isolate macrocycles of the (1 + 1) type on interaction of dap with 3-oxa-1,5-diaminopentane in the presence of metal salts [90], but magnesium(II), calcium(II) or barium(II) perchlorates with a molar ratio of reagents of 1:2 in methanol, give $M(L719)(ClO_4)_2$ (Eq. 3.39) [91]. Transmetallation of $M(L719)(ClO_4)_2$ with Mn^{II},

Fe^{II}, Co^{II}, Ni^{II}, Cu^{II} or Zn^{II} perchlorates in methanol at 30°C yields the corresponding complexes in 70–80% yield.



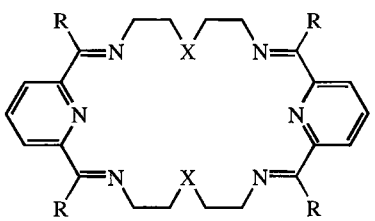
L719 (3.39)

From the denticity of L719, magnetic measurements, and Mössbauer, ESR and electron absorption spectra, these complexes are considered to have pentagonal-bipyramidal geometries (Eq. 3.40). This coordination was confirmed by X-ray diffraction for the nitrogen-containing analogue L678 in $Cu(L678)(ClO_4)_2$, having similar geometric parameters [69].



(3.40)

On heating $Ba(L719)(ClO_4)_2$ in dry methanol at 60°C, $Ba(L720)(ClO_4)_2$ is formed in 35–40% yield. The mononuclear barium(II) macrocyclic complex in the presence of an excess of copper(II) perchlorate in methanol undergoes transmetallation, yielding binuclear $Cu_2(L720)(ClO_4)_4 \cdot H_2O$ (Eq. 3.41).



$R = CH_3, X = O$ L720
$R = H, X = O$ L721
$R = CH_3, X = S$ L722 (3.41)

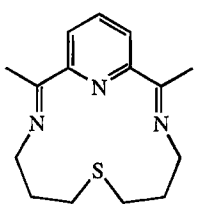
If imidazole (Himid) is added to the latter in boiling methanol, then $Cu_2(L720)(imid)(ClO_4)_3 \cdot H_2O$ can be isolated. Attempts to obtain similar products containing manganese(II), iron(II), iron(III), cobalt(II) or nickel(II) by metal ion exchange were unsuccessful [91].

The macrocycle L721, closely related to L720, can also be assembled by 2 + 2 condensation of 2,6-dfp and 3-oxa-1,5-diaminopentane, if silver(I) is used as template [92]. X-Ray diffraction of $[Ag_2(L721)CN]ClO_4 \cdot 0.275H_2O$, crystallised from acetonitrile, showed two silver(I) ions being linked with the two pyridyl-diimine moieties of a folded macrocycle, in which the pyridyl units lie almost parallel to each other. The oxygen atoms are not involved in coordination. The CN^- group, the origin of which is thought to be slightly contaminated solvent, bridges two

symmetry-related metal ions of two neighbouring molecules, forming dimers. The latter are further associated in a polymeric chain through silver–silver intermolecular interactions at 34.04 nm. The intramolecular silver–silver separation is markedly larger.

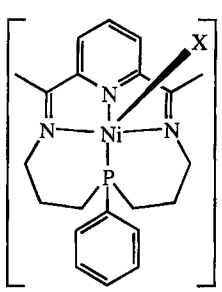
Template syntheses of macrocyclic systems from primary diaminothioethers by condensation with 2,6-pyridinedicarbonyl compounds have also been carried out. The reaction between the simplest ligson, 3-thia-1,5-diaminopentane, and dap on a silver(I) matrix produces the 24-membered macrocyclic ligand L722, isolated as $[Ag_2(L722)]X_2$ ($X = ClO_4$, BPh_4) in 55–65% yield [93]. The compound $Cu_2(L722)(ClO_4)_4 \cdot 2H_2O$ has been obtained by transmetallation of $[Ag_2(L722)]X_2$. Dissolving the compound $Cu_2(L722)(ClO_4)_4 \cdot 2H_2O$ in boiling CH_3OH-CH_3CN (3:1 mixture), followed by the addition of an equimolar amount of aqueous imidazole, leads to the formation of $[Cu_2(L722)(imid)(ClO_4)_3(H_2O)]$ whose structure has been established by X-ray diffraction. The coordination number of each copper(II) ion is six, resulting from equatorial coordination of the macrocycle through four nitrogen atoms, one of which is derived from bridging imidazole and axially positioned oxygen atoms of the perchlorate groups and a water molecule.

The product $Cu(L723)(ClO_4)_2 \cdot 2H_2O$ is obtained by heating stoichiometric amounts of copper(II) perchlorate, dap and 4-thia-1,7-diaminoheptane in aqueous ethanol [94]. The absence of stretching vibrations $\nu_{C=O}$ and ν_{N-H} and the presence of $\nu_{C=N}$ at 1609 cm^{-1} provide evidence for the macrocyclic nature of L723 (Eq. 3.42).



L723 (3.42)

Macrocyclic products with N and P donor atoms have also been synthesised by the template technique. The first tetradentate macrocyclic ligand containing a phosphine donor, L724, was obtained by refluxing an ethanolic solution of $PhP(CH_2CH_2CH_2NH_2)_2$, dap, and $NiX_2 \cdot 6H_2O$ (X = Br, I), followed by addition of NH_4PF_6. As a result the complex $[Ni(L724)X]PF_6$ is isolated (Eq. 3.43) [95]. When X = Cl the reaction yields the four-coordinate product $[Ni(L724)](PF_6)_2$. The five-coordinate $[Ni(L724)Cl]PF_6$ species may be obtained easily, however, by using '$NiCl(PF_6)$' as template source.

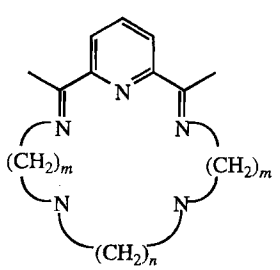


PF_6 $[Ni(L724)X]PF_6$ (3.43)

3.3 Macrocycles based on 2,6-dicarbonylpyridines and diamines containing two additional supporting donor atoms

Ligsons with terminal $-NH_2$ groups, containing four nitrogen atoms in positions suitable for complexation, appear to be very effective for condensation with dap in the presence of metal ions as matrices. Their special feature is that macrocyclic (1 + 1) products result from these template processes [11, 96–118]. The first representatives of a series of these compounds were described long ago [98, 99]. They were obtained by interaction of dap with triethylenetetramine (trien) on an iron(II) matrix in the presence of atmospheric oxygen. The substances isolated were originally characterised as iron(III) mononuclear complexes with the 15-membered macrocyclic ligand L30. Later, X-ray diffraction study of two of those substances established one of them to be the monomeric complex $[Fe(L30)(NCS)_2]ClO_4$, and the second to be the μ-oxodimer $[(H_2O)(L30)Fe^{III}-O-Fe^{III}(L30)(H_2O)](ClO_4)_2$ [96]. In both cases pentagonal-bipyramidal coordination to the central atom was realised, with the pentadentate macrocyclic ligand L30 in the basal plane and the axial positions occupied by two NCS^- and μ-oxoion and oxygen atoms of water molecules, respectively. The synthesis of other iron(III) compounds with L30, containing different inner- and outer-sphere anions has been reported [100]. By using manganese(II) chloride as a pattern in the dap reaction with trien in methanol, and with subsequent crystallisation from water, $Mn(L30)Cl_2 \cdot 6H_2O$ was isolated [97]. Thus, unlike iron(II), manganese(II) does not change its oxidation state.

Other complexes of iron(III), as well as of magnesium(II), iron(II) or zinc(II), with L30 have also been obtained by template reactions [101–103, 105]. For cadmium(II), mercury(II), silver(I) [104, 109–111], manganese(II) [72, 106, 107], lead(II) and tin(IV) [11, 112, 113, 117], the respective coordination compounds with L30, as with the related 16- and 17-membered ligands L725 and L726, have been obtained (Eq. 3.44).

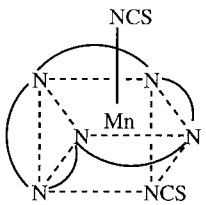


$m = n = 2$ L30
$m = 2,\ n = 3$ L725
$m = 3,\ n = 2$ L726

(3.44)

X-Ray diffraction studies have established [11, 96, 101, 107, 110, 111, 114–118] that L30 and L725 act in these complexes as planar pentadentate ligands, whereas L726, being more flexible, can also adopt other conformations. Thus, for the complexes of magnesium(II), manganese(II), iron(II), iron(III), zinc(II), cadmium(II)

and tin(IV) with L30 and L725, pentagonal-bipyramidal coordination to the central atom is realised, whereas in the cobalt(II), silver(I) and mercury(II) compounds, the central atom has a pentagonal-pyramidal geometry. As X-ray diffraction investigation of $Mn(L726)(NCS)_2$ showed [106], the 17-membered macrocyclic ligand L726 is also pentadentate, and the geometry of the complex itself can be considered as pentagonal bipyramidal. The five donor atoms of 15- and 16-membered macrocyclic ligands are only slightly displaced from the pentagonal plane containing the metal, but L726, being more flexible than L30 and L725, deviates from this plane in $Mn(L726)(NCS)_2$ so considerably that four nitrogen atoms are coplanar with the metal ion, with the pyridine nitrogen atom being out-of-plane by 9.2 nm. The manganese(II) environment in this substance has the form of a square-capped trigonal prism (Eq. 3.45).

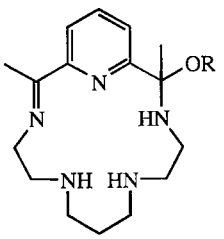


(3.45)

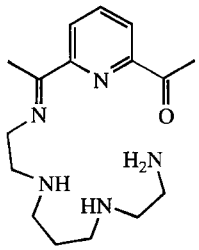
The macrocyclic ligand in the complex [Pb(L726)(SCN)](SCN) is also folded. Moreover, its geometry closely resembles that of the corresponding cadmium(II) compound [117]. The angle between the plane of the other macrocycle donor atoms and the pyridine ring is 63.1° in $[Pb(L726)(SCN)]^+$, 49.7° in $[Cd(L726)Br]^+$ and 41.8° in $[Mn(L726)(NCS)_2]$. These results reflect correlation between the degree of folding of L726 and metal ion size (Pb 13.3, Cd 10.3, Mn 9.0 nm) [14]. Ligand L726 undergoes similar conformation changes in coordination compounds $[Cd(L726)Br]Br \cdot H_2O$, $[Hg(L726)Br][Hg_2Br_6]$ and $[Ag(L726)]ClO_4$, where the pyridine nitrogen atom is out of the plane of the other four nitrogen atoms by 13.1, 13.8 and 9.4 nm, respectively [110].

Ions of Mn^{II}, Pb^{II}, Hg^{II}, Ag^{I} and Sn^{IV} act as matrices for building up the above-mentioned 15-(L30)-, 16-(L725)- and 17-(L726)-membered macrocyclic pentadentate ligands, whereas ions with smaller radii, such as magnesium(II), iron(II), iron(III) and zinc(II), make it possible to synthesise the ligand with the lesser cavity size. It has also been reported [11] that the 16-membered macrocyclic ligand has been obtained by using lanthanum(III) as a template for condensation of the respective ligsons.

Attempts to use nickel(II) and copper(II) ions for template assembly of these macrocyclic compounds were unsuccessful [115]. Transmetallation of the silver(I) perchlorate complex with L725 by nickel(II) ion in dry alcohols gave the octahedral coordination compound of ligand L727 (Eq. 3.46). The latter is a product of addition of ROH to one of the azomethine bonds of the original ligand. Carrying out the reaction in the presence of water, C=N bond hydrolysis takes place, and a complex of the open-chain ligand L728 is formed, giving the octahedral coordination expected for the divalent nickel [115].



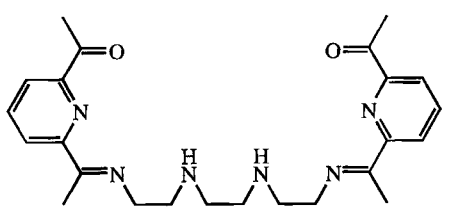
L727



L728

(3.46)

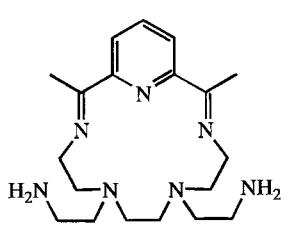
In the two examples shown, the formation of ligands L727 and L728 is dictated by the stereochemical requirements of the central atom, whereas the template synthesis of L30, L725 and L726 is conditioned to a certain extent by their ability to impose an unusual geometry on the coordination unit of the metals concerned [11, 115]. In the presence of strontium(II) and barium(II) perchlorates, condensation of dap with trien proceeds by the (2 + 1) path to give chelates with the open-chain ligand L729 (Eq. 3.47). The latter, however, is not an intermediate for (2 + 2) macrocycle formation, because its subsequent interaction with a series of diamines of different chain length does not lead to ring closure [119]. The possible reason for the process stopping at the (2 + 1) step follows from the result of the X-ray diffraction study of $Ba(L729)(ClO_4)_2$. This showed that the 10-coordinate barium atom chelates via the carbonyl groups, so that those groups are disposed at an angle 80.2° to each other, forming a cleft 52.1 nm wide. If such a conformation is assumed to remain intact in solution, then a steric barrier to bifunctional nucleophilic attack by the $-NH_2$ groups cannot be excluded. This illustrates the influence of ligand conformation on its reactivity.



L729

(3.47)

The complex $Mn(L730)(PF_6)_2$ has been prepared by template condensation of dap with *N*,*N*,*N*′,*N*′-tetrakis(2-aminoethyl)ethylenediamine in the presence of manganese(II) (Eq. 3.48) [120].

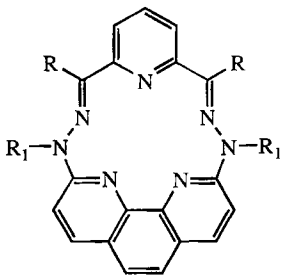


L730

(3.48)

Assembling L730 may serve as a prototype for the synthesis of macrocyclic species with pendant arms starting from dap, 2,6-dfp or related ligsons and polyfunctional polyamines.

By template interaction of dap or 2,6-dfp with 2,9-di(1-methylhydrazino)-1,10-phenanthroline in the presence of salts of d elements, the appropriate metal complexes with L731 and L732 can be synthesised (Eq. 3.49) [121–127].

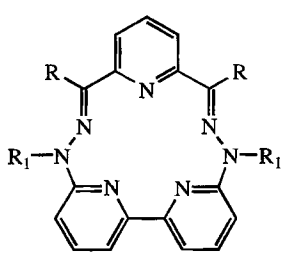


$R = H, R_1 = CH_3$	L731
$R = R_1 = CH_3$	L732
$R = CH_3, R_1 = CH_2CH_2OH$	L733

(3.49)

X-Ray diffraction studies of $[Co(L731)(H_2O)_2][SiF_6]\cdot 6H_2O$ [123], $[M(L732)(H_2O)_2][BF_4]_2\cdot nH_2O$ (where M = Co [128], Fe [124]), $[Co(L732)(CH_3OH)_2][BF_4]_2$ [125], $[Mn(L732)Cl][BF_4]$ [122] and $[Mn(L733)Cl][BF_4]\cdot 4H_2O$ [126] showed these macrocyclic ligands to be pentadentate, with azomethine, pyridine, and 1,10-phenanthroline nitrogen atoms forming the pentagonal plane of a bipyramid or pyramid, whose vertices are occupied by monodentate ligands. The functional group CH_2CH_2OH is not coordinated in the manganese(II) complex of L733 [126], although it has been shown [79] that in the nickel(II) compound with L698 this group can coordinate to the central atom.

Template synthesis of zinc(II), cadmium(II) and mercury(II) complexes with L731 and L734 was also carried out [129, 130]. As in other cases, absence of the corresponding metal ions leads to formation of polymeric products. When attempting to obtain the macrocyclic compounds L731 and L734 in the presence of magnesium(II), polymeric products are also isolated, which confirms the inability of this ion to function as a matrix in this case (Eq. 3.50) [129].



$R = R_1 = CH_3$	L734
$R = R_1 = H$	L735
$R = H, R_1 = CH_3$	L736
$R = H, R_1 = CH_2CH_2OH$	L737
$R = CH_3, R_1 = H$	L738

(3.50)

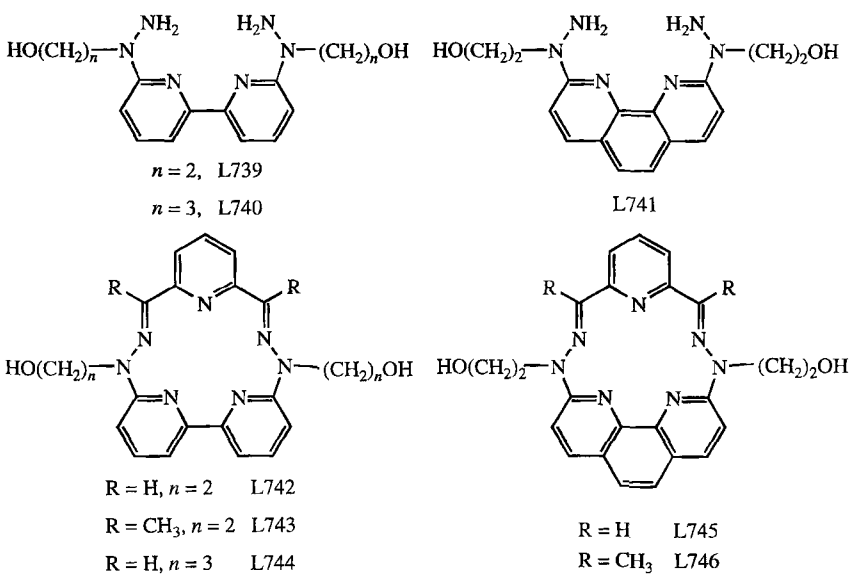
Template synthesis of these macrocyclic compounds is catalysed by acids, and isolation of the final products depends on the metal salts used [129]. This is most clearly manifested in the case of zinc(II) as template. Carrying out the reaction in the presence of NH_4NCS gives a complex of Zn(II) with an open-chain ligand, which is a (1 + 2) product of condensation of 2,6-dfp with the dihydrazine derivative of 1,10-phenanthroline. Using chromium(III) or tin(IV) as the patterns yields metal-free macrocyclic compounds L731–L734 [131, 132].

The condensation of L48 and its derivatives with 2,6-dfp in the presence of aqueous chromium(III) chloride led to the formation of the metal-free macrocycles L735–L737 [133]. Reaction of the phenanthroline analogue, 2,9-bis(1-methylhydrazino)-1,10-phenanthroline, occurs in a similar way. In no case could a chromium(III)-containing complex of either initial or final ligands be isolated from the reaction mixture. Identical yields of metal-free macrocycles were obtained when the reaction was conducted in the presence of chromium(III) chloride, chromium(III) chloride and hydrochloric acid (pH = 1), or hydrochloric acid alone. Only low yields of macrocycles were obtained in the absence of acid (pH = 6) or in acetate buffer. This indicates that the proton is the 'true' template in these chromium-mediated reactions.

Zinc(II) complexes of pentadentate ligands L735 and L738 were isolated from template condensation of 2,6-dfp or dap with L48 in the presence of $Zn(NO_3)_2 \cdot H_2O$ [134].

When hydrated chromium(III) chloride reacts with L739 in ethanol, the compound $[Cr(L739)Cl_2]Cl$ is formed (Eq. 3.51). Treatment of the latter with 2,6-dfp under conditions of the transient template reaction mentioned above gives rise unexpectedly to $[Cr(L742)(H_2O)_2]Cl_3 \cdot 2H_2O$, the structure of which was established by X-ray diffraction methods. In this compound the central atom is in a regular pentagonal-bipyramidal environment, with the axial positions occupied by water molecules. This is a rare example of a seven-coordinate macrocyclic complex of chromium(III) [133].

The template condensation of L739 and L741 with 2,6-dfp or dap proceeds smoothly in the presence of iron(II) chloride in aqueous medium under an inert atmosphere with formation of iron(II) complexes of L742 and L743, and of L745 and L746, respectively. The latter are easily oxidised into iron(III) complexes by atmospheric dioxygen [135].

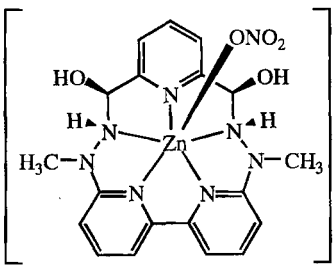


(3.51)

Vanadium(III) complexes with L742 and L744 have been obtained in a similar way, by condensation of L739 and L740 with 2,6-dfp in the presence of vanadium trichloride [136].

The metal-free ligands L742 and L745 are prepared by a transient template condensation of the corresponding ligsons in the presence of chromium(III) chloride [135].

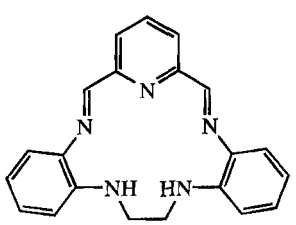
6,6′-Di(*N*-methylhydrazino))-2,2′-bipyridyl (*N*-methyl derivative of L48) reacts with 2,6-dfp in the presence of zinc(II) nitrate in a large volume of ethanol at room temperature to give $Zn(L747)(NO_3)_2$ (Eq. 3.52) [137].



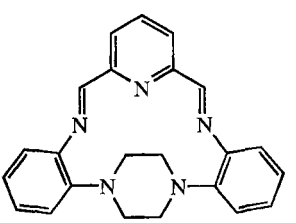
NO_3 $[Zn(L747)NO_3]NO_3$ (3.52)

X-Ray structure determination confirmed the presence of ligand L747, in which the expected nitrogen atoms are coordinated to the zinc(II) ion, and showed that the carbinolamine C–O and N–H bonds are all disposed to the same side of the macrocycle [137]. The isolation of $[Zn(L747)NO_3]NO_3$ suggests that the template formation of L736 and related macrocyclic systems may proceed through formation of a dicarbinolamine before any elimination of water occurs. This might be expected when the ligand precursors are both relatively rigid, because the cyclisation step becomes less favourable once one imine bond has formed and the approach of the second amine nitrogen atom on a line perpendicular to the carbonyl group becomes less probable. Molecular models show that such an effect will be particularly significant when the macrocyclic product has an unstrained planar central ring [137].

Manganese(II), iron(II), nickel(II) and zinc(II) coordination compounds with L748 and manganese(II) compounds with L749 are synthesised by template interaction of 2,6-dfp with corresponding aromatic amines (Eq. 3.53) [138].



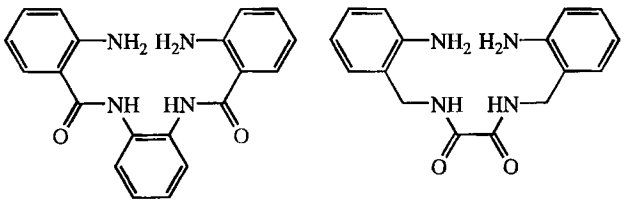
L748



L749

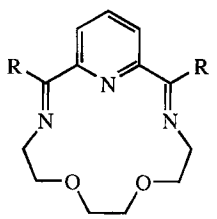
(3.53)

The diamidodiamines L750 and L751, which possess greater framework rigidity, proved to be unsuitable for template condensation with dap [73] presumably because of non-complementarity with the corresponding building blocks (Eq. 3.54).



L750 L751 (3.54)

In contrast to 3-oxa-1,5-diaminopentane, 3,6-dioxa-1,8-diaminooctane undergoes condensation with dap or 2,6-dfp on matrices of a number of metal ions (Mg^{2+}, Fe^{3+}, Fe^{2+}, Mn^{2+}, Zn^{2+}, Cd^{2+}), with formation of products of the (1 + 1) type (Eq. 3.55) [90, 102, 107].



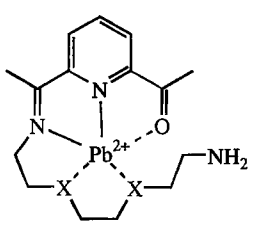
R = CH_3 L752
R = H L753 (3.55)

In the presence of Mg^{2+} ions, $[Mg(L752)(H_2O)_2]Cl_2 \cdot H_2O$ is obtained in more than 75% yield [90]. Formation of the macrocyclic ligand is confirmed by the presence of a peak with $m/z = 275$ in the mass spectrum, corresponding to $[L752]^{+\cdot}$. The pentagonal bipyramidal geometry of magnesium(II) has been proved by X-ray diffraction study of $[Mg(L752)(H_2O)_2](ClO_4)_2$ [139]. $[Fe^{III}(L752)Cl_2][FeCl_4]$ was obtained by reaction of $FeCl_2 \cdot 4H_2O$ with dap and 3,6-dioxa-1,8-diaminooctane in methanol (molar ratio of reagents 1:1:1) at 40–50°C, with subsequent oxidation by an aqueous solution of $Na_2S_2O_8$ and treatment with one equivalent of $FeCl_3$ in methanol acidified with HCl [107]. If this substance is treated with an excess of sodium perchlorate in methanol-acetone mixture $[Fe^{III}(L752)Cl_2]ClO_4$ is obtained. Treatment of a hot aqueous solution of the latter with an excess of sodium thiocyanate in the presence of perchloric acid gives $[Fe^{III}(L752)(NCS)_2]ClO_4$. The reaction of $FeCl_2 \cdot 4H_2O$ with dap and the diamine ligson at the same reagent ratio, followed by $Na_2S_2O_4$ in aqueous methanol under heating, and finally with sodium thiocyanate and $Na_2S_2O_4$, gives $[Fe^{II}(L752)(NCS)_2]$. If sodium cyanide is used instead of thiocyanate, then it is possible to synthesise the complex $[Fe^{II}(L752)(CN)_2] \cdot H_2O$ [140]. Compound $[Mn^{II}(L752)(NCS)_2]$ and $[Zn(L752)(NCS)_2]$ have been synthesised by template condensation of dap with 3,6-dioxa-1,8-diaminooctane in methanol at 50°C in the presence of $MnCl_2 \cdot 4H_2O$ or $ZnBr_2$, with subsequent treatment of the solution with an excess of sodium thiocyanate. In the case of $CdBr_2 \cdot 4H_2O$, reaction occurs in boiling methanol and $[Cd(L752)Br_2] \cdot H_2O$ can be isolated. Treatment of this with an excess of sodium thiocyanate in methanol converts it into $[Cd(L752)(NCS)_2]$. Formation of L752 on a Cd^{II} matrix, as in the case of Mg^{II}, is confirmed by the presence of a peak corresponding to $[L752]^{+\cdot}$ in the mass spectra of complexes. X-Ray diffraction of $[Mn^{II}(L752)(NCS)_2]$ [107] established that the manganese ion is in a pentagonal-

bipyramidal environment, with the donor atoms of L752 in the equatorial plane and nitrogen atoms of thiocyanate groups in the axial positions. The metal ion lies in the plane of the macrocycle donors. Similar structures for all the other complexes may be suggested on the basis of available data. An octahedral structure was proposed for $[Fe(L752)(CN)_2]\cdot H_2O$ on the basis of its Mössbauer spectrum. One of the oxygen atoms of L752 would be uncoordinated [140].

In the absence of metal ions, condensation of dap or 2,6-dfp with 3,6-dioxa-1,8-diaminooctane, even under high dilution conditions, results in formation of amorphous precipitates or viscous oils, in the mass spectra of which peaks of ions with $m/z = 275$ and 247, corresponding to $[L752]^{+\cdot}$ and $[L753]^{+\cdot}$, are seen. On interaction of these products with $MgCl_2\cdot 6H_2O$ it is possible to isolate $[Mg(L752)(H_2O)_2]Cl_2\cdot H_2O$, although only in about 5% yield; in the second case (L753 from 2,6-dfp) no complex can be isolated [90]. This result, together with IR data confirming the presence of the unreacted C=O groups in the products of condensation, indicates that in the absence of a template the macrocyclic ligands L752 and L753 are formed either in very low yield or not at all.

If Pb^{II} is used as the pattern, then it is possible to carry out (2 + 2) condensation. Thus reaction in methanol at 40°C in the presence of $Pb(SCN)_2$ gives $Pb_2(L16)(SCN)_4$ [112, 113], whose structure has been proved by X-ray diffraction. All the donor atoms of L16 are involved in coordination to lead(II) ions. The coordination polyhedron around each Pb(II) ion is a hexagonal bipyramid, with one equatorial site unoccupied. One possible reason is the presence of stereo-active lone-pairs in this complex. The sulphur atoms of the thiocyanate groups are in the axial positions. We should also note that it is impossible to carry out a (1 + 1) process on a Pb^{II} matrix with the formation of L752 [112, 113]. This fact cannot be explained by the mismatch of the Pb^{2+} ion size with the L752 cavity, because synthesis of the analogous 15-membered macrocycle L30 is successfully realised in the presence of Pb^{II} [11]. Taking into account the strong preference of lead to form bonds to nitrogen rather than to oxygen atoms (the Pb–N, and Pb–O separations in $Pb_2(L16)(SCN)_4$ are equal to 25.4, 25.6 and to 29.6, and 28.8 nm, respectively [112]), the course of the template process is assumed to be controlled by ligand conformation during the initial steps of complexation and determined by the nature of X in the intermediate species (Eq. 3.56).



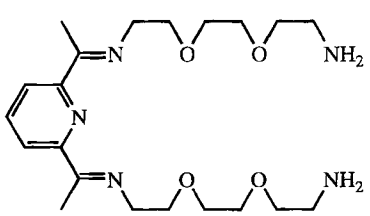
X = NH, O (3.56)

If reasonably strong bonds are formed between the central ion and X, then the carbonyl group and a terminal primary amine group approach closer to each other, so that intramolecular condensation producing the (1 + 1) macrocycle is possible. Such a situation presumably occurs when X = NH. On the other hand, the more weakly coordinated donors X (for example, ether oxygen atoms) are not able to compete effectively with solvent molecules in occupation of the coordi-

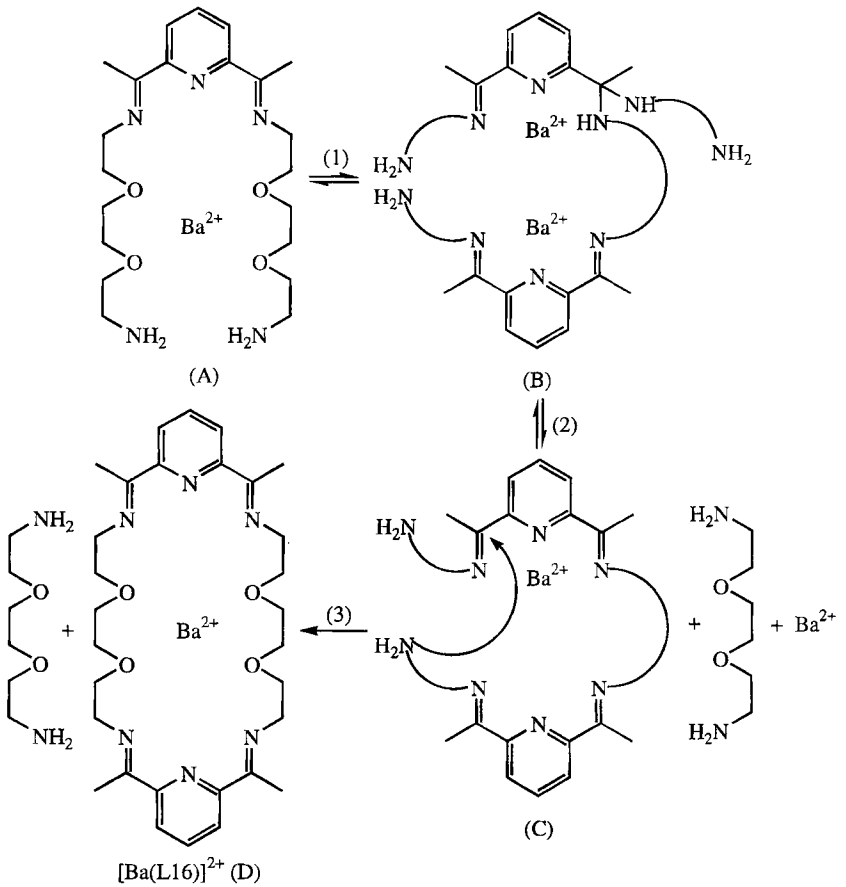
nation sites around lead(II). Therefore the C=O and $-NH_2$ groups involved in the reaction cannot take up positions that make their direct interaction possible. As a result, the process of intermolecular condensation of two molecules of intermediate proceeds with higher probability and produces the (2 + 2) macrocyclic product [112].

Attempts to isolate metal-free L16 failed, so transmetallation reactions were employed to obtain complexes of other metals with this ligand. For example, complexes $[M(L16)](ClO_4)_2 \cdot H_2O$, where M = Fe^{II}, Co^{II} or Ni^{II}, have been obtained by reaction of $Pb_2(L16)(SCN)_4$ with iron(II), cobalt(II) and nickel(II) perchlorates in boiling ethanol [141]. The X-ray structure determination of the iron(II) and cobalt(II) complexes indicated that the metal ions are in a distorted octahedral environment of nitrogen donor atoms [142], with no oxygen atoms coordinated to the central ion. Treatment of $Pb_2(L16)(SCN)_4$ with silver(I) perchlorate results in the formation of the binuclear product $[Ag_2(L16)](ClO_4)_2 \cdot H_2O$ [143]. Upon addition of silver(I) perchlorate to a hot methanolic solution of $[Co(L16)](ClO_4)_2 \cdot H_2O$ or on reaction of $[Ag_2(L16)](ClO_4)_2 \cdot H_2O$ with a cobalt(II) salt, the cobalt(III) compound $[Co(L13)](ClO_4)_3 \cdot H_2O$ is formed [143, 144]. If no more than one equivalent of copper(II) perchlorate reacts with $[Ag_2(L16)](ClO_4)_2 \cdot H_2O$, then as a result of metal ion exchange the mononuclear complex $[Cu(L16)](ClO_4)_2 \cdot H_2O$, presumably also having an octahedral structure, can be obtained. An excess of copper(II) perchlorate gives rise to the binuclear compound $[Cu_2(L16)](ClO_4)_4 \cdot 2H_2O$ [143, 145]. Binuclear $[Cu_2(L16)(OH)](ClO_4)_3 \cdot H_2O$ is obtained on reaction of the latter with one equivalent of NaOH or $NaOCH_3$. This compound can be converted back into the initial tetraperchlorate by reaction with one equivalent of perchloric acid. In accordance with X-ray data [145] the copper(II) ions in $[Cu_2(L16)(OH)](ClO_4)_3 \cdot H_2O$ are bridged by a single OH group. The products $[Cu_2(L16)(N_3)_3]ClO_4$ and $[Cu_2(L16)(imid)](ClO_4)_3$ result from reaction of $[Cu_2(L16)](ClO_4)_4 \cdot 2H_2O$ with NaN_3 and imidazole, respectively, in methanol. Their structures have been solved by X-ray diffraction [143, 145]. In the second case $[Cu_2(L16)(Himid)_2](ClO_4)_4 \cdot 2H_2O$ is formed after isolation of $[Cu_2(L16)(imid)](ClO_4)_3$ and concentration of the filtrate. The binuclear copper(I) complex is also obtained by metal ion exchange. $[Pb_2(L16)(SCN)_2](ClO_4)_2 \cdot H_2O$, formed by reaction of $Pb_2(L16)(SCN)_4$ with sodium perchlorate, is used as starting salt, the source of Cu(I) being $[Cu(CH_3CN)_4]ClO_4$. This transmetallation reaction is carried out in methanol in an inert atmosphere [145].

The template effect of alkaline earth metal ions on the condensation reaction of dap with 3,6-dioxa-1,8-diaminooctane is now discussed in more detail. The products $[M(L754)](ClO_4)_2$ are formed in 15–20% yield on reaction of dap with the diamine in methanol (in molar ratio 1:1) in the presence of barium(II) or strontium(II) perchlorates (Eq. 3.57) [144, 146].



L754 (3.57)

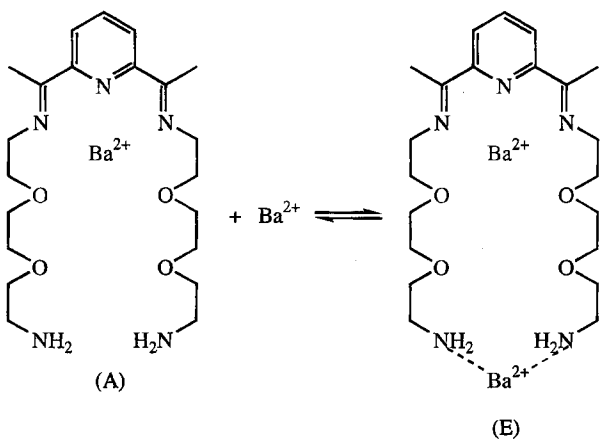


Scheme 3-2. The formation of [Ba(L16)]$^{2+}$ by two consecutive transamination steps.

The yield can be increased considerably (up to 65% in respect to the dap) if one equivalent excess of diamine is employed. Complex $[Ba(L16)](ClO_4)_2$ is formed at room temperature upon dissolving $[Ba(L754)](ClO_4)_2$ in methanol containing one equivalent of dap (30–40% yield) [144]. In addition, the conversion of $[Ba(L754)](ClO_4)_2$ into the macrocyclic product $[Ba(L16)](ClO_4)_2$, in 25–30% yield, occurs on dissolving in methanol without adding dap. The complexity of this process is obvious. The possibility of hydrolysis of L754 followed by recombination of resultant fragments and formation of L16 is excluded by the observation that carrying out the reaction in a dry solvent gives the same yield of the final product. The formation of L16 can be explained provided that the template transformations include two transamination acts (Scheme 3-2).

Bimolecular reaction involving nucleophilic attack by an uncoordinated amine

group of one molecule on the coordinated C=N bond of a second molecule, to give the addition compound B, proceeds during the first step. Regeneration of the azomethine bond occurs by splitting off the diamine molecule (step 2). Then the second (intramolecular) nucleophilic attack by a primary amine group in compound C on a C=N bond occurs, followed by deamination and the formation of compound D (step 3). Since A is an intermediate in the preparation of D, it seems surprising, at first sight, that the template reaction stops at this step even if the reagent ratio is 1:1. Under such conditions an excess of dap, required for performing the cyclisation, must be present in the reaction mixture. However, the yield of A is quite low (15–20%) under these conditions. Therefore, the concentration of primary amine groups is sufficiently high in the reaction medium. As a result, the probability of interaction between $-NH_2$ and imine carbon atoms in A is increased. Then the low yield of D may be explained by the fact that these reactions and the process of bimolecular condensation (step 1) proceed simultaneously. The process A → D is completely suppressed by the presence of free diamine even if the molar ratio of the above compounds is 1:1. Moreover, the conversion A → D is reversible as A is formed in 30% yield as a result of treatment of D with two equivalents of 3,6-dioxa-1,8-diaminooctane in methanol at 65°C [144]. An excess of Ba^{2+} ions also suppresses the process A → D, but less effectively. The existence of equilibrium between A and E could be a reason for this, the terminal amine groups in E being coordinated to Ba^{2+} (Eq. 3.58). As a consequence, these are less effective for nucleophilic attack on neighbouring C=N bonds (Scheme 3-2).



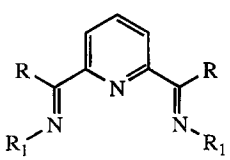
(3.58)

In contrast to $[Ba(L754)](ClO_4)_2$, the corresponding strontium(II) complex of L754 does not undergo any transformations that would result in the formation of products with L16, neither in the absence of diamine nor in its presence in the reaction medium. The reason for this may be the different strength of the metal–amine bonds. Strontium(II), having a higher charge density, is bonded more effectively. Calcium(II) is not suitable as a template for yielding Schiff bases based on dap and 3,6-dioxa-1,8-diaminooctane, or related complexes. Magnesium(II)

is a suitable template for carrying out (1 + 1) condensation, and also mediates the formation of (2 + 2) products [144]. For instance, $[Mg(L16)](ClO_4)_2 \cdot H_2O$, which can readily be transformed into $[Mg(L16)](BPh_4)_2$ by metathesis, is formed in 25% yield on slow evaporation of a methanol solution at room temperature. If the reaction mixture is treated with $NaBPh_4$ before perchlorate crystallisation occurs, the magnesium(II) complex of the 1 + 1 condensation product $[Mg(L752)(H_2O)_2](BPh_4)_2$, with an IR spectrum identical to that of an authentic sample [90], can be isolated. Formation of L16 during the process of template synthesis has been proved both by obtaining $[Fe(L16)](ClO_4)_2$ from $[Mg(L16)](ClO_4)_2 \cdot H_2O$ as a result of metal ion exchange, and by the comparison of its infrared and Mössbauer spectra with those of an authentic sample [142].

Magnesium(II) complexes of L754 have not been obtained, even when an excess of diamine was used. However, the possibility of formation of L754 in solution as an intermediate in the synthesis of both 15- and 30-membered macrocycles cannot be excluded, as treatment of $[Mg(L16)](ClO_4)_2 \cdot H_2O$ with two equivalents of diamine in dry methanol, followed by addition of an excess of $NaBPh_4$, leads to the isolation of $[Mg(L752)(H_2O)_2](BPh_4)_2$, where L752 is the 1 + 1 condensation product, in 30% yield. In this case, transamination is believed to play a key role.

The following data provide evidence in favour of transamination during multistep template processes. The products L755, L756 and L757 form copper(II) and zinc(II) complexes with composition $M(ligand)_2^{2+}$, having approximately octahedral geometry (Eq. 3.59) [144].

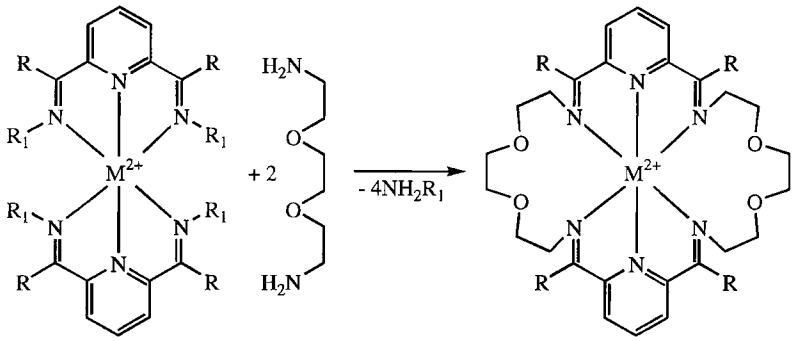


$R = CH_3, R_1 = CH_2CH_2OCH_3$ L755
$R = CH_3, R_1 = CH_2CH_2CH_3$ L756
$R = H, \quad R_1 = CH_2CH_2CH_3$ L757 (3.59)

In the case of L755 the ether oxygen atoms remain uncoordinated. The compound $[Cu(L16)](ClO_4)_2$ is formed in 70% yield on reaction of $[Cu(L755)_2](ClO_4)_2 \cdot H_2O$ with a fivefold excess of 3,6-dioxa-1,8-diaminooctane in dry methanol at 55°C. Treatment of this compound with an excess of copper(II) perchlorate yields $[Cu_2(L16)(ClO_4)_4] \cdot 3H_2O$ which, according to IR data, is identical to the sample synthesised by transmetallation of $[Ag_2(L16)]^{2+}$ [143]. The copper(II) complexes with L756 and L757 and the zinc(II) compound $[Zn(L757)](ClO_4)_2 \cdot H_2O$, undergo analogous transformations. As a result of these reactions, four monodentate amine molecules are exchanged for two diamine molecules and 30-membered macrocycles are formed (Scheme 3-3).

Macrocyclic complexes are also prone to amine exchange reactions. For instance, the action of a tenfold excess of ethane-1,2-diamine on $[Pb_2(L16)(SCN)_4]$ in boiling dry methanol produces [Pb(L646)(NCS)(SCN)], as considered in Section 3.2.

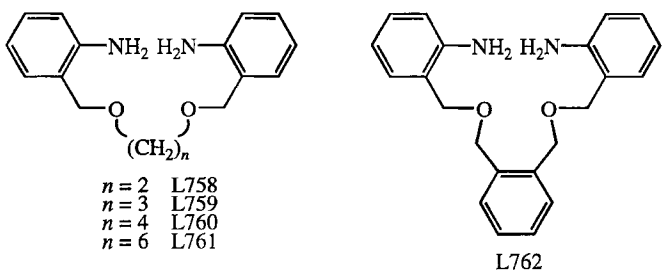
The involvement of the aromatic analogues of 3,6-dioxa-1,8-diaminooctane, i.e. L758–L761, as ligsons permits (1 + 1) template condensation between the latter and either 2,6-dfp or dap (Eq. 3.60).



$R = CH_3$, $R_1 = CH_2CH_2CH_3$ $M(L756)^{2+}$ (M = Cu)

$R = H$, $R_1 = CH_2CH_2CH_3$ $M(L757)^{2+}$ (M = Cu, Zn)

Scheme 3-3. Synthesis of macrocyclic complexes by amine exchange.

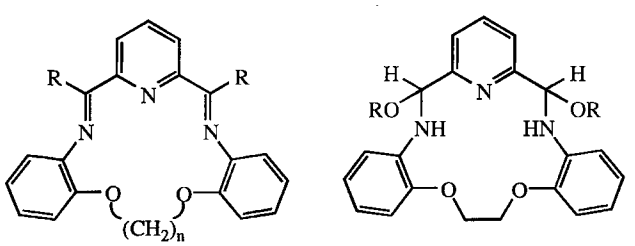


$n = 2$ L758
$n = 3$ L759
$n = 4$ L760
$n = 6$ L761

L762

(3.60)

Lanthanide(III) ions promote the condensation of H_2L758 and 2,6-dfp or dap yielding 15-membered N_3O_2 macrocycles L763 and L764 (Eq. 3.61), isolated as metal complexes [147]. Complexes $M(L763)X_2$ ($M = Mn^{II}$, Zn^{II}; $X = ClO_4$, NO_3) have been prepared in 25% yield from methanolic solutions in the presence of manganese(II) or zinc(II) perchlorates or nitrates [108]. If the reaction proceeds on an $MnCl_2$ matrix in ethanol, $Mn(L763)(H_2O)_2Cl_2$ is formed, L768 crystallising after the separation of this complex [148]. Manganese(II) also promotes the formation of larger macrocycles L765–L767 from L759–L761 and 2,6-dfp [149].



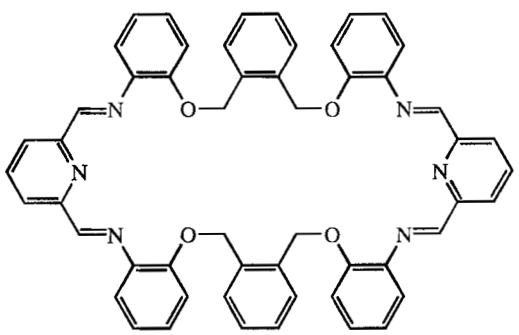
R = H, $n = 2$ L763
R = CH_3, $n = 2$ L764
R = H, $n = 3$ L765
R = H, $n = 4$ L766
R = H, $n = 6$ L767

$R = C_2H_5$ L768
$R = CH_3$ L769
$R = n\text{-}C_4H_9$ L770

(3.61)

The formation of L768 is not associated with the template action of manganese(II) chloride because, in the absence of metal ions, 2,6-dfp reacts with primary aromatic diamines in ethanol, methanol or *n*-butanol to form L768–L770, respectively. The use of propan-2-ol, *tert*-butyl alcohol, or benzyl alcohol instead of the above-mentioned solvents does not yield any macrocyclic products. The most intense peak in the mass spectra of L768–L770 is that corresponding to $[M-2ROH]^+$ [148]. The ease of ROH addition across azomethine bonds is likely to be caused by a decrease of conformational strain in the macrocycle, whereas the formation of these macrocycles in the absence of template centres is explained by a slight decrease in internal entropy in the macrocyclisation process [148].

In the presence of manganese(II), calcium(II), strontium(II), barium(II), lead(II) or silver(I), the Schiff base condensation of L762 and 2,6-dfp yields the 2 + 2 macrocycle L771 (Eq. 3.62), isolated as mononuclear $[M(L771)]^{2+}$, where M = Mn, Ca, Sr, Ba or Pb, or binuclear $[Ag_2(L771)]^{2+}$ [150–152]. In the absence of metal ions, solids of unidentifiable composition result from condensation reactions at normal and high dilution conditions.



L771 (3.62)

Transmetallation of $[Ag_2(L771)]^{2+}$ with an excess of $M(ClO_4)_2 \cdot 6H_2O$ (M = Co, Ni, Zn) in acetonitrile results in mononuclear complexes $[M(L771)]^{2+}$. According to X-ray crystallographic data the 34-membered macrocycle L771 is prone to adopt a double helical configuration in approximately isostructural $[M(L771)]^{2+}$ (M = Co, Ni, Zn) (Figure 3-5), as well as in $[Cd(L771)]^{2+}$ and $[Pb(L771)]^{2+}$. The occurence of the double helix is determined by the ability of L771 to accommodate the preferred coordination mode of the template by meridional arrangement of pyridinediimine moieties around the metal ion and by favourable intramolecular π–π interactions between aromatic fragments of the ligand. The N_6 coordination in a double helix has been found in $[M(L771)]^{2+}$ (M = Co, Ni, Zn) as shown in Figure 3-5 and with N_6O_4 coordination in $[Pb(L771)]^{2+}$. Note that the more flexible related macrocycle L16 does not exhibit analogous behaviour. The combination of a certain flexibility, ambidentate coordinating ability and the presence of aromatic units in the 34-membered ring make its properties unique for development of molecular helicity. Note the metal ion size is not crucial for double helix formation. It only has influence on the secondary structure of the helicate.

2,6-Diacetylpyridine reacts with 4,7-dithia-1,10-diaminodecane in methanol in the presence of silver(I) perchlorate or nitrate to produce [Ag(L772)]X (X = ClO_4,

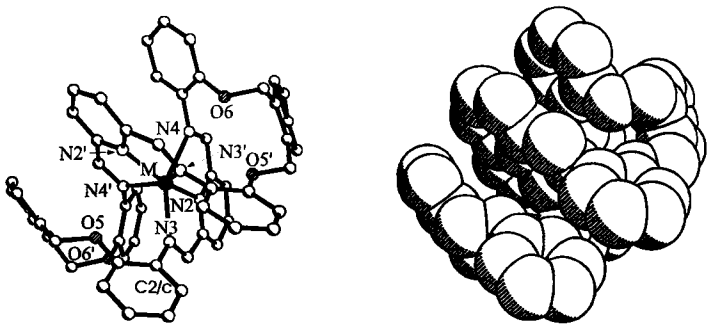
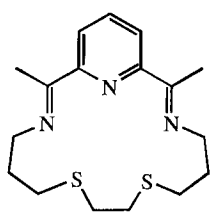


Figure 3-5. The structure of the $[M(L771)]^{2+}$ cation (M = Co, Ni, Zn).

BPh_4) in 50–60% yield (Eq. 3.63). Viscous oils of unidentifiable composition are formed in the absence of a template [153].



L772 (3.63)

The reaction of $[Ag(L772)]ClO_4$ with $NaBPh_4$ in methanol results in the simultaneous reduction of both azomethine bonds and Ag(I). Treatment of $[Ag(L772)]ClO_4$ with an excess of copper(II) perchlorate in boiling methanol yields $[Cu^{II}(L772)](ClO_4)_2$. Note that in this case the direct template synthesis technique is not appropriate to obtain $[Cu^{II}(L772)](ClO_4)_2$. An X-ray structure of this compound showed [154] that the copper atom is bonded to all donor atoms. The coordination polyhedron approximates to a square pyramid; one of the sulphur atoms of L772 occupies an apical position.

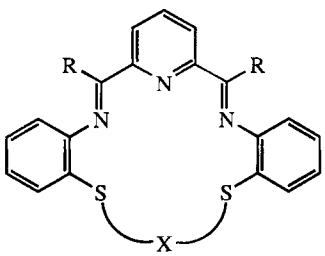
From the reaction of $[Cu(L772)](ClO_4)_2$ with two equivalents of $NaBPh_4$ in methanol at room temperature, one can readily isolate $[Cu(L772)](BPh_4)_2$. On boiling this reaction mixture, the copper(I) complex $[Cu(L772)]BPh_4$ is formed in 55% yield, the BPh_4^- anion acting as the reducing agent. Decreasing the amount of $NaBPh_4$ to one equivalent enables the corresponding perchlorate derivative $[Cu(L772)]ClO_4$, to be obtained. $[Cu^{II}(L772)](BPh_4)_2$ is reduced to $[Cu^{I}(L772)]BPh_4$ in acetonitrile, in contrast to $[Cu^{II}(L772)](ClO_4)_2$, which remains intact in acetonitrile.

X-Ray diffraction studies of $[Cu(L772)]ClO_4$ and $[Ag(L772)]ClO_4$ [153] revealed that in both cases all donor atoms of L772 are involved in coordination to the metal ion. The coordination environment of the metal ion is close to trigonal pyramidal, with sulphur atoms in the equatorial plane.

Two series of iron(II) complexes, which are either high spin or low spin depending on the nature of the anions or neutral molecules required to complete the

coordination number of the Fe(II) of 6 [155], are obtained by transmetallation of [Ag(L772)]X (X = ClO_4, BPh_4) with iron(II) salts in dry methanol. An X-ray crystal structure indicated distorted octahedral coordination of donor atoms both in low spin [Fe(L772)(NCS)]BPh_4 and in high spin [Fe(L772)Cl(CH_3OH)]ClO_4. All nitrogen and sulphur atoms of L772 are involved in coordination to iron(II) in the former, with the nitrogen atom of the thiocyanate group occupying the *trans* position with respect to one of the sulphur atoms. The equatorial plane in the latter is formed by nitrogen atoms of the trimethylene fragment of L772 and a chloride ion, and the axial positions are occupied by the oxygen atom of a methanol molecule and one of the sulphur atoms of the macrocyclic ligand.

As in the case of diamino ethers, unsaturated thioanilines can be employed for template condensation with dap or 2,6-dfp. For example, 2,6-dfp and 1,2-bis(aminophenylthio)alkanes react in methanol or acetonitrile in the presence of some transition metal ions to form (1 + 1) products L773–L775 (Eq. 3.64), isolated in the form of the respective complexes [138]. The macrocycle L773 is formed on manganese(II), zinc(II) and nickel(II) matrices and L774, L775 in the presence of zinc(II) ions.



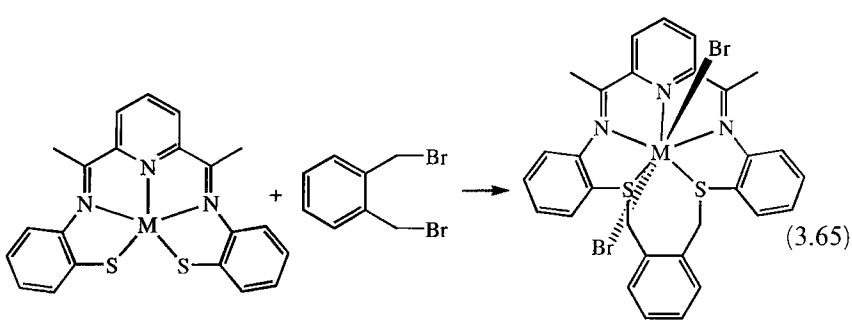
R = H, X = $(CH_2)_2$	L773
R = H, X = $(CH_2)_3$	L774
R = H, X = $(CH_2)_4$	L775
R = CH_3, X = *o*-xylene	L776
R = CH_3, X = $(CH_2)_4$	L777

(3.64)

To obtain coordination compounds of N_3S_2 ligands, alkylation template reactions of open-chain precursors can also be employed. For instance, the macrocyclic complexes of zinc(II) and of cadmium(II) with L776 have been synthesised by the action of 1,2-bis(bromomethyl)benzene on the metal complexes of the appropriate open-chain ligand in acetone (Eq. 3.65) [156].

If 1,4-diiodobutane is used as alkylating agent, [Zn(L777)I_2] can be obtained in the same manner [156].

Consideration of the series of compounds formed by zinc(II) with L774, L775

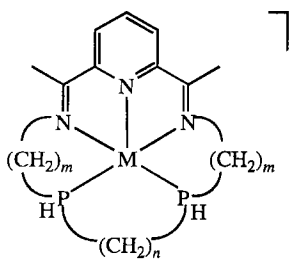


(3.65)

[M(L776)Br_2], M = Zn, Cd

and L777, can probe the effect of polymethylene chain length X on the structure of the corresponding complexes. For instance, X-ray diffraction studies of $[Zn(L774)(ClO_4)_2]$, $[Zn(L775)(H_2O)_2](ClO_4)_2 \cdot CH_3CN$ [138] and $[Zn(L777)I_2]$ [157] indicated that the first compound and the complex cation of the second have a pentagonal-bipyramidal geometry. In both cases, macrocycle donor atoms determine the equatorial planes of the polyhedron. The axial positions are occupied by ClO_4^- and water molecules, respectively. Lengthening of the polymethylene chain results in an elongation of the Zn-S bonds in $[Zn(L775)(H_2O)_2]^{2+}$ (27.52 and 26.67 nm) as compared with $[Zn(L774)(ClO_4)_2]$ (26.35 and 25.13 nm). The increase in the number of $-CH_2-$ groups by one leads to a situation in which pentagonal-equatorial coordination becomes impossible on account of the steric effect of the tetramethylene bridge connecting the sulphur atoms as well as of the low affinity of zinc(II) for thioether groups [157]. The coordination polyhedron for $[Zn(L777)I_2]$ is square pyramidal with three nitrogen atoms and an I^- arranged in a plane and another I^- positioned axially [157]. A similar structure cannot be excluded for $[Zn(L776)Br_2]$.

The coordination compounds formed by Cd^{II} or Ag^{I} and L778 or L779 result from reaction of dap with diphosphinodiamines on cadmium(II) or silver(I) matrices in boiling methanol (Eq. 3.66) [158].



$m = 2,\ n = 3$ $[M(L778)]^{q+}$

$m = 3,\ n = 2$ $[M(L779)]^{q+}$

M = Cd, Ag (3.66)

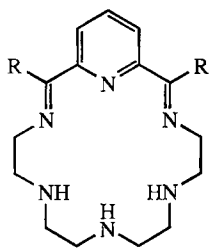
The macrocyclic nature of L778 and L779 has been confirmed by the absence of stretching vibrations $\nu_{C=O}$ and ν_{N-H} in the IR spectra of the complexes and by the presence of stretching vibrations $\nu_{C=N}$ at 1650 cm^{-1}.

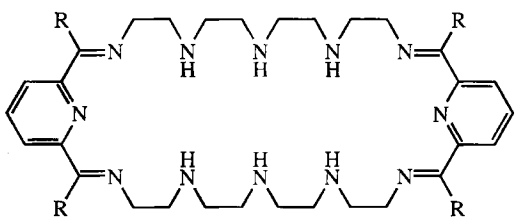
Manganese(II), iron(II), zinc(II) and mercury(II) are not effective as template centres for the assembly of L778 and L779. Products of unidentifiable composition containing carbonyl groups not involved in the reaction are formed in the presence of these ions.

3.4 Macrocycles based on 2,6-dicarbonylpyridines and diamines containing three additional supporting donor atoms

The simplest amine ligson containing two terminal NH_2 groups and three additional nitrogen donor atoms in its chain is tetraethylenepentamine

$H_2N(CH_2CH_2NH)_3CH_2CH_2NH_2$ (tetraen). Data on the employment of the tetraen ligson for template building of 1 + 1 macrocyclic condensation products (H_3L780, H_3L781) by reaction with dap or 2,6-dfp are rather scarce in the literature [98, 159, 160], and the synthesis of 2 + 2 macrocycles such as L782, L783 has not been reported so far (Eq. 3.67). A search of the Crystallographic Database at Daresbury showed a lack of structural data for H_3L780, H_3L781, their metal complexes or related derivatives. It has been reported, however, that the reaction of $FeCl_2 \cdot 4H_2O$ with dap and tetraen in water in the presence of dioxygen followed by addition of an excess of KI as counter anion supplier results in the formation of the iron(III) complex of the 1 + 1 macrocyclic ligand product $[Fe^{III}(H_2780)]I_2$ [98]. The flexibility and potential denticity of H_3L780 presumably permitted its octahedral coordination to iron(III). It was also reported that europium(II) promotes the formation of H_3L780, isolated as $Eu^{II}(H_3L780)(ClO_4)_2 \cdot 4H_2O$ [159,160]. The oxidation state of europium has been proved by redox titration with $K_2Cr_2O_7$.





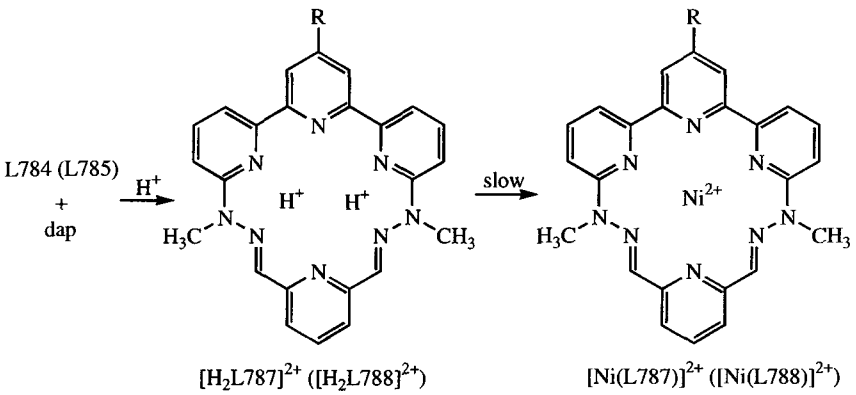
(3.67)

$R = CH_3$ H_3L780 $R = CH_3$ L782

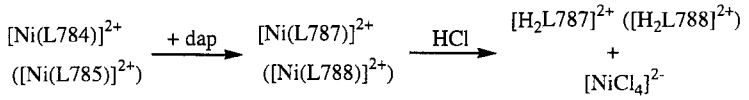
$R = H$ H_3L781 $R = H$ L783

Like tetraen, terpyridine derivatives L784–L786 contain two terminal $-NH_2$ groups able to enter Schiff base condensation reactions and three potential donors in the ligson framework (Eq. 3.68). However, in contrast to tetraen these systems possess high rigidity. This circumstance introduces some peculiarities into the course of template reactions involving their participation. Treatment of a methanolic solution of L784 or L785 with nickel(II) acetate, with subsequent addition of an equivalent amount of dap and an excess of hydrochloric acid, results in the rapid formation of a deep orange solution from which, upon addition of NH_4PF_6, the metal-free macrocyclic salts $H_2L787(PF_6)_2$ and $H_2L788(PF_6)_2$ are deposited [161].

The formation of the free ligands in these reactions is not surprising, if one takes into account the lack of complementarity between geometrical parameters of the nickel(II) (6.9 nm) ion and ligand cavity (11 nm). This mismatch causes the labilisation of the metal complex, permitting an easy liberation of the metal ion. This was fully confirmed by a range of spectroscopic techniques (EI and FAB mass spectra, ^1H NMR spectra). It was found that the metal-free ligands were obtained easily if the reaction solutions were moderately concentrated and strongly acidic. In dilute or weakly acidic solution the products were the nickel(II) complexes $[Ni(L787)(MeOH)_2](PF_6)_2$ or $[Ni(L788)(MeOH)_2](PF_6)_2$. Two possible mechanisms have been suggested:

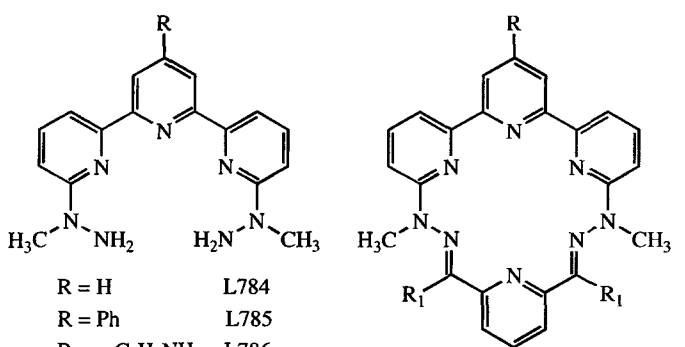


Scheme 3-4. Possible route to $[Ni(L787)]^{2+}$ and $[Ni(L788)]^{2+}$.



Scheme 3-5. The synthesis of ligand products $[H_2L787]^{2+}$ and $[H_2L788]^{2+}$ by transient template route.

(i) the reaction might be specific and catalysed, with the proton acting as true template, with slow incorporation of nickel(II) into the macrocyclic product (Scheme 3-4);
(ii) the reaction might involve a true transient template effect with a nickel(II)-mediated condensation followed by an acid-dependent demetallation (Scheme 3-5) [161].



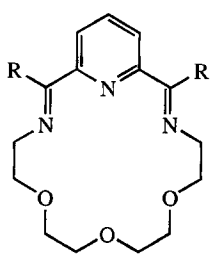
(3.68)

It is believed [161] that the key step in the formation of the metal-free macrocy-

clic ligands is an acid-catalysed chloride ion-specific demetallation. This explains why the reaction is specific to HCl, and why the metal ion must be present.

Europium(III) has proved to be a suitable template with which to control the 1 + 1 condensation of dap with L786 in the presence of a small amount of concentrated HCl, promoting the formation of $[Eu^{III}(HL789)(H_2O)_2Cl]Cl_3 \cdot 2H_2O$ in 44% yield [162]. X-Ray diffraction of the latter revealed the coordination of all six nitrogen donor atoms, which form a slightly distorted boat due to tight binding to the metal ion and in order to minimise the repulsion between the neighbouring methyl groups attached at the non-coordinating hydrazine atom and pyridine diimine moiety. The two H_2O molecules bonded to Eu^{III} are accommodated on the concave side of the coordinated macrocycle, and the chloride ion on the convex side of the complex.

For templated synthesis of the 18-membered N_3O_3 macrocycles L790 and L791 (Eq. 3.69), the most effective proved to be lead(II), alkaline earth and lanthanide(III) ions. For example, $Pb(L790)X_2$ and $Pb(L791)X_2$ (X = NCS, $ClO_4 \cdot \frac{1}{2}H_2O$) are obtained on template condensation of dap or 2,6-dfp with 3,6,9-trioxa-1,11-diaminoundecane in hot aqueous ethanol in the presence of lead(II) thiocyanate or lead(II) perchlorate [113, 163].



R = CH_3 L790
R = H L791

(3.69)

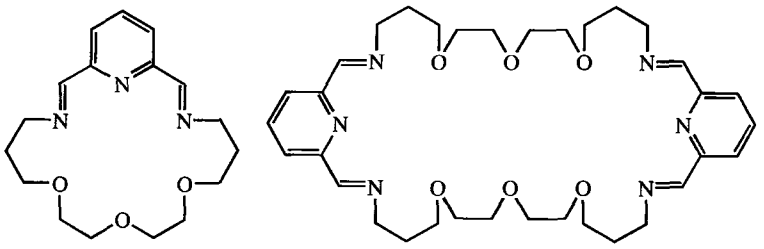
According to the X-ray diffraction study of [Pb(L791)(NCS)(SCN)] [163,164], the central ion is bonded to all donor atoms (on average, the Pb–O and Pb–N separations are 30.7 and 26.0 nm, respectively). The thiocyanate groups are positioned above and below the macrocyclic ligand plane, one of them being coordinated through its sulphur atom and the other through its nitrogen atom. The lead(II) ion is coplanar with the pyridine ring. The donor atoms of L791 are displaced from the pyridine ring plane, the oxygen atoms being the most displaced from this plane.

Complexes $[M(L790)X_2] \cdot nH_2O$ (X = NCS; M = Ca, Sr, Ba; n = 0. X = ClO_4 with M = Ca, Sr; n = 0 or with M = Ba, n = 1) and complexes $[M(L791)X_2] \cdot nH_2O$ (X = NCS with M = Ca; n = 0 or with M = Sr, Ba; n = 1. X = ClO_4 with M = Ca; n = 0 or with M = Sr, Ba; n = 1) are obtained on reaction in 1:1 ratio in ethanol or butanol [165]. (Note that Mg^{II} does not promote the assembly of L790 and L791.) The X-ray analyses of $[Ca(L791)(NCS)_2]$ and $[Sr(L791)(NCS)_2(H_2O)]$ showed [166] that in both complexes the central atoms are bonded to all donor atoms of the macrocycle. The smaller calcium(II) is located approximately within the median plane determined by the donor oxygen and

nitrogen atoms of L791, whereas the strontium(II) is displaced from this plane by 5.3 nm. The M–O and M–N distances are approximately equal (27.8 nm for the strontium and 26.4 nm for the calcium complexes, respectively). The difference in the average distance between metal and donor atoms (1.4 nm) is attributed to the difference between the cation radii (Ca^{2+} 10.0 nm, Sr^{2+} 11.8 nm). The coordination number of the Ca^{II} in the complex is eight, due to two extra thiocyanate groups coordinated above and below the L791 plane, through their sulphur atoms. The coordination number of the Sr^{II} is nine, with two SCN groups on one side of the macrocycle and a water molecule on the opposite side. The complex $[Ba(L791)(NCS)_2(H_2O)]$ is isostructural with the strontium compound [166]. Upon heating these alkaline earth metal complexes in aqueous ethanol with $Pb(SCN)_2$, transmetallation takes place with formation of [Pb(L791)(NCS)(SCN)]. The formation of the latter may be explained by the preference of lead(II) to form bonds with nitrogen rather than oxygen atoms [166].

Lanthanum(III) nitrate and cerium(III) nitrate have been found to promote the 1 + 1 condensation of dap with 1,11-diamino-3,6,9-trioxaundecane in ethanol, to form $[M(L790)(NO_3)_3]$ (M = La, Ce) in 10–13% yield [167]. Transmetallation of barium(II) in $Ba(L790)(ClO_4)_2 \cdot H_2O$ by samarium(III) nitrate or neodymium(III) nitrate yielded $M(L790)(NO_3)_2ClO_4 \cdot H_2O$, where M = Sm or Nd. An X-ray crystal structure determination for $[La(L790)(NO_3)_3]$ revealed 12-coordinated lanthanum(III), the metal ion being bonded to all donor atoms of the macrocycle, and the three bidentate nitrate groups, two on one side and one on the other side of the macrocycle [167].

It has been shown [168, 169] that even copper(II) can promote the construction of large 1 + 1 macrocycles such as 20-membered L792 (Eq. 3.70), if its template effect is combined with the effect of high dilution. Thus, slow addition of one equivalent of 1,13-diamino-4,7,10-trioxatridecane to a methanol solution containing one equivalent each of 2,6-dfp and copper(II) chloride, followed by addition of an excess of NH_4PF_6, affords the copper(II) complex $[Cu^{II}(L792)Cl(H_2O)]PF_6$. An X-ray structure determination showed L792 to be coordinated to the copper(II) only through the nitrogen atoms. The coordination polyhedron around the copper(II) is a nearly square pyramidal with a water molecule occupying an axial site (Figure 3-6).



L792 L793 (3.70)

Using nickel(II) as the template and changing the ratio of interacting ligsons from 1:1:1 to 1:2:2 permitted the assembly of the 2 + 2 macrocycle L793, isolated

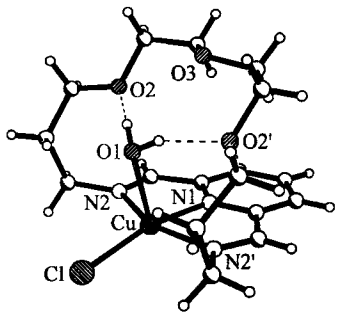
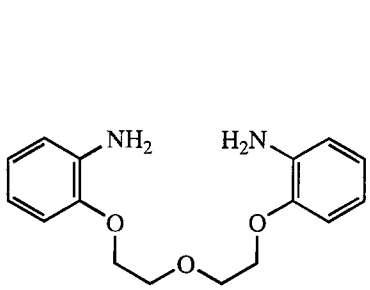


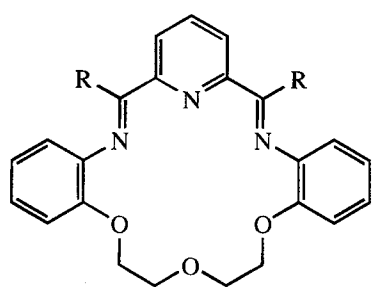
Figure 3-6. The structure of $[Cu(L792)Cl(H_2O)]^+$.

as $[Ni(L793)](PF_6)_2$ in 31% yield [169]. According to X-ray structure analysis L793 is hexadentate, coordinating only through nitrogen donor atoms to octahedral nickel(II). These results indicate that the metal ion size is not crucial for the success of the macrocyclisation process as long as the developing ligand product is able to provide the preferred mode of coordination of the templating metal ion.

The reaction of 2,6-dfp and L794 (Eq. 3.71) in methanol yields a yellow solid which proved to be a mixture of 1 + 1 condensation products (cyclic and acyclic), as well as polymeric products. Attempts to separate the macrocyclic compound failed [165]. However, the synthesis of macrocyclic compound L795, isolated in the form of metal complexes, has been carried out in the presence of manganese(II) [149], calcium(II), strontium(II), barium(II) [165], lead(II) [170, 171] and lanthanide(III) [172]. A template method using Ln^{III} ions (Ln = La, Ce, Pr, Nd and Gd) was found to be effective in the formation of metal complexes of the macrocycle L796 [147].



L794



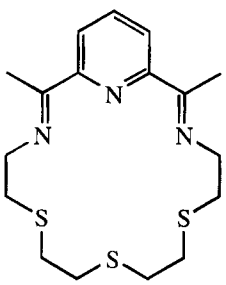
(3.71)

R = H L795

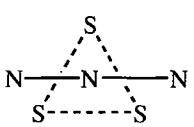
R = CH_3 L796

Condensation of 3,6,9-trithia-1,11-diaminoundecane with dap in the presence of silver(I) nitrate followed by addition of $NaClO_4$ gives rise to $Ag(L797)ClO_4$ (Eq. 3.72). Addition of the stoichiometric amount of $NaBPh_4$ leads to isolation of $Ag(L797)BPh_4$ [173]. The complex $Ag(L797)ClO_4$ is also obtained directly from $AgClO_4$ [174]. The $[Ag(L797)]^+$ cation has been structurally characterised as its tetraphenylborate [173] and perchlorate [174] salts (Eq. 3.73). Both salts contain the same N_3S_3 ligand donor set, which may be considered as comprised of the same

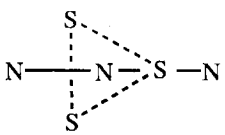
pair of moieties: (i) an essentially planar *mer*-triaza system, and (ii) an essentially *fac*-triangular trithia donor set. These two units may, in principle, adopt any rotational position relative to each other; in fact, the results of the two structure determinations show dispositions approaching the two symmetrical arrays which contain (quasi-) mirror planes normal to, and containing, the triaza array, respectively [174].



L797 (3.72)



Perchlorate and

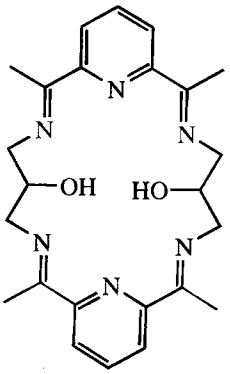


Tetraphenylborate (3.73)

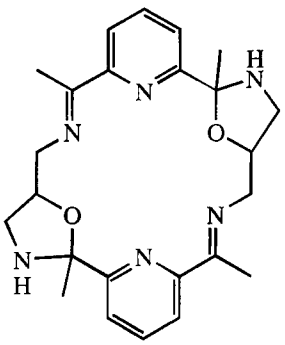
3.5 Macrocycles derived from 2,6-dicarbonylpyridines, 2,5-diformylpyrrole and 1,3-diaminopropan-2-ol

Insertion of an –OH group into the framework of ligsons with primary terminal amino groups was performed in order to favour the formation of polynuclear macrocyclic compounds by templated synthesis. Unexpectedly, this structural modification led to new stoichiometries for the condensation reactions in which they participate. The ligsons considered so far react in the presence of a metal template with dap or 2,6-dfp to give, as a rule, 1 + 1 and/or 2 + 2 macrocyclic ligand products. Examples of 2 + 2, 3 + 3 and 4 + 4 condensations and of metal-controlled ring contraction or expansion rearrangements are discussed in this section.

Mononuclear barium(II) complexes of H_2L798 (Eq. 3.74) are obtained by reaction of dap with 1,3-diaminopropan-2-ol in methanol in the presence of $Ba(ClO_4)_2$ or $Ba(NCS)_2$, in molar ratio 2:2:1. The peak with *m/z* 434 corresponding to metal-free H_2L798 is the most intense in the mass spectra of these complexes [175]. An X-ray diffraction study of $[Ba(H_2L798)(H_2O)_2](ClO_4)_2$ showed [175] that all donor atoms of H_2L798 and two water molecules are involved in coordination to form a square antiprism with two extra vertices.



H_2L798



L799

(3.74)

If lead(II) [175, 176] or calcium(II) [177] is employed as the matrix, complexes with the 'contracted' ligand product L799 are formed. The X-ray data for [Pb(L799)(NCS)]NCS·CH_3OH favour the structure shown above [175, 176]. In this case a nucleophilic addition of an OH group across a neighbouring azomethine bond, followed by proton migration to the nitrogen atom, occurs as a result of reaction directed by the metal ion assembling the final product. This leads to a better match between metal and ligand size. That this is a metal-induced rearrangement has been confirmed by transmetallation reactions. Thus refluxing a mixture of $Pb(L799)^{2+}$ with two equivalents of silver perchlorate resulted in ring expansion and formation of $Ag_2(H_2L798)(ClO_4)_2 \cdot 2H_2O$. The product is identical with the sample obtained from $Ba(H_2L798)(ClO_4)_2 \cdot 2H_2O$ and $AgClO_4$ using the same metal exchange procedure.

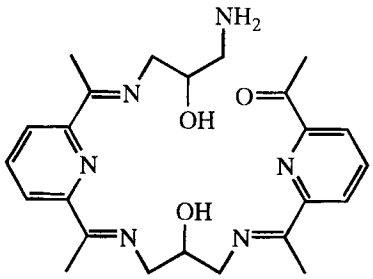
Similarly, transmetallation of $[Ba(H_2L798)(H_2O)_2](ClO_4)_2$ by copper(II) perchlorate in ethanol gave the binuclear species $Cu_2(HL798)(ClO_4)_3 \cdot 2H_2O$ which, after recrystallisation from acetonitrile, was characterised by X-ray diffraction to be $[Cu_2(HL798)(CH_3CN)H_2O](ClO_4)_3$ [178]. Each copper atom has a nearly square-pyramidal geometry. The macrocycle is coordinated to each of them through three nitrogen atoms, the bridging alkoxide, and an axial H_2O and CH_3CN molecule respectively. Interestingly the OH group of the macrocycle is not involved in coordination to the metal ions.

The barium(II) in $[Ba(H_2L798)(H_2O)_2](ClO_4)_2$ has also been claimed to have been replaced by iron(III) to form the corresponding binuclear complex of $(L798)^{2-}$, containing two seven-coordinated iron(III) ions bridged by both alkoxide groups [179].

Transmetallation of $[Ba(H_2L798)(H_2O)_2](ClO_4)_2$ by VCl_3 in methanol gives $[V^{III}_2(L798)(H_2O)_4](ClO_4)_4 \cdot 2H_2O$ [180]. X-Ray crystal structure determination showed a highly symmetrical cation with a centre of inversion in the middle of the binuclear species. The coordination geometry of each V^{III} is a pentagonal bipyramid made up of two H_2O molecules in the axial positions and N_3O_2 set of donors of the macrocycle in the equatorial pentagonal plane. Each of the alkoxide groups bridges two V^{III} centres intramolecularly. It is worth noting that the same product has been obtained when $VOSO_4 \cdot 3H_2O$ is employed as the metal exchange salt

[181]. The transmetallation process is accompanied by reduction of V^{IV} to V^{III}. This indicates the stabilising effect of the H_2L798 for vanadium(III). Two vanadium(III) ions can also be incorporated within the macrocyclic cavity by direct template condensation of the corresponding ligsons in the presence of oxovanadium(IV) [181].

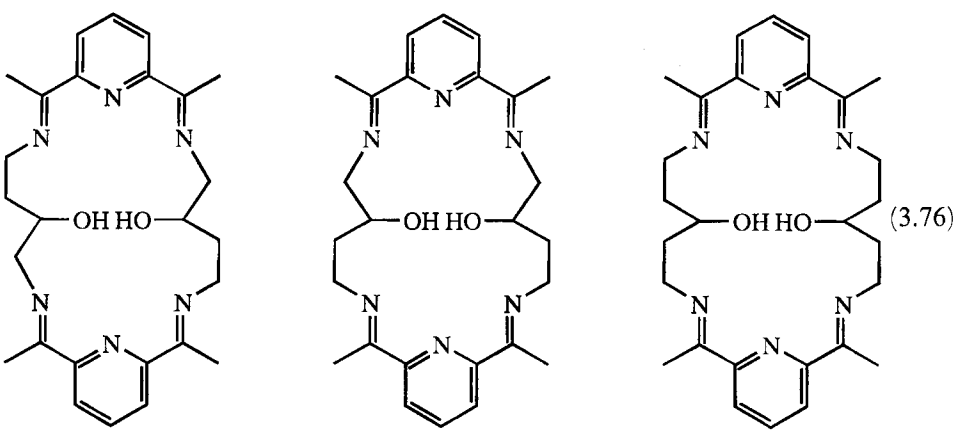
If condensation is assisted by strontium(II) perchlorate in methanol at room temperature, the complex $Sr(H_2L800)(ClO_4)_2 \cdot 3H_2O$ is produced (Eq. 3.75).



H_2L800 (3.75)

The strontium(II) complex with the contracted 18-membered ligand L799 is prepared by dissolving the above product in CH_3OH–CH_3CN (10:1 mixture) followed by prolonged stirring of the solution at room temperature [175].

Dap reacts with 1,4-diaminobutan-2-ol in hot methanol in the presence of $Pb(ClO_4)_2$ to form binuclear $Pb_2(H_2L801)(ClO_4)_3(OH)$; the reagents are taken up in 1:1:1 molar ratio. The ^1H NMR data indicate the existence of H_2L801 in the form of two isomers A and B (Eq. 3.76) [175].



A B H_2L802 (3.76)

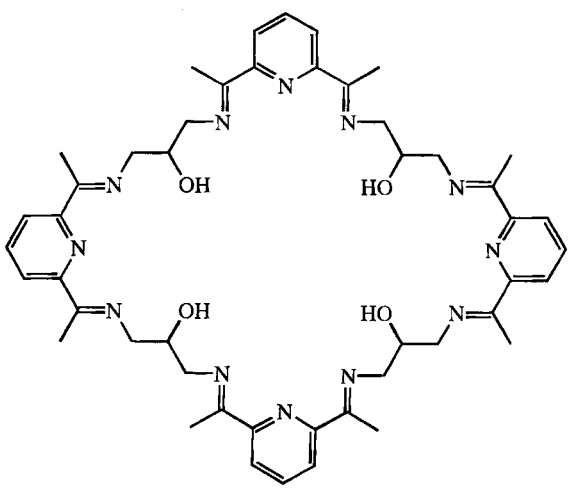
H_2L801

The complexes $Pb_2(H_2L802)(ClO_4)_3(OH)$ and $Pb_2(H_2L802)(NCS)_4$ are obtained by template condensation between dap and 1,5-diaminopentan-3-ol on $Pb(ClO_4)_2$

and $Pb(NCS)_2$ respectively [175]. The peak with $m/z = 490$, corresponding to $[H_2L802]^+$, is the most intense in the mass spectrum of the thiocyanate complex. Thus, an increase in the size of the macrocycle results in accommodation of two lead(II) ions within the macrocycle cavity.

Note that in all cases considered above polymeric compounds are formed in the absence of metal ions at normal concentrations of reagents as well as at high dilution. In addition, metal-free ligand products cannot be obtained by demetallation, so the cation exchange technique is most explored for the synthesis of other metal complexes. For instance, $[Cu_2(HL801,A)(H_2O)_2](ClO_4)_3$ and $[Cu_2(HL802)(H_2O)_2](ClO_4)_3$ are prepared from the corresponding dilead(II) complexes by transmetallation with copper(II) salt in methanol. The structures of the copper(II) complexes with H_2L801 and H_2L802 have been established by X-ray diffraction [182].

Complicated and peculiar transformations occur when Ba^{II} is replaced by Mn^{II}. Thus, for example, a perchlorate product is formed by the action of an excess of $Mn(ClO_4)_2 \cdot 6H_2O$ on a methanolic or ethanolic solution of $[Ba(H_2L798)(H_2O)_2](ClO_4)_2$. If an excess of NaNCS is added to the boiling reaction mixture, a thiocyanate complex is isolated [179]. By crystallization of the latter from acetonitrile $[Mn_4(L803)(ClO_4)_4] \cdot 2H_2O$ and $[Mn_4(HL798)(L798)(NCS)_4]NCS$ have been obtained. Tetranuclear structures for these substances were proved by X-ray diffraction studies [179]. The H_4L803 formed (Eq. 3.77) is a product of 4 + 4 condensation between dap and 1,3-diaminopropan-2-ol; it is coordinated to four manganese(II) ions via all 16 donor atoms.



H_4L803 (3.77)

The alcohol groups are deprotonated and each bridges three manganese ions, forming a central cubane-type structure with stoichiometry $Mn_4(alkoxide)_4$. Every metal ion is seven-coordinate, bonded to three alkoxide oxygen donors, three nitrogen atoms from a pyridine-diimine unit, and one perchlorate oxygen. The coordination polyhedron approximates to a pentagonal bipyramid (Figure 3-7) [179, 183].

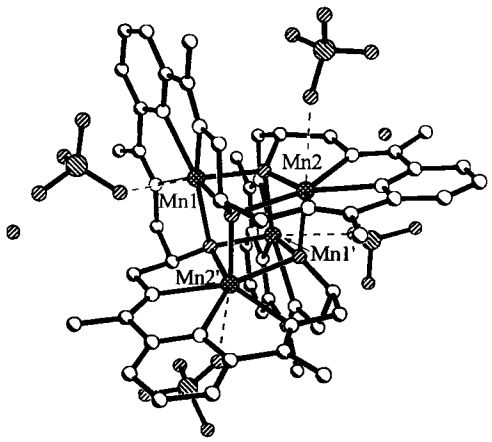


Figure 3-7. The structure of $[Mn_4(L803)(ClO_4)_4]\cdot 2H_2O$

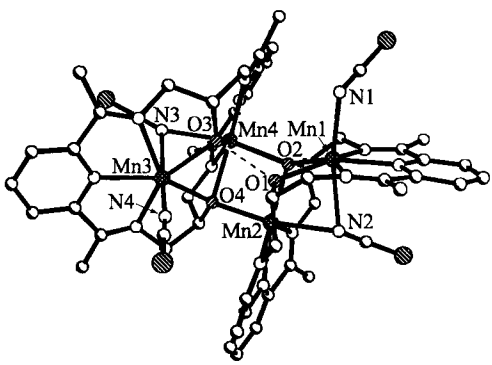


Figure 3-8. The structure of the cation $[Mn_4(HL798)(L798)(NCS)_4]^+$.

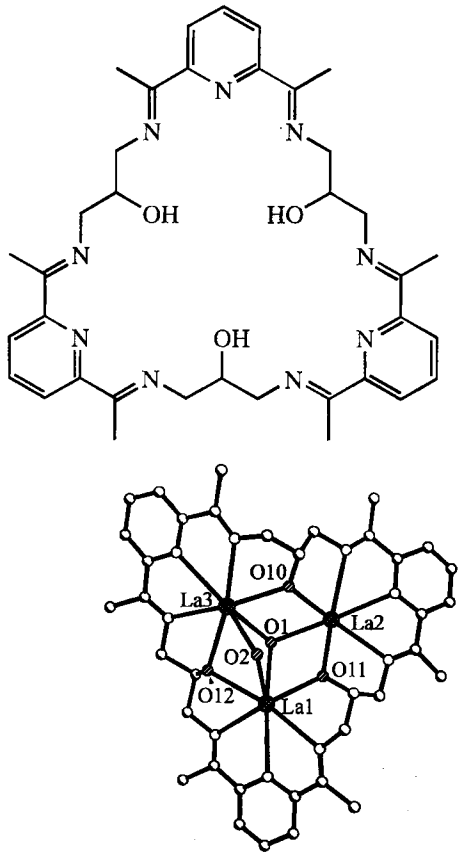
The thiocyanate complex has a dimeric structure with two (2 + 2) macrocyclic units linked together as shown in Figure 3-8. The two halves of the dimeric structure are crystallographically independent and have significant geometrical differences. Like the perchlorate complex, each manganese ion has an approximately pentagonal-bipyramidal geometry. Three atoms of a pyridine-diimine fragment and two oxygen atoms of the same macrocycle are arranged in the pentagonal plane. A thiocyanate bridging group is coordinated by its nitrogen atom in one of the axial positions. The central Mn1 and Mn2 are bound to N2, and Mn3 and Mn4 to N3. The coordination numbers of Mn1 and Mn3 are made up to seven by N1 and N4 donor atoms of terminal NCS groups respectively, and Mn2 and Mn4 by oxygen atoms O4 and O2 of a neighbouring macrocycle. The dimeric structure is maintained by these Mn2–O4 and Mn4–O2 intermolecular interactions [179]. The alkoxides O1 and O3 are doubly bridging, while O2 and O4 are triply bridging. The atoms O1 and O3 are linked by a hydrogen bond.

The preparation of H_4L803 was quite accidental [183], so the question of the mechanism of its formation arose. A small amount of the compound has been

supposed to be formed by reaction of dap with 1,3-diaminopropan-2-ol on the Ba^{II} matrix and isolated mainly as a result of the subsequent transmetallation by Mn^{II}. Such a route appeared possible because Ba^{II} binds preferentially to alkoxide donors rather than to the softer imine nitrogens. However, another pathway to the formation of H_4L803, namely during the transmetallation reaction with manganese(II), cannot be ignored. Indeed, mass spectrometry has proved unambiguously that the second route was effective [179]. More precisely, the mass spectrum of non-recrystallised barium(II) compound was found to have no peak assignable to the ions corresponding to $[Ba_2(H_4L803)]^{4+}$, H_4L803 or to products of their fragmentation. However, the signals corresponding to the Mn_4L803 fragment and to products of $Mn_2(L798)$ fragmentation ($m/z = 1400$ and 540 amu) have been observed in the mass spectrum of a manganese perchlorate complex obtained by transmetallation. A peak assignable to a molecular ion with $m/z \approx 1200$ amu is present in the mass spectrum of the thiocyanate complex, which gives evidence in support of significant strength of the metal–ligand bonds linking the macrocyclic halves into a single dimeric unit.

The pseudo-cubane cluster $Mn_4(alkoxide)_4$ is supposed [179] to hold ligsons in positions suitable for their mutual interaction and therefore to play the role of templating moiety in the process of (4 + 4) ligand product formation. The picture presented above indicates that tetranuclear manganese compounds are the most stable of the reaction products, at least kinetically, and that these substances could also be prepared via direct template synthesis using Mn^{II} as the matrix [179]. In accordance with mass spectrometry data, a perchlorate complex similar to that obtained by transmetallation of the barium(II) complex with H_4L803 is actually produced by the condensation between dap and 1,3-diaminopropan-2-ol in the presence of manganese(II) perchlorate. The addition of sodium thiocyanate to the reaction mixture yields $[Mn_4(HL798)(L798)(NCS)_4]\cdot 2H_2O$. The effectiveness of manganese(II) as template is reduced presumably because of the blocking of coordination positions around the central ion, which could otherwise be occupied by $-NH_2$ and C=O groups or NCS^- ions with high coordination ability.

Lanthanides(III) can be used as template centres to promote the condensation between dap and 1,3-diaminopropan-2-ol to give macrocyclic ligand products [184–186]. The process can be directed to different pathways (3 + 3 and 2 + 2) depending on the sequence of reagents added. Specifically, if equimolar amounts of $La(NO_3)_3\cdot 6H_2O$ and dap were added successively to a methanolic solution of 1,3-diaminopropan-2-ol and then the reaction mixture heated to boiling and left in a stoppered flask for 24 h, $La_3(L804)(NO_3)_6\cdot 3CH_3OH$ was formed. The presence of a peak in the FAB mass spectrum with $m/z = 1375$ assigned to $[La_3(L804)(NO_3)_6{-}NO_3]^+$ was the first reliable evidence of its formation. ^1H NMR and nuclear Overhauser effect difference spectra were consistent with the 3 + 3 ligand product being formed. The same condensation reaction was recently reported [177] to produce $[La_3(L804)(OH)_2(NO_3)_4]\cdot 7H_2O$. The X-ray diffraction study confirmed the 3 + 3 pathway of template condensation and revealed the triangular arrangement of lanthanum(III) ions within the macrocycle cavity (Figure 3-9) [177]. The difference in composition between the two products obtained by different groups, $La_3(L804)(NO_3)_6\cdot 3CH_3OH$ [186] and $[La_3(L804)(OH)_2(NO_3)_4]\cdot$



H_3L804

Figure 3-9. The structure of the fragment $La_3(L804)(OH)_2$ in $[La_3(L804)(OH)_2(NO_3)_4]\cdot 7H_2O$.

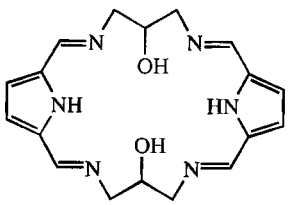
$7H_2O$ [177], may be attributed to partial hydrolysis of the former compound during its preparation. Praseodymium(III), europium(III) and gadolinium(III) have also been found to promote the 3 + 3 condensation pathway.

If, however, the 1,3-diaminopropan-2-ol is added to a methanolic solution of lanthanide(III) nitrate or thiocyanate and dap (in the molar ratio 1:1:1), and the reaction mixture refluxed for 2–3 h, kinetically stable $Ln_2(L798)(NO_3)_4(H_2O)_5$ (Ln = La, Pr) or $Ln_2(L798)(NCS)_4(H_2O)_4$ (Ln = La, Pr, Nd, Sm, Eu) respectively are claimed to have been isolated [185]. Unfortunately, the products were characterised only by elemental analysis, IR and ^{13}C NMR spectra, which do not permit a reliable assignment of the macrocycle formed as the 2 + 2 condensation product. For labile metal ions such as the lanthanides the sequence in which reagents are added should not have a critical influence on the stoichiometry of condensation. Nevertheless the occurence of a 2 + 2 condensation mechanism initiated by coordination of dap to a lanthanide(III) ion (in accordance with synthetic procedure employed) could not be totally excluded.

It should be noted that viscous oils of oligomeric or polymeric composition [175,

179] are formed in the absence of metal ions at normal concentrations of reagents or at high dilution.

If pyrrole-2,5-dicarbaldehyde is used as a dicarbonylheterocyclic ligson, it condenses with 1,3-diaminopropan-2-ol with formation of H_2L805 in the absence of a metal centre (Eq. 3.78) [187].

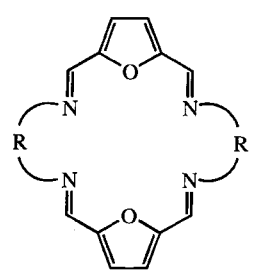


H_2L805 (3.78)

A small amount of resin-like polymer, produced when the reaction mixture is refluxed, may readily be separated by filtration. The macrocyclic nature of H_2L805 has been confirmed by the presence of the peak corresponding to the parent ion in its mass spectrum.

3.6 Macrocycles derived from 2,5-diformylfuran, 2,5-diformylthiophene and 1,*n*-diamines

2,5-Diformylfuran (dff) and 1,*n*-diamines also give macrocyclic compounds in the presence of appropriate template centres. Viscous oils of a polymeric nature are produced in the absence of metal ions. Complexes of the macrocyclic ligands L806–L808 (Eq. 3.79) [188] with a 1:1 metal–ligand composition are synthesised by reaction of the corresponding ligsons on an Ln^{III} matrix (Ln = Lu–Eu).



$R = (CH_2)_2$	L806
$R = (CH_2)_3$	L807
$R = CH_2CH(CH_3)$	L808
$R = o\text{-}C_6H_4$	L809

(3.79)

The macrocyclic structure of the ligands has been verified by the absence of bands assignable to stretching vibrations of carbonyl and primary amino groups and by the presence of $\nu_{C=N}$ in the IR spectra, as well as by the mass spectra of template synthesis products in which peaks assignable to $[L806]^{+\cdot}$, $[L807]^{+\cdot}$ and $[L808]^{+\cdot}$ were apparent.

The template reaction of dff with en in the presence of lanthanide(III) (Gd-Lu)

nitrate results in the isolation of complexes with a metal–ligand ratio of 3:2. As in the cases considered above, a peak with $m/z = 296$ assigned to $[L806]^{+\cdot}$ is present in the mass spectra of these compounds. In contrast to the compounds based on dap and diamine ligsons, these products decompose on dissolving in water. The complex $Lu(L807)(NO_3)_3$ undergoes transmetallation by copper(II) perchlorate to form $Cu_2(L807)(ClO_4)_2$ [188].

Products formed by the metal ion and L807 in a 1:1 ratio are obtained, in 60–95% yield, on reaction of the corresponding ligsons on Ca^{II}, Sr^{II}, Ba^{II} or Pb^{II} matrices. Resins or amorphous powders of variable composition are produced in the presence of Mg^{II} [189].

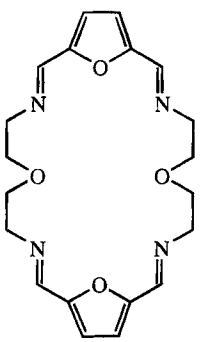
Barium(II) compounds with 1:2 metal–ligand stoichiometry are prepared by addition of $NaBPh_4$ and $Co(NCS)_2$ to acetonitrile–ethanol solutions containing $[Ba(L807)(ClO_4)_2]\cdot C_2H_5OH$. The structure of $[Ba(L807)_2(H_2O)_2][Co(NCS)_4]$ has been established, and the central atom has been shown to be 11-coordinate. It is bound to all six donor atoms of the first macrocyclic ligand, three atoms of the second one (O and two N) and two water molecules. The formation of such a product is a consequence of the large size of Ba^{II} and the tendency of this ion to have high coordination numbers. It should be noted that coordination number 12 is not reached, perhaps because in a sandwich structure atoms of two non-planar macrocycles L807 come into extremely close contact [189].

Alkaline earth metal ions in their complexes with L807 are replaced by lead(II), silver(I), copper(I), copper(II), cobalt(II) and zinc(II) [189–194]. The reactions involving Pb^{II} and Ag^{I} yield mononuclear products, whereas the transition metals form binuclear compounds. The fact that the macrocycle remains unchanged in the transmetallation reaction has been verified by X-ray diffraction study of $[Cu_2(L807)(SCN)_2]$ [190], $[Cu^{I}_4(L807)_2(CCC_6H_5)](ClO_4)_3\cdot\frac{1}{2}A$ (A = diphenyldiacetylene) [191], $[Cu_2(L807)(OC_2H_5)_2(NCS)_2]$ [192], $[Co_2(L807)(OC_2H_5)(NCS)_3]$ and $[Co_2(L807)(OCH_3)(N_3)_3]$ [193, 194]. The oxygen atoms of the furan ring are not coordinated to the central atom in binuclear compounds.

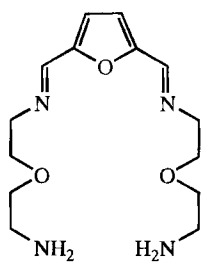
2,5-Diformylfuran condenses with *o*-phda in methanolic solutions of calcium(II), strontium(II) or barium(II) thiocyanate, perchlorate or halide, or lead(II) perchlorate, to give L809 in the form of complexes $M(L809)^{2+}$ (M = Ca, Sr, Pb) and $Ba(L809)_2{}^{2+}$. The peak with $m/z = 392$, present in the mass spectra of thiocyanate complexes and assigned to $[L809]^{+\cdot}$, is the most intense. The macrocyclic structure of L809 has been proved by X-ray diffraction of $[Ba(L809)_2](BPh_4)_2$. The complex cation has a sandwich structure. The barium ion is 12-coordinated, by all the donor atoms of the two L809 molecules [195]. The macrocycle L809 is also formed on a K^+ matrix. The smaller Mg^{II}, Li^{I} and Na^{I} do not promote macrocyclisation. On the basis of IR spectra it was suggested that 2 + 2 condensation occurs in the presence of Rb^{I} and Cs^{I}, but the products isolated are of variable composition [195]. It has been reported that template condensation of *o*-phda and dff in the presence of RbBr in methanol, followed by anion metathesis with $NaBPh_4$, permitted the isolation of two products $[Rb_2(L809)_3](BPh_4)_2$ and $[Na(L809)(CH_3OH)]_2(BPh_4)_2$. The first is of uncommon stoichiometry, but has been confirmed by a preliminary X-ray diffraction study [196]. The formation of the sodium complex presumably occurs by partial transmetallation of rubidium(I) from its complex with L809.

The alkaline earth metal complexes obtained by template synthesis undergo demetallation on reaction with perchloric acid to produce $H_2L809(ClO_4)_2$. The identical product is formed on substitution of alkali and alkaline earth metal ions for iron(III) or copper(II). If $H_2L809(ClO_4)_2$ is treated with a 2–3-fold excess of an aqueous solution of NaOH or NH_4OH in methanol, $Na(L809)ClO_4$ and $NH_4(L809)ClO_4$ are formed, respectively. By heating the reaction mixture to reflux $L809{\cdot}2CH_3OH$ has been obtained, which could also be produced by recrystallisation of the sodium and ammonium compounds from hot methanol.

Reaction of dff with 1,5-diaminopentan-3-ol in the presence of calcium(II), strontium(II), or barium(II) perchlorates yields either the complexes of the (2 + 2) macrocycle L810 or of the open-chain (1 + 2) condensation product L811 (Eq. 3.80). In the absence of a template centre one fails to obtain macrocyclic or open-chain Schiff bases by using these ligsons [197].



L810

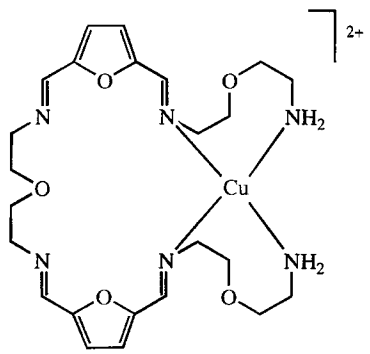


L811 (3.80)

If Ba^{II} is used as template, only $Ba(L810)(ClO_4)_2{\cdot}C_2H_5OH{\cdot}H_2O$ is obtained, but $Sr(L811)(ClO_4)_2{\cdot}H_2O$ is the sole product formed in the presence of strontium(II). Both $Ca(L810)(ClO_4)_2{\cdot}C_2H_5OH{\cdot}H_2O$ and $Ca(L811)(ClO_4)_2{\cdot}H_2O$ are produced in the presence of calcium(II) as matrix. The latter precipitates from ethanol at room temperature due to its poor solubility. The addition of 10% acetonitrile (by volume) to an ethanolic solution to avoid the precipitation of the non-cyclic product, followed by boiling the reaction mixture, produces the macrocyclic complex $Ca(L810)(ClO_4)_2{\cdot}C_2H_5OH{\cdot}H_2O$. The open-chain species L811 is likely to be an intermediate in the synthesis of L810 [197].

Treatment of $Ba(L810)(ClO_4)_2{\cdot}C_2H_5OH{\cdot}H_2O$ with silver(I) perchlorate in acetonitrile leads to the isolation of $[Ag_2(L810)(H_2O)_2](ClO_4)_2$. The latter undergoes demetallation on reaction with $NaBPh_4$ in an acetonitrile–ethanol mixture to form $HL810(BPh_4)$, which gives a peak in its mass spectrum of $m/z = 384$ corresponding to $[L810]^{+\cdot}$.

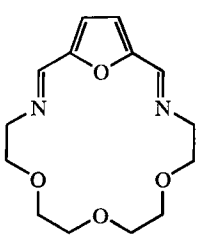
The copper(I) compound $[Cu_2(L810)(H_2O)_2](ClO_4)_2{\cdot}H_2O$ is obtained in good yield on reaction of $Ba(L810)(ClO_4)_2{\cdot}C_2H_5OH{\cdot}H_2O$ with $[Cu(CH_3CN)_4]ClO_4$ in methanol. If copper(II) perchlorate in acetonitrile is used to replace barium in the presence of $NaBPh_4$, the copper(II) complex $[Cu(L812)](BPh_4)_2$ will be the main product. The structure of this complex has been established by X-ray diffraction (Eq. 3.81) [197].



$[Cu(L812)]^{2+}$ (3.81)

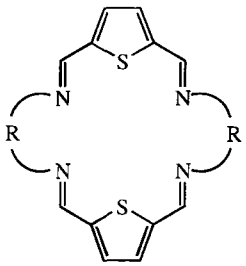
The environment of the central atom has a geometry intermediate between square-planar and tetrahedral. This product has been also synthesised by a template pathway starting from the corresponding ligsons in acetonitrile containing copper(II) perchlorate and $NaBPh_4$, as well as by transmetallation of $M(L811)(ClO_4)_2 \cdot H_2O$ (M = Ca, Sr) with copper(II) perchlorate in the presence of $NaBPh_4$ [197].

The coordination compounds $M(L813)X_2 \cdot nH_2O$ (M = Ca, X = NCS, $n = 0$; M = Sr, X = NCS, $n = 1$; M = Ba, X = NCS, $n = 1$; M = Ba, X = NCS, $n = 1$; M = Pb, X = NCS, $n = 0$; M = Ca, X = ClO_4, $n = 0$; M = Sr, X = ClO_4, $n = 0$; M = Ba, X = ClO_4, $n = 1$) are obtained on reaction of dff with 3,6,9-trioxa-1,11-diaminoundecane in the presence of calcium(II), strontium(II) or barium(II) perchlorate or thiocyanate [198], or lead(II) thiocyanate [113], with the reagents present in 1:1:1 ratio in a mixture of butanol and triethyl orthoformate. The structure of $Sr(L813)(NCS)_2 \cdot H_2O$ (which is essentially isostructural to its pyridyl analogue $Sr(L660)(NCS)_2 \cdot H_2O$ [166]), solved by X-ray diffraction, together with mass spectra of thiocyanate complexes which contain peaks with m/z assigned to $[Ca(L813)NCS]^+$, $[Sr(L813)]^+$ and $[L813]^{+\cdot}$, can be considered as good evidence for the formation of L813 (Eq. 3.82) [199].



L813 (3.82)

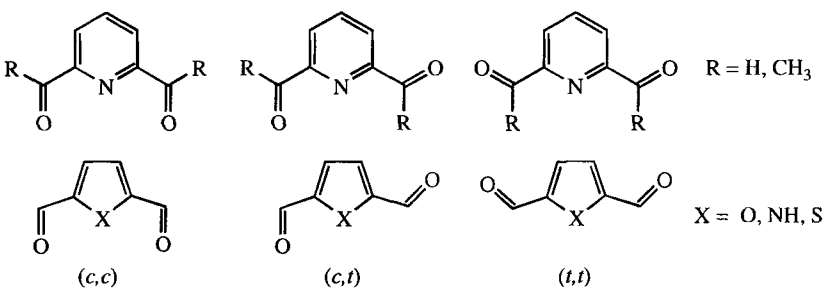
The heterocyclic dicarbonyl-containing ligsons discussed above (with a few exceptions [187]) form macrocyclic compounds by reaction with primary 1,*n*-diamines only in the presence of suitable template centres. In contrast, condensation of 1,*n*-diamines with 2,5-thiophenedialdehyde yield a whole series of macrocyclic systems (L814–L817, L33–L35, L818–L820) in the absence of template ions (Eq. 3.83) [200–202].



$R = (CH_2)_3$	L814
$R = (CH_2)_4$	L815
$R = (CH_2)_5$	L816
$R = (CH_2)_6$	L817
$R = (CH_2)_2S(CH_2)_2$	L33
$R = (CH_2)_2NH(CH_2)_2$	L34
$R = (CH_2)_3NH(CH_2)_3$	L35
$R = (CH_2)_2O(CH_2)_2$	L818
$R = (CH_2)_2O(CH_2)_2O(CH_2)_2$	L819
$R = (CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2$	L820

(3.83)

The study of the heterocyclic dicarbonyl compounds by ^1H NMR and dipole moment measurements demonstrated that they exist in solution in the form of a mixture of the conformers *cis,cis* (*c,c*), *cis,trans* (*c,t*) and *trans,trans* (*t,t*) (Eq. 3.84) [187].



(3.84)

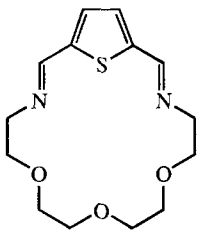
The (*t,t*) conformers dominate in a solution of dfp and dap. In the case of dff the *c,t*:*t,t*:*c,c* ratio is 2:1:1, whereas 2,5-thiophene dialdehyde exists mainly in the *c,c* form.

Note that in the macrocyclic systems derived from heterocyclic carbonyl compounds and primary diamines, C=N bonds are situated in *cis* positions with respect to donor atoms (N or X) [200, 201]. In the light of this it becomes obvious that thiophenedialdehyde, which exists in solution in the *c,c* conformation, is the most suitable with which to form macrocycles. In the cases of other heterocyclic dialdehydes the required *c,c* conformation is achieved on coordination to a template centre.

The macrocyclic compounds L814–L817, L33–L35, and L818–L820 form binuclear silver(I) complexes. The latter can also be obtained *in situ* from 2,5-thiophenedialdehyde and the corresponding 1,*n*-diamine in the presence of Ag(I). The structure of $L819{\cdot}2AgClO_4{\cdot}H_2O$, solved by X-ray analysis, confirmed the binucleating ability of the system considered above. The binuclear compounds $Ba_2(L819)(NCS)_4$, $Ba_2(L820)(NCS)_4$ and $Ba_2(L34)(NCS)_4$ have also been synthesised *in situ* [201].

The Ag^I template effect operates in the reaction of 2,5-thiophenedialdehyde with 3,6,9-trioxa-1,11-diaminoundecane. Prolonged boiling of the reaction mixture

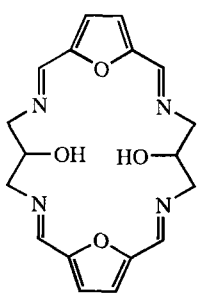
followed by filtration and addition of the filtrate to an excess of $NaClO_4$ gives $Ag(L821)_2ClO_4$, where L821 (Eq. 3.85) is the product of (1 + 1) condensation of the ligsons [201]. The presence of a peak in the mass spectrum with $m/z = 296$, assignable to $[L821]^{+\cdot}$ supports the formation of such a product in the course of the template reaction.



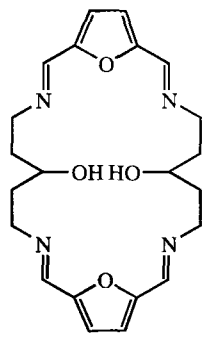
L821 (3.85)

After the isolation of this product the binuclear compound $Ag_2(L820)(ClO_4)_2$ can be separated from the reaction mixture.

As in the case of dap, the reaction of equimolar amounts of dff and 1,3-diaminopropan-2-ol in the presence of $Ba(ClO_4)_2$ (2:2:1 molar ratio) gives the product $Ba(L822)(ClO_4)_2$ (Eq. 3.86).



L822



L823 (3.86)

In a similar way, by using dff and 1,5-diaminopentan-3-ol as ligsons, $Ba(L823)(ClO_4)_2$ was obtained [175]. Structures of both $Ba(L822)(ClO_4)_2$ and $Ba(L823)(ClO_4)_2$ were determined by X-ray diffraction [175].

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Chapter 4

Template synthesis of three-dimensional macrocyclic systems

The coordination template effect is widely used for the preparation of various monomacrocyclic compounds synthesised in two-dimensional space, as exemplified by the material presented in the previous chapters. Examples of reactions between ligsons positioned around a matrix in three-dimensional space are much less common. This chapter illustrates the use of the template effect in elegant syntheses of three-dimensional polymacrocyclic systems.

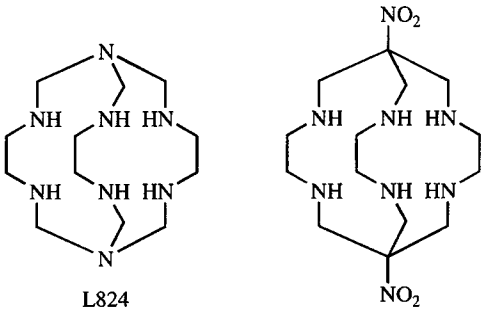
4.1 Clathrochelates

Clathrochelates are polymacrocyclic ligand systems of three-dimensional structure able to encapsulate a metal ion [1]. Strictly, the term 'clathrochelate' applies to the complex formed between a metal ion and an encapsulating ligand, but it is also commonly used for the free ligand. Metal ion-containing molecules, in contrast to metal-free clathrochelates, cannot be drawn in two dimensions without any bond crossing and fall in the category of topologically non-planar systems [2].

4.1.1 Clathrochelates based on 1,2- and 1,3-diaminoalkanes

The synthesis of three-dimensional macrocyclic systems (cryptands, clathrochelates) using common techniques is hindered by the decrease in internal entropy of large flexible fragments condensing during macrocyclisation. One way to overcome this obstacle is to carry out the organic synthesis in the presence of metal ions. The formation of large macrocycles is thus achieved in several individually less unfavourable stages. This strategy has been a very fruitful one for obtaining clathrochelates with meridional nitrogen atoms and apical carbon or nitrogen atoms (sepulchrates, sarcophagines) [3, 4]. The template pathway for assembling cage-like molecules can be very simple and effective. Kinetically inert metal ions cobalt(III), rhodium(III), iridium(III) and platinum(IV) are the most suitable template centres.

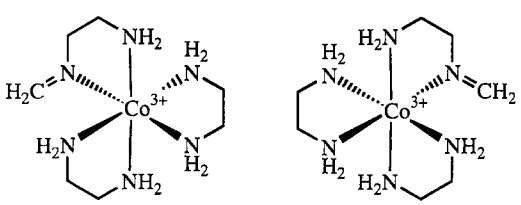
Generally, the two main template strategies exploited are: 'sides + caps' and 'caps + sides' [5], of which the first is used more extensively. Thus the cage-like systems L824 and L825 (Eq. 4.1) are isolated in 40–90% yield by reaction of ethane-1,2-diamine complexes containing these metals with formaldehyde and ammonia or nitromethane [6–11].



L824 L825 (4.1)

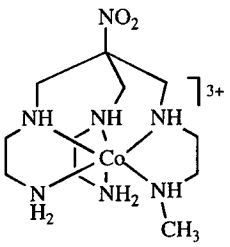
Several reports on X-ray diffraction studies of cobalt(III) complexes of L824 and L825 are available [12–17].

The formation of macrocyclic encapsulated complexes is assumed to proceed as shown in Scheme 4-1 [3] for Rh^{III}, Ir^{III}, Pt^{IV} and, as illustrated, for Co^{III}. The isolation of $[Co(L826]^{3+}$ formed by reaction of $[Co(en)_3]^{3+}$ with formaldehyde [3], and shown in Equation (4.2) in the form of two possible enantiomers (Λ and Δ) due to the helical arrangement of bidentate ligands, provides evidence in favour of the proposed mechanism.



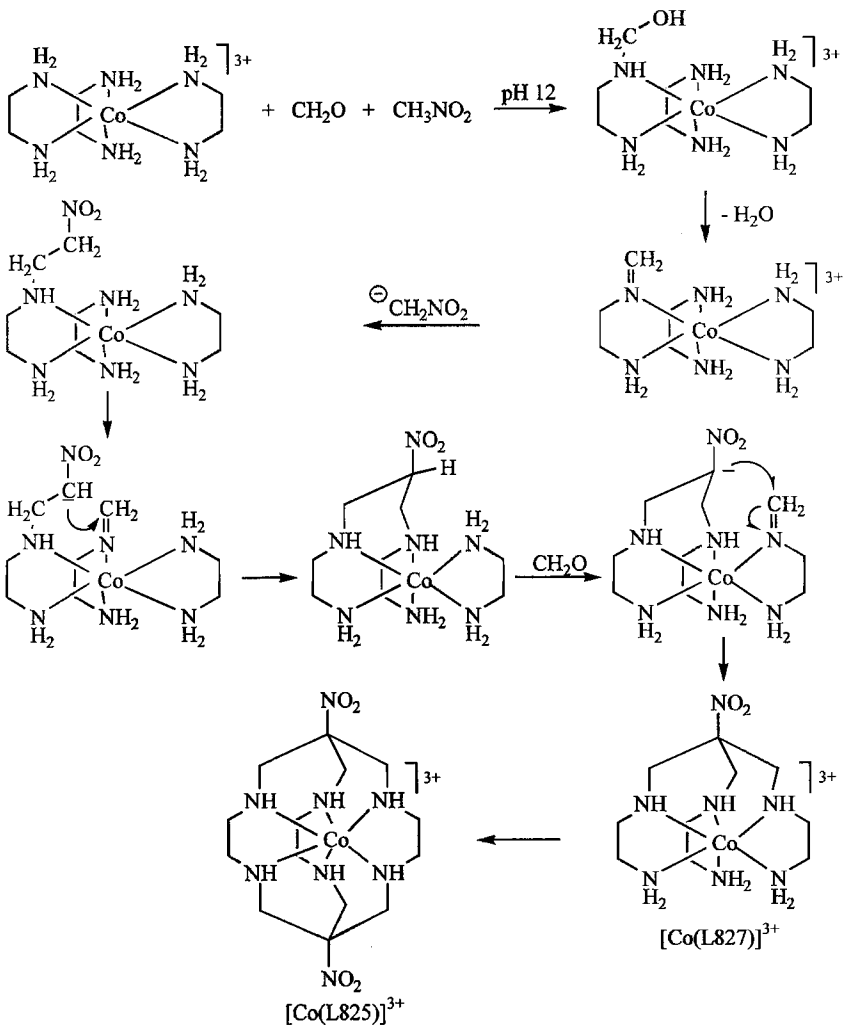
Λ-[Co(L826)]$^{3+}$ Δ-[Co(L826)]$^{3+}$ (4.2)

The encapsulation process is initiated by attack of the nitromethane carbanion on this chelate. As soon as the second imine bond is formed in the neighbourhood of a nitroethyl unit coordinated to a metal, intramolecular cyclisation occurs to form the first capping six-membered metallocycle (Scheme 4-1). The subsequent condensations and cyclisations result in completion of the first cap and assembly of the second, to give the final product $[Co(L825)]^{3+}$. A series of other intermediates may be isolated by quenching the process represented in Scheme 4-1 at certain times. Some of these compounds, for example $[Co(L827)]^{3+}$ and $[Co(L828)]^{3+}$ (Eq. 4.3), have been identified and their structures have been established by X-ray diffraction [17]. The preparation of $[Co(L827)]^{3+}$ provides evidence for a successive capping process.



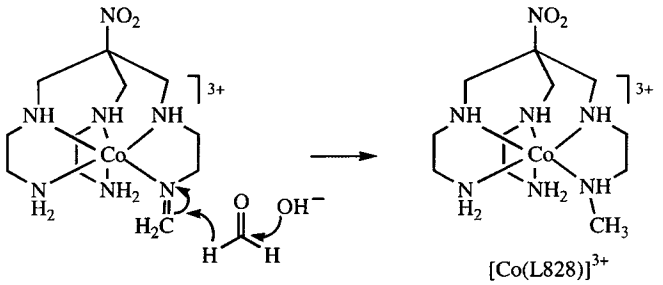
$[Co(L828)]^{3+}$ (4.3)

However the template process can deviate from that represented in Scheme 4-1.



Scheme 4-1. A possible mechanism for the stepwise formation of $[Co(L825)]^{3+}$ by the sides + caps template strategy.

In particular, $[Co(L828)]^{3+}$ is likely to arise from the crossed-Cannizzaro reaction (Eq. 4.4) [8].



(4.4)

Thus, the role of cobalt(III) as template is associated with control of the behaviour of iminium ion by the activation of an imine to nucleophilic attack as a result of its coordination to the central ion [3].

The high regiospecificity of the template encapsulation reaction should be noted. Eleven molecules (three en, six HCHO, and two NH_3 or two CH_3NO_2) participate in the formation of the chelate rings of the final macrocyclic product. In the absence of a matrix a cage-like molecule is believed to be formed in 0.1% yield at best [10]. Moreover, if a chiral octahedral (Table 4-1) ethane-1,2-diamine

Table 4-1. Structural parameters and conformations of $\Lambda(\delta\delta\delta)$-$[Co(en)_3]^{3+}$ and some half and fully encapsulated cobalt(III) species.

Compound	Co–$N_{average}$ (nm)	ϕ or 2θ[a] (°)	α[b] (°)	Cap conformation[c]	Reference
$[Co(en)_3]^{3+}$	19.63	55.0	47.4 50.2 49.8	–	18, 19
$[Co(L827)]^{3+}$	19.67	53.8	51.5 53.6 53.3	λ_{Ncap}	17
$[Co(L825)]^{3+}$	19.92	54.4	55.7 54.5 54.6	$\lambda_{Ncap}\lambda_{Ncap}$	17
$[Co(L824)]^{3+}$	19.90	56.7	55.4 53.6 56.2	$\lambda_{Ncap}\lambda_{Ncap}$	13

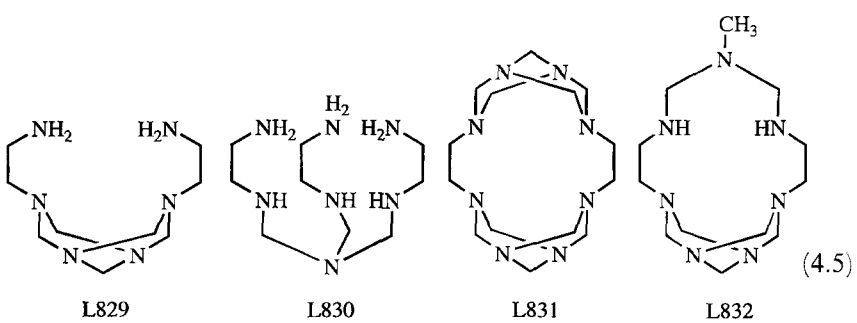
[a] θ = twist angle, characterizing the coordination polyhedron between octahedral ($2\theta = \phi = 60°$) and trigonal prismatic ($\phi = 0°$) [20].

[b] α = torsion angle HN–CH_2–CH_2–NH, characterizing the deviation of the corresponding chelate ring from planarity.

[c] Defined in terms of the projection of the C–N bond on the pseudo-C_3 axis of the complex; in terms of Cahn, Ingold and Prelog (CIP) nomenclature all six stereogenic nitrogen atoms have *S* configuration.

complex Λ-$[Co(en)_3]^{3+}$ having the δ conformation for all three en chelate rings (homoconformational $\Lambda(\delta\delta\delta)$ enantiomer) is involved in the sides + caps template process, a chiral clathrochelate $[Co(L824)]^{3+}$ or $[Co(L825)]^{3+}$ of configuration $\Lambda(\delta\delta\delta)\lambda_{Ncap}\lambda_{Ncap}$ results from the synthesis. The notation $\delta\delta\delta$ indicates the conformations of the five-membered en chelate rings and $\lambda_{Ncap}\lambda_{Ncap}$ the conformations of both top and bottom caps that are built up. Note that this is in spite of the fact that six nitrogen-ligand coordinated atoms become stereogenic upon cage formation and, as a consequence, the number of theoretically possible conformers of the cage increases markedly when compared to the $[Co(en)_3]^{3+}$ case. The structural data given in Table 4-1 clearly demonstrate that the formation of $[Co(L824)]^{3+}$ and $[Co(L825)]^{3+}$ via the monocapped intermediate occurs with minor distortion of the geometry of the starting $[Co(en)_3]^{3+}$ chelate. The situation can be explained by the very specific stereochemistry of the complex cation as well as by the high density and small mobility of the framework of a cage-like molecule [8, 13, 21]. The energy barrier for inversion of one en chelate ring in $[Co(L824)]^{3+}$ has been estimated at 21.6 kJ mol^{-1} [22].

When attempting to carry out the encapsulation of chromium(III), difficulties arise because the formation of an imine bond from the reaction of $[Cr(en)_3]^{3+}$ with HCHO causes the breaking of a Cr–N bond and loss of an adjacent ethane-1,2-diamine ligand [9]. However, it has been reported [23] that $[Cr(L824)](ClO_4)_3$ can be synthesised in 10% yield, although the authors do not present elemental analysis data but merely point out that there are some stretching vibrations characteristic of cage-like systems (ν_{C-H}, ν_{N-H}) in the IR spectrum. Complete encapsulation involving labile ethane-1,2-diamine complexes of bivalent metals has proved elusive. For example, Zn^{II} and Cu^{II} are not suitable for the construction of sepulchrates and sarcophagines [9], although nickel(II) proves to be an exception. As well as nickel(II) complexes with L829 and L830, $[Ni(L824)](ClO_4)_2$ has been isolated in 1% yield as a result of the template condensation of ethane-1,2-diamine with formaldehyde and ammonia [24–26]. The formation of this substance, and of $[Ni(L829)](ClO_4)_2$, has been verified by X-ray structure analysis (Eq. 4.5) [24, 25].



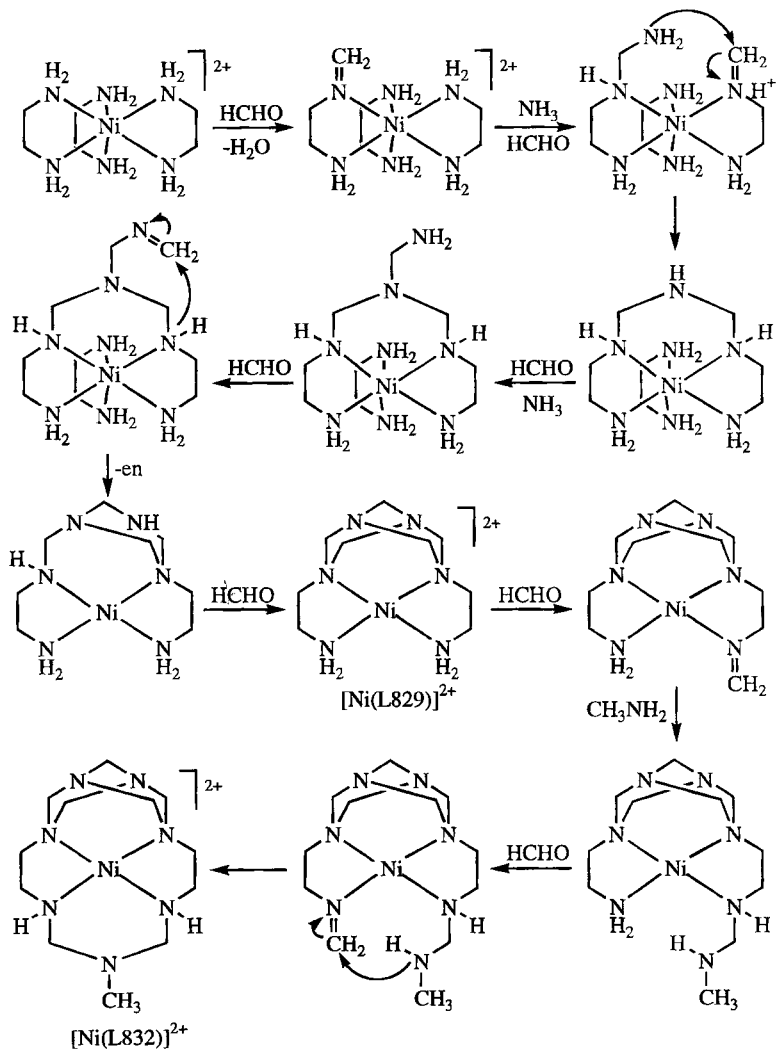
(4.5)

L829 L830 L831 L832

The complex $[Ni(L829)](ClO_4)_2$ is the main product of the template condensation involving a large excess of formaldehyde and ammonia. Note that $[Ni(L824)](ClO_4)_2$ is not formed on heating a dimethyl sulphoxide solution of $[Ni(L830)](ClO_4)_2$ with HCHO and NH_3; $[Ni(L829)](ClO_4)_2$ is produced during

this reaction. Moreover, the $[Ni(L829)](ClO_4)_2$ isolated from the reaction mixture does not undergo subsequent condensation involving HCHO and NH_3. Numerous attempts to assemble the symmetric macrocyclic product L831 were unsuccessful [25]. The macrocyclic complex $[Ni(L832)](ClO_4)_2$, whose structure was established by X-ray structure analysis [25], is formed by reaction of $[Ni(L829)](ClO_4)_2$ with formaldehyde and methylamine. The proposed mechanism for the synthesis of $[Ni(L829)]^{2+}$ and $[Ni(L832)]^{2+}$ is shown in Scheme 4-2 [25].

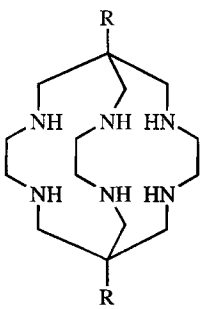
Complete encapsulation of ruthenium(III) and osmium(III) would seem to be



Scheme 4-2. The proposed mechanism for the formation of $[Ni(L829)]^{2+}$ and $[Ni(L832)]^{2+}$.

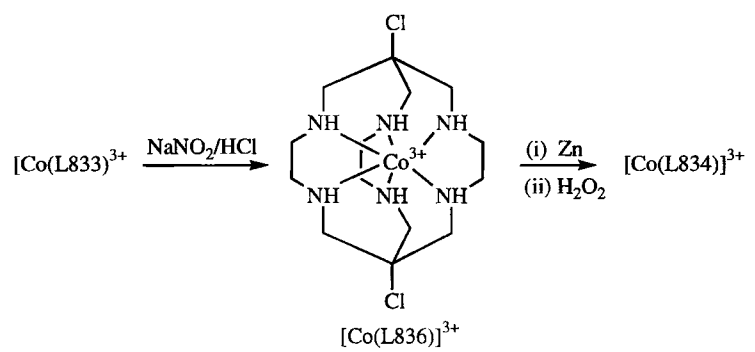
possible, but the complexes $[M(en)_3]^{3+}$ (M = Ru, Os) undergo disproportionation to form M^{II} and M^{IV} products on reaction with HCHO in alkaline medium [3].

In connection with the preparation of cage-like metal coordination compounds in cases where the direct template synthesis is difficult or impossible, the possibility of sepulchrate and sarcophagine demetallation and remetallation has been studied. Sepulchrates appear to be less stable than sarcophagines, and are decomposed by concentrated mineral acids [27]. However the metal-free bicyclic species L833 and L834 (Eq. 4.6) have been obtained by heating the cobalt(II) complexes of L833 and L834 in concentrated hydrochloric or hydrobromic acid at 130–150°C [3, 24]. The substances thus obtained give coordination compounds with Ti^{IV}, V^{IV}, V^{III}, Cr^{III}, Mn^{III}, Mn^{II}, Fe^{III}, Fe^{II}, Ni^{III}, Ni^{II}, Cu^{II}, Zn^{II}, Cd^{II}, Hg^{II}, Ag^{II}, Ga^{III}, In^{III}, Mg^{II}, Ru^{III} and Ru^{II} [3, 28–36]. The cobalt(II) complexes of L833 and L834 are synthesised by reduction of the corresponding Co^{III} compounds with zinc amalgam in aqueous solution. The complex $[Co^{III}(L833)]^{3+}$ is formed by the reduction of nitrosarcophagine complex $[Co(L825)]^{3+}$ with zinc in concentrated hydrochloric acid, followed by addition of H_2O_2 to reoxidise the complex to trivalent cobalt. Equation (4.7) shows the pathway to $[Co^{III}(L834)]^{3+}$ [9].



R = NH_2 L833
R = H L834
R = NHOH L835

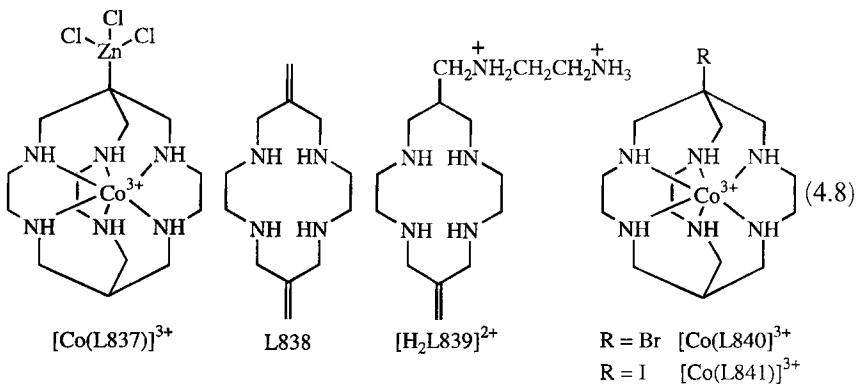
(4.6)



(4.7)

It should be noted that an unusual, relatively stable, complex $[Co(L837)]^{3+}$ with a zinc-carbon bond, for which X-ray structural evidence has been reported [37], is formed on treating $[Co(L836)]^{3+}$ with zinc dust. It is supposed [38] that reduction of the cobalt(III) to cobalt(II) in the dichloro cage species $[Co(L836)]^{3+}$, followed by oxidative addition of Zn^0 to the C–Cl bonds and finally addition of two Cl^-

and reoxidation, generate the $[Co(L837)]^{3+}$ complex (Eq. 4.8). In addition, small amounts of the complex containing two $-ZnCl_3$ groups and $[Co(L834)]^{3+}$, as well as cobalt(III) complexes of monomacrocyclic ligands L838 and $[H_2L839]^{2+}$ resulting from rupture of the cage, have been isolated and characterised [38].



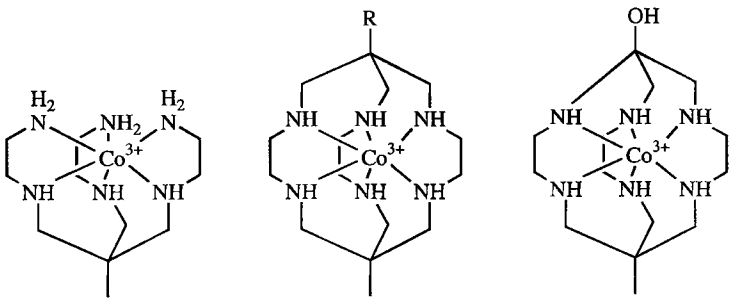
Although the Zn-C bond appears to be quite stable, it is sensitive to electrophilic reagents. The sarcophagines $[Co(L840)]^{3+}$ and $[Co(L841)]^{3+}$ result from reaction of $[Co(L837)]^{3+}$ with Br_2 or I_2 respectively [37]. Heating $[Co(L837)]^{3+}$ in the presence of acid or base results in the elimination of zinc and protonation of the capping carbon atom, giving $[Co(L834)]^{3+}$ [3].

Syntheses based on the reaction of $[Pt(en)_3]^{4+}$ with formaldehyde and ammonia or nitromethane yielded the macrocyclic complexes of Pt^{IV} with L824 and L825, respectively [4]. On reduction of $[Pt(L825)]^{4+}$ with $SnCl_2/HCl$, a complex believed to be $[Pt(L833)]^{4+}$ was isolated [4]. However, it was later suggested [39] that the latter could be the bis(hydroxylamine) species $[Pt(L835)]^{4+}$. The synthesis from $[Pt(en)_3]^{4+}$ [4] was repeated and the reduction of the platinum(IV) complex with L825 was studied [40]. X-Ray analysis of the product obtained by the last procedure and subsequent recrystallisation from CF_3SO_3H revealed the composition $[Pt(L835)](CF_3SO_3)_4 \cdot H_2O$ [40]. The diamagnetism of the complex gave evidence for the Pt^{IV} oxidation state.

A detailed study of the redox behaviour of the cobalt(III) cage complex $[Co(L825)](CF_3SO_3)_3 \cdot H_2O$ has been reported [41]; the redox behaviour of the nitro groups is very diverse. Nitroso, hydroxylamine, amine and nitro radical anions are formed as primary products from reduction, depending on the nature of reductants, pH, solvent, and the amount of reductant employed. The reduction products with Zn/HCl contain amine substituents, whereas reductions with $SnCl_2/HCl$ (or $S_2O_4^{2-}$ [42]), or electrochemical reductions at an Hg-pool electrode, yield hydroxylamine-substituted cage complexes as the final products [41]. The type of product obtained on reduction of these nitro derivatives cannot be rationalised a priori or by analogy [40–42].

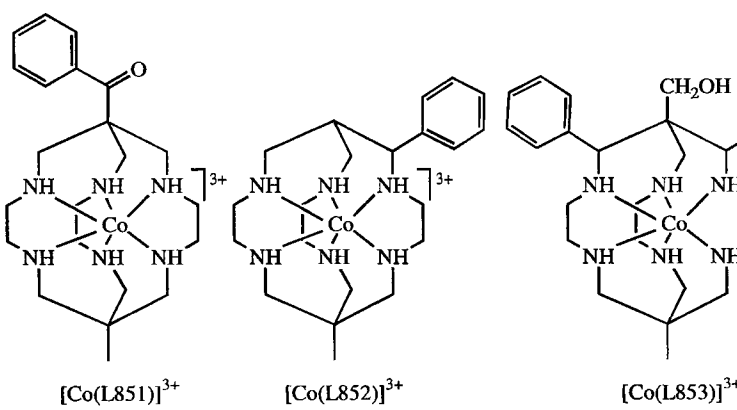
Another approach within the sides + caps general strategy for template synthesis of organic metal ion cages is called cup + cap [5, 43]. This consists of using, as initial building blocks for metal ion encapsulation, monocapped complexes such

as $[Co(L842)]^{3+}$ (Eq. 4.9). The construction of the second cap can be performed smoothly using the standard ligsons (HCHO and NH_3 or CH_3NO_2) to give $[Co(L843)]^{3+}$ and $[Co(L844)]^{3+}$, respectively [43]. The latter have also been obtained using more devious procedures [9, 37]. The nitro-capped cobalt(III) cage complex reacts with base providing the formation of a contracted cage species $[Co(L845)]^{3+}$, whose X-ray diffraction structure and mechanism of formation have been reported [44].

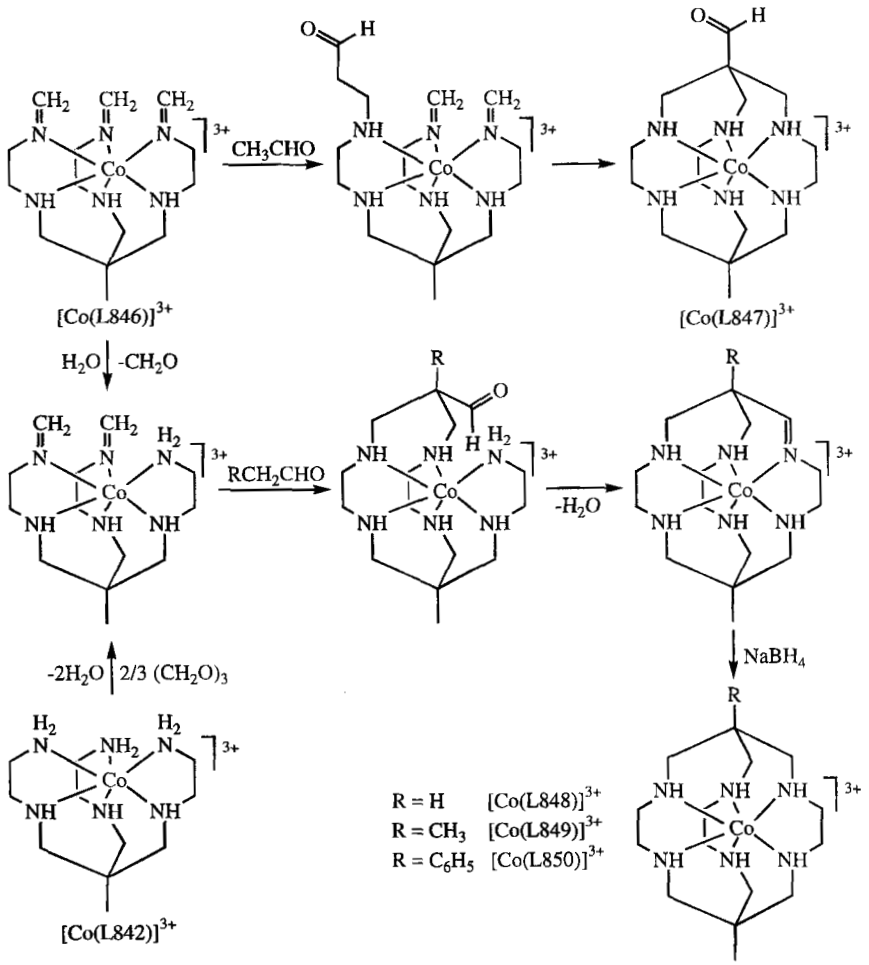


(4.9)

Employment of other capping agents, such as primary aldehydes [43], aromatic ketones or diketones [45], *N*-alkylated pyridinium analogues [46], phosphines [47] and arsines [48], has broadened the possibilities of this synthetic route, providing a versatile synthetic strategy for the derivatisation of metal ion cages. For example, the three-dimensional cobalt(III) species $[Co(L847)]^{3+}$–$[Co(L850)]^{3+}$ can be synthesised from $[Co(L842)]^{3+}$ and $[Co(L846)]^{3+}$ following the reactions depicted in Scheme 4-3 [43]. Note that $[Co(L846)]^{3+}$ is a rather stable species, which is easily prepared by treating $[Co(L842)]^{3+}$ with an excess of paraformaldehyde and quenching the reaction with hydrochloric acid [48]. Reactions of equimolar amounts of $[Co(L842)]^{3+}$ and acetophenone or dibenzoylmethane, and a small excess of paraformaldehyde in the presence of diisopropylethylamine in acetonitrile, produce the encapsulated species $[Co(L851)]^{3+}$, $[Co(L852)]^{3+}$ and $[Co(L853)]^{3+}$, respectively, in 27, 46 and 46% yield (Eq. 4.10) [45].

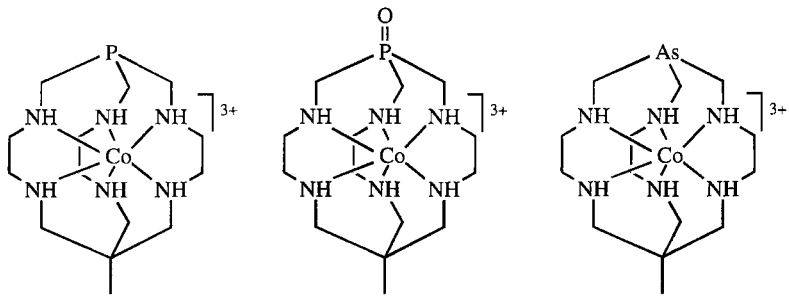


(4.10)



Scheme 4-3. Synthetic pathway to $[Co(L846)]^{3+}$–$[Co(L849)]^{3+}$.

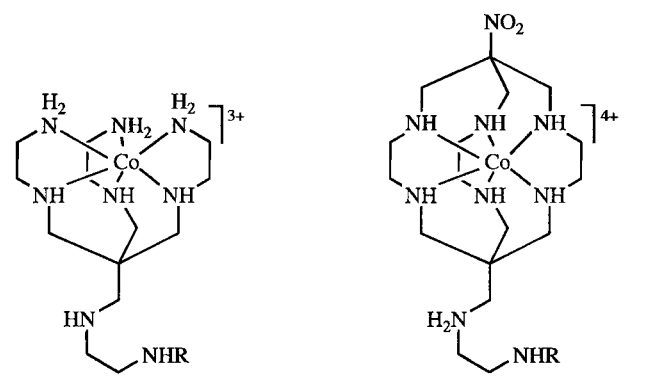
Base-induced condensation of $[Co(L842)]^{3+}$ with paraformaldehyde and phosphine leads to the phospha-capped bicyclic cage complex $[Co(L854)]^{3+}$ and its phosphine oxide derivative $[Co(L855)]^{3+}$ (Eq. 4.11) [47]. The condensation of $[Co(L846)]^{3+}$ with AsH_3 yields the arsa-capped $[Co(L856)]^{3+}$ [48]. X-Ray diffraction studies of the cobalt(III) complexes of L855 and L856 have been reported [47, 48].



(4.11)

$[Co(L854)]^{3+}$ $[Co(L855)]^{3+}$ $[Co(L856)]^{3+}$

Encapsulated complexes $[Co^{III}(L859)]^{4+}$ and $[Co^{III}(L860)]^{4+}$ have been obtained analogously by reaction of appropriate precursors $[Co^{III}(L857)]^{3+}$ and $[Co^{III}(L858)]^{3+}$ with nitromethane and aqueous formaldehyde (Eq. 4.12) [49, 50].



(4.12)

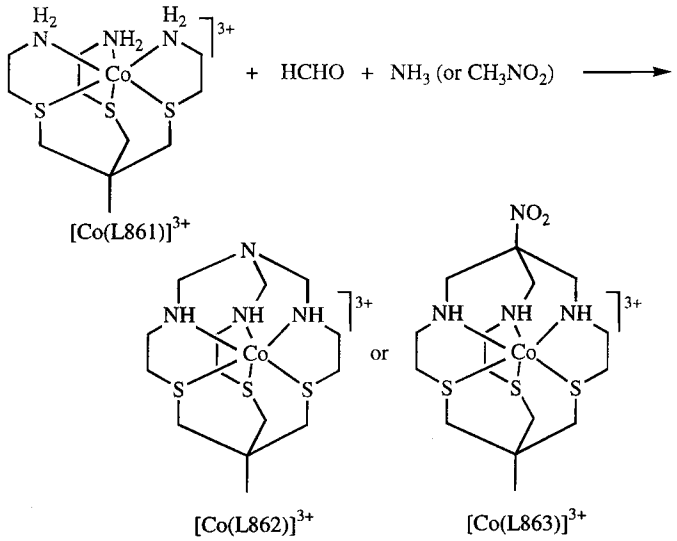
R = H $[Co(L857)]^{3+}$ R = H $[Co(L859)]^{4+}$

R = $C_6H_4SO_2$ $[Co(L858)]^{3+}$ R = $C_6H_4SO_2$ $[Co(L860)]^{4+}$

Clathrochelates containing an N_3S_3 set of donor atoms can also be assembled by exploiting the same technique. For this purpose one should select the starting building blocks of defined stereochemistry and required stability and perform the reaction under the conditions appropriate for successful encapsulation. One such complex is $[Co(L861)]^{3+}$, which gives the macrobicyclic systems $[Co(L862)]^{3+}$ or $[Co(L863)]^{3+}$ by reaction with HCHO and ammonia or nitromethane respectively (Scheme 4-4) [51].

Template synthesis, properties and suggested mechanisms of formation for a number of related cage complexes with N_3S_3 donor sets have been reported [52].

Following the same synthetic pathway, encapsulated cobalt(III) complexes with ligands containing N_5S [53, 54] or N_4S_2 [55, 56] have been prepared and charac-



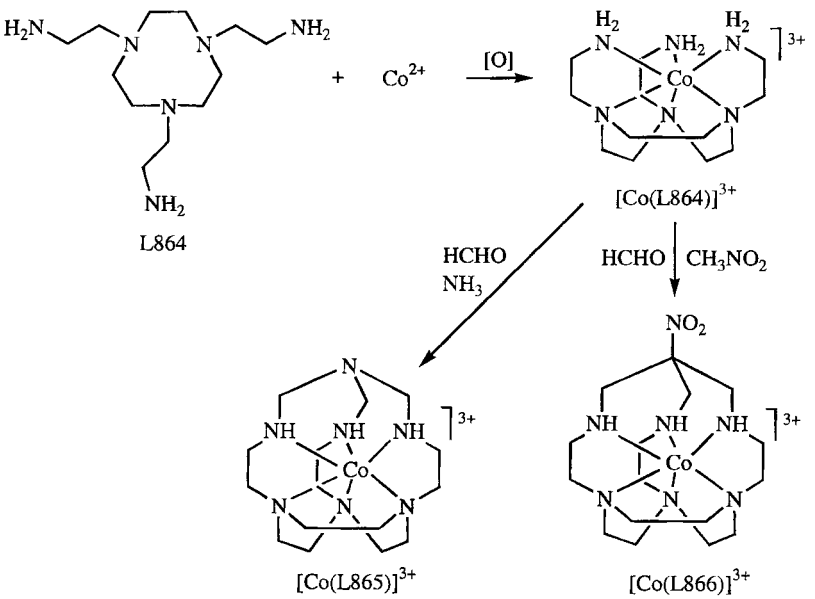
Scheme 4-4. Synthesis of N_3S_3 cobalt(III) cage complexes.

terised. Complexes of other metals, for example nickel(II), can be obtained by direct complexation reaction with metal-free ligands obtained by demetallation of the corresponding cobalt(II) complexes with sodium cyanide [57]. The synthesis of a homoleptic S_6 cage has been achieved by a caesium carbonate-mediated ring-closure reaction [58]. The encapsulation of both cobalt(II) and cobalt(III) results from direct complexation reactions and is confirmed by X-ray crystallographic analysis of the cobalt(II) complex [58]. A larger-cavity homoleptic thioether cage and its cobalt(III) complex have also been reported [59].

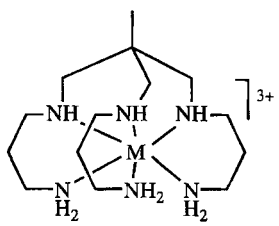
An analogous route has been explored for the assembly of the macrocyclic cryptands isolated in the form of complexes $[Co(L865)]^{3+}$ and $[Co(L866)]^{3+}$ from $[Co(L864)]^{3+}$ (Scheme 4-5) [60].

An important direction for development in clathrochelate chemistry is the search for the synthesis of cage-like molecules with large cavity sizes appropriate to the stabilisation of metal ions in lower oxidation states [3, 4]. The obvious strategy is to carry out the encapsulation reaction with complexes $[M(1,3\text{-pn})]^{3+}$ or to use coordination compounds containing a hexadentate semisarcophagine ligand, such as $[M(L867]^{3+}$ (Eq. 4.13). (Note that the analogous substance containing 1,2-diaminoethane fragments is readily capped under conditions suitable for carrying out encapsulation reactions on cobalt(III) ion matrices [8].) However, attempts to perform the encapsulation process starting from $[M(1,3\text{-pn})]^{3+}$ has not yet proved successful, mainly due to the ease with which $[Co(1,3\text{-pn})_3]^{3+}$ in aqueous solution in the presence of base loses its ligands.

Encapsulation of $[M(L867)]^{3+}$, where M = Co or Cr, does not go to completion, due to unfavourable spatial arrangements of imine fragments with respect to the neighbouring nucleophilic centres. From analysis of molecular models, it can be

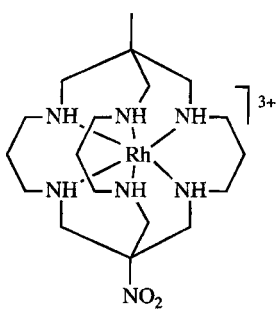


Scheme 4-5. Synthetic route to $[Co(L865)]^{3+}$ and $[Co(L866)]^{3+}$.



(4.13)

deduced that M–N bonds longer than Co^{III}–N (19.8 nm) should favour formation of the second cap. Indeed, the sarcophagine complex $[Rh(L868)]^{3+}$ (Eq. 4.14), whose structure was established by X-ray diffraction, has been assembled in good yield by reaction of $[Rh(L867)]^{3+}$ with HCHO and CH_3NO_2 [4] or even more efficiently by treating $[Rh(L867)]^{3+}$ with paraformaldehyde and nitromethane in molar ratio 1:10:2 in the presence of triethylamine as base in acetonitrile [61].



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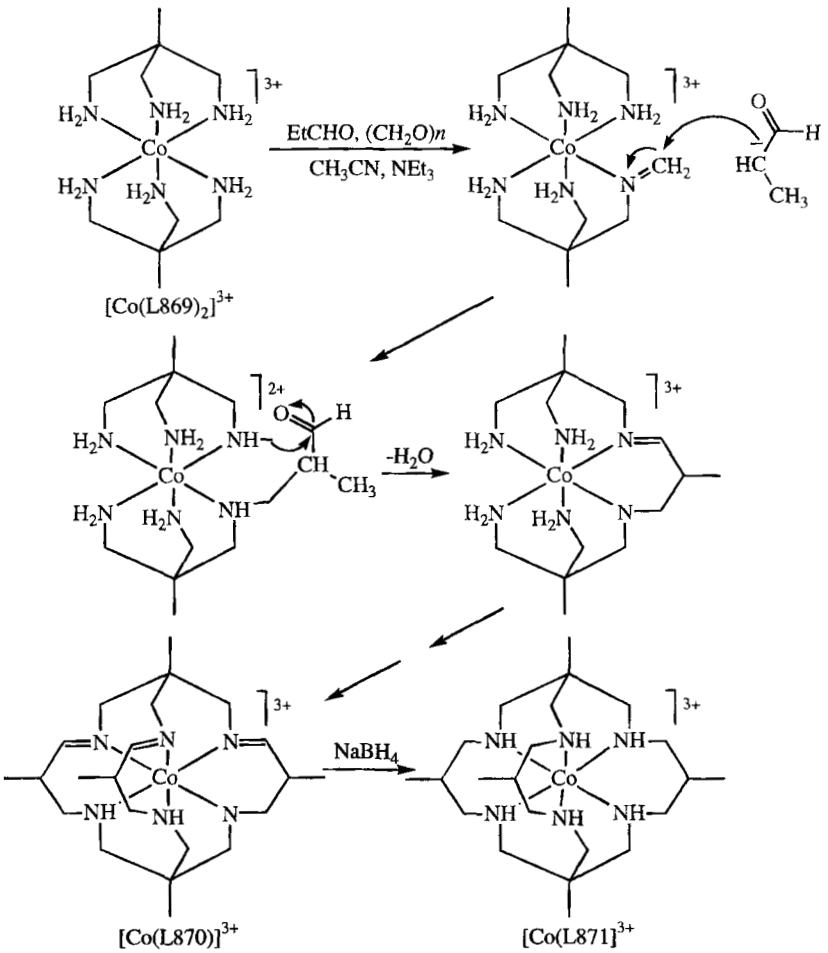
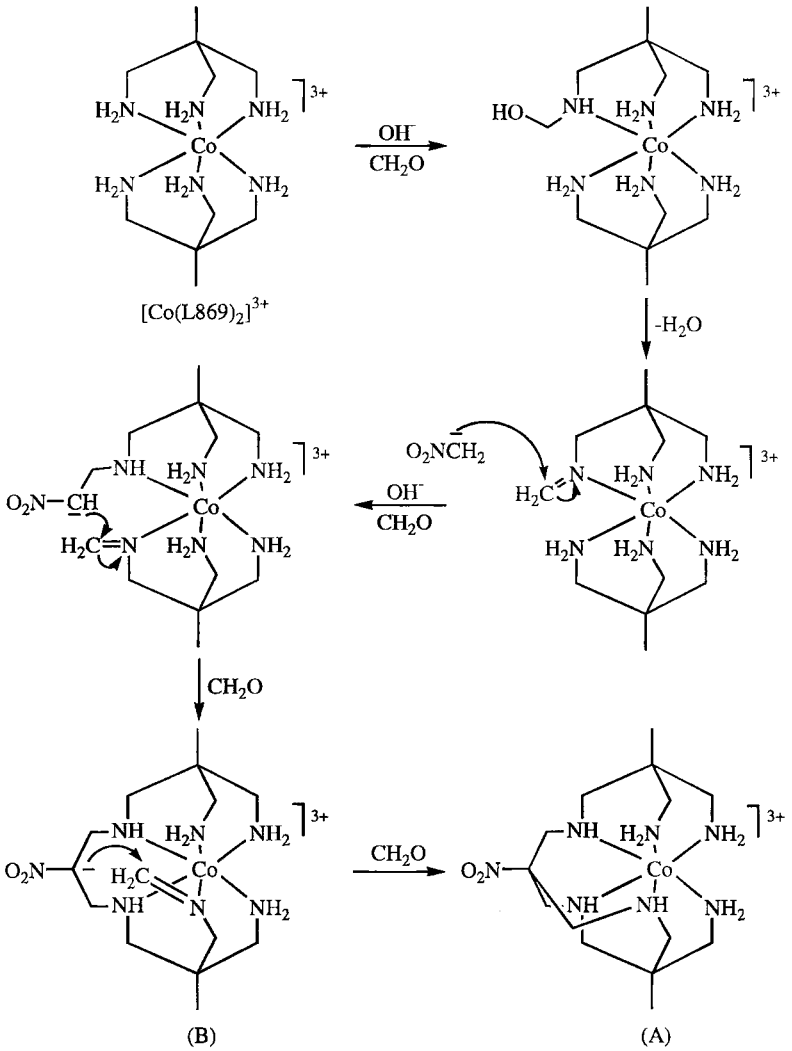


Scheme 4-6. Synthetic route to large cavity cobalt(III) cage species.

Cobalt(III) has also proved effective for organising intramolecular encapsulation chemistry within an alternative caps + sides synthetic strategy [3, 62]. For example, condensation of paraformaldehyde and propionaldehyde with $[Co(L869)_2]^{3+}$ readily encapsulates the metal ion (Scheme 4-6) leading to $[Co(L870)]^{3+}$ [62]. Subsequent reduction of the imine functions results in an expanded-cavity cage species $[Co(L871)]^{3+}$. The reaction is very stereospecific. Only one form from 92 possible diastereomers has been found. The X-ray diffraction structure analysis revealed all six stereogenic N atoms have the same *S* (or *R*) configuration linked to the Λ (or Δ) arrangement of the three 2-methyl-propane-1,3-diamine moieties, the overall structure being essentially C_3 symmetric.

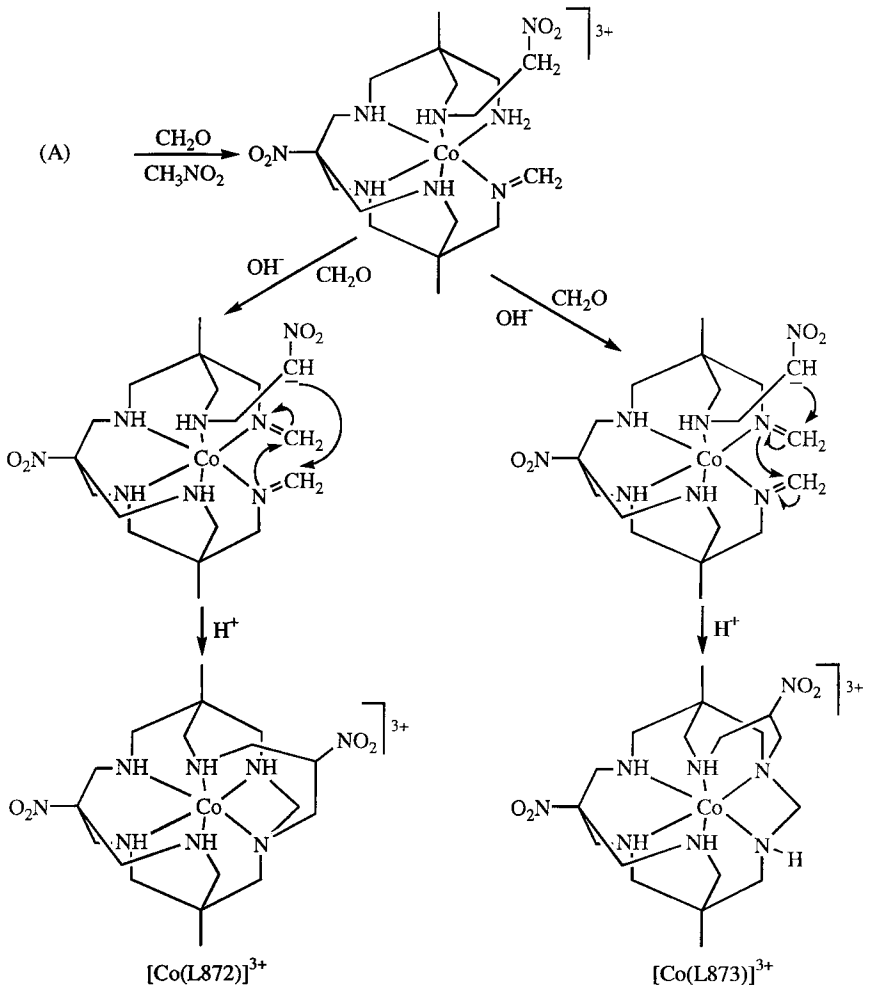
An alternative route has been suggested, based on the use of $[Co(L869)_2]^{3+}$



Scheme 4-7. Branched routes of successive transformations resulting in cage-like complexes $[Co(L872)]^{3+}$ to $[Co(L875)]^{3+}$ - formation of intermediate species (A) and (B).

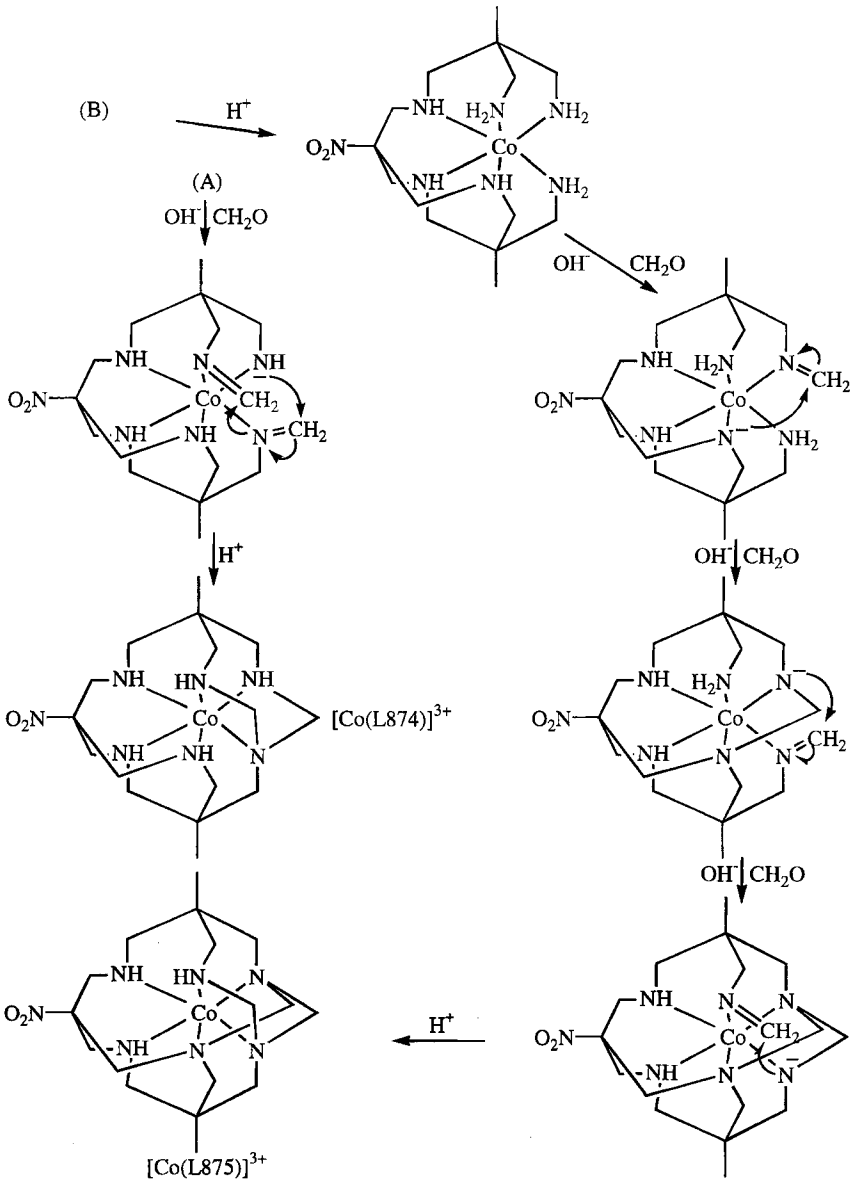
[3, 63, 64]. The template condensation of $[Co(L869)_2]^{3+}$ with formaldehyde and nitromethane in aqueous solution, followed by separation of the reaction mixture by ion-exchange chromatography, is represented in Schemes 4-7–4-9. Branched routes of successive transformations result in the formation of four main products, $[Co(L872)]^{3+}$ to $[Co(L875)]^{3+}$ [63, 64].

The structures of $[Co(L872)]^{3+}$, $[Co(L873)]^{3+}$ and $[Co(L874)]^{3+}$, have been established by X-ray diffraction. It is easy to see that one face of the polyhedron



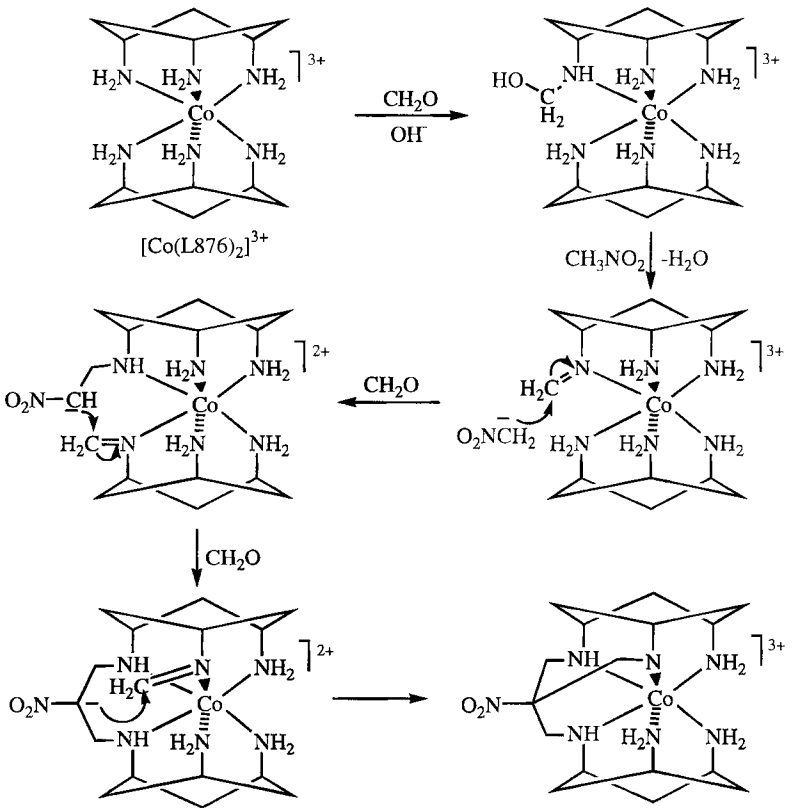
Scheme 4-8. Development of speciers (A) (Scheme 4-7) to complexes $[Co(L872)]^{3+}$ and $[Co(L873)]^{3+}$.

$[Co(L869)_2]^{3+}$ is involved in the condensation reaction with one nitromethane and two formaldehyde molecules to form a trigonal cap, typical for sarcophagines. The second side reacts with either two or three formaldehyde molecules and yields two or three new four-membered chelate cycles, respectively (the complexes $[Co(L874)]^{3+}$ and $[Co(L875)]^{3+}$), or one nitromethane molecule and three HCHO molecules to construct one six-membered and one four-membered metallocycle ($[Co(L872)]^{3+}$ and $[Co(L873)]^{3+}$). The clathrochelate hole size does not change significantly because an increase in size in one direction in the ligand results in a decrease in another direction. In general, the structures of these systems are considerably dis-



Scheme 4-9. Development of species (A) and (B) (Scheme 4-7) to complexes $[Co(L874)]^{3+}$ and $[Co(L875)]^{3+}$.

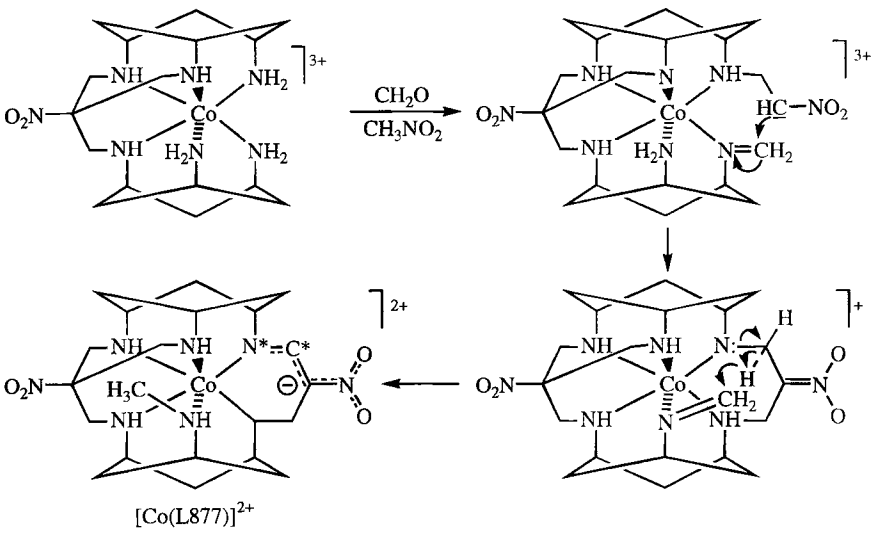
torted, but the four-membered chelate rings are quite stable. However the strongly deformed macro(tetra)cyclic complex $[Co(L875)]^{3+}$ undergoes slow hydrolysis at pH > 9 and room temperature, the bonds being broken in a trigonal cap containing six-membered rings [63]. The mechanism of cobalt(III) clathrochelate assembly



Scheme 4-10. The template construction of $[Co(L877)]^{2+}$ species – part 1.

represented in Schemes 4-7–4-9 is proposed on the basis of Co^{III}-imine chemistry and the nature of compounds like Co^{III}–N=CH_2 isolated in the course of the reaction of $[Co(L869)_2]^{3+}$ with HCHO by quenching it at appropriate times. Note, however, that the sequence of imine bond formation and ring closure may differ from that shown in these schemes [63, 64].

Owing to the required stereochemistry and considerable stability, the chelate $[Co(L876)_2]^{3+}$ appears to be suitable for assembling a relatively rigid cage-like system $[Co(L877)]^{2+}$ having an enhanced cavity size (Schemes 4-10 and 4-11) [65]. An X-ray diffraction study of the complex showed that in the multistep process one face of the octahedral $[Co(L876)_2]^{3+}$ was involved as if it had been a matrix for the required trigonal cap, whereas the second face appeared to be unsuitable for this purpose. The formation of a six-membered chelate ring containing a stable carbanion embedded in its framework resulted from the reaction of two amino groups of the second face with one nitromethane molecule and two formaldehyde molecules, whereas the third $-NH_2$ group underwent methylation. This formation of a



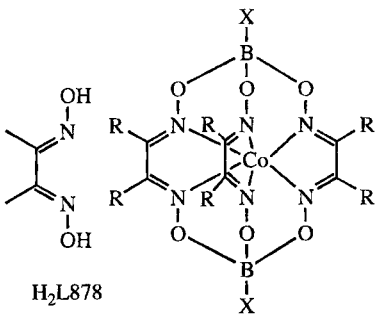
Scheme 4-11. The template construction of $[Co(L877)]^{2+}$ species – part 2.

carbanion in basic medium is not too surprising, but the persistence of the deprotonated form in acid solution is extremely unusual. This can probably be ascribed to both electron density delocalisation over the near-planar fragment N*–C*–NO_2, as a result of proton loss from $CHNO_2$ and deprotonation of the N* and C* atoms, and to strain produced as a result of ligand coordination [65]. The lengths of five Co–N bonds (except Co–N*) are more than 20.0 nm, longer than is normal (19.6–19.8 nm) for cobalt(III) hexamine complexes. This is best explained by the relatively strict requirements of the ligand and the strains produced by this ligand in the complex.

4.1.2 Macrobicyclic tris(mono- and di-)oximates and other cage complexes

Another type of clathrochelate successfully assembled by taking advantage of the kinetic coordination template effect comprises d metal tris(mono- and di-)oximates obtained by replacement of the hydrogen bonds in oxime starting complexes with Lewis acids containing such elements as B, Sn, Ge, Si. Cobalt(III), iron(II), ruthenium(II) and technetium(III) tris(dioximato) precursors have been found to be most suitable for Lewis acid/oxime capping reactions. As for the sepulchrates and sarcophagines discussed in the previous section, the sides + caps synthetic strategy proved to be extremely efficient for building up this kind of cage-like assembly. For example, the first representative of this class of compounds, $[Co(L879)]BF_4$, has

been prepared by the reaction of $K_3[Co(L878)_3]$ with $BF_3{\cdot}(C_2H_5)_2O$ in dimethyl ether (Eq. 4.15) [66]. The complex $[Co(L879)]BF_4$ can also be synthesised by oxidation of a reaction mixture consisting of a cobalt(II) salt, dimethylglyoxime (H_2L878) and $BF_3{\cdot}(C_2H_5)_2O$ in *n*-butanol with atmospheric dioxygen in the presence of a base [67], but its construction presumably proceeds via the formation of a cobalt(III) tris(dioximato) intermediate.



H_2L878

X = F, R = CH_3	$[Co(L879)]^+$
X = C_6H_5, R = CH_3	$[Co(L880)]^+$
X = C_4H_9, R = CH_3	$[Co(L881)]^+$
X = C_4H_9, R = $(C_4H_8)_{0.5}$	$[Co(L882)]^+$ (4.15)
X = R = C_6H_5	$[Co(L883)]^+$
X = C_6H_5, R = $(C_4H_8)_{0.5}$	$[Co(L884)]^+$
X = F, R = C_6H_5	$[Co(L885)]^+$

However, it should be noted that the complex anion $[Co^{III}(L878)_3]^{3-}$ is more suitable as a template than Co^{II} ions. In the former case the yield of the required product is twice as large as in the latter, amounting to approximately 60% [68]. This can be explained by the fact that the oxime oxygen atoms of the trisdimethylglyoximate complex are held in positions suited to enclose a three-dimensional cavity with boron trifluoride. The arrangement of oxime oxygen atoms results from the coordination of three identical ligands H_2L878 positioned in an *anti* configuration by nitrogen atoms. A reduced reaction yield when starting from Co^{II} and dioximes can supposedly be explained by other concurrent reactions, as for example formation of square planar cobalt(II) dioximato complexes, which will be subsequently converted, at least in part, to thermodynamically stable species other than tris(dioximato)cobalt(III) intermediates.

Although cobalt(II) forms square planar complexes with oximes, and as consequence cannot be used as a three-dimensional template, the cobalt(II) encapsulated species $[Co^{II}(L879)]$ has been prepared by reduction of $[Co^{III}(L879)]BF_4$ with NaI in acetonitrile-acetone mixture. Macrobicyclic clathrochelate structures for both complexes have been proved by X-ray diffraction [69].

By using other cobalt(III) alicyclic and aromatic trisdioximates along with dimethyl glyoxime as starting building blocks, and $C_6H_5BCl_2$, n-$C_4H_9BCl_2$, $C_6H_5B(OH)_2$ as capping reagents, the synthesis of the clathrochelates from $[Co(L880)]BF_4$ to $[Co(L884)]BF_4$ has been performed [70]. The complex $[Co(L885)]BF_4$ was obtained as a result of addition of $BF_3{\cdot}(C_2H_5)_2O$ to the oxidised mixture of $CoCl_2$, diphenylglyoxime and KOH in *n*-butanol [71].

Following the same route, but employing $SnCl_4$ as capping reagent instead of $BF_3{\cdot}(C_2H_5)_2O$, the synthesis of H[Co(L886)]–H[Co(L890)] was carried out (Eq. 4.16) [72]. The clathrochelate K[Co(L886)] is formed by reaction of $K_3[Co(L878)]$

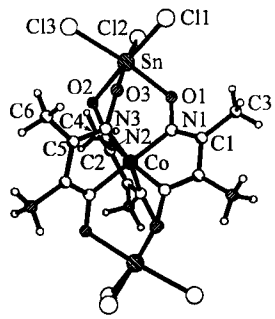
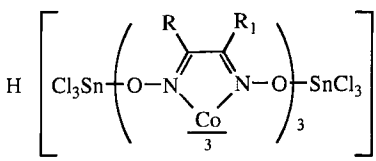


Figure 4-1. Perspective view of the $[Co(L886)]^-$ anion.

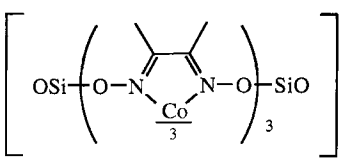


$R = R_1 = CH_3$	H[Co(L886)]	
$R = R_1 = (C_4H_8)_{0.5}$	H[Co(L887)]	
$R = R_1 = H$	H[Co(L888)]	(4.16)
$R = H, R_1 = CH_3$	H[Co(L889)]	
$R = R_1 = C_6H_5$	H[Co(L890)]	

with $SnCl_4$ in methylene chloride. This compound is converted into $[(n\text{-}C_3H_7)_4N]$-[Co(L886)] by a double-exchange reaction. This latter has been isolated as a crystalline solid in 18% yield [68].

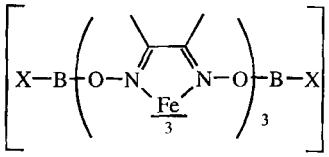
An X-ray diffraction study of $H[Co(L886)]\cdot 2C_6H_6$ has been reported [72]. Cobalt(III) is surrounded by six nitrogen atoms disposed in a trigonal antiprismatic manner. The distortion angle is 42.3° with respect to the trigonal prismatic coordination for which ϕ is 0° (Figure 4-1).

The complex $[Co(L891)]HPF_6$ (Eq. 4.17) is obtained on reaction of $K_3[Co(L878)_3]$ with $SiCl_4$. The isolation and purification of the product are tedious due to the formation of gels upon its precipitation.



HPF_6 $[Co(L891)]HPF_6$ (4.17)

Despite the fact that the first representatives of clathrochelates based on dioximates have been assembled in the presence of kinetically inert cobalt(III), the kinetically labile iron(II) is the most suitable template with which to control this kind of encapsulation reaction. The cage-like, and now low-spin, boron-containing iron(II) coordination compounds [Fe(L892)] to [Fe(L900)] are prepared in good yield from alcoholic or aqueous solution on reaction of the iron(II) salt, dimethyl-



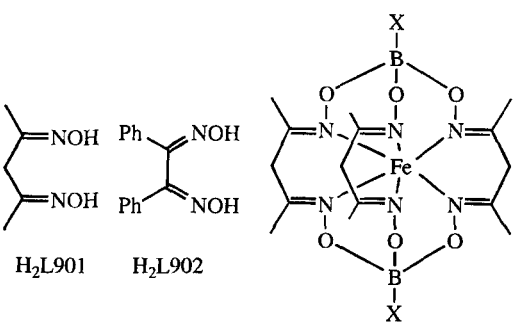
X = F	[Fe(L892)]	X = O-*iso*-C_3H_7	[Fe(L896)]
X = OH	[Fe(L893)]	X = O-*n*-C_4H_9	[Fe(L897)]
X = OCH_3	[Fe(L894)]	X = CH_3	[Fe(L898)]
X = OC_2H_5	[Fe(L895)]	X = C_6H_5	[Fe(L899)]
		X = H	[Fe(L900)]

(4.18)

glyoxime and BF_3 or $B(OH)_3$ (Eq. 4.18). If BF_3 is involved, [Fe(L892)] is formed. When boric acid is selected as a ring closure agent, [Fe(L893)] to [Fe(L897)] are synthesised depending on the solvent (H_2O, C_2H_5OH, CH_3OH, *iso*-C_3H_7OH or *n*-C_4H_9OH) [73, 74]. The $[P]^+$ peaks are the most intense in the mass spectra of [Fe(L893)] to [Fe(L897)].

The formation of the corresponding iron(II) complexes occurs even if iron(III) salts are used instead of $FeCl_2$. As might be expected, attempts to obtain iron(III) clathrochelates by the oxidation of these iron(II) compounds failed [74]. Reaction of $FeCl_2 \cdot 4H_2O$ with H_2L878 and methylboric or phenylboric acids in methanol yields the products [Fe(L898)] and [Fe(L899)], respectively [75]. Compound [Fe(L900)], containing inert B–H bonds, has been synthesised by the reaction of anhydrous $FeBr_2$ with dimethylglyoxime and $NaBH_4$ in dry acetonitrile [75].

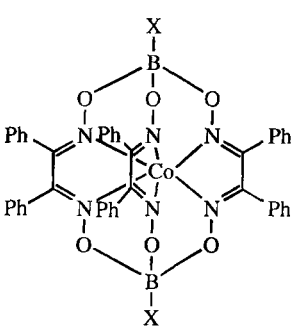
Two groups of complexes, [Fe(L903)] to [Fe(L907)] (Eq. 4.19) and [Fe(L908)] to [Fe(L912)] (Eq. 4.20), were obtained in a similar way starting from $FeCl_2 \cdot 4H_2O$,



H_2L901 H_2L902

X = OH	[Fe(L903)]
X = OCH_3	[Fe(L904)]
X = OC_2H_5	[Fe(L905)]
X = O-*iso*-C_3H_7	[Fe(L906)]
X = O-*n*-C_4H_9	[Fe(L907)]

(4.19)



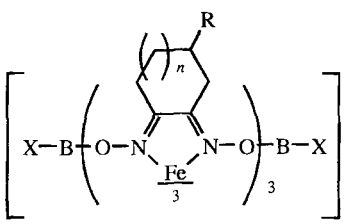
X = OH	$[Fe(L908)]^+$
X = OCH_3	$[Fe(L909)]^+$
X = OC_2H_5	$[Fe(L910)]^+$
X = O-*iso*-C_3H_7	$[Fe(L911)]^+$
X = O-*n*-C_4H_9	$[Fe(L912)]^+$
X = CH_3	$[Fe(L913)]^+$
X = F	$[Fe(L914)]^+$
X = C_6H_5 (Ph)	$[Fe(L915)]^+$

(4.20)

dioxime H_2L901 or H_2L902, and boric acid in the corresponding ROH, where R = H, CH_3, C_2H_5, *iso*-C_3H_7 or *n*-C_4H_9 [76].

The product [Fe(L913)] has been isolated by the reaction of $FeCl_2 \cdot 4H_2O$ with diphenylglyoxime and methylboric acid in *n*-butanol [75]. The chelate $Fe(HL902)_2(CH_3imid)_2$ is formed by the reaction of $FeSO_4 \cdot 7H_2O$ with H_2L902 and *N*-methylimidazole (CH_3imid) in aqueous dimethylformamide in an inert atmosphere with the reagents in the ratio 1.1:2:4. Treatment of this chelate with an excess of $BF_3 \cdot (C_2H_5)_2O$ results in its rearrangement into the clathrochelate [Fe(L914)] [77]. Upon boiling a mixture of $Fe(HL902)_2(CH_3imid)_2$, H_2L902, and $C_6H_5B(OH)_2$ in ether in molar ratio 1:1:4, [Fe(L915)] has been obtained [77].

The macrobicyclic boron-containing iron(II) nioximates [Fe(L916)] to [Fe(L926)] resulted from the reaction of iron(II) and nioxime with the corresponding capping agents, namely $NaBH_4$, $B(OH)_3$, $CH_3B(OH)_2$, *n*-$C_4H_9B(OH)_2$, $C_6H_5B(OH)_2$, $B(OH)_3 + CH_3OH$, $B(OH)_3 + C_2H_5OH$, $B(OH)_3 + n$-C_4H_9OH, BF_3, BCl_3 and BBr_3 [67, 78–81]. By analogous procedures the products [Fe(L927)] to [Fe(L932)] [82, 83], [Fe(L933)] to [Fe(L935)] [84] and [Fe(L936)] to [Fe(L941)] [85] were obtained (Eq. 4.21).



R = H, *n* = 1:

X = H	[Fe(L916)]
X = OH	[Fe(L917)]
X = CH_3	[Fe(L918)]
X = *n*-C_4H_9	[Fe(L919)]
X = C_6H_5	[Fe(L920)]
X = OCH_3	[Fe(L921)]
X = OC_2H_5	[Fe(L922)]
X = O-*n*-C_4H_9	[Fe(L923)]
X = F	[Fe(L924)]
X = Cl	[Fe(L925)]
X = Br	[Fe(L926)]

R = CH_3, *n* = 1:

X = OH	[Fe(L927)]
X = CH_3	[Fe(L928)]
X = O-sec-C_3H_7	[Fe(L929)]
X = O-sec-C_4H_9	[Fe(L930)]
X = O-*n*-C_4H_9	[Fe(L931)]
X = F	[Fe(L932)]

R = H, *n* =2:

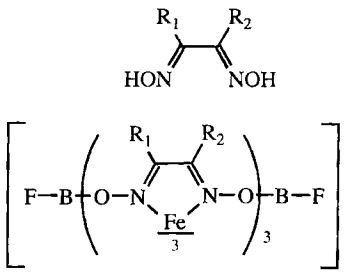
X = F	[Fe(L933)]
X = CH_3	[Fe(L934)]
X = OH	[Fe(L935)]

R = H, *n* = 3:

X =F	[Fe(L936)]
X = OH	[Fe(L937)]
X = O-*n*-C_4H_9	[Fe(L938)]
X = CH_3	[Fe(L939)]
X = C_6H_5	[Fe(L940)]
X = *n*-C_4H_9	[Fe(L941)]

(4.21)

Template synthesis of the macrocyclic systems [Fe(L945)] to [Fe(L947)] has been carried out by reaction of $FeCl_2 \cdot 4H_2O$, with the corresponding oxime (glyoxime H_2L942, methylglyoxime H_2L943 or furildioxime H_2L944) and $BF_3 \cdot (C_2H_5)_2O$ in *n*-butanol (Eq. 4.22) [86].



$R_1 = R_2 = H$ [Fe(L942)]
$R_1 = CH_3, R_2 = H$ [Fe(L943)]
$R_1 = R_2 =$ [FeL944)]
$R_1 = R_2 = H$ [Fe(L945)]
$R_1 = CH_3, R_2 = H$ [Fe(L946)]
$R_1 = R_2 =$ [FeL947)]

(4.22)

Gas-phase fragmentation pathways for clathrochelates [Fe(L917)], [Fe(L927)], [Fe(L935)] and [Fe(L937)] have been investigated by FAB mass spectrometry [87]. The most intense peaks in the spectra belong to protonated molecular ions $[P + H]^+$. The presence of this peak ion confirms formation of the corresponding complexes. The fragmentation of $[P + H]^+$ occurs mainly at the expense of the dioximate fragments.

X-Ray diffraction studies have been reported for [Fe(L914)] and [Fe(L935)]·$3H_2O$ [82, 88, 89]. The structure of the latter is illustrated in Figure 4-2. The iron atom is encapsulated by the macrobicyclic ligand and is in distorted trigonal prismatic coordination: the prism bases (N1, N3, N5) and (N8, N4, N6) are almost parallel (the dihedral angle between the base planes is less than 0.2°, the distance between them is 23.3 nm) and the distortion angle is 23.4°. Bond lengths and angles in the macrobicyclic ligands resemble those for cobalt analogues [69].

The kinetics and mechanism of template formation of clathrochelate structures

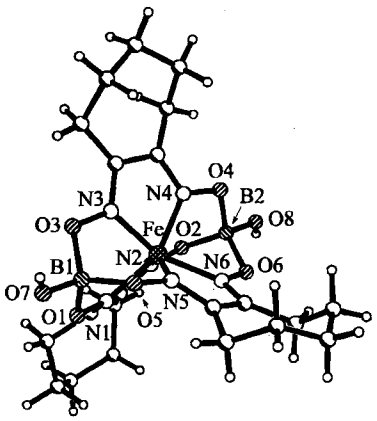
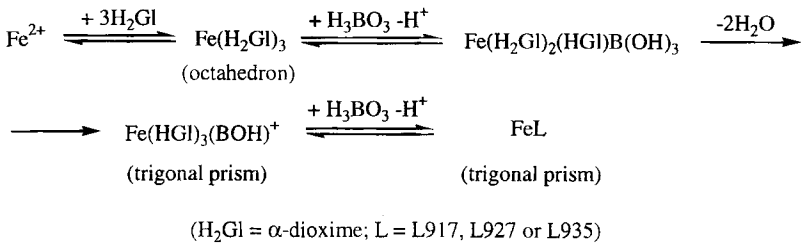


Figure 4-2. The structure of [Fe(L935)].

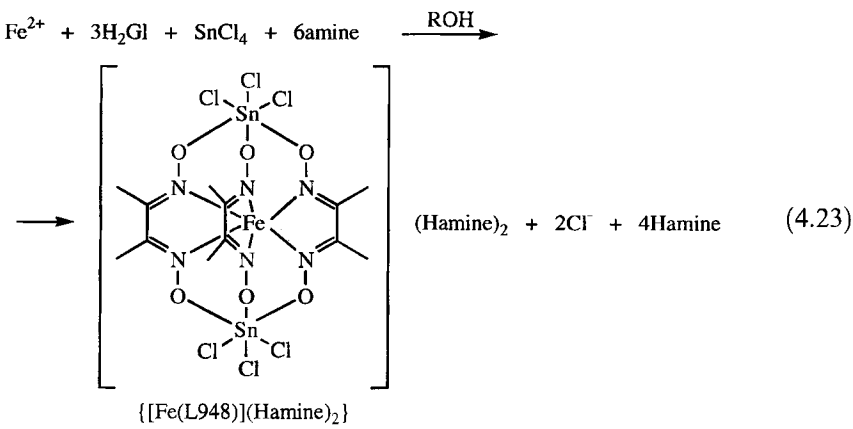


Scheme 4-12. Supposed mechanism of formation of iron(II) clathrochelates.

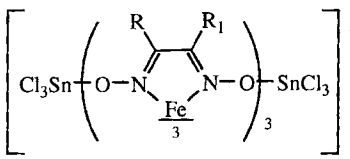
by the encapsulation of iron(II) tris-dioximates with boron-containing fragments has been studied in detail [82, 83, 90–93] in the case of [Fe(L917)], [Fe(L927)] and [Fe(L935)], the assembly of which occurs in quantitative yield in dilute aqueous solution at room temperature.

The results obtained indicate that the process of final product assembly includes formation of the protonated trisdioximate complex, addition of one molecule of acid with loss of a proton, followed by the rate-determining step consisting of splitting off two water molecules with change of coordination geometry from octahedral to trigonal-prismatic, and reversible addition of the second molecule of boric acid, according to Scheme 4-12.

The encapsulation of iron(II) tris-dioximates can be achieved not only by using boron-containing capping reagents, but also other Lewis acids such as derivatives of tin [94] and germanium [95]. The synthesis of clathrochelate tin-containing iron(II) trisdioximates can be performed by two main methods: direct interaction of iron(II), dioxime and $SnCl_4$ (Eq. 4.23) or encapsulation of preliminary synthesised non-macrocyclic iron(II) trisdioximate (Eq. 4.24).



The direct reaction (Eq. 4.23) appears to proceed via a protonated tris complex. Although the product yield in the case of Equation (4.24) is higher, the difficulty of separating non-macrocyclic iron(II) trisdioximates makes the former synthesis more attractive. Tin-containing complexes can also be obtained by the interaction of tin(IV) tetrachloride with bisdioximates $Fe(HGl)_2(amine)_2$, and by treatment of labile boron-containing complexes (such as [Fe(L908)], [Fe(L917)], [Fe(L927)] and [Fe(L937)]) with a large excess of $SnCl_4$. In addition to $[Fe(L948)][H_2N(C_2H_5)_2]_2$



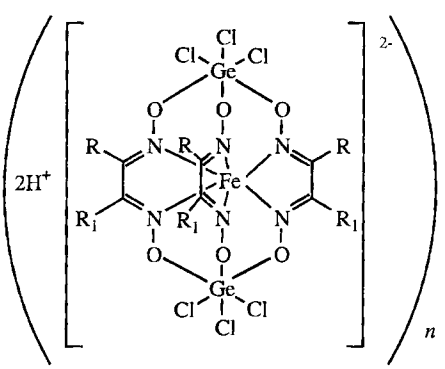
$R = R_1 = H$	$[Fe(L949)]^{2+}$
$R = H, R_1 = CH_3$	$[Fe(L950)]^{2+}$
$R = R_1 = C_6H_5$	$[Fe(L951)]^{2+}$
$R\frown R_1 = (CH_2)_4$	$[Fe(L952)]^{2+}$
$R\frown R_1 = (CH_2)_2CH(CH_3)CH_2$	$[Fe(L953)]^{2+}$
$R\frown R_1 = (CH_2)_6$	$[Fe(L954)]^{2+}$

(4.25)

the macrobicyclic iron(II) complexes $[Fe(L949)]^{2+}$ to $[Fe(L954)]^{2+}$ have been obtained (Eq. 4.25) [94].

Iron-57 Mössbauer spectroscopic data suggest these complexes to have a trigonal-antiprismatic geometry with a distortion angle of 40–55°. The parameters of the ^{119}Sn-Mössbauer and NMR spectra indicate a highly symmetrical octahedral geometry for the capping tin-containing fragment [94].

The encapsulation of iron(II) trisdioximates by germanium tetrachloride proceeds by a somewhat unexpected route: instead of the clathrochelate dianion $[Fe(Gl)_3(GeCl_3)_2]^{2-}$, the polymeric complexes $\{H_2[Fe(L955)]\}_n$ to $\{H_2[Fe(L959)]\}_n$ were obtained (Eq. 4.26) [95].



$R = R_1 = H$	$\{H_2[Fe(L955)]\}_n$
$R = H, R_1 = CH_3$	$\{H_2[Fe(L956)]\}_n$
$R = R_1 = CH_3$	$\{H_2[Fe(L957)]\}_n$
$R = R_1 = C_6H_5$	$\{H_2[Fe(L958)]\}_n$
$R\frown R_1 = (CH_2)_4$	$\{H_2[Fe(L959)]\}_n$

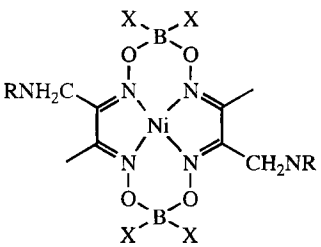
(4.26)

According to the ^{57}Fe Mössbauer spectroscopic data the coordination polyhedron of the iron(II) atoms approaches an octahedron. The macrocyclic ligand field-increasing effect in germanium-containing complexes is close to that in boron-

containing clathrochelates and is much more pronounced than in their tin-containing analogues [95].

The ruthenium(II) clathrochelate [Ru(L920)] has been isolated from the template reaction of $RuCl_3 \cdot 3H_2O$ with nioxime and phenylboric acid in dry ethanol in an inert atmosphere in 12.5% yield [96, 97]. In addition, template syntheses of [Ru(L881)], [Ru(L894)], [Ru(L909)], [Ru(L918)], [Ru(L919)] and [Ru(L921)] to [Ru(L924)] were reported [97]. Similar compounds containing nickel(II), cobalt(II), copper(II) and palladium(II) were not obtained. The reason for this may be the preferential formation by these metals of square-planar bis(dioximato) complexes rather than octahedral or distorted octahedral tris(dioximato) complexes and not the mismatch of the size of a clathrochelate cavity to the radii of these metal ions, as has been suggested [81, 86].

Square planar nickel(II), cobalt(II), copper(II), palladium(II) and platinum(II) macrocyclic dioximates result from replacement of the hydrogen bonds in oxime complexes with boron bridging reagents (Eqs. 4.27 and 4.28) [98–109].

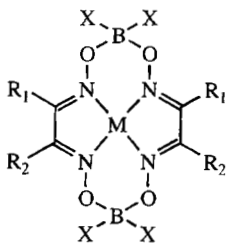


$R = CH_3$, $X = F$	[Ni(L960)]	
$R = C_2H_5$, $X = F$	[Ni(L961)]	(4.27)
$R = CH_3$, $X = C_2H_5$	[Ni(L962)]	
$R = X = C_2H_5$	[Ni(L963)]	

Neither Fe^{II} nor Co^{III} ions show a preference for the formation of macrocyclic boron-containing bisdioximates, but such systems are sometimes produced. In particular, the cobalt(III) complex $[CH_3Co(L964)(H_2O)]$ has been isolated in 62% yield by the reaction of $CH_3Co(HL878)_2 \cdot H_2O$ with $BF_3 \cdot (C_2H_5)_2O$ in ether [110]. The compound [Fe(L969)] results from the reaction of $[Fe(HL878)_2]$ with the aminoethyl ester of diphenylboronic acid [100], and $[Fe(L969)(CH_3imid)_2]$ from the reaction of $[Fe(HL878)_2(CH_3imid)_2]$ with diphenylboron bromide in the presence of *N*-methylimidazole. The structure of the latter has been proved crystallographically [77].

Binuclear complexes $[Ni_2(L986)]$ and $[Ni_2(L987)]$ (Eq. 4.29) have been prepared from monomeric bis(dioximato)nickel(II) precursors by treatment with the corresponding bridging reagents $F_2B\text{-}R\text{-}BF_2$ ($R = 1,4\text{-}C_6H_4$ or $\text{-}(CH_2)_4\text{-}$) [105].

An interesting class of capping reagents based on 3d metal complexes of 1,4,7-triazacyclononane has recently been discovered [111–113]. It is well known that manganese(III), iron(III) or chromium(III) form octahedral complexes with 1,4,7-triazacyclononane or its derivatives with 1:1 stoichiometry [114]. The macrocyclic amine in these complexes has been shown to be coordinated facially to the central metal ion, the remaining three coordination sites being occupied by monodentate ligands. The latter, in contrast to the tridentate macrocyclic amine, can easily be



M = Ni, Co; $R_1 = R_2 = CH_3$; X = F [M(L964)]

M = Ni; $R_1 = R_2 = CH_3$; $X = CH_3$ [Ni(L965)]

M = Ni, Pd; $R_1 = R_2 = CH_3$; X = n-C_3H_7 [M(L966)]

M = Ni; $R_1 = R_2 = CH_3$; X = n-C_4H_9 [Ni(L967)]

M = Ni; $R_1 = R_2 = CH_3$; X = iso-C_4H_9 [Ni(L968)]

M = Ni, Cu, Pd; $R_1 = R_2 = CH_3$; $X = C_6H_5$ [M(L969)]

M = Ni; $R_1 = R_2 = H$; X = F [Ni(L970)]

M = Ni; $R_1 = CH_3$, $R_2 = H$; X = F [Ni(L971)]

M = Ni, Co, Cu; $R_1 = R_2 = C_6H_5$; X = F [M(L972)]

M = Ni; $R_1 = R_2 = NH_2$; X = OH [Ni(L973)]

M = Ni, Co, Pd, Pt; $R_1 = R_2 =$; X = F [M(L974)]

M = Ni, Cu; $R_1 = R_2 = CH_3$; X = C_2H_5 [M(L975)]

M = Ni, Cu; $R_1 = R_2 = C_6H_5$; X = C_2H_5 [M(L976)]

M = Ni; $R_1 = R_2 =$ n-C_3H_7; X = F [Ni(L977)]

M = Ni; $R_1 = R_2 = C_2H_5$; X = F [Ni(L978)]

M = Ni; $R_1 = CH_3$, $R_2 = C_2H_5$; X = F [Ni(L979)]

M = Ni; $R_1 = R_2 = (CH_2)_4$; $X = C_6H_5$ [Ni(L980)]

M = Ni; $R_1 = R_2 = (CH_2)_5$; $X = C_6H_5$ [Ni(L981)]

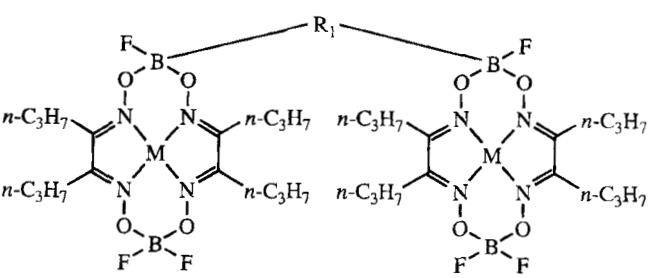
M = Ni; $R_1 = R_2 = NH_2$; $X = C_6H_5$ [Ni(L982)]

M = Ni; $R_1 = R_2 = H$; $X = C_6H_5$ [Ni(L983)]

M = Ni; $R_1 = R_2 = C_6H_5$; $X = C_6H_5$ [Ni(L984)]

M = Ni; $R_1 = R_2 =$; X = F [Ni(L985)]

(4.28)

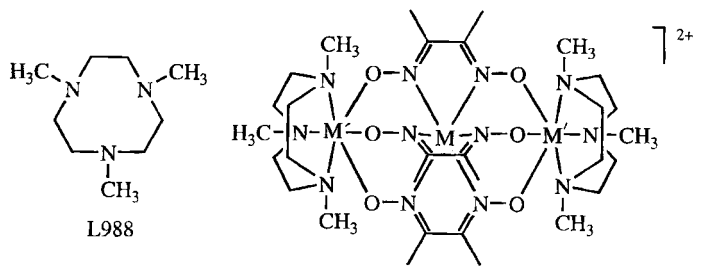


(4.29)

R_1 = 1,4-C_6H_4 [Ni_2(L986)]

$R_1 = (CH_2)_4$ [Ni_2(L987)]

replaced under appropriate conditions by other ligands preferred by the central metal ions. All this makes the above complexes extremely appealing for using as capping reagents for tris(dioximato) metal chelates. Indeed, the clathrochelates $[M(L989)]^{2+}$ and $[M(L990)]^{2+}$ with M = Zn^{II}, Cu^{II}, Ni^{II}, Fe^{II} or Mn^{II}, in which the metal is encapsulated in a tris(dioximato) ligand cage system capped by manganese(III) or iron(III) complexes of 1,4,7-trimethyl-1,4,7-triazacyclononane (L988), have been prepared [111–113]. The structures of $[Zn(L989)]^{2+}$ [113], $[Cu(L990)]^{2+}$ [111] and $[Ni(L990)]^{2+}$ [112] have been established by X-ray diffraction (Eq. 4.30).

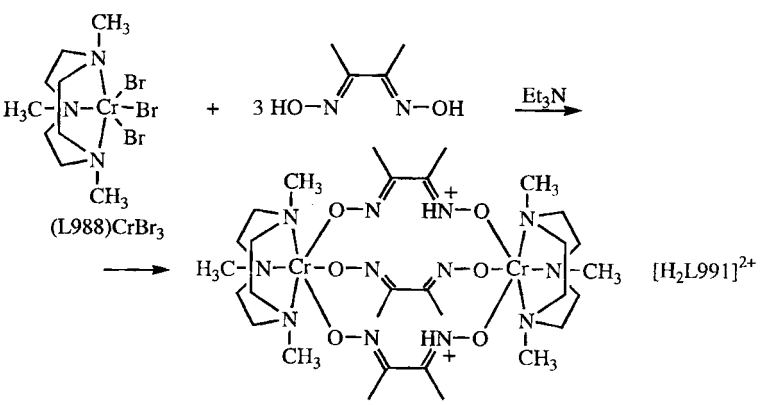


L988

$M' = Mn^{III}$ $[M(L989)]^{2+}$
$M' = Fe^{III}$ $[M(L990)]^{2+}$
$M = Zn^{II}, Cu^{II}, Ni^{II}, Fe^{II}, Mn^{II}$

(4.30)

Recalling that metal(II) ions such as nickel(II) or copper(II) preferentially form square-planar bis(dioximato)complexes, it is arguable that the metal(II) tris(dioximato) core is responsible for the control of the encapsulation process, acting as a three-dimensional template. The metal-free cage ligand system $[H_2L991](ClO_4)_2 \cdot CH_3OH$ has been isolated by refluxing a mixture of $(L988)CrBr_3$ with dimethylglyoxime and triethylamine in the molar ratio 2:3:6 in methanol, followed by addition of triethylammonium perchlorate (Eq. 4.31) [115].

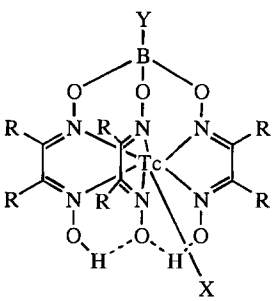


$(L988)CrBr_3$ $[H_2L991]^{2+}$

(4.31)

The structure has been proved by X-ray diffraction methods [115]. This unexpected reaction showed that the presence of three substitution-labile coordination sites, disposed in an appropriate facial manner around a metal(III) centre for a capping reaction to occur, combined with the preference of chromium(III) ions for oxime oxygen donor atoms rather than azomethine nitrogens, ensure a combination of steric and functional prerequisites for ultimate self-assembly involving both (L988)$CrBr_3$ and dimethylglyoxime ligsons. Both partners in this case act as template for each other, to provide the final cage-like ligand product. Template complementarity is crucial for the success of this peculiar self-assembly. It is concluded that the metal(II) ions play a secondary role in assembly of $[M(L989)]^{2+}$ and $[M(L990)]^{2+}$.

Technetium complexes monocapped by boronic acid/oxime capping, $[Tc^{III}(L992)X]$ to $[Tc^{III}(L996)X]$ (X = Cl, Br) (Eq. 4.32), have been prepared by template synthesis starting from pertechnetate $(TcO_4)^-$, stannous (Sn^{2+}) ions, and from $[N(C_4H_9)_4][TcOCl_4]$ or $M_2[TcX_6]$ (M = NH_4, K; X = Cl, Br) [116–118]. Crystal structures have been determined by X-ray diffraction studies for [Tc(L992)Br], [Tc(L993)Br] and [Tc(L994)Br] [116], [Tc(L995)Cl] [118] and [Tc(L996)Cl] [117].



X = Br, Y = CH_3, R = $(CH_2)_2$	[Tc(L992)Br]
X = Cl, Y = CH_3, R = $(CH_2)_2$	[Tc(L992)Cl]
X = Br, Y = n-C_4H_9, R = CH_3	[Tc(L993)Br]
X = Cl, Y = n-C_4H_9, R = CH_3	[Tc(L993)Cl]
X = Br, Y = n-C_4H_9, R = $(CH_2)_2$	[Tc(L994)Br]
X = Cl, Y = n-C_4H_9, R = $(CH_2)_2$	[Tc(L994)Cl]
X = Cl, Y = m-$C_6H_5CH_3$, R = CH_3	[Tc(L995)Cl]
X = Cl, Y = CH_3, R = CH_3	[Tc(L996)Cl]

(4.32)

As is shown in Figure 4-3 for the typical case of [Tc(L992)Br], the technetium atom is heptacoordinated by a hexadentate monocapped ligand and a halogen atom. The six ligating nitrogen atoms form a monocapped distorted trigonal prism, which can be characterised by the geometry of the triangles of nitrogen or oxygen atoms at the capped and uncapped ends of the complex. These triangles are nearly parallel (dihedral angles range from from 0° to 3°). Triangles at the capped end are smaller than the corresponding triangles at the uncapped end due to the pinching constraints of the cap (the average Tc–N distance at the capped end is 1 nm smaller than the average Tc–N distance at the uncapped end). The dioxime oxygen atoms at the uncapped end are involved in hydrogen bonding with two protons. The distortion of the structure from strict trigonal prismatic symmetry is to a great extent dictated by the coordination of the halogen to the technetium atom. These structural distortions probably preclude the addition of a second boron cap. The formation of [Tc(L996)Cl] from $^{99}TcO_4^-$ and $SnCl_2$ is believed [117] to proceed

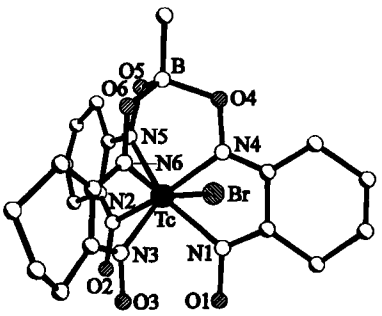
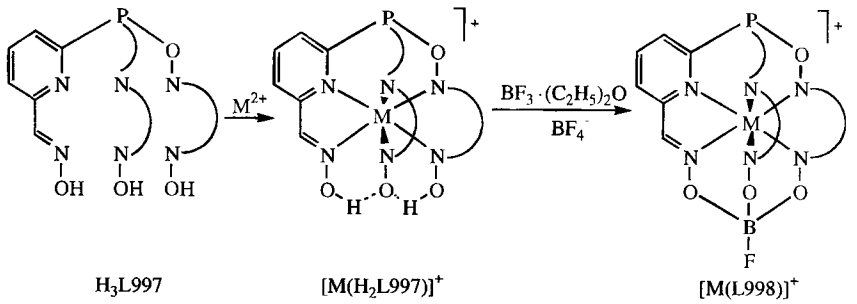


Figure 4-3. The structure of [Tc(L992)Br].



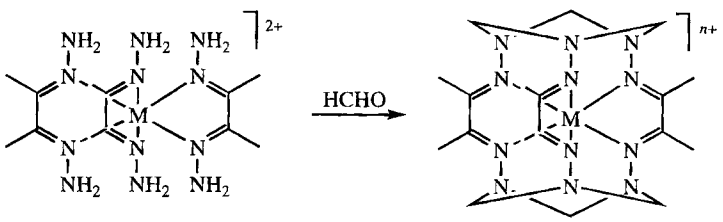
Scheme 4-13. Synthesis of phosphabora-capped clathrochelates.

through two Tc^{III} intermediate species. The first, $[Tc^{III}(HL878)_3(\mu\text{-}OH)Sn^{IV}Cl_3]$, assigned previously on the basis of X-ray structure analysis, which did not permit the establishment of the degree of protonation of the oxime ligands, as a $Tc^{V}Sn^{IV}$ compound [119], is converted into the second species, $[Tc^{III}(HL878)_2(H_2L878)Cl]$, in acid solution. The loss of the tin cap causes the rearrangement of the structure, which becomes favourable for interaction with boronic acid. The coordination kinetic template effect is operative at this stage and results in fast capping of the tris(dioximato) technetium(III) complex with ultimate formation of [Tc(L996)Cl].

The phosphorus-containing macrobicyclic 3d metal complexes assembled on iron(II), cobalt(II), nickel(II), and zinc(II) matrices in good yield, following Scheme 4-13 [120–122], form another class of clathrochelates, similar in structure and properties. It should be noted that not only $BF_3{\cdot}(C_2H_5)_2O$ but also alkaline metal tetrafluoroborates can be employed as capping reagents; in both cases the yield of the final product, except for $[Zn(L998)]^+$, is 50–75%. (Upon closing the cavity in $[Zn(H_2L997)]^+$ with sodium tetrafluoroborate the yield of $[Zn(L998)]BF_4$ is 31%.) All attempts to perform the conversions represented in Scheme 4-13 in the presence of Cu^{II} and Mn^{II} were unsuccessful [121]. X-Ray diffraction studies of the clathrochelates $[M(L998)]^+$, where M = Fe, Co, Ni or Zn, revealed [123–126]

structures in which the metal(II) coordination sphere approaches the ideal trigonal prismatic case for Co^{II} d^7 ($\phi_{av.} = 0.9°$), Ni^{II} d^8 ($\phi_{av.} = 1.6°$) and Zn^{II} d^{10} ($\phi_{av.} = 1.2°$) or is intermediate between trigonal prismatic and trigonal antiprismatic (octahedral), as for Fe^{II} d^6 ($\phi_{av.} = 21.7°$). Note that of these metal ions the low-spin Fe^{II} has the smallest radius (6.1 nm), compared to Co^{II}, Ni^{II} and Zn^{II} (7.4, 7.0 and 7.5 nm, respectively).

Another type of clathrochelate, namely $[M(L1000)]^{n+}$, is obtained on reaction of tris(butan-2,3-dione)dihydrazonato-nickel(II), -iron(II) or -cobalt(II) with formaldehyde in acetonitrile (Eq. 4.33) [127, 128].



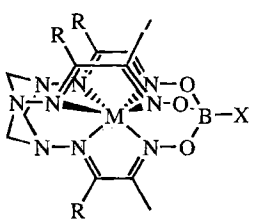
$[M(L999)_3]^{2+}$
M = Ni, Fe, Co

$[M(L1000)]^{2+}$ (M = Ni, Fe)
$[Co(L1000)]^{3+}$

(4.33)

The complex $[Co(L1000)]^{3+}$ is obtained from $[Co(L999)_3]^{2+}$ and oxidation occurs even if the reaction is carried out under an inert atmosphere. The cobalt(II) complex with L999 is produced by treatment of $[Co^{III}(L999)](BF_4)_3$ with hydrazine. A large excess of hydrazine should be avoided as cobalt(II) may than be reduced to cobalt(I).

The Lewis acid/oxime [66] and the formaldehyde/hydrazone [127, 128] capping processes permit the assembly of clathrochelate iron(II) or cobalt(II) complexes $[M(L1001)]^+$ to $[M(L1006)]^+$ based on miscellaneous oxime-hydrazone ligand systems (Eq. 4.34) [129, 130].

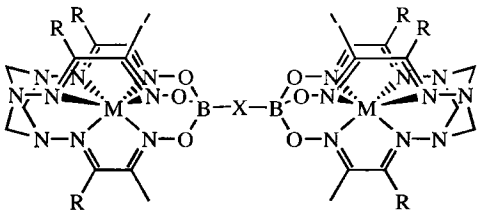


M = Fe, Co; R = CH_3; X = C_6H_5	$[M(L1001)]^+$
M = Fe, Co; R = C_6H_5; X = C_6H_5	$[M(L1002)]^+$
M = Fe, Co; R = H; X = C_6H_5	$[M(L1003)]^+$
M = Fe; R = CH_3; X = Fc	$[Fe(L1004)]^+$
M = Fe; R = C_6H_5; X = Fc	$[Fe(L1005)]^+$
M = Fe; R = H; X = Fc	$[Fe(L1006)]^+$

(Fc = ferrocenyl)

(4.34)

The employment of both benzene-1,4-diboronic and 1,1′-ferrocenediyldiboronic acids as capping agents produces trinuclear species $[M_2(L1007)]^{2+}$ to $[M_2(L1009)]^{2+}$, in which two clathrochelate iron(II) or cobalt(II) complexes are linked through a 1,4-benzene or 1,1′-ferrocenediyl bridging group (Eq. 4.35) [129, 130].



(4.35)

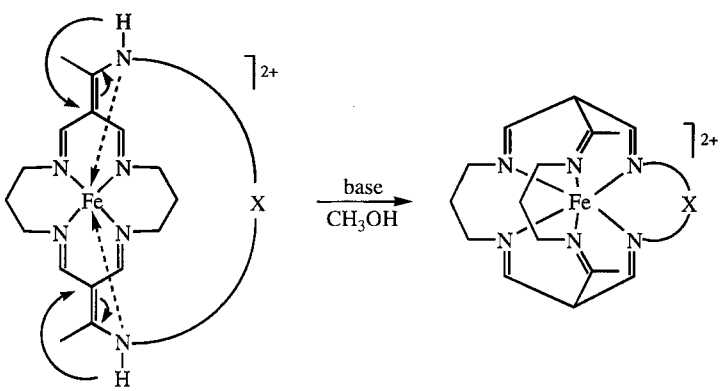
M = Fe, Co; R = CH_3, X = 1,4-C_6H_4 $[M_2(L1007)]^+$

M = Fe, Co; R = C_6H_5, X = 1.4-C_6H_4 $[M_2(L1008)]^+$

M = Fe; R = CH_3; X = 1,1′-Fc $[Fe_2(L1009)]^+$

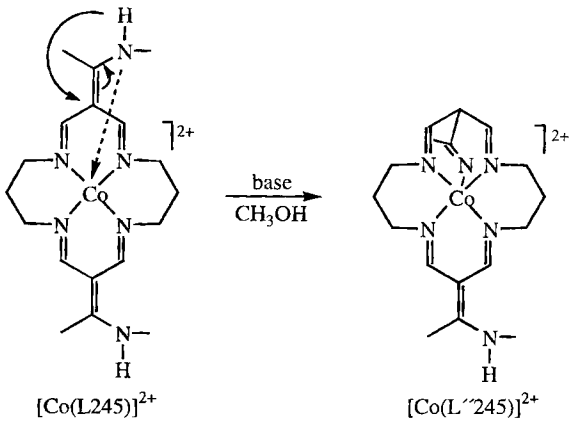
An original pathway for producing reversible iron(II) clathrochelated structures has been discovered [131]. In particular, the clathrochelate systems $[Fe(L'245)]^{2+}$, $[Fe(L'1010)]^{2+}$, $[Fe(L'244)]^{2+}$ and $[Fe(L'1011)]^{2+}$ were produced by treating complexes of superstructural macrocyclic ligands $[Fe(L245)]^{2+}$, $[Fe(L1010)]^{2+}$, $[Fe(L244)]^{2+}$ and $[Fe(L1011)]^{2+}$ with base in methanol in an inert atmosphere (Scheme 4-14).

The complexes with hexadentate cage-like ligands result from tautomeric conversion of conjugated π systems of quadridentate macrocycles catalysed by bases due to the migration of protons of two secondary amino groups to γ-carbon atoms, followed by coordination of the two C=N groups produced (Scheme 4-14). Poten-



X = $-(CH_3)_2$	$[Fe(L245)]^{2+}$	X = $-(CH_3)_2$	$[Fe(L'245)]^{2+}$
X = $(CH_2)_5$	$[Fe(L1010)]^{2+}$	X = $(CH_2)_5$	$[Fe(L'1010)]^{2+}$
X = $(CH_2)_6$	$[Fe(L244)]^{2+}$	X = $(CH_2)_6$	$[Fe(L'244)]^{2+}$
X = $(CH_2)_3$ $(CH_2)_3$	$[Fe(L1011)]^{2+}$	X = $(CH_2)_3$ $(CH_2)_3$	$[Fe(L'1011)]^{2+}$

Scheme 4-14. Base-induced tautomeric isomerisation of tetradentate macrocycles into cage ligand systems.



$[Co(L245)]^{2+}$ $[Co(L''245)]^{2+}$

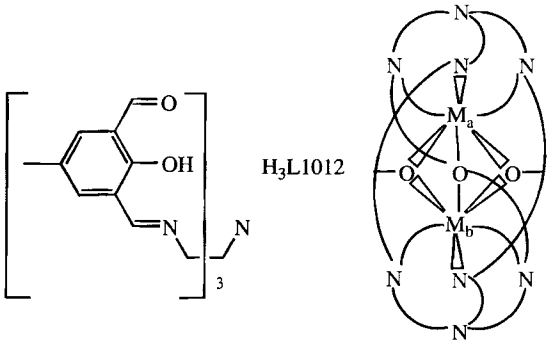
Scheme 4-15. Base-induced isomerisation of $[Co(L245)]^{2+}$ into $[Co(L''245)]^{2+}$.

tial donor NH groups initially not bound to the metal become the coordinated imines. X-Ray diffraction proved the clathrochelate nature of one of the hexaene compounds, $[Fe(L'1010)]^{2+}$. Six imine groups are coordinated to Fe^{2+} forming a slightly distorted octahedron, the Fe–N bond length being within the range 19.3–19.9 nm. The similarity of spectroscopic features in the series $[Fe(L'245)]^{2+}$, $[Fe(L'1010)]^{2+}$, $[Fe(L'244)]^{2+}$ and $[Fe(L'1011)]^{2+}$ suggests that all these substances have a cage-like structure [131]. By using carbon monoxide as an incoming nucleophile the reverse clathro rearrangement has also been studied under appropriate conditions [131].

Analogous transformations of $[Co(L245)]^{2+}$ are also well documented. In this case in the presence of an excess of base (acetate ion) an internal rearrangement of one peripheral secondary amine moiety of $[Co(L245)]^{2+}$ occurs and this allows an additional nitrogen atom to coordinate to the metal centre, forming a five-coordinate cobalt(II) complex $[Co(L''245)]^{2+}$ (Scheme 4-15) [132].

An X-ray diffraction examination of $[Co(L''245)(CH_3CN)](PF_6)_2$ has shown [132] that the macrocyclic ligand occupies five vertices of a slightly distorted square pyramid, with an acetonitrile molecule weakly interacting at the sixth coordination site. Ligand L''245 is thus pentadentate, half of whose structure corresponds to that of a clathrochelate, whereas the other half retains the characteristic structural features of a cyclidene [132].

A remarkable clathrochelate that ensures a relatively compact environment of two metal ions has been reported [133, 134]. This compound is obtained in high yield on reaction of H_3L1012 with one equivalent of tris(aminoethyl)amine and $NaNO_3$ as mononuclear $Na(H_3L1013)^+$. Transmetallation and formation of complexes $[M_a(H_3L1013)]^{2+}$ take place upon the action of bivalent metal salts on this latter compound. Binuclear clathrochelates $[M_aM_b(L1013)]^+$ are formed by addition of the corresponding metal salt to $[M_a(H_3L1013)]^{2+}$ solution in the presence of triethylamine (Eq. 4.36).

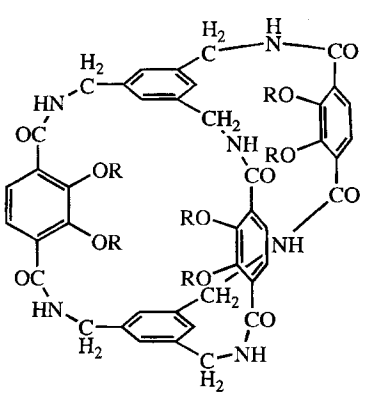


(4.36)

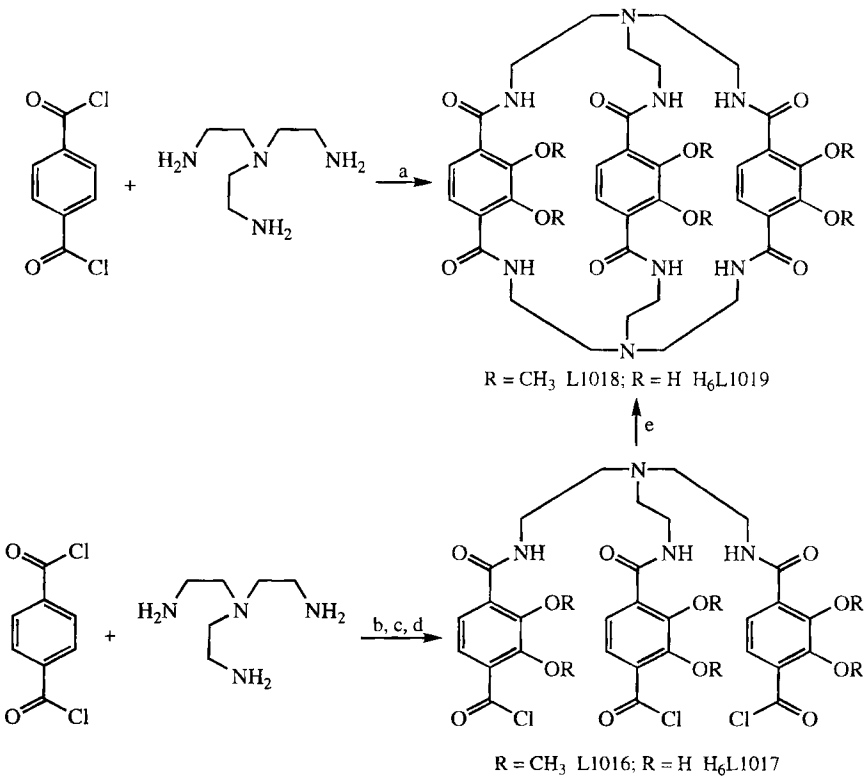
When copper(II) is involved the compound $[Cu_2(HL1013)]^{2+}$, which undergoes deprotonation with diisopropylamine, can be synthesised. The crystal structure determination of the heteronuclear clathrochelate $[CoFe(L1013)]BF_4$ showed that the high-spin Co^{II} and Fe^{II} ions were in strongly distorted environments, intermediate between octahedral and trigonal prismatic. These distortions are attributed to steric interactions between the atoms in the ligand. Analysis of space-filling molecular models demonstrated that steric interactions did not allow a cage-like ligand to be coordinated to a central atom in an octahedral manner. Each metal atom is bound to three imine nitrogens and three bridging oxygens.

4.1.3 Siderophore models and cryptands

The macrobicyclic catechoylamide ligands L1014, H_6L1015 [135–138] and other related compounds, discussed in this section are topologically similar to the clathrochelates. Interest in macrobicyclic catechoylamide compounds like L1014 and H_6L1015 (Eq. 4.37) is stimulated by the similarity of their properties to those of naturally occuring siderophores. In particular, both enterobactin and three-



(4.37)



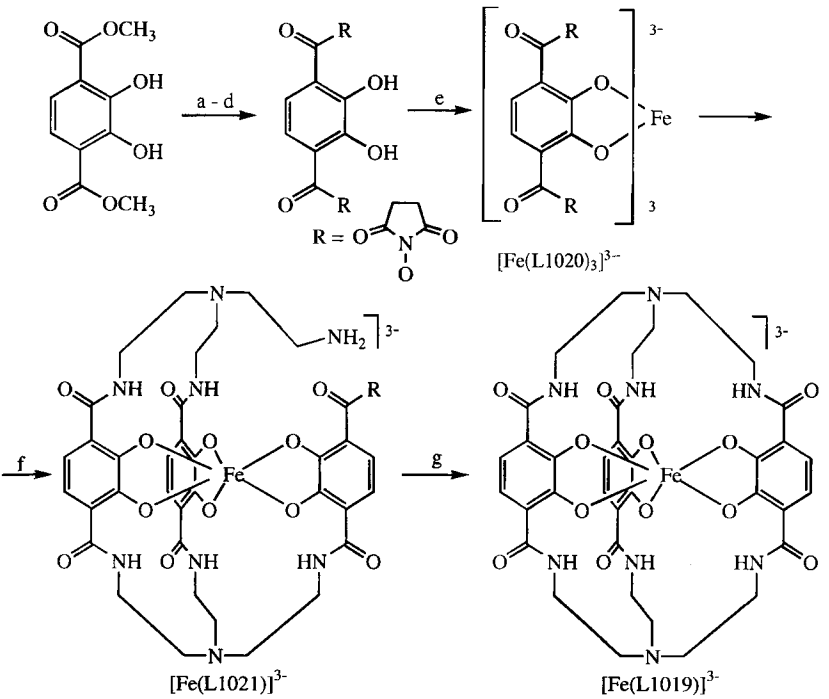
Scheme 4-16. High-dilution routes for construction of L1018: (a) THF, $(C_2H_5)_3N$, high dilution, 3.5%; (b) Schotten-Baumann, aqueous KOH, not isolated; (c) CH_3OH, aqueous NaOH, 2 h, 89%; (d) $SOCl_2$, THF, catalytic DMF; (e) tris(2-aminoethyl)amine (1 equivalent), THF, $(C_2H_5)_3N$, high dilution, 27%.

dimensional catechoylamide systems bind Fe^{3+} ions very strongly. Stability constants of the iron(III) complexes with enterobactin and $[Fe(L1015)]^{3-}$ are 10^{52} and 10^{59}, respectively [138, 139].

As a rule, the macrobicyclic catechoylamide compounds have been obtained by high-dilution techniques [135–138, 140]. However, the yield of these products is low. In particular, methyl-protected bicapped L1018 can be prepared via two high-dilution routes (Scheme 4-16) in 3.5% and 27% yields. The product H_6L1019 is obtained by treatment of L1018 with boron tribromide in CH_2Cl_2 [140].

It should be emphasised that the template method is extremely effective for the assembly of H_6L1019 [140], and quite promising for other similar products.

Reaction of an iron(III) preassembled complex $[Fe(L1020)_3]^{3-}$ with tris(2-aminoethyl)amine proceeds to form the partially encapsulated product $[Fe(L1021)]^{3-}$ in 90% yield (Scheme 4-17).

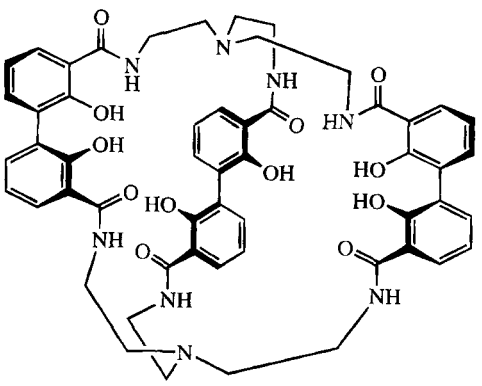


Scheme 4-17. Template synthesis of $[Fe(L1019)]^{3-}$: (a) $C_6H_5CH_2Cl$, KI, K_2CO_3, acetone reflux, 72 h, 85%; (b) NaOH, DMF/H_2O, reflux, 9 h, 94%; (c) *N*-hydroxysuccinimide, dicyclohexylcarbodiimide, dioxan, 72%; (d) H_2/5% Pd–C, ethyl acetate, room temperature, 1 h, 100%; (e) $FeCl_3$, $(C_2H_5)_3N$, DMF or DMSO, not isolated; (f) tris(2-aminoethyl)amine (2 equivalents), room temperature, 14 h; (g) 4-(dimethylamino)-pyridine, 65°C, 5 days, 70%.

Subsequent heating in the presence of 4-dimethylaminopyridine results in complete closure of $[Fe(L1021)]^{3-}$ to produce $[Fe(L1019)]^{3-}$ in 70% yield. According to an X-ray diffraction study [138] the Fe^{3+} ion in $[Fe(L1019)]^{3-}$ is positioned in a non-typical trigonal-prismatic environment formed by six pyrocatechol oxygen atoms, with each Fe–O bond being 20.12 nm. Every pyrocatechol group is planar, and the *trans* configuration of amide groups provides strong hydrogen bonding between amide protons and coordinated oxygens. Treatment of $[Fe(L1019)]^{3-}$ with $Na_2S_2O_4$/HCl solution yields a metal-free compound showing a peak with m/z 779, assigned to $[H_6L1019 + H]^+$, in the FAB mass spectrum [140].

Poly(ethylene imine) (PEI) has also been employed for capping a preassembled octahedral iron(III) complex with H_2L1020 (Scheme 4-17) in DMSO in the presence of triethylamine [141]. The formation of amide linkages has been proved by the presence of a band at 1641 cm^{-1} in the IR spectra. However, the formation of a bicapped cage structure remains uncertain.

Synthesis of macrobicyclic H_6L1022 possessing six convergent hydroxy groups, and which is thus a potential siderophore, has been achieved (Eq. 4.38) [142].



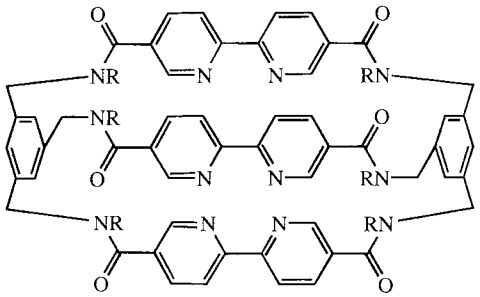
H_6L1022 (4.38)

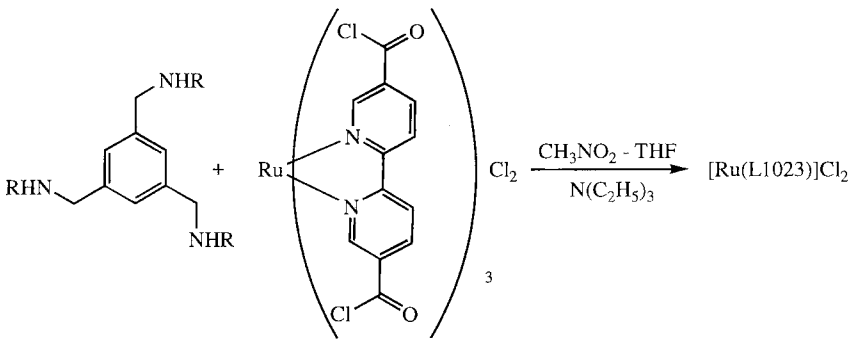
The synthesis of H_6L1022 was carried out by the high dilution technique (yield 18%), as well as in nearly quantitative yield through a template reaction using a published [140] procedure. Iron(III) is bound even more strongly in $[Fe(L1022)]^{3-}$ than to EDTA or natural siderophores, as shown by competition experiments in water at pH 11.5 [142]. The effectiveness of these applications of the coordination template effect is attributed to a number of favourable factors:

- according to the HSAB principle, pyrocatechol donor oxygens, as hard bases, will have an affinity for such metals as Al, Fe and U [136];
- a remarkably stable five-membered chelate ring is formed in metal complexes with pyrocatechol and related ligsons;
- three pyrocatechol units can be arranged around the Fe^{3+} ion in an appropriate geometry [143];
- the orientation of the reactive groups of pyrocatechoylamide ligsons is appropriate for interaction with trifunctional encapsulators.

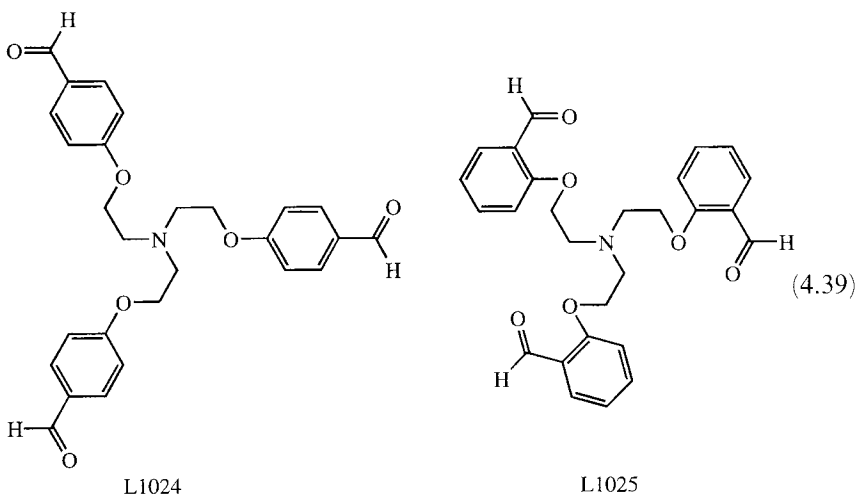
The ligand L1023 was synthesised both via a high dilution procedure [144] and via a template reaction according to Scheme 4-18 [145].

Condensation of tripodal trialdehydes L1024 or L1025 (Eq. 4.39) with 1,2-diaminobenzene in the molar ratio 2:3 in the presence of Cs^I as template, followed by reduction of the resulting Schiff bases with $NaBH_4$, produces the cryptands L1026 and L1027 in 35% and 30% yield, respectively (Eq. 4.40) [146]. Note that in the absence of Cs^I a mixture of unidentifiable composition is formed.

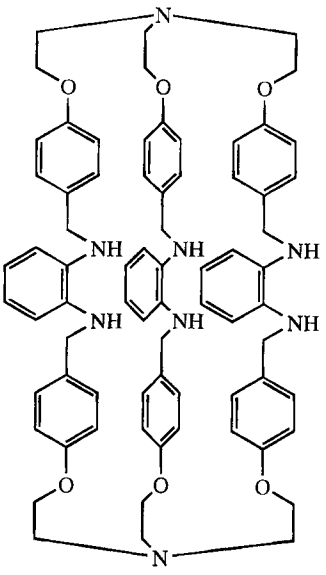




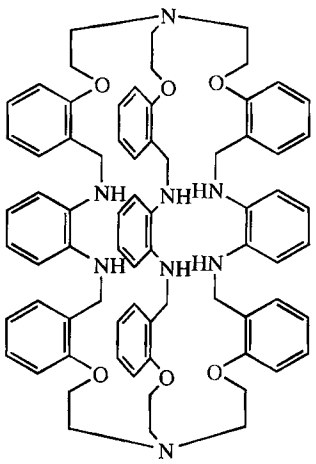
Scheme 4-18. Template assembly of [Ru(L1023)]Cl_2.



(4.39)



L1026

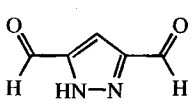


L1027

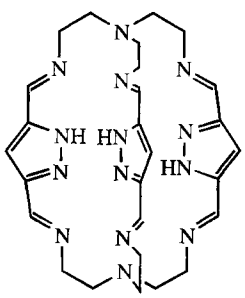
(4.40)

Both cryptands form mononuclear cryptates with Cu^{II}, Ni^{II}, Co^{II} and Fe^{III}. It is believed that the central metal ion is bonded to six nitrogen donor atoms of the 1,2-diaminobenzene residues.

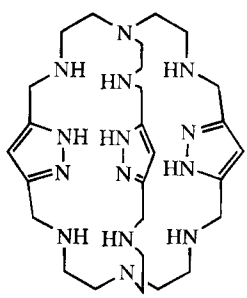
Reaction of HL1028 with tris(2-aminoethyl)amine (L685) in acetonitrile-methanol (25:1) affords the macrobicyclic Schiff base H_3L1029 in 65% yield [147]. Reduction of the latter in methanol gives the cryptand H_3L1030 (Eq. 4.41).



HL1028



H_3L1029



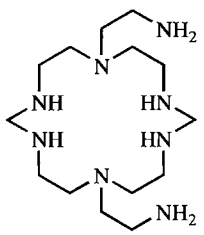
H_3L1030

(4.41)

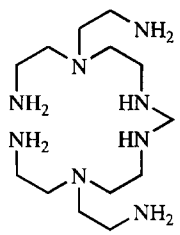
When the condensation reaction was carried out in the presence of two equivalents of Ag^+ the same ligand product was isolated as the binuclear complex $[Ag_2(H_3L1029)]^{2+}$ in 50% yield. Although the role of silver(I) in this reaction has not been elucidated, it is tempting to consider this reaction according to the classification given in Chapter 1 as *in situ*, and not a template process.

The interaction of tris(2-aminoethyl)amine (L685) with bis(dimethylamino)-methane in the presence of trifluoromethanesulfonate salts of lanthanides(III),

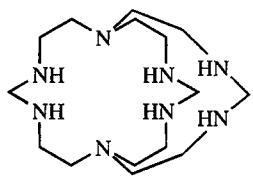
as well as of complexes $Ln(L685)_2(CF_3SO_3)_3$ with bis(dimethylamino)methane, was studied. Depending on the reaction conditions a number of products can be obtained. For instance, the reaction of two equivalents of L685 with two equivalents of bis(dimethylamino)methane in the presence of one equivalent of the lanthanide(III) triflate in acetonitrile gave the complexes $Ln(L1031)(CF_3SO_3)_3(CH_3CN)$ (Ln = La, Yb, Ce, Pr, Eu, Y) (Eq. 4.42) [148, 149].



L1031



L1032

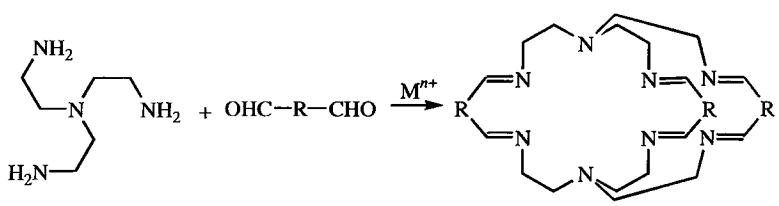


L1033

(4.42)

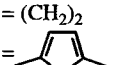
With only one equivalent of bis(dimethylamino)methane and the reaction mixture heated at reflux for only 30 min rather than overnight, lanthanide complexes of L1032 (Ln = Ce, Pr, Eu, Y) are formed [149]. The fully encapsulated complex $Yb(L1033)(CF_3SO_3)_3CH_3CN$ was prepared by using a large excess of coupling reagent and a long reaction time. It was produced in low yield and was separated from a mixture of the dibridged complex and other impurities by crystallization [149].

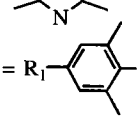
A simple one-pot synthesis of a new family of cryptands, based on reaction (4.43) has been described [150–157].



L685

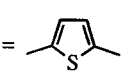
R = $(CH_2)_2$ L1034

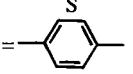
R =  L1035

R = R_1-  -OH : $R_1 = CH_3$ L1036

$R_1 = OCH_3$ L1037

$R_1 = t\text{-}C_4H_9$ L1038

R =  L1039

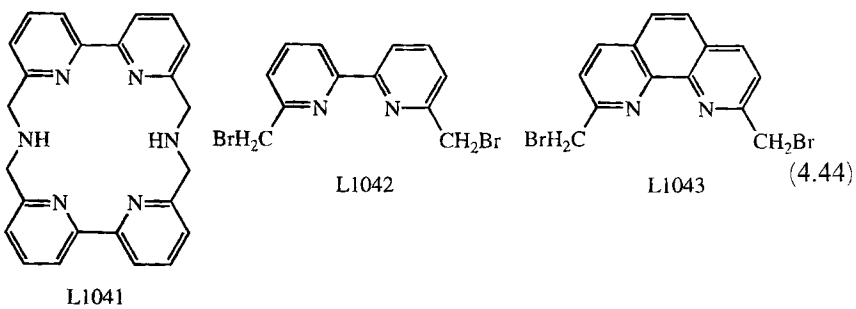
R =  L1040

(4.43)

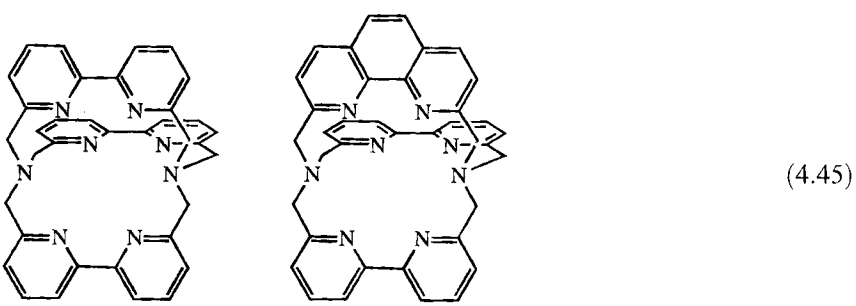
Following this procedure L1034 [152], L1035, L1036 [153], L1037 [156], L1038 [157], L1039 [150, 155], and L1040 [154] have been obtained. Metal ion templates of

Group II have been used to assemble L1034; L1035 and L1036 have been produced on Ba^{II} and Na^{I}; L1037 and L1038 are formed in the presence of Na^{I}; and L1039 is readily formed on Ag^{I}. The corresponding complexes are easily demetallated. Metal-free macrocyclic compounds L1034–L1039 form very stable complexes with 3d elements. X-Ray diffraction of $Co(L1034)(ClO_4)_2$ revealed that the metal ion is bound to all six imine donors [152]. Kinetically stable lanthanide cryptates are produced by treatment of the sodium complexes of L1036–L1038 with Ln^{3+} [156,158]. Compound L1040 was isolated as $Ag_2(L1040)(CF_3SO_3)_2$ when using silver(I) triflate as template source, and as $(H_2L1040)(ClO_4)_2$ when carrying out the reaction in the presence of copper(II) perchlorate [154]. These cryptands can also be obtained by non-template routes from the corresponding ligsons, but the yield is then much lower. Analogous furan- and pyridine-based cryptands are readily prepared by non-template procedures [150, 159].

Alkali metal ions are used as templates for the assemblage of macrobicyclic cryptands containing heterocyclic fragments [160–164]. Thus reaction of L1041 with L1042 or L1043 (Eq. 4.44) in the presence of Na_2CO_3 gave the sodium complexes of L1044 or L1045, respectively, as bromides (Eq. 4.45) [160].



L1041 L1042 L1043 (4.44)



L1044 L1045 (4.45)

Cryptand L1046, containing three phenanthroline moieties, was obtained from the phenanthroline analogue of L1041 plus L1043 under similar conditions. Synthesis of L1049 and L1050 was performed by condensation of L1047 and L1048 with L1043 under analogous conditions. In this case the corresponding products were also isolated as sodium complexes (Eq. 4.46) [160].

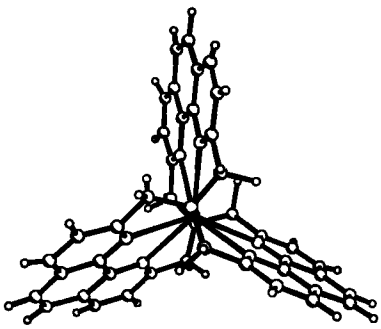
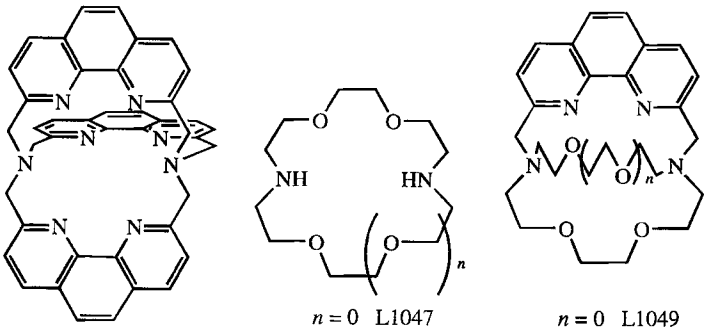


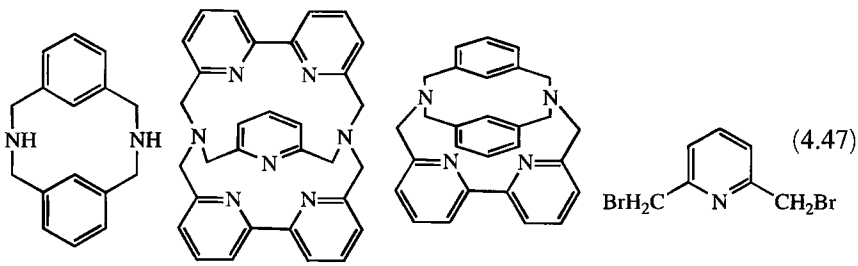
Figure 4-4. The structure of $[Na(L1046)]^+$.



L1046 $n = 0$ L1047 $n = 1$ L1048 $n = 0$ L1049 $n = 1$ L1050 (4.46)

The structure of $Na(L1046)Br \cdot 2CHCl_3$ has been established by X-ray diffraction [161]. The complex is of the cryptate type (Figure 4-4), the Na^+ cation being accommodated in the molecular cavity of L1046 and bound through all eight nitrogen atoms. The ligand has a propeller shape.

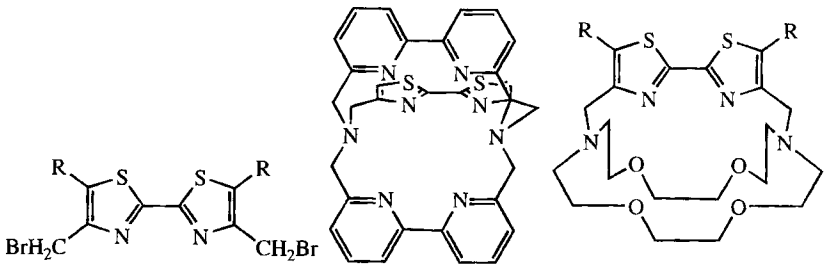
Addition of L1042 to a solution of L1051 in acetonitrile in the presence of Li_2CO_3 yielded the complex Li(L1053)Br. Under similar conditions L1052 was prepared from L1041 and L1054 employing Na_2CO_3 as template (Eq. 4.47) [163].



L1051 L1052 L1053 L1054 (4.47)

Similar synthetic routes have been employed to obtain other tricyclic systems

containing bipyridine and bisisoquinoline groups [163]. From template reactions (Na_2CO_3) of L1055 with L1041 or L1048, compounds L1056 and L1057 were isolated, respectively (Eq. 4.48) [164]. In all the cases mentioned, marked cation template effects have been found that facilitate the cyclisation processes. All the ligands were isolated as their cryptates with the corresponding alkali metal cations.



(4.48)

L1055 L1056 L1057

The template syntheses of a number of aliphatic cryptands is considered in Section 6.3.

4.2 Catenanes, rotaxanes and knots

4.2.1 Introduction

These three types of three-dimensional macrocyclic compounds are characterised by the threading of one molecule through another (catenanes, rotaxanes and pseudorotaxanes), or of a molecule through itself (knots). Their main characteristics [165] are outlined in Figure 4-5; their general topological [166] and chiral [167] features are discussed elsewhere. They, and their biological, nanostructural, and molecular recognition relevance, have been reviewed several times [168] – most fully (289 references) in [169]. Catenanes have interlocking rings (Latin *catena* = chain). The number of molecular (ring) components is indicated in brackets, as in [2]-catenane.

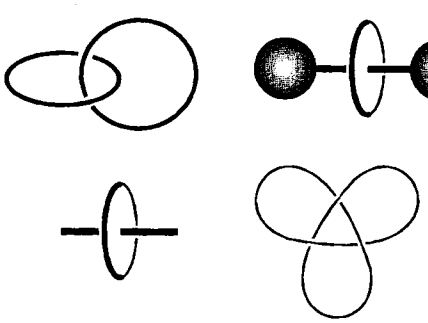


Figure 4-5. The main characteristics of catenanes, rotaxanes, pseudorotaxanes and knots.

In rotaxanes (Latin *rota* = wheel and *axis* = axle) a linear molecule is threaded through a macrocyclic ring, with the linear molecule having bulky groups at each end to prevent it slipping out of the ring. Pseudorotaxanes lack the bulky groups – they might perhaps better be termed pre-rotaxanes, as they are formally, often actually, precursors for true rotaxanes. For all these species a key feature is the need to be able to thread a molecular strand through a macrocyclic ring. Strictly the components of a catenane or rotaxane should be linked mechanically rather than by covalent or coordinate bonding. Knots are somewhat different in character [170], although linked by the need to thread molecular strands appropriately. Formally defined, a knot is a polygonal or smooth closed curve in three-dimensional space that cannot be embedded in a plane without crossings [171].

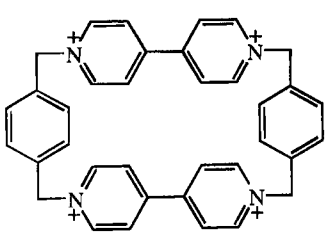
Successful synthetic work in this area depends on assembling the components in a suitable mutual orientation and arrangement. This is usually achieved by molecular preorganisation in one (or more) of three ways:

- by templating, in which metal ions may be used to bind the potential reacting ligands in close proximity and suitably positioned, or suitable guest molecules or ions may be used to organise their host thus;
- the π-stacking of electron-deficient and electron-rich aromatic units;
- by hydrogen-bonding interactions, often involving amide groups.

Cyclisation is the other important ubiquitous feature. Again there are three common ways of achieving ring formation:

- formation of ether linkages;
- formation of amide linkages;
- generation of quaternary ammonium centres.

There are many types of rings in catenanes and (pseudo)rotaxanes. They may be flexible, as in rings that combine a metal-binding moiety [172], such as 1,10-phenanthroline, or an aromatic stacking unit, with a long hydrocarbon or poly-oxyethylene chain. They may be rigid, as in the square ligand L1058 (Eq. 4.49; itself best prepared by template synthesis [173]). This was the first all-organic square ring, and is probably the most frequently encountered ring component of (pseudo)-rotaxanes and catenanes [174]. They may be not only rigid but also provide the added constraint of having a cylindrical rather than a toroidal gap to be threaded, as in the case of cyclodextrins, where the width of the gap varies from 57 to 78 to 95 nm as one goes from α- to β- to γ-cyclodextrin [175].



(4.49)

L1058

A wide range of instrumental techniques are needed to characterise products fully – X-ray crystallography, mass spectrometry (especially FAB-MS and electrospray MS), ^{1}H and ^{13}C NMR, UV-Vis spectroscopy, and electrochemistry – in the solid state and in solution. As much information as possible is needed in order to establish both the exact nature and long-range structural features (superstructure) of rotaxanes, catenanes and knots. As noted at appropriate points in the text, there is considerable interest in applications for these classes of compounds, particularly in respect to molecular switching devices.

It has been impossible to be anywhere near comprehensive in providing references to relevant literature. The field is relatively new, but very rapidly growing – with, it must be said, a regrettable degree of fragmentation and overlap. In order to keep this section within bounds, it has sometimes been necessary to restrict the mention of lengthy and detailed papers to a few words, adumbrating their main feature. However, almost all the papers cited appear in widely available journals, and are themselves generously referenced.

4.2.2 Threading: pseudorotaxanes

Threading a linear molecule through a ring is a key step in the generation of rotaxanes. The capping of a threaded molecule at both ends then converts the pseudorotaxane into a true rotaxane (Figure 4-6). Alternatively, the two ends of the thread may be joined to give a catenane [176]. Several approaches to threading have proved successful, and are outlined in the following paragraphs. Capping methods are dealt with in Section 4.2.3. The alternative route to rotaxanes is to form the ring from two components suitably positioned in relation to the (potential) thread. This route, known as clipping, appears in Section 4.2.3 because it does not involve a pseudorotaxane intermediate.

The first approach is to use copper(I) to thread a linear multinitrogen-donor molecule, such as the 2,9-diphenyl-1,10-phenanthroline [177] derivative L1059 [178]

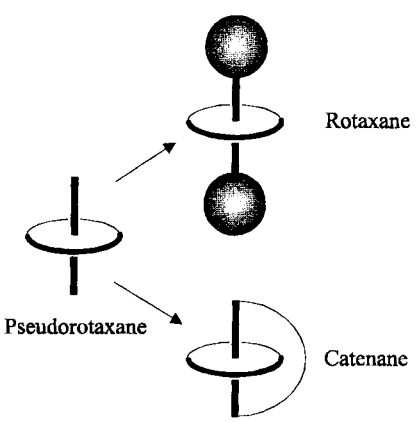
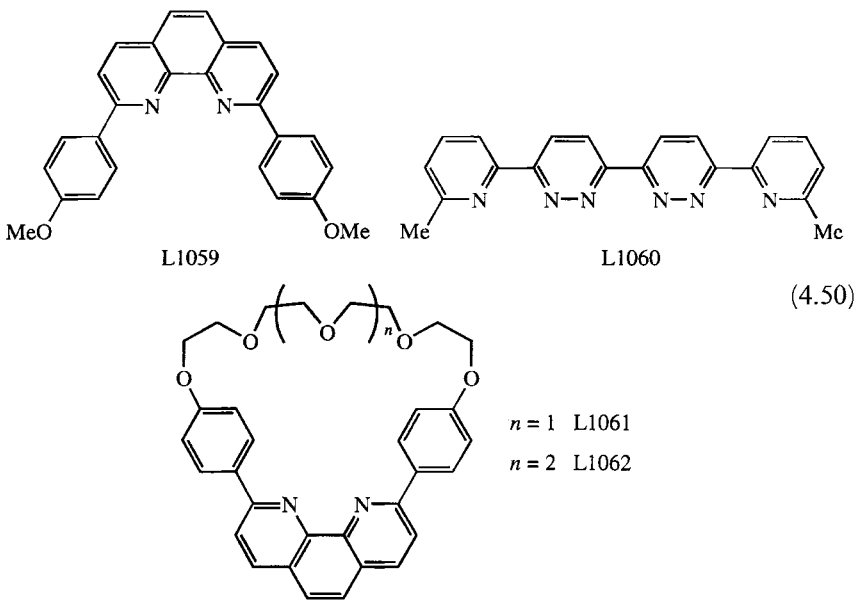


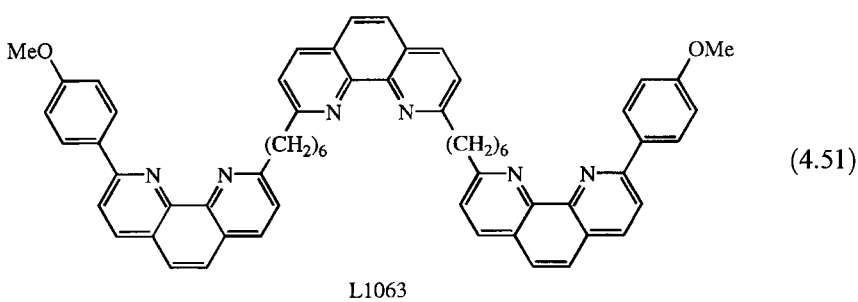
Figure 4-6. Threading as a key step in generation of rotaxanes and catenanes.

or the pyridazine-based L1060, through fused crown ether/1,10-phenanthroline macrocycles such as L1061 or L1062 (Eq. 4.50) (Some relevant background organic



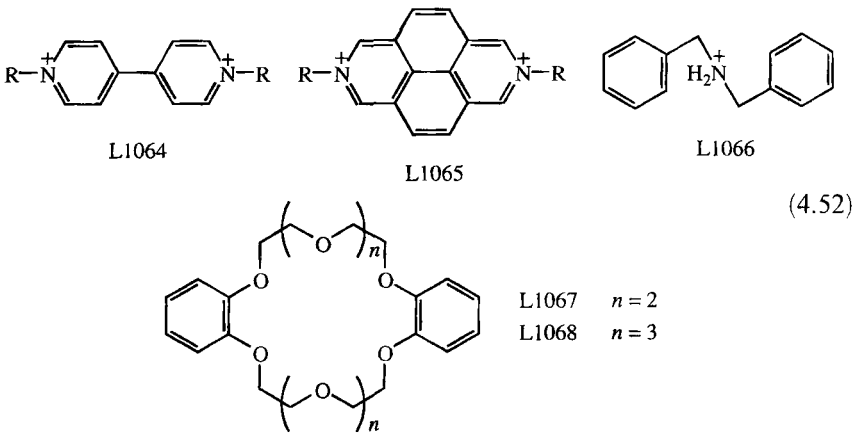
(4.50)

chemistry may be found in Scheme 4-21 near the start of Section 4.2.4.) Each Cu^+ is coordinated to two phenanthroline nitrogens from a macrocycle and to two diimine nitrogens from the garland ligand, thus threading the latter through a series of molecules of the former. The reaction between L1059 and L1061 in dichloromethane/nitromethane occurs in greater than 80% yield [179]. Threading through two or three rings can be achieved by using threads containing two or three (L1063) phenanthroline units (Eq. 4-51) [178], or by electropolymerisation of a rotaxane containing a bis(bithienyl)-1,10-phenanthroline thread. This gives short polyrotaxane wires threaded with a phenanthroline/polyether ring (L1062) at each copper(I) [180].



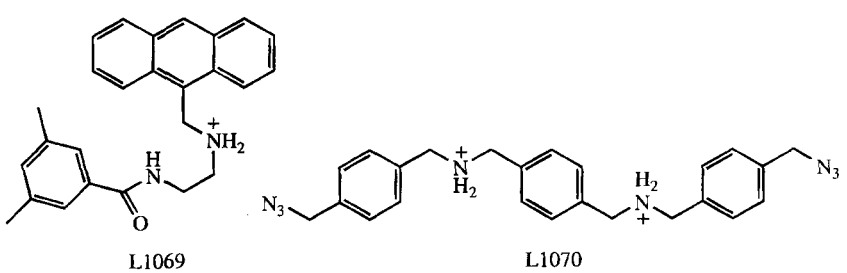
(4.51)

The second approach is to thread π-electron-deficient bipyridinium cations (L1064, L1065) or secondary diarylalkylammonium cations (e.g. L1066) through macrocyclic polyethers such as L1067 or L1068 (Eq. 4.52). More recently, porphyrin derivatives containing ether and ketone oxygen donor functions [181] have been used.

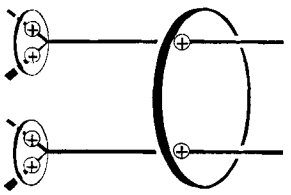


(4.52)

Strong hydrogen-bonding interactions facilitate the threading of, for instance, protonated amines of the type L1069 (Eq. 4.53) through dibenzo-24-crown-8 (L1067). This system is noteworthy for the reported increase in yield in biphasic media, which implies that the interfacial region may be a favourable site for reactions of this type [182]. The two $-NH_2^+-$ groups in L1070 permit two dibenzo-24-crown-8 rings to be accommodated around this thread [183]. It is possible to have several electron-deficient centres along a thread, and thus have several electron-rich rings. It has also proved possible to insert more than one thread through a sufficiently large ring with several potential interaction sites [184]. These exotic species have been termed (for 2:1 cases) doubly-encircled and doubly-stranded pseudorotaxanes, respectively [185]. In L1071 (Eq. 4.54) these two phenomena are com-

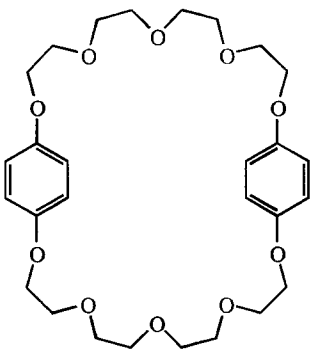


(4.53)

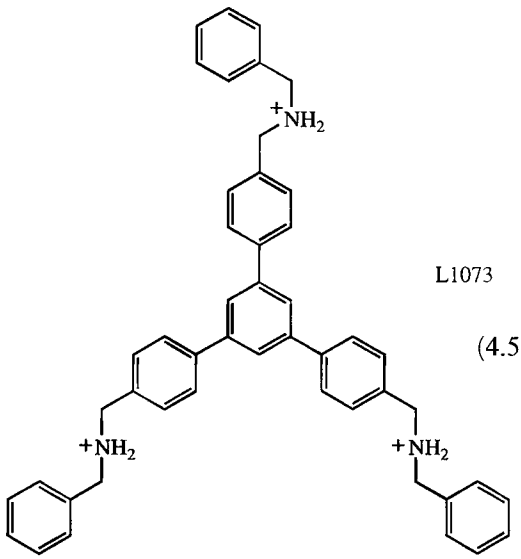


L1071

(4.54)



L1072



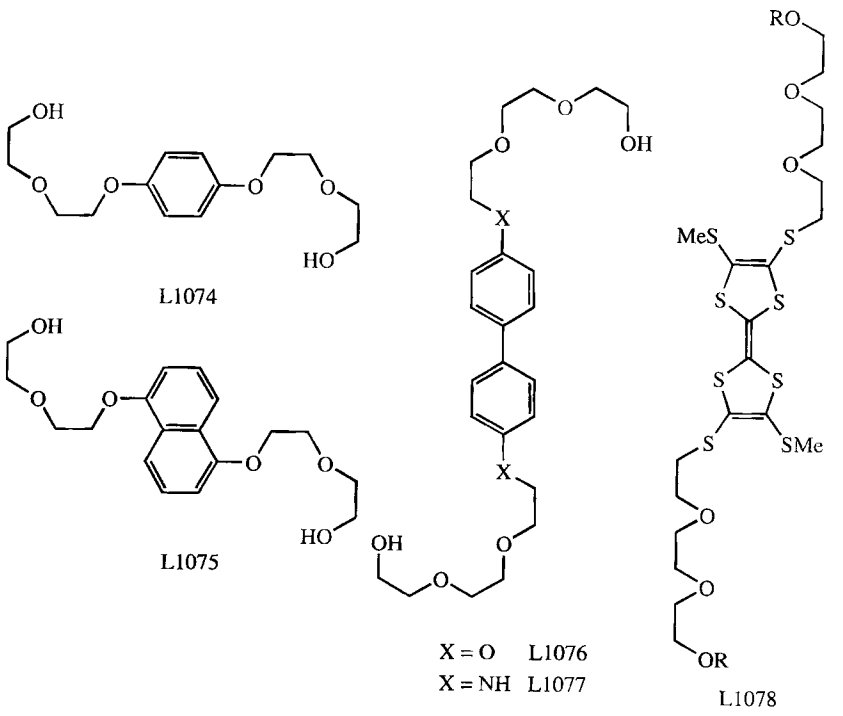
L1073

(4.55)

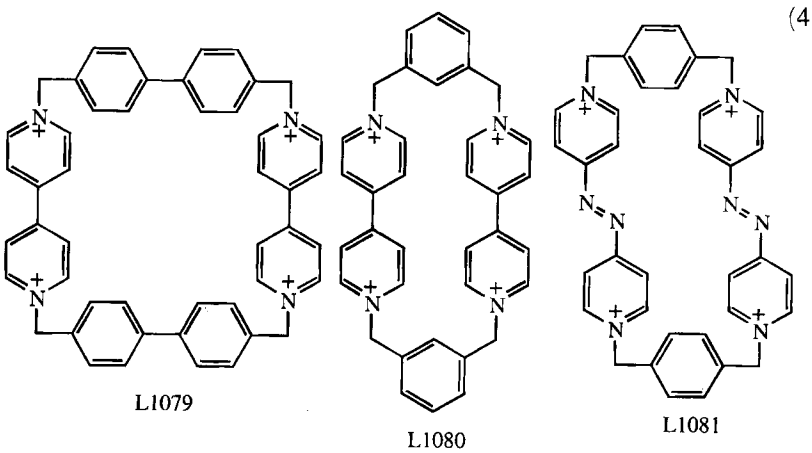
bined. Thanks to the small radius of the $-NH_2^+-$ group it is possible to thread two of them through a bis-*p*-phenylene-34-crown-10 ring (L1072); this can be repeated three times for the three-armed tris($-NH_2^+-$) thread L1073 (Eq. 4.55) [186].

Complementary to this approach is the threading (sometimes by clipping) of an electron-rich π-donor unit, such as the aromatic rings of L1074 or L1075 [174], L1076 or L1077 [187], or L1078 (Eq. 4.56) [188], through the π-electron-deficient cyclobis(paraquat-*p*-phenylene) tetracationic ring system L1058 or one of its analogues, such as L1079, L1080, or the diazo-compound L1081 with its built-in chromophoric reporters (Eq. 4.57) [189]. Inter-ring π–π interactions and hydrogen-bonding between electron-donor and electron-acceptor are important both in the initial interaction and in stabilising the pseudorotaxane once formed.

A special case of threading of this type is illustrated by the compound L1082, where there is intramolecular threading as shown, with the electron-acceptor phenylene ring in the cyclophane cavity (Eq. 4.58) [190]. The nature and extent of charge-transfer interactions in tetrathiafulvalene-cyclophane and tetrathiafulvalene–bipyridinium systems has been probed through models, such as L1083 [191] and L1084 [192]. In these bipyridinium and tetrathiafulvalene units are covalently linked in macrocyclic rings, containing linkages that are sufficiently long and flexible


OH
O
O
O
O
HO
L1074
OH
O
O
O
O
HO
L1075
O
OH
O
X
X
OH
O
O
X = O L1076
X = NH L1077
RO
O
O
O
MeS
S
S
S
S
S
S
SMe
S
O
O
OR
L1078

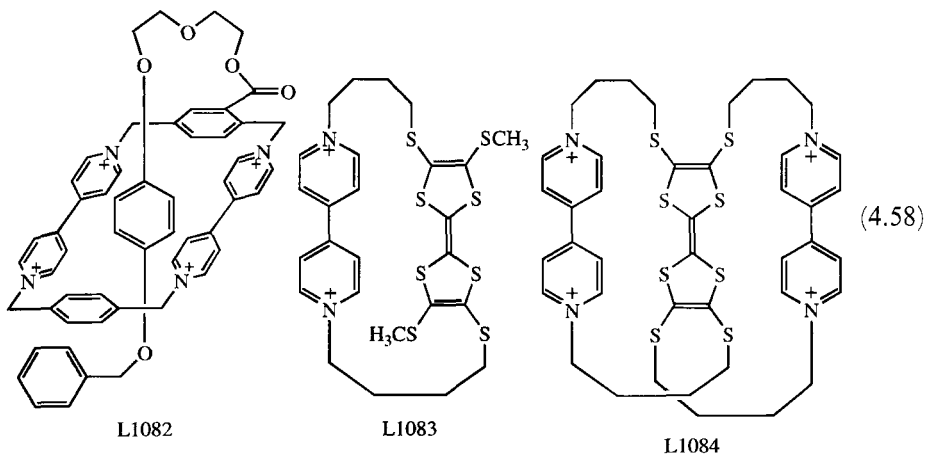
(4.56)


L1079
L1080
L1081

(4.57)

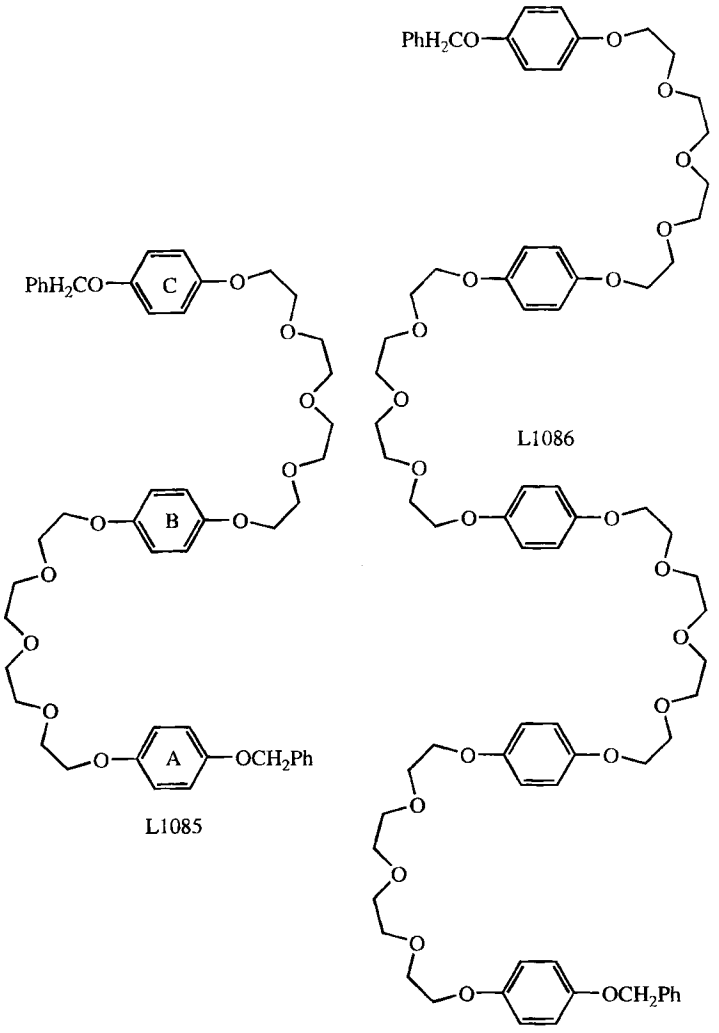
for non-covalent transannular interactions to be assessed. The crystal structure of $[L1083](PF_6)_2 \cdot MeCN$ has been determined. The reversible threading/dissociation equilibrium can be monitored electrochemically or optically, as has been documented for the interaction between the parent tetrathiafulvalene and the cyclophane L1058 [193].

Alternatively, NMR or UV–Vis spectroscopy can be used to determine association and dissociation rate constants, and thence estimate association constants, as in the study of the threading of L1074 through L1058 [194]. Kinetic and equilibrium characteristics of association have also been monitored for model systems in which 1,4-disubstituted benzenes interact with the ubiquitous cyclophane L1058 [195].



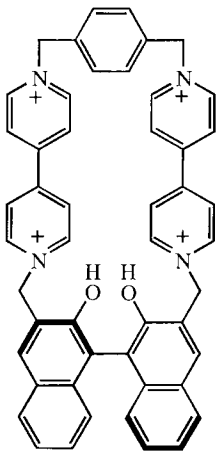
L1082 L1083 L1084 (4.58)

When one ring is associated with a thread containing several potential interaction sites, then several isomers may be possible. Thus, for example, two positional isomers are possible for the compound between the cyclophane ring L1058 and the tris-phenylene polyether L1085 (Eq. 4-59), according to whether the ring interacts with the central or a terminal phenylene ring. Barriers to translational isomerisation (movement of the cyclophane ring from ring A or C to ring B, or *vice versa*) in this and related systems, including the pentafunctional L1086, can be estimated from coalescence temperatures from variable-temperature NMR spectroscopy. Such barriers are of the order of 60 kJ mol^{-1}. Pirouetting, the process which exchanges the positions of rings A and C in the translational isomer with the cyclophane circling ring B, is, as one might expect, too fast to be monitored on the NMR time-scale. A further type of isomerisation is possible for analogues containing naphthylene links in place of phenylene links in the threads, and that involves reorientation of the naphthylene ring. Rate constants and activation barriers for this type of rearrangement can also be estimated by NMR spectroscopy [196].

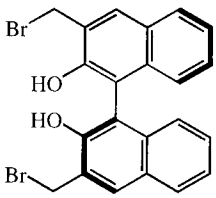


(4.59)

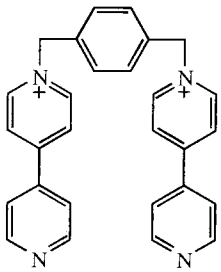
Optically active (pseudo)rotaxanes can be built up by the use of a rigid chiral unit L1087 in place of one or both phenylene units in the cyclophane L1058. L1087 may be prepared from L1088 and L1089 on a 1,4-bis{2-(2-hydroxyethoxy)ethoxy}benzene template (Eq. 4.60) [197].



L1087



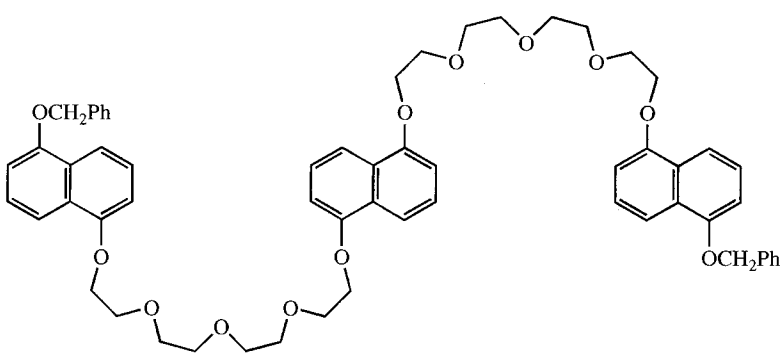
L1088



L1089

(4.60)

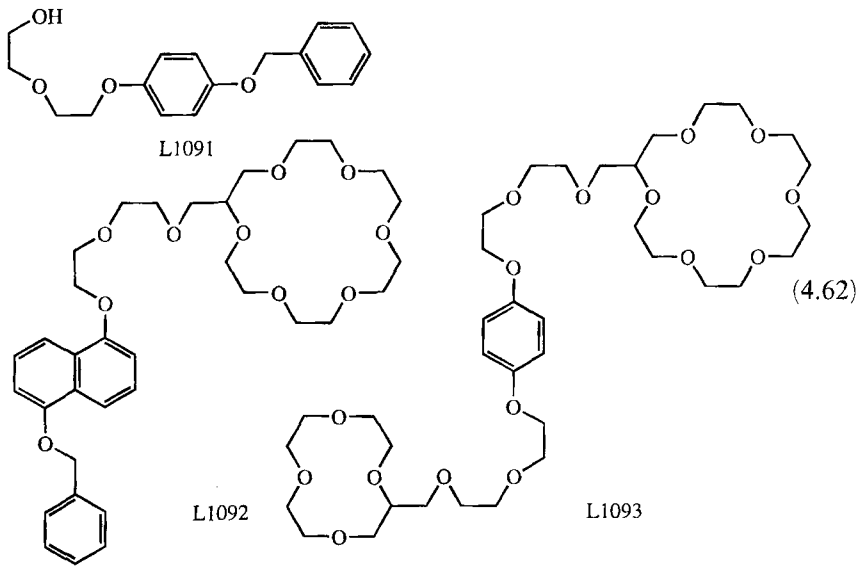
It is possible to build up a layered superstructure consisting of an array of pseudorotaxanes, by using a thread incorporating three aromatic π-electron donors (L1090; Eq. 4.61) sandwiching the two π-acceptor 4,4-bipyridylium moieties of L1079 [198]. Further extensions to polymeric analogues brings us into the fields of so-called 'supramolecular weaving' [199] or of 'molecular mosaics' [200].



L1090

(4.61)

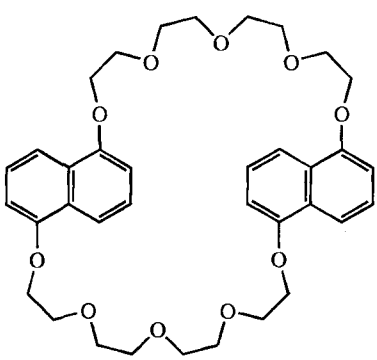
Molecular switching based on pseudorotaxanes may be based either on coupled equilibria involving two (or more) threads competing for insertion, on reversible capping to form a non-robust rotaxane, or on interaction with a third component. Thus, for example, there may be competition between L1091 and L1092 for the standard cyclic bis-paraquat host (L1058); this competition is tunable by reversible complexation of K^+ by the crown ether ring of L1092 (Eq. 4.62) [201].



(4.62)

Assembly and dissociation of the pseudorotaxane formed from L1058 and L1093 may be controlled by alkali metal cations. Addition of $LiPF_6$ or $NaPF_6$ to a solution of the pseudorotaxane (L1058)(L1093) gives the alk^+ complex of the L1093 moiety and results in disassembly [202]. Threading and unthreading of a pseudorotaxane based on L1065 (with R = $-CH_2C_6H_5$) and L1094 may be controlled by amines such as 1-hexylamine or the bicyclic compounds L1095 or L1096 (Eq. 4.63). Amine addition causes the pseudorotaxane (L1065)(L1094) to unthread; neutralisation of the added base permits rethreading to occur [203]. An intra–intermolecular variant of competition involves the self-complexed L1082 with L1075 competing for the site at the centre of the cyclophane ring [190].

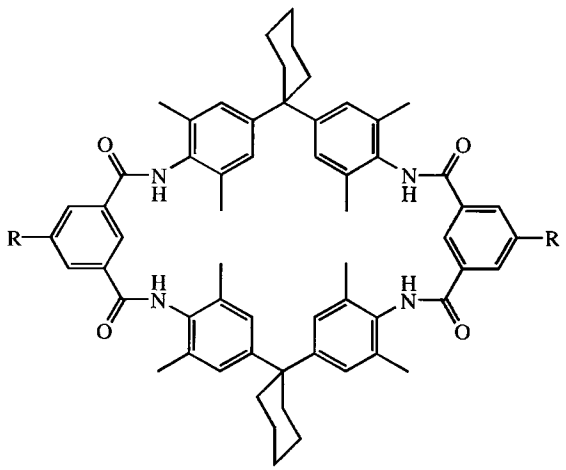
A further type of threading is involved in amide (pseudo)rotaxanes. In this class of compounds both components are amides (e.g. L1097 with L1098; Eq. 4.64) [204]. There are many sites for hydrogen-bonding and π–π (stacking, donor–acceptor) non-covalent interactions between the components [205].



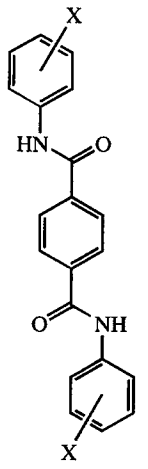
L1094

L1095 X = N
L1096 X = CH

(4.63)



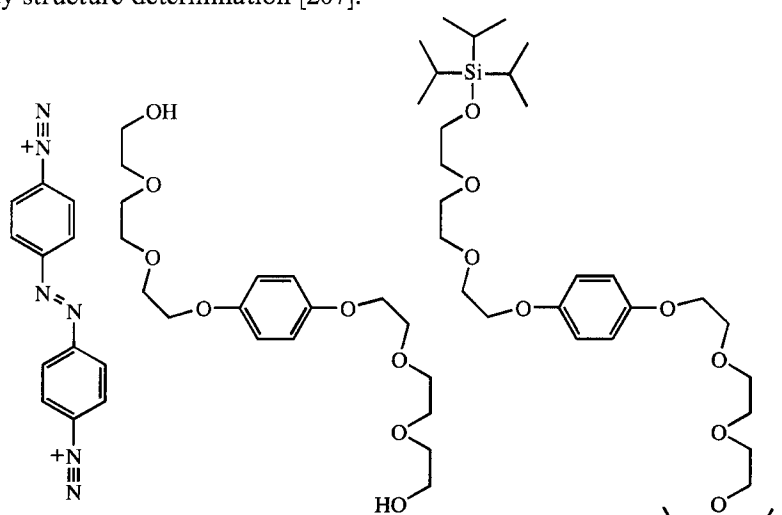
L1097



L1098

(4.64)

Diazonium compounds (e.g. L1099; Eq. 4.65) can be threaded through cyclodextrins. The cyclodextrins confer water solubility (maintained in the subsequent rotaxanes by the presence of, for example sulphonate groups in the caps). The conjugated azo-chromophores confer high optical absorbance [206]. Judging from the paucity of determined structures, it seems that it is very difficult to grow crystals of X-ray diffraction quality of (pseudo)rotaxanes consisting of threaded cyclodextrins. However, curcurbitural, a cavitand closely related to cyclodextrins, can be threaded by spermine, $H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$, to give a pseudorotaxane, and subsequently a rotaxane, both of which formed crystals satisfactory for X-ray structure determination [207].



L1099 L1100

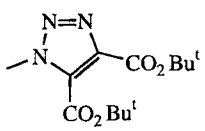
L1101

(4.65)

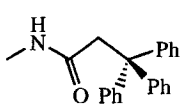
Finally, polyacetylene threads can be constructed through certain macrocyclic rings, as detailed in the rotaxane section below.

4.2.3 Rotaxanes

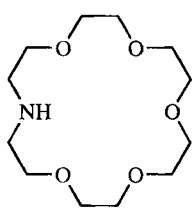
There are a variety of ways of capping pseudorotaxanes to give rotaxanes. If the thread has terminal hydroxides it is a straightforward matter to derivatise, for example by replacing –H by $-Si(CHMe_2)_3$ groups (e.g. L1100 → L1101 [208]). Terminal azides can be capped by reaction with di-*tert*-butyl acetylenedicarboxylate (giving L1102; Eq. 4.66) [183]. Terminal diazonium groups, as in L1099, can be capped by standard diazonium-dye chemistry [206]. Terminal amine groups can be capped with 3,3,3-triphenylpropionyl chloride, giving L1103 [181]. Conversely, terminal –COCl can react with a primary or secondary amine, as in the generation of adamantyl caps by the use of aminoadamantane and of azacrown ether caps by the use of L1104 [209]. The properties of rotaxanes with caps of this last type can be tuned *via* reversible complexing with alkali metal cations, as in the case of (L1058)(L1093) above. Carbohydrate stoppers confer water solubility [210], unless they are furnished with appropriate lipophilic substituents [211].



L1102



L1103



L1104

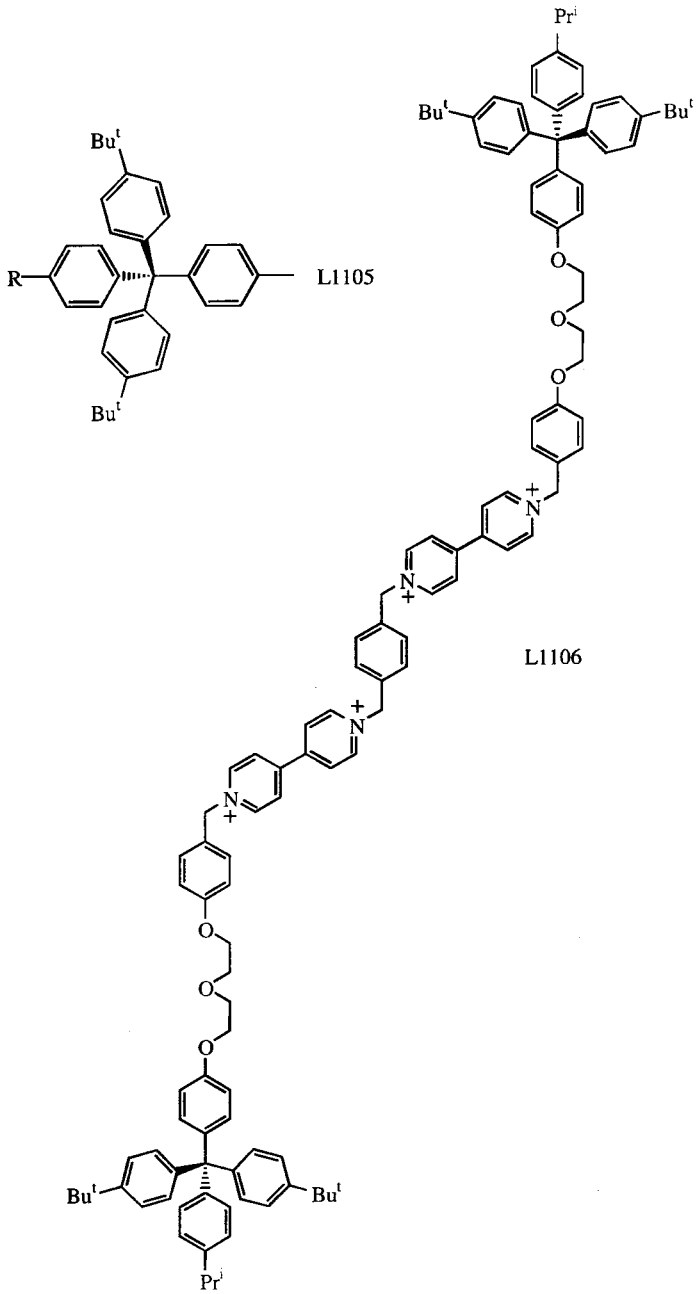
(4.66)

The initial threading process is usually spontaneous, but the equilibrium

$$\text{pseudorotaxane} + \text{caps} \rightleftharpoons \text{rotaxane}$$

does not always lie predominantly to the right. Indeed, possibilities for molecular switching lie in tuning the equilibrium constant and displacing the equilibrium to one side then the other. Equilibrium constants may be tuned through their solvent-dependence, but a more effective route is through tuning the redox properties of the two components of the (pseudo)rotaxane, because they control the level of the donor–acceptor interactions that hold the components together. Such redox tuning may be achieved photochemically, preferably with the photoactive entity incorporated into the thread cap. An extension of this idea is to design a molecular shuttle in which a suitable photosensitizer can cause the electron-donor ring to move between two different electron-acceptor sites on the thread [212]. Rate constants for such shuttling can be obtained from variable-temperature ^{1}H NMR spectroscopy. They are significantly solvent-sensitive with, for example, shuttling taking place over 100 times faster in deuteroacetone than in deuterochloroform [213]. Very small differences between the two sites can result in a large difference in the relative stabilities of the two translational shuttle isomers [214].

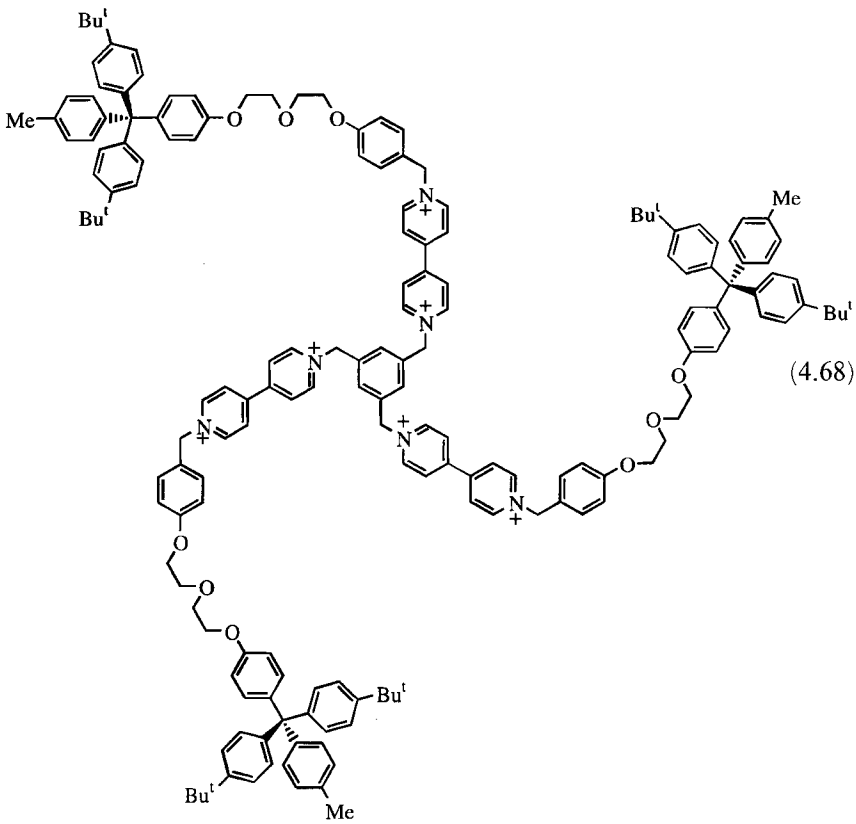
Formation and dissociation of a rotaxane will, of course, be critically dependent on the bulk of the caps and the size of the cavity of the electron-donor ring. Ring cavity size can be varied through phenylene–naphthylene variation (compare L1072 and L1094). Cap size can often be varied by simply varying the bulk of alkyl groups, as in the sequence R = H to R = Pr^i for caps L1105 (Eq. 4.67). Careful



(4.67)

matching of cavity and cap sizes has permitted the preparation of species such as rotaxanes based on the capped thread L1106 with two different rings on the two electron-acceptor bipyridinium units. The synthetic strategy involves standard self-assembly for threading the first ring, whereas the second ring attaches itself by slippage [215] when its cavity is just large enough to pass over the cap. In this case the use of one isopropyl and two *tert*-butyl substituents on the cap are appropriate for the larger cavity in L1094 [216].

Just as the incorporation of two electron-acceptor units in a thread permits the assembly of a two-ringed rotaxane, so the synthesis of multi-electron-acceptor ligsons permits the synthesis of more complicated multi-ring rotaxanes. Thus reaction of L1107 (Eq. 4.68) with bis-*p*-phenylene-34-crown-10 (L1072) gives a mixture of rotaxanes, with one, two, or three rings on the branches of this three-legged



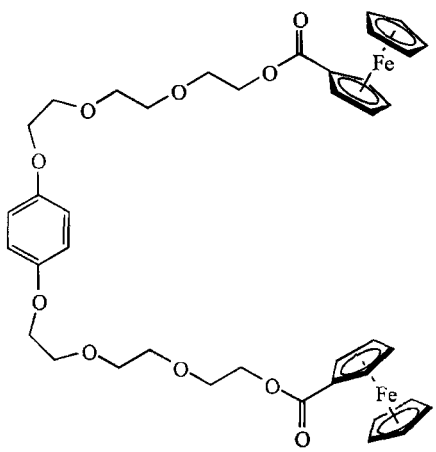
(4.68)

L1107

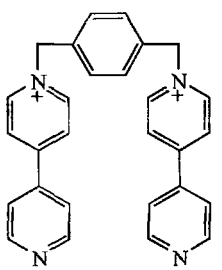
electron-acceptor [217]. In line with the size considerations outlined above, the caps here are marginally smaller (they have one smaller alkyl group) than those appropriate for slippage of the analogous bis-1,5-naphthylene crown. Further extension leads to rotaxanes with dendritic stoppers [213]. An alternative route to high-mo-

lecular-weight rotaxanes involves the formation of polymeric units from appropriate multifunctional ligsons, for example by joining cyclophane electron-donor rings by flexible hexyl links [218]. Polymeric rotaxanes have been prepared from polyglycols [219].

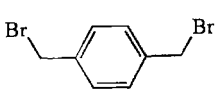
Threading followed by capping is the normal route for the generation of rotaxanes, but the alternative approach of closing the ring around the already-capped thread (clipping) is also possible, as for example in rotaxane formation from the tetrathiafulvalene-containing thread mentioned earlier [188], and in the reaction of the bis-ferrocenyl-capped thread L1108 with L1089 and L1109 (Eq. 4.69), the precursors of the L1058 ring [220]. Ferrocenyl and anthracenyl stoppers are useful for the study of photoexcitation processes and of the detailed mechanism of electron transfer within rotaxanes. Studies of these classes of compound have suggested a significant role for conformational change in determining such intramolecular electron transfer rates [221]. If anthracenyl stoppers close a flexible thread, there is the possibility of these stoppers interacting π-wise with the central cyclophane ring. Such interactions are relatively weak and offer thermal/photochemical switching opportunities [222].



L1108



L1089

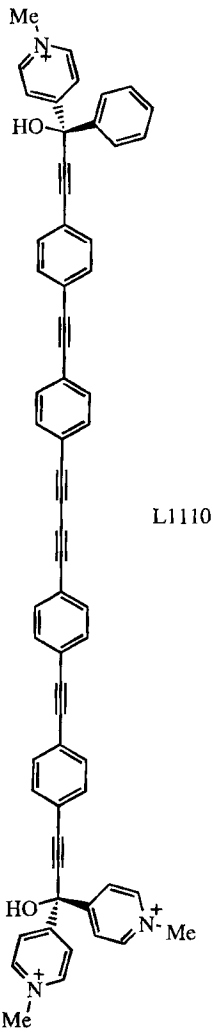


L1109

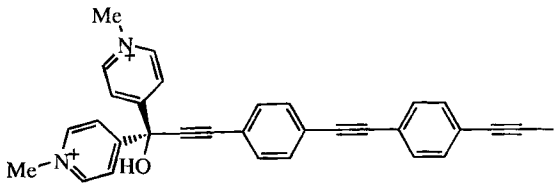
(4.69)

An alternative to the threading, slipping and clipping routes dealt with so far, is to join two half-threads in the presence of a potential ring. This synthetic method was successfully applied to the preparation of singly- and doubly-ringed polyacetylenic threads (L1110 from L1111; Eq. 4.70). Diedrich's cyclophane (L1112) conferred water solubility on these rotaxanes [223].

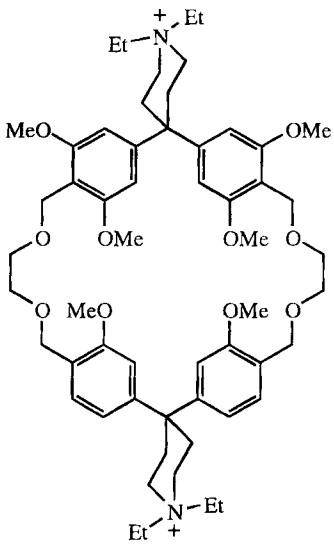
Amide-rotaxanes [224] are generally capped by triphenylmethyl, bis-*tert*-butylphenyl, or similar moieties. In the earlier preparations, ring, thread and capping agent were reacted in a one-pot manner. Subsequently, temperature and cap size control were used to get the correct balance for the ring to slip over the cap and along the thread, but not to slide off again [204]. The temperature control was considered to operate through brief melting of the wheel and axle (ring and



L1110



L1111

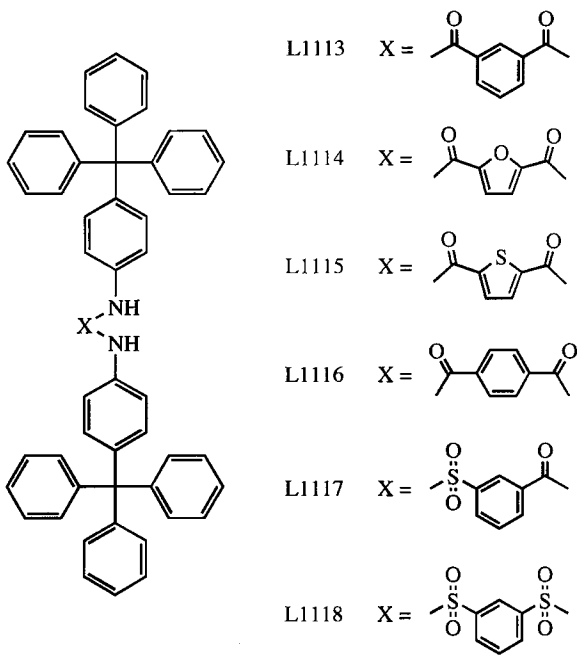


L1112

(4.70)

thread). Hydrogen-bond clipping has been used to generate peptido-rotaxanes on glycylglycine-containing templates. Solvent control is also important in these syntheses [225]. Amide-rotaxanes have proved useful intermediates in the synthesis and solubilisation of amide-containing macrocycles [226]. The possibility of incorporating a variety of subunits in the threads (e.g. L1113 to L1118) makes these amide-based rotaxanes a versatile group of compounds (Eq. 4.71) [227].

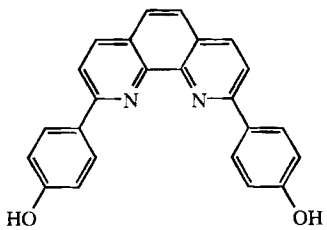
Copper(I)-threaded pseudorotaxanes can be capped by such large moieties as porphyrins [228] or fullerenes [229] – indeed there is a tris-Cu^{I} pseudorotaxane which can be deemed a rotaxane if the two terminal copper-bonded centres are considered as caps for the central unit [179]. Porphyrin-capping is of particular interest as providing a means to have an electron donor and electron acceptor



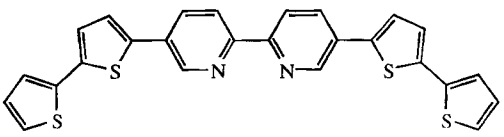
(4.71)

pair at the two ends of a threaded system. More conventional capping methods can be illustrated by the reaction of L1062 with L1119 in the presence of $[Cu(MeCN)_4]BF_4$, with subsequent reaction with $(4\text{-}tert\text{-}BuC_6H_4)_2PhC(CH_2)_3I/K_2CO_3$ to replace the terminal protons of L1119 with very bulky caps (Eq. 4.72) [230]. The large symmetrical units $(Me_3CC_6H_4)_3CC_6H_4-$ have also been used as caps, for example in a rotaxane incorporating both bidentate and terdentate copper-chelating units in the thread [231]. Polymeric rotaxanes have been developed in efforts to synthesise supramolecular sensors. The tetrathiophen-bipyridyl thread L1120 (compare the bis-bithienyl-1,10-phenanthroline analogue mentioned near the start of Section 4.2.2) can be threaded through L1062 using Cu^+ or Zn^{2+} as template. This product has been established by X-ray crystallography. The pseudo-rotaxand produced can then be electropolymerised to give the thread L1121 with an L1062 ring attached by Cu^+ at each bipyridyl section [232]. Copper(I) (or zinc(II), which is occasionally used as template) can be removed from all these rotaxands by cyanide to give the corresponding metal-free rotaxanes.

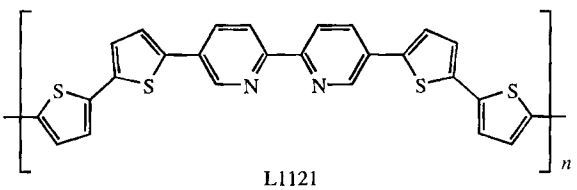
The differing stereochemical requirements of Cu^+ and Cu^{2+} can be coupled with shuttling to give a potential redox-driven switch. This is achieved by building a phenanthroline and a terpyridyl unit into the thread. The former combined with the phenanthroline unit of the ring gives the tetrahedral coordination environment favoured by Cu^+, whereas the latter, taken with the phenanthroline unit of the ring, gives a five-coordinate environment more appropriate to Cu^{2+} [233].



L1119



L1120



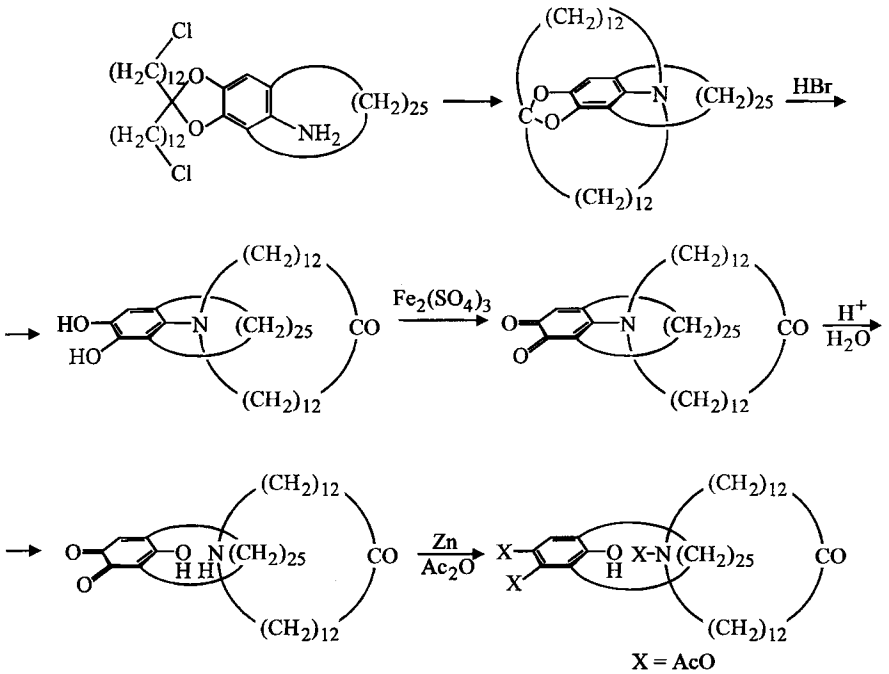
L1121 (4.72)

Free radical-initiated polymerisation of acrylonitrile in the presence of 60-crown-20 leads to further examples of polymeric rotaxanes, and provides yet another route to rotaxanes [234].

4.2.4 Catenanes

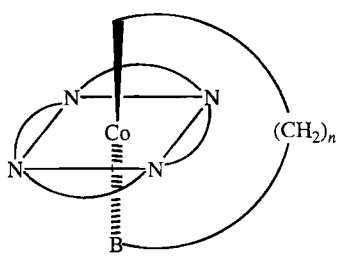
Introduction

The synthesis of catenanes from preformed macrocycles is restricted by ring-size restraints, being feasible only from macrocyclic compounds with ring sizes which allow an appropriate linear molecule to be threaded through prior to cyclisation. Catenanes can also be obtained by cyclisation of linear difunctionalised molecules, preliminarily arranged in such a manner that a chain of two or more rings can be generated. There are several basic routes to catenanes, these being the statistical and the controlled (directed) approach, and the Möbius strip approach, which is intermediate in character [165, 235, 236]. Statistical methods give the desired products in low yields, essentially as byproducts to an unwanted main reaction, since the probability of cyclisation of a linear molecule at the moment that the molecule penetrates a macrocycle is extremely low. Controlled synthesis involves the assembly of the potential catenane components in such a spatial arrangement that intra-annular cyclisation to form a precatenane is the only way to close a cycle. Specific templates, or 'scaffolds', were employed in early syntheses of [2]-catenanes [237], to hold the functional groups in the required positions for assembly (Scheme 4-19). Thereafter the scaffolds are removed selectively, leaving the required molecule. Transition metal complexes provide suitable scaffolds for the formation of catenane-type structures. Indeed their role in such reactions was proposed before the term 'template synthesis' came into general use in coordination chemistry [238]. The idea was initially presented [235] for a system consisting of cobalt bound to a planar tetradentate ligand, with a long alkyl chain spanning the *trans* axial positions of the



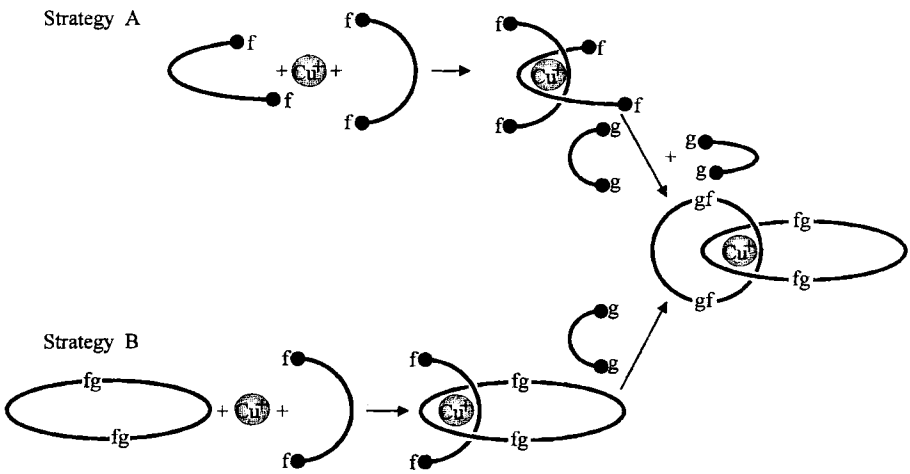
Scheme 4-19. Specific templating in the early syntheses of catenanes.

cobalt, carbon-bonded to cobalt at one end, and with a nitrogen or phosphorus donor at the other (Eq. 4.73).

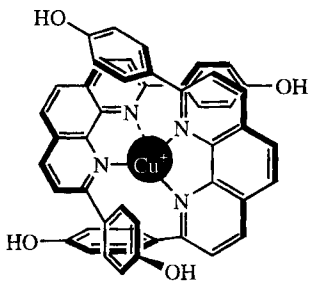


(4.73)

The tetraazamacrocycle and the cobalt-alkyl-macrocycle are interlocked, but the above species is not strictly a catenane since there are cobalt-nitrogen coordinate bonds forming a chemical linkage between the two rings.



Scheme 4-20. Two strategies for the assembly of catenanes.



$[Cu(L1119)_2]^+$

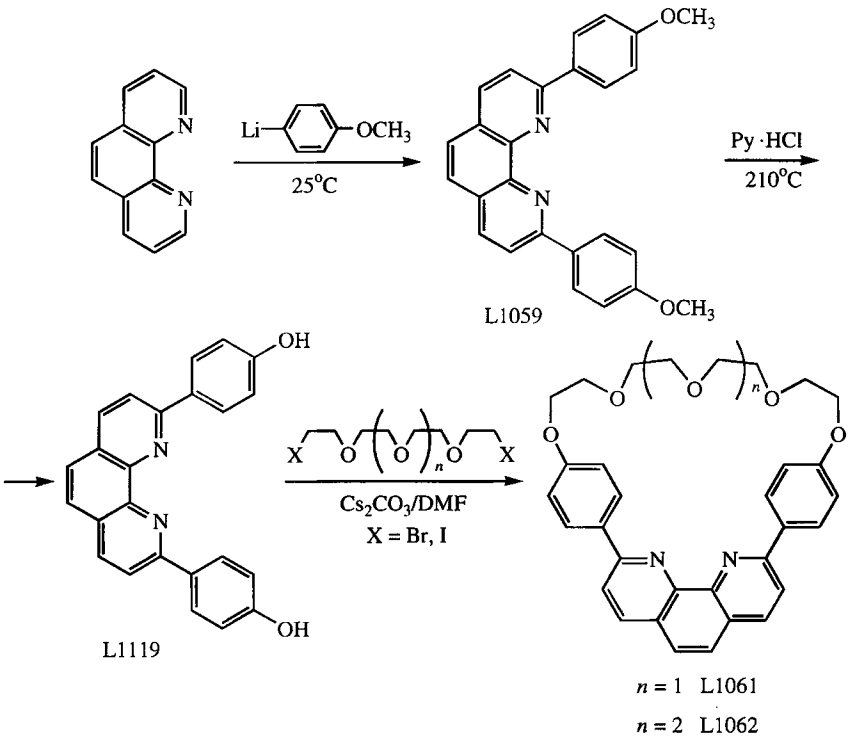
Figure 4-7. The structure of the cation $[Cu(L1119)_2]^+$.

Metal ion template syntheses

The two strategies proposed for the three-dimensional assembly of catenanes using a metal ion as template are depicted in Scheme 4-20 [239]. At first sight route A appears the simpler, but it involves simultaneous pair binding of eight reaction centres. Route B requires preliminary macrocycle synthesis, but in the second stage interlocking the second cycle involves only four functional groups, and is thus more favourable on statistical grounds.

A large number of catenanes have by now been synthesised with the aid of copper(I), whose favoured tetrahedral coordination environment provides a suitable template [240]. 2,9-Disubstituted-1,10-phenanthrolines form fairly stable complexes with copper(I). The complex $[Cu(L1119)_2]^+$, whose structure is shown in Figure 4-7 [241], has hydroxy substituents available in positions appropriate for cyclisation, which has been achieved as shown in Scheme 4-21 [242].

Employing the strategy of Route B (the statistically favoured route) of Scheme 4-20, $[Cu(L1119)(L1062)]^+$ is obtained in quantitative yield on reaction of stoichio-

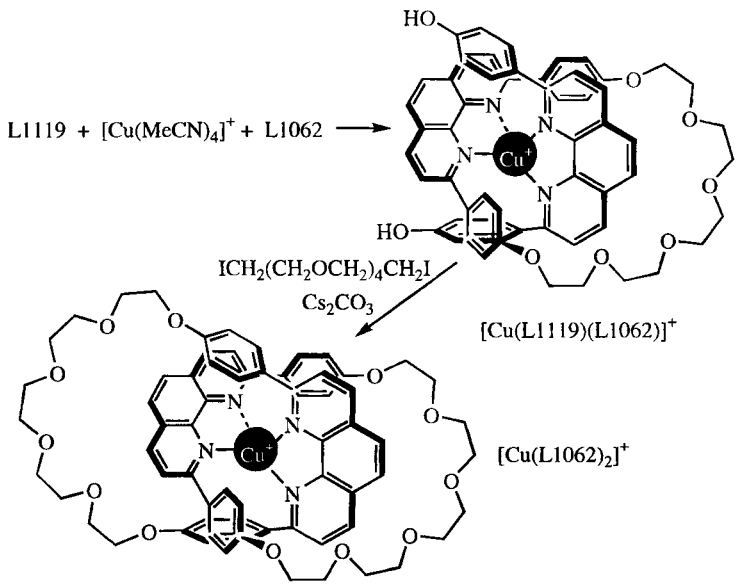


Scheme 4-21. Synthesis of macrocycles L1061 and L1062.

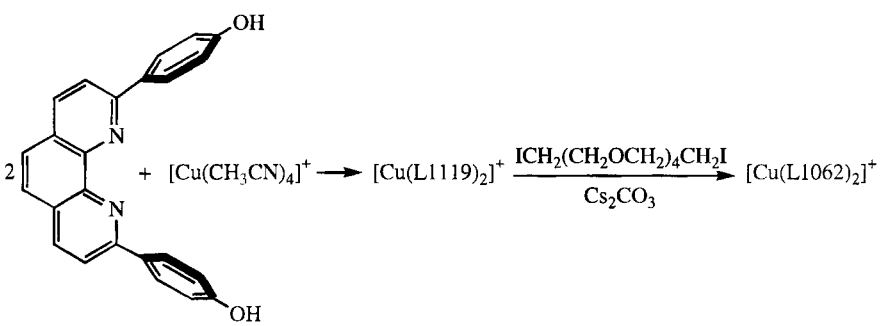
metric amounts of L1119, $[Cu(MeCN)_4]BF_4$ and L1062 [239]. In the final step, an equimolar mixture of $[Cu(L1119)(L1062)]^+$ and pentaethyleneglycol diiodide (1,14-diiodo-3,6,9,12-tetraoxotetradecane) is added to a large excess of caesium carbonate in DMF. The second ring is thus formed, giving $[Cu(L1062)_2]^+$ (in 42% yield; Scheme 4-22). It has been established by ^1H NMR spectroscopy that the two L1062 ligands are indeed arranged around the copper in perpendicular planes and are interlocked like two links in a chain.

The complex $[Cu(L1062)_2]^+$ can also be prepared by the method of strategy A of Scheme 4-20 [239]. The stable chelate $[Cu(L1119)_2]^+$, prepared from $[Cu(MeCN)_4]BF_4$ and L1119, reacts with pentaethyleneglycol diiodide under high dilution conditions in the presence of a large excess of caesium carbonate in DMF [243]. The catenate $[Cu(L1062)_2]^+$ is obtained in 27% yield (Scheme 4-23), together with free L1062 (20%) and a species of linear structure and high molecular weight. The yield of $[Cu(L1062)_2]^+$ from 1,10-phenanthroline is higher by route A (3 steps, 20% yield) than by route B (4 steps, 14% yield). Route A is thus better here, but more often it is strategy B which proves to be the more reliable.

On treatment of $[Cu(L1062)_2]^+$ with tetramethylammonium or potassium cyanide, in MeCN–water, a metal-free catenand is obtained (Scheme 4-24). Judging from ^1H NMR spectroscopy and mass spectrometry, it consists of two L1062

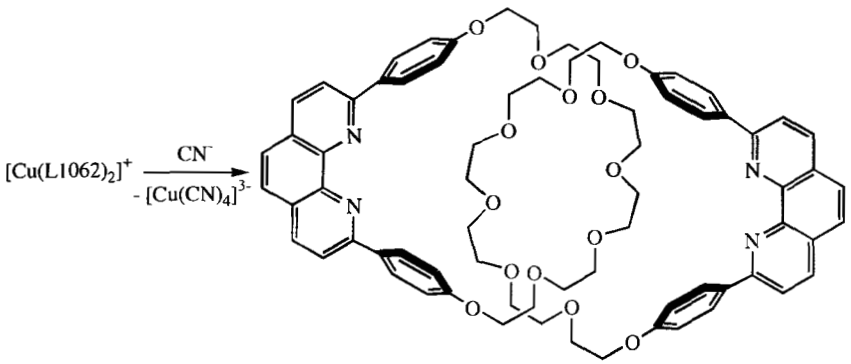


Scheme 4-22. Template assembly of $[Cu(L1062)_2]^+$ by strategy B of Scheme 4-20.



Scheme 4-23. Template assembly of $[Cu(L1062)_2]^+$ by route A of Scheme 4-20.

macrocycles interlocked mechanically. An X-ray crystallographic examination of $[Cu(L1062)_2]^+$ and of the corresponding catenand [244] showed completely different ligand geometries in the coordinated and metal-free forms (Figures 4-8 and 4-9). The conformational differences between catenand and catenate result from mutual sliding of the two macrocyclic rings in the course of demetallation. This sliding can be prevented by the incorporation of bulky ring substituents, giving a combination of catenane and rotaxane characteristics. There may then be two isomers, as depicted in Figure 4-10. If fragments (a) and (b) are different, then the compounds



Scheme 4-24. Synthesis of catenand (L1062)(L1062).

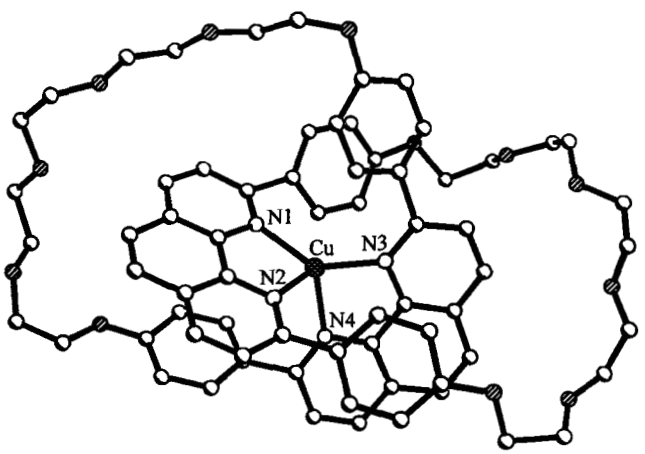


Figure 4-8. Structure of the catenate $[Cu(L1062)_2]^+$.

(C) and (D) must also be different. The interconversion (C) ⟷ (D) will be virtually impossible, thanks to the large steric barriers imposed by the bulky substituents (a) and (b).

The situation shown in Figure 4-10 may be exemplified by the mixed-ring catenate $[Cu(L1062)(L1122)]^+$. The precursor, $[Cu(L1119)(L1122)]^+$, can be obtained in essentially quantitative yield from $[Cu(MeCN)_4]^+$, L1119 and L1122 (Eq. 4.74). Onward reaction with the appropriate diiodo-compound gives the catenate $[Cu(L1062)(L1122)]^+$ as its BF_4^- salt, in 7% yield (Scheme 4-25) [245]. The corresponding metal-free catenand has been obtained by demetallation of the catenate with potassium cyanide [246]. The rate constant for demetallation is quite low, due to the positioning of one of the polyoxyethylene chains between the bulky phenyl groups, which restricts conformational mobility (compare with (D) in Figure 4-10).

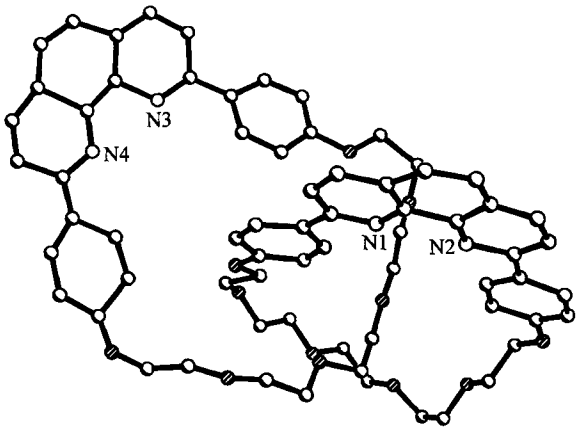


Figure 4-9. Structure of the catenand (L1062)(L1062).

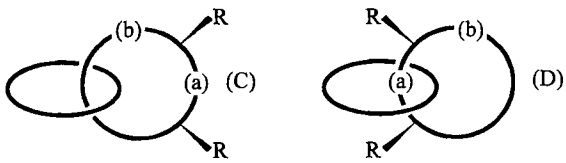
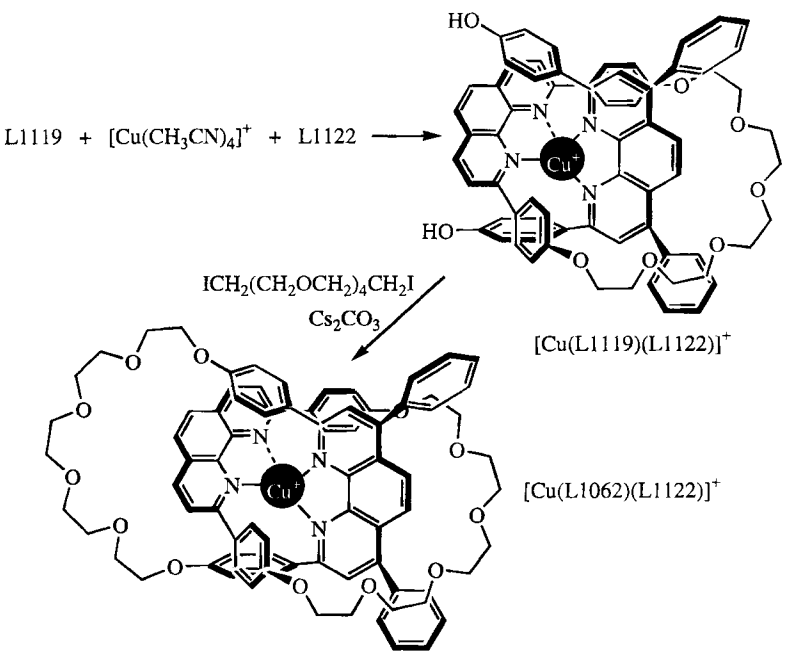
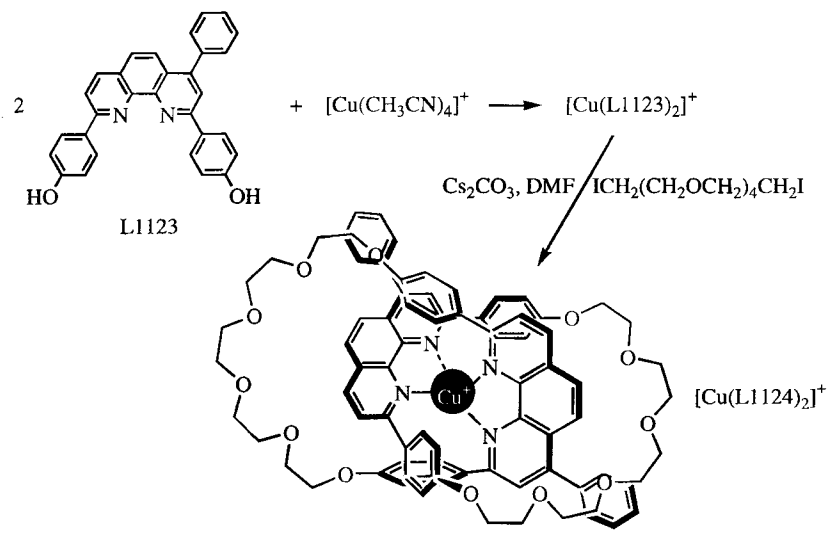


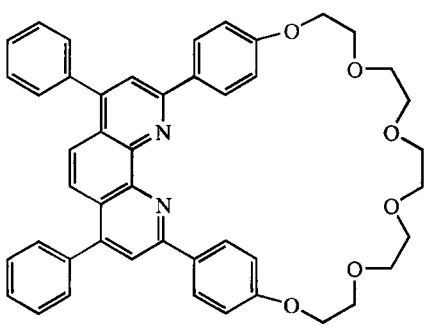
Figure 4-10. Possible translational isomers of [2]-catenanes.



Scheme 4-25. Synthesis of the mixed ring catenate $[Cu(L1062)(L1122)]^+$.



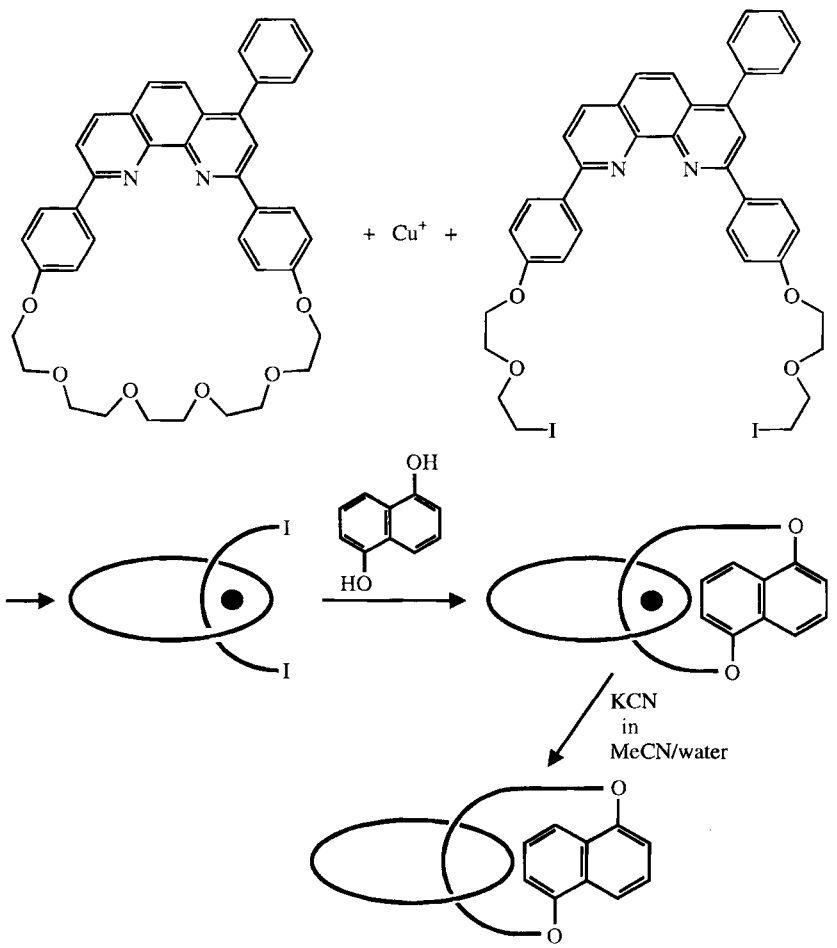
Scheme 4-26. Synthesis of the topologically chiral catenate $[Cu(L1124)_2]^+$.



(4.74)

Chiral catenanes can be obtained by the use of an unsymmetrically substituted 1,10-phenanthroline derivative such as L1123 in the Cu^+-template method. Thus the catenate $[Cu(L1124)_2]^+$, generated in 12% yield as shown in Scheme 4-26 [247], is topologically chiral.

The enantiomers cannot be interconverted except by cleaving and reforming a C–C or C–O bond. The chirality of $[Cu(L1124)_2]^+$ was demonstrated by ^1H NMR spectroscopy. In the presence of one of Pirkle and Hoekstra's fluoroalcohol chiral reagents [248] most of the signals corresponding to the aromatic protons were split. The threading, ring closure and demetallation reaction sequence shown in Scheme 4-27 produce a chiral catenane, whose chirality stems from the fact that its two component rings, each of which has C_s symmetry, are unable to become coplanar. This catenane is claimed to be the first example of a molecule whose molecular



Scheme 4-27. Synthesis of the catenane with rigid geometrical chirality.

graph exhibits rigid geometrical chirality in every presentation [249]. Zinc(II) has been used as template for the assembly of a [2]-catenane from five components, with chirality introduced by a metallomacrocycle [250].

Various forms of geometrical isomerism are possible for catenanes of the type generated by using copper(I) templates. The preparation of the doubly-interlocked isomer of a normal singly-interlocked [2]-catenane requires three copper(I) centres, and can be achieved by the use of the tris-phenanthroline ligand L1063 (Figure 4-11) [251]. Electrospray and FAB mass spectrometry were required to confirm the identities of the singly- and doubly-intelocked forms [252]. The use of the ruthenium complex denoted here as L1125 (Eq. 4.75) in the ring closure of L1126 coordinated to Cu^+ has permitted incorporation of an ethylenic linkage in one or both rings of a [2]-catenane; *cis* and *trans* isomers are thus possible [253]. The incorpo-

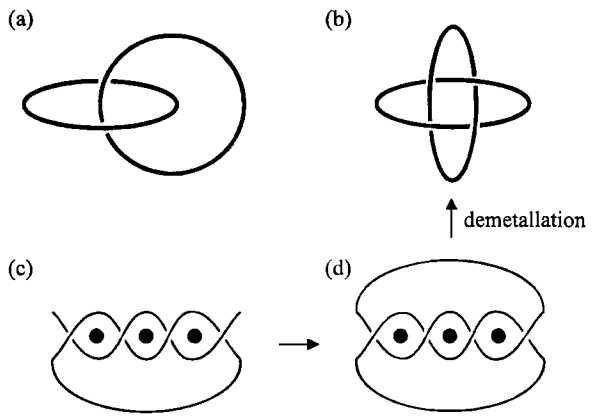
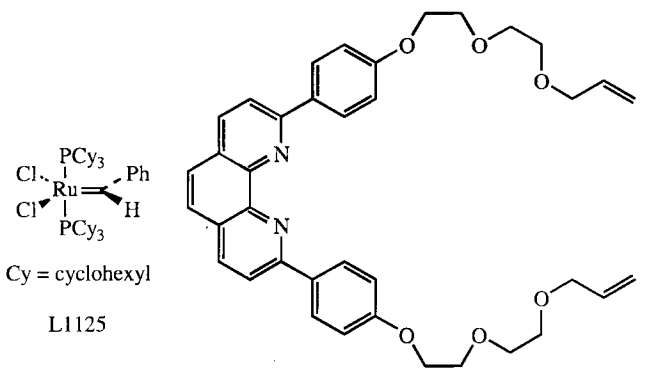


Figure 4-11. (a) Singly and (b) doubly interlocked [2]-catenanes; (c), (d) three Cu^{+} templates are required to generate (b).



L1126 (4.75)

ration of both a phenanthroline and a terpyridyl entity in each ring of a copper [2]-catenand introduces the possibility of linkage isomers. In view of the preference of Cu^{+} for tetrahedral coordination, of Cu^{2+} for octahedral, such a catenand should be redox switchable [254].

The synthesis of catenates containing relatively small rings is more difficult. Thus on going from L1062 to L1061, which has one less $-CH_2CH_2O-$ unit in the ring, the yield of catenate decreases [255]. Attempted demetallation of the $[Cu(L1061)_2]^{+}$ produced under the conditions successfully used for demetallation of $[Cu(L1062)_2]^{+}$ results in decomposition of the catenand skeleton and production of mono-macrocyclic L1061. Under conditions of lower concentration it is possible to demetallate $[Cu(L1061)_2]^{+}$, but the structure characteristic of catenates, namely phenanthroline fragments at right angles as if interpenetrating, is not realised. Rather, the catenand undergoes substantial conformational changes during the demetallation reaction.

One line of interest in catenanes is to use them to study details of electron transfer, by having an electron donor in one ring, an electron acceptor in another (Figure 4-12). The first step in this programme was the synthesis of a [2]-catenane with a tetrathiafulvalene unit incorporated into one of the rings. The required catenane

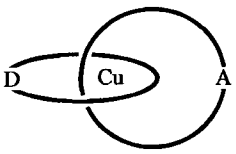
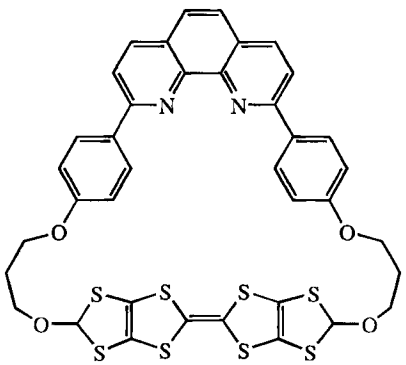


Figure 4-12. The linking of donor (D) and acceptor (A) units in a copper(I) [2]-catenand.

was assembled in the usual manner from copper(I), L1127 (Eq. 4.76) and L1119, which gave $[Cu(L1127)(L1062)]^+$ [256]. An alternative approach is to have metal complex units as the electron donor and acceptor – such species are mentioned below, in the section on multi-metal catenanes.



(4.76)

L1127

Almost all metal template-based syntheses of catenanes use Cu^+, but there are a few instances of other metal ion templates, including Zn^{2+}, Pd^{2+}, and Pt^{2+}. The relative substitution-lability of Pd^{2+} makes it suitable as a preparative template; the substitution-inertness of Pt^{2+} has been used as the basis for a temperature-switchable catenane 'molecular lock' [257]. This mode of switching is based on platinum–nitrogen bond dissociation at elevated temperatures.

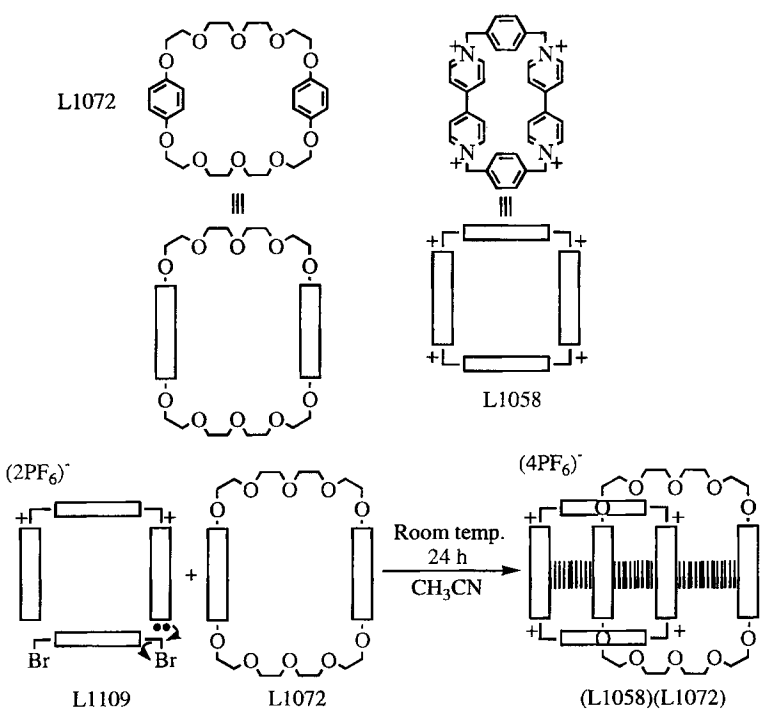
Catenates of a number of other metal ions have been prepared by using cyanide to demetallate Cu^+ catenates, giving catenands which can be then used to complex a range of other metal ions. In particular, Li^+, Ag^+, Zn^{2+}, Cd^{2+}, Co^{2+}, and Ni^{2+} – all metal ions more or less comfortable in tetrahedral geometry – form complexes with the [2]-catenand consisting of two interlocked L1062 rings. Electrochemical reduction of the Ni^{2+} complex gives a stable Ni^+ catenate [258]. Crystal structures of these Ni^{2+} and Ni^+ catenates show that the Ni^+ is in as near tetrahedral geometry as the bite of 1,10-phenanthroline allows, but that the coordination environment of the Ni^{2+} is far from tetrahedral, despite the occurence of near-tetrahedral geometry in many Ni^{2+} complexes. It appears that the highly distorted tetrahedral arrangement in the Ni^{2+} catenane permits strong π–π interactions between phenyl rings and phenanthroline rings, which are not possible if the phenanthrolines adopt tetrahedral geometry [259]. Metal ions with a strong preference for octahedral coordination are unlikely to form stable catenate complexes. $(L1062)_2$ reacts with Fe^{2+} in solution but, although it was possible to study its electrochemical behaviour, it proved impossible to isolate the complex formed. Electrochemical reduction

of $[Fe(L1062)_2]^{2+}$, in methylene chloride solution at a platinum or mercury electrode, occurs in two reversible steps, presumably giving $[Fe(L1062)_2]^{+}$ and $[Fe(L1062)_2]^{0}$, but it was impossible to oxidise the complex to the Fe^{III} state.

Kinetics of catenand complexation have been established for some metal ions [260, 261]. Formation of Cu^{+} and Ag^{+} catenates obeys the classical second-order rate law, as is the case for model open-chain or monomacrocyclic models. On the other hand, Li^{+}, Zn^{2+}, Cd^{2+} and Co^{2+} catenates are formed in two distinct steps. The first step is second-order, presumably corresponding to the initial binding of the catenand to the metal ion. The second step is independent of metal ion concentration, indicating an intramolecular rearrangement. This may be one ring moving within the other to permit the coordination of the second chelating moiety to the metal ion which would be a novel manifestation of the SCS (sterically controlled substitution) mechanism [262] for metal chelate formation. The kinetics of demetallation of a copper(I) catenand have been established. The rate law indicates parallel attack by cyanide at the copper, which is still fairly accessible in the catenand, and dissociation. Both processes are about 10 times slower in the case of the monomacrocyclic analogue [263].

Cyclophane–polyether catenanes

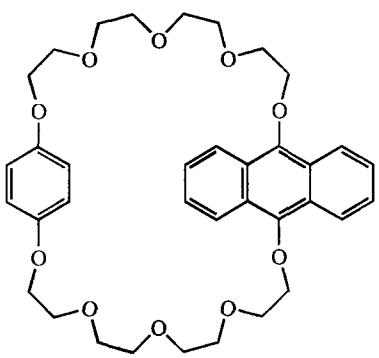
Scheme 4-28 shows an alternative approach to the use of metal ion templates, with the templating furnished by electron donor-acceptor interactions. Bis-4,4′-



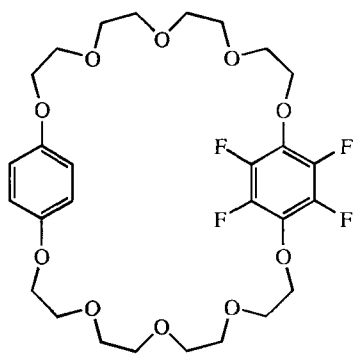
Scheme 4-28. Synthesis of the catenane (L1058)(L1072).

bipyridinium (paraquat) electron acceptor units, often clipped through the other ring as indicated in Scheme 4-28, π-interact with polyether rings containing benzene ring donors. Catenane (L1058)(L1072) was obtained in this way in 70% yield. FAB mass spectrometry, ^{1}H NMR spectroscopy and X-ray crystallography not only characterised the interlocked tetracationic cyclobis(paraquat)-*p*-phenylene) and bis(*p*-phenylene-34-crown-10) rings, but further showed that the catenane entities were stacked both in the solid state and in solution [264].

A great variety of analogous catenanes can be prepared similarly from appropriate starting materials, varying one ring or the other (or both). Thus the *p*-phenylene groups in L1058 can be replaced by naphthalene equivalents derived from 1,5-, 1,6-, 2,6- or 2,7-dihydroxynaphthalenes [265, 266], giving rise to a series of isomeric luminescent catenanes containing polyether rings such as L1094 [267]. In like vein, one phenylene group can be replaced by the anthracene chromophore, giving L1128 as one ring component (Eq. 4.77) [268]. A marked reduction in the π-electron donor power of the hydroquinone–polyether ring has been engineered by



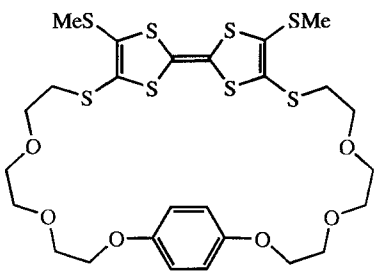
L1128



L1129

(4.77)

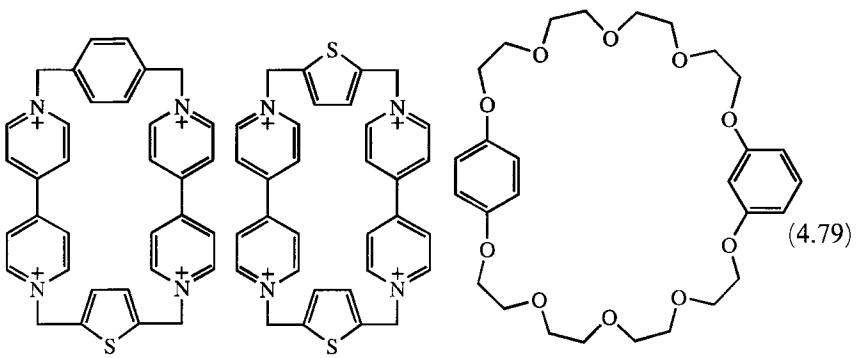
having a perfluoro-ring, L1129 [269]. A marked increase in π-electron donor power can be arranged by the inclusion of a tetrathiafulvalene, as in the ring L1130 (Eq. 4.78), again threaded through the usual cyclophane ring of L1058 [188]. Inevitably fullerenes had to be brought into this area of chemistry (compare with pseudorotaxane capping). This was achieved with the preparation of a [2]-catenane with C_{60} attached to one of the phenylene rings of L1072, which was threaded through the standard cyclophane L1058 [270].



L1130

(4.78)

In a similar manner, the nature of the cyclobis(paraquat-*p*-phenylene) (L1058) ring may be varied, either at the phenylene or at the bipyridinium site. The simplest change is the replacement of one or both *p*-phenylene links by *m*-phenylene, as for L1080. Such a change has a small but significant steric effect. A much more significant electronic effect may be made by replacing one or both phenylene links by thiophen, to give the rings L1131 and L1132 (Eq. 4.79). The dynamic properties of the catenanes $(L1072)(L1058)^{4+}$, $(L1072)(L1131)^{4+}$ and $(L1072)(L1132)^{4+}$ have been investigated by ^1H NMR spectroscopy. Barriers to the cyclophane moving through the crown ether cavity are approximately 50 kJ mol^{-1} (in deuteroacetone solution), to the crown ether moving through the cyclophane cavity approximately 65 kJ mol^{-1} (in deuteroacetonitrile). There is also a rocking movement with a lower barrier, of about 40 kJ mol^{-1} [271].



L1131 L1132 L1133 (4.79)

Implicit in the preceding paragraphs is the possibility of isomerism in many catenanes of this type. Thus there are four sites in the parent catenane $(L1058)(L1072)^{4+}$ where *p*-phenylene may be replaced by *m*-phenylene [272]. These are indicated in Figure 4-13. For the unsymmetrical L1133, isomeric catenanes are

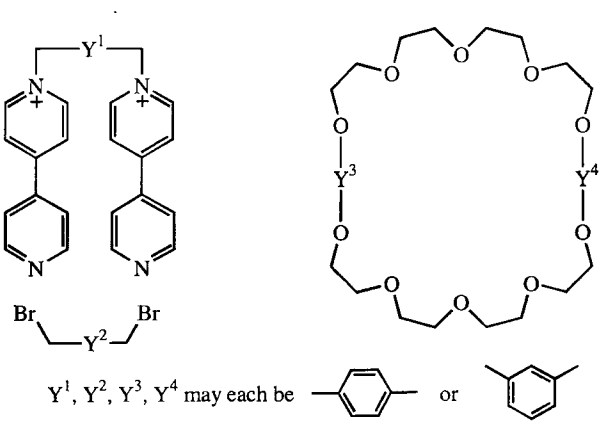
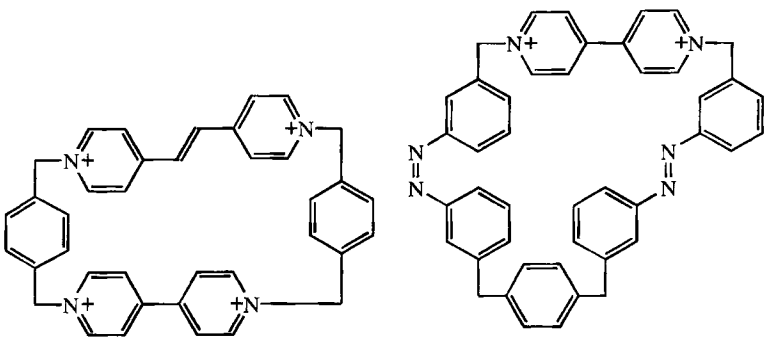


Figure 4-13. Possibilities of isomers in the catenanes $(L1058)(L1072)^{4+}$ according to the combina-

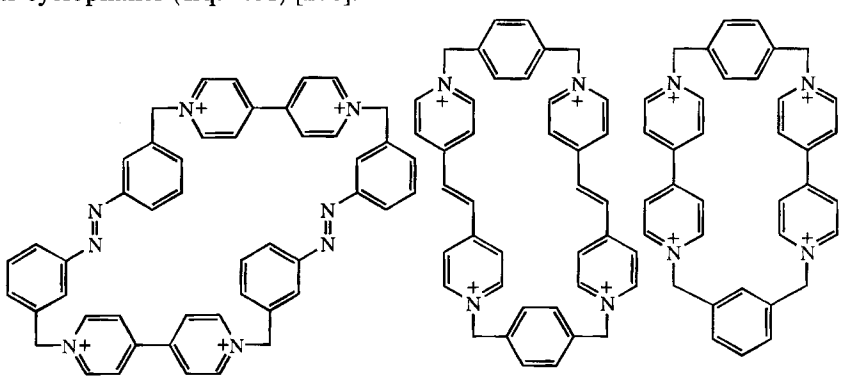
possible in which either the *p*- or the *m*-phenylene group is within the cyclophane cavity [273]. Similarly, either the bipyridinium or the bis-pyridiniumethylene units of L1134 may be in the cavity of L1072 in the catenane $(L1072)(L1134)^{4+}$ (Eq. 4.80) [274]. Structural and kinetic aspects of such isomerism have been extensively investigated and established by ^1H NMR spectroscopy [196, 275]. Kinetic barriers are between 45 and 75 kJ mol^{-1}, and appear to be significantly solvent sensitive – as indeed are equilibrium ratios of such translational isomers [276].



(4.80)

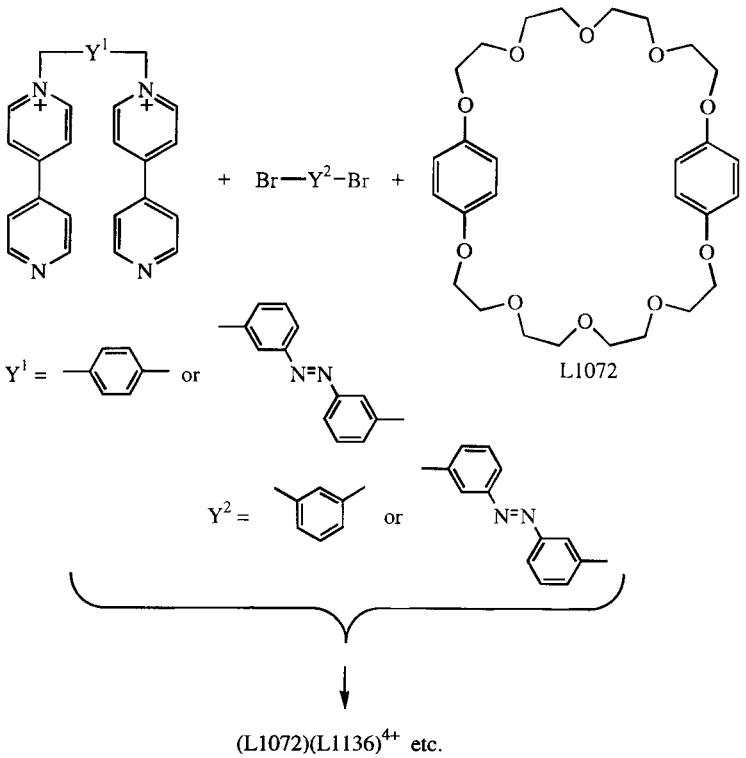
L1134 L1135

Cis ↔ *trans* (*E* ↔ *Z*) isomerism is possible at the ethylene link of L1134, and therefore for the catenane $(L1072)(L1134)^{4+}$. The photophysics and photochemistry of interconversion of such isomers has been considered [275]. One or both phenylene units may be replaced by bis-pyridyldiazo units; the latter are shown as L1135 and L1136. Catenanes such as $(L1072)(L1136)^{4+}$ may be prepared as shown in Scheme 4-29. They are potentially photoswitchable, on the basis of *cis* ↔ *trans* (*E* ↔ *Z*) photoisomerisation in the azobenzene unit [277]. Replacement of the bipyridinium moieties is less frequently encountered, although one or both may be replaced by bis-pyridylethylene units, as in L1134 and L1137 [275], or again by analogous bis-pyridyldiazo units, as in L1081. Kinetic aspects of catenane formation have been probed in relation to catenanes containing rings of various sizes, namely consisting of L1058 or L1094 together with L1134, L1137, L1138 and similar cyclophanes (Eq. 4.81) [278].



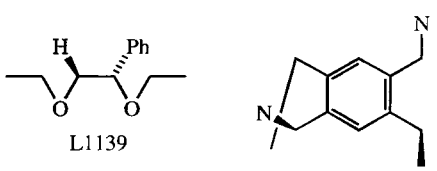
(4.81)

L1136 L1137 L1138



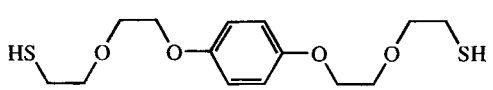
Scheme 4-29. Synthesis of photoswitchable catenane (L1072)(L1136)$^{4+}$ etc.

Chirality may be introduced into catenanes of the cyclophane-polyether type by replacement of the *p*-phenylene unit in the starting material L1089 with a chiral entity such as L1139 [279] or L1140 (Eq. 4.82) [280].



L1139 L1140 (4.82)

Of considerable electrochemical importance is the tethering of L1058 to a gold surface in what is essentially a [2]-catenane. Thus, L1141 (Eq. 4.83) spontaneously threads itself through L1058 ($K_{assoc} = 253$ (molar scale)), whereafter the –SH ends are attached to the gold surface by established technology, to give the species shown in Figure 4-14 [281].



L1141 (4.83)

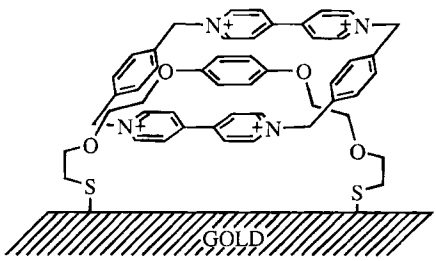


Figure 4-14. A [2]-catenane incorporating a gold surface in one ring.

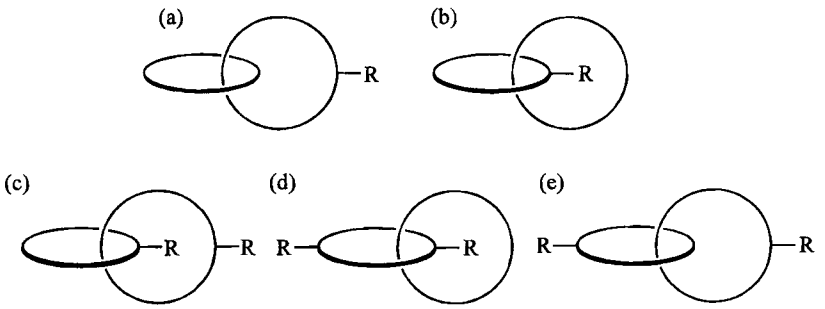
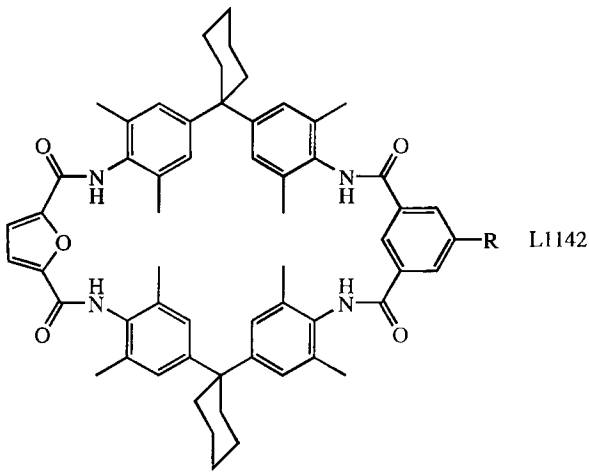


Figure 4-15. Geometrical isomers for lactam-based catenanes: (a), (b) monosubstituted; (c), (d) and (e) disubstituted.

Amide-based catenanes

A third type of catenane synthesis involves amide starting materials. The first octa-lactam catenanes consisted of two interlocked L1097 rings (R = H, OMe variously) [282, 283]. A number of isomers are possible for this type of catenane, as shown in Figure 4-15 [284]. The rings may be modified by replacing one of the benzene rings of L1097 by a furan ring, to give the catenane $(L1142)_2$ [285]. This will have three isomers (see the disubstituted catenanes in Figure 4-15). Alternatively, one of the benzene rings in each of the catenane rings may be replaced by a short poly-methylene chain, $-(CH_2)_n-$, to give $(L1143)_2$. For this [2]-catenane, polar solvents favour one isomer, non-polar the other (Figure 4-16) [286]. In these synthetic routes, hydrogen-bonding interactions in reaction intermediates are important in determining whether catenation or macrocyclisation predominate [287]; hydrogen-bonding interactions are also important in stabilising the final product [288]. The last-mentioned study includes details of an interesting problem in the interpretation of X-ray diffraction data for certain catenanes – when two linked macrocycles are symmetry-related in the crystal, the interlocking may only be clear when the packing diagram is inspected.

Early attempts to develop this particular route ran into difficulties over the problem of non-availability of starting materials. However it was discovered by



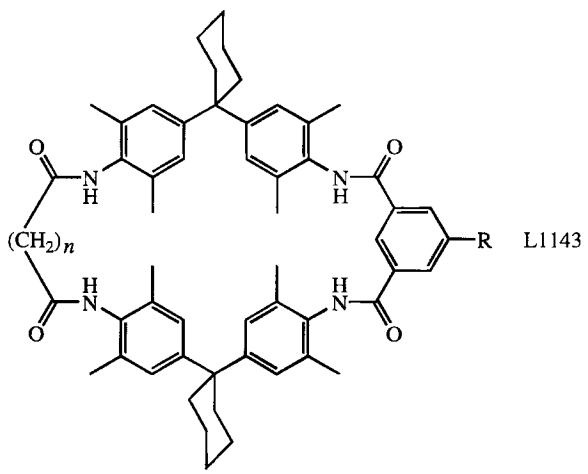
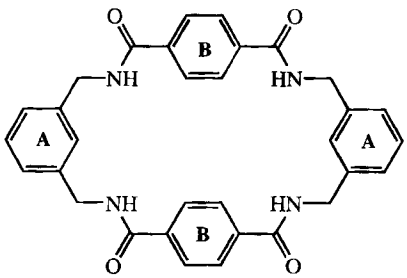


Figure 4-16. Solvent control of translational isomerism in [2]-catenanes having a hydrogen link ($-(CH_2)_n-$; shown as ⬬) in place of one *p*-phenylene link in each ring.

chance that a synthesis meant to produce an amide macrocycle able to bind carbon dioxide actually gave the [2]-catenane $(L1144)_2$ (Eq. 4.84). Two noteworthy features are the 20% yield in one step from commercially available materials and the small size of the rings, which are only 26-membered with a cavity of approximate dimensions 40 nm × 60 nm [289]. It is possible to make a variety of catenanes, with a wide range of ring sizes, by this method. Thus, for example, substituents may be

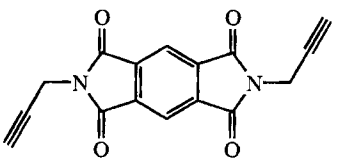
introduced into ring A of L1144, the benzene of ring A may be replaced by pyridine or thiophen, and the phenylene ring B by biphenylene or naphthylene [290].



L1144 (4.84)

Alkyne-derived catenanes

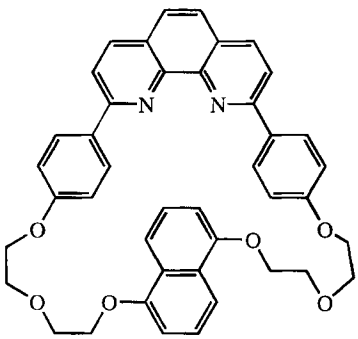
Ring-clipping can also be achieved by oxidative coupling of pairs of α, ω-dialkynes (the Glaser reaction). Thus two molecules of L1145 (Eq. 4.85) can be clipped around the dinaphtho-crown ether L1094 to give an uncharged [2]-catenane. This reaction works well thanks to good interactions between complementary π-donor and π-acceptor units [291]. Several further examples of the usefulness of the Glaser reaction are given in the section on multi-ring catenanes below.



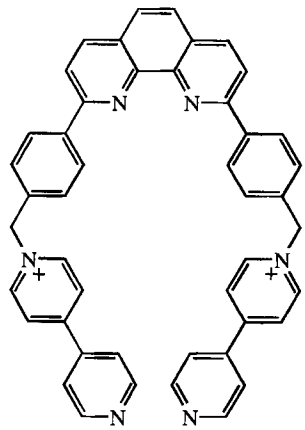
L1145 (4.85)

Hybrid catenanes

A hybrid catenane combining a copper(I) site and a π-electron donor-acceptor site has been reported. Product L1146 (Eq. 4.86), prepared from L1119, and L1147, prepared from L1148, were reacted with $[Cu(MeCN)_4]^+$ in CH_2Cl_2/MeCN solution, and the two ends of the coordinated L1147 ligand were clipped together by reaction with L1149 under high dilution conditions, giving the L1150 ring to complete the [2]-catenane. Treatment of $[Cu(L1146)(L1150)]^{5+}$ with KCN in aqueous MeCN results in the expected demetallation, but also results in a large topological change in which the π-acceptor and π-donor sites move together to maximise interaction, but the two phenanthroline moieties move rather far apart. The catenane framework undergoes reversible switching between these two forms according to the presence of cations Cu^+, Li^+ or H^+, or their removal. The switching can be monitored by NMR spectroscopy; there is also a detectable difference in the optical spectrum [292].

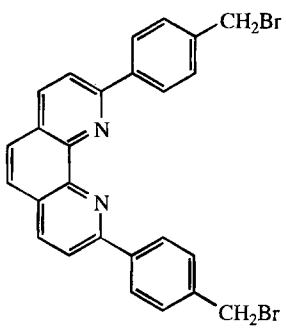


L1146

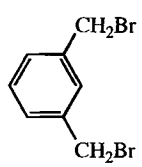


L1147

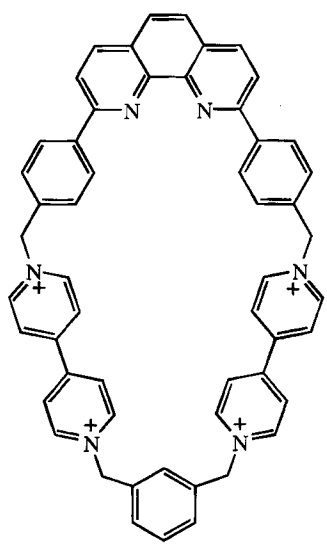
(4.86)



L1148



L1149



L1150

Multi-metal [2]-catenanes

Usually, [2]-catenates contain just one metal ion, but with appropriate ring substituents they can coordinate further metal ions. In order to provide a metal-chelating unit on the periphery of a catenate, a 2,2′-bipyridyl unit may be used in place of one of the phenylene units of L1058. Catenane synthesis using L1072 and L1151 in place of L1089 leads to the product (L1072)(L1152) which can coordinate bis(2,2′-bipyridyl)ruthenium(II), to give a complex of the form shown in Figure 4-17 [293], whose close relationship to $[Ru(bipy)_3]^{2+}$ and consequent photochemical

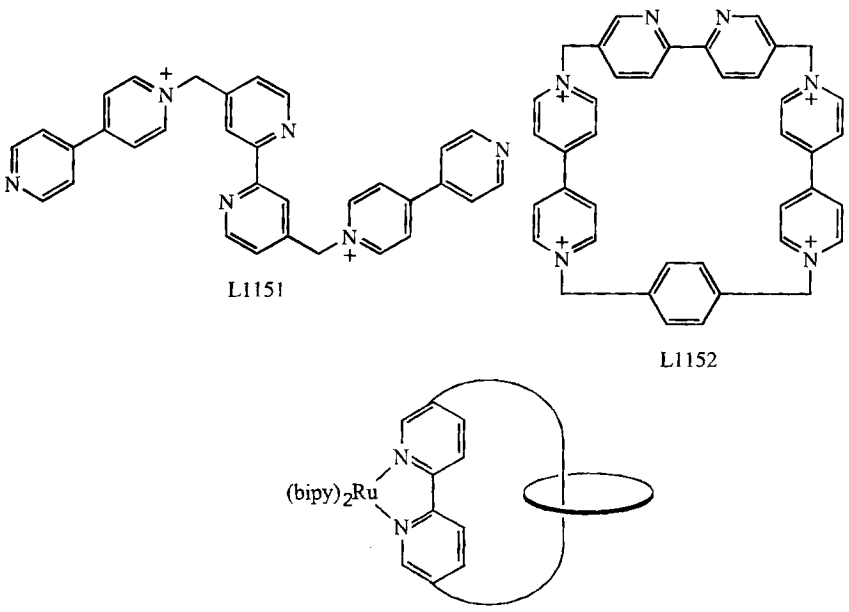


Figure 4-17. Diagrammatic representation of $[(L1072)(L1152)Ru(bipy)_2]^{6+}$.

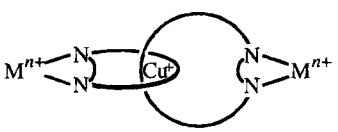
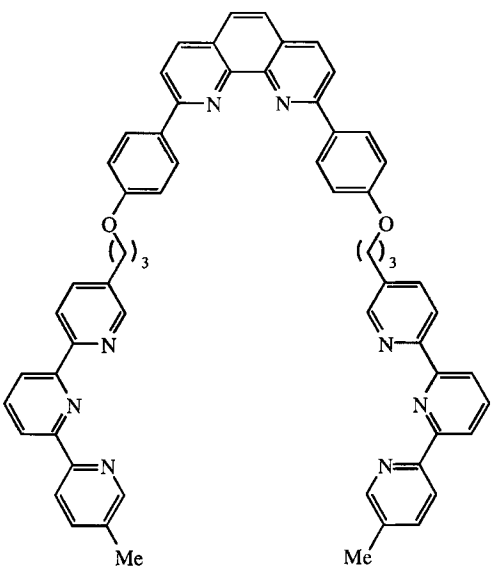


Figure 4-18. Trimetallic [2]-catenane constructed from rings containing 2,2′-bipyridyl units.

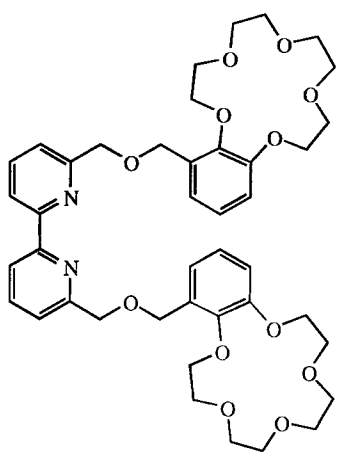
importance is immediately apparent. A symmetrical [2]-catenate, with one chelating unit in each ring (such as 2,2′-bipyridyl unit borne by L1151 as illustrated in Figure 4-17) could contain three metal ions, as indicated in Figure 4-18. For particularly strong cation binding the ring substituents might be porphyrins. By building the catenane in two stages different metal ions could be incorporated, as in the reported zinc(II)/gold(III) catenate with, as usual, copper(I) linking the two rings [294]. In this compound the porphyrins are pendant groups, but they may also be built into the rings, as in the catenane derived from L1119 linked with di(2-methoxyphenyl)-octaethylporphyrin [295]. This was again a Cu^+-template synthesis, in which the porphyrins were complexed with Zn^{2+} prior to reaction to avoid copper being incorporated. Porphyrin-[2]-catenanes have also been prepared using the paraquat/stacking method, which produced a basket porphyrin with its hydroquinol–polyether handle threaded through the standard bis(4,4′-pyridinium) ring of L1058. These catenanes are of particular interest in relation to dynamic processes [296] and

conformational changes consequent on the electrostatic effects of protonating the porphyrin entities [297].

It is possible to use metal ions to link two arms of a threaded molecule to form a ring and thus produce a catenane. This has been achieved using the bis-terpyridyl derivative of the standard Cu^+-complexing building block of L1119, namely L1153 (Eq. 4.87). This ligand reacts with $[Ru(DMSO)_2Cl_2]$ under conditions of high dilution to give a ruthenocycle, the two terpyridyl units of L1153 completing the octahedral coordination shell of the ruthenium(II). This metallomacrocycle reacts with another molecule of L1153 and Cu^+ to give L1153 threaded through the ruthenium-containing ring (i.e. a pseudorotaxane). Further reaction, with iron(II), cobalt(II), copper(II) or zinc(II) chloride, forms the second ring and thus gives a [2]-catenane, again by the M^{2+} drawing together the two ends of the thread to complete its octahedral coordination shell. This sequence is outlined in Scheme 4-30. Alternatively, $[Cu(L1153)_2]^+$ can be reacted with $[Ru(DMSO)_2Cl_2]$ to give the [2]-catenane consisting of two ruthenocycles. The advantage of the diruthenium compound is that ruthenium(II) is so substitution inert that this catenand can be treated with cyanide to remove the copper(I), while leaving the interlocked ruthenium-containing rings intact (Scheme 4-31) [298].



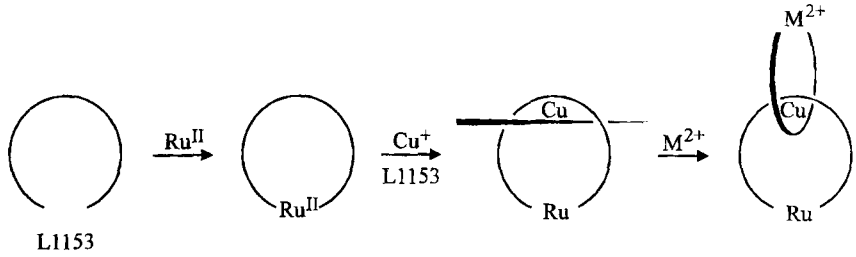
L1153



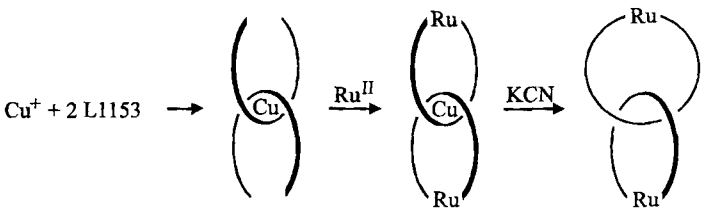
L1154

(4.87)

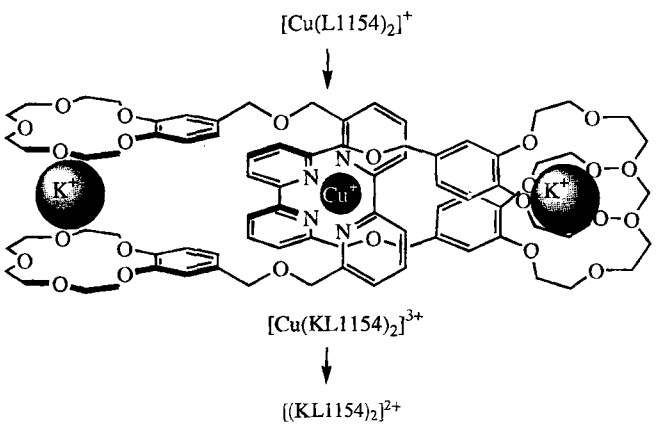
The two ends of the bipyridyl–bis-crown ether ligand L1154 can be clipped together by K^+. Reaction of $[Cu(MeCN)_4]^+$ with two equivalents of L1154 gave the precursor $[Cu(L1154)_2]^+$, which with an excess of KPF_6 gave the novel alkali-metallated catenate $[Cu(KL1154)_2](PF_6)_3$. The potassium binds the benzo-15-crown-5 units sufficiently tightly for demetallation, with potassium or tetramethylammonium cyanide, to be feasible, giving the [2]-catenane $(KL1154)_2$ as its hexafluorophosphate salt [299] (Scheme 4-32).



Scheme 4-30. Outline of synthesis of [2]-catenanes clipped by metal ion complexation of terminal terpyridyl groups.



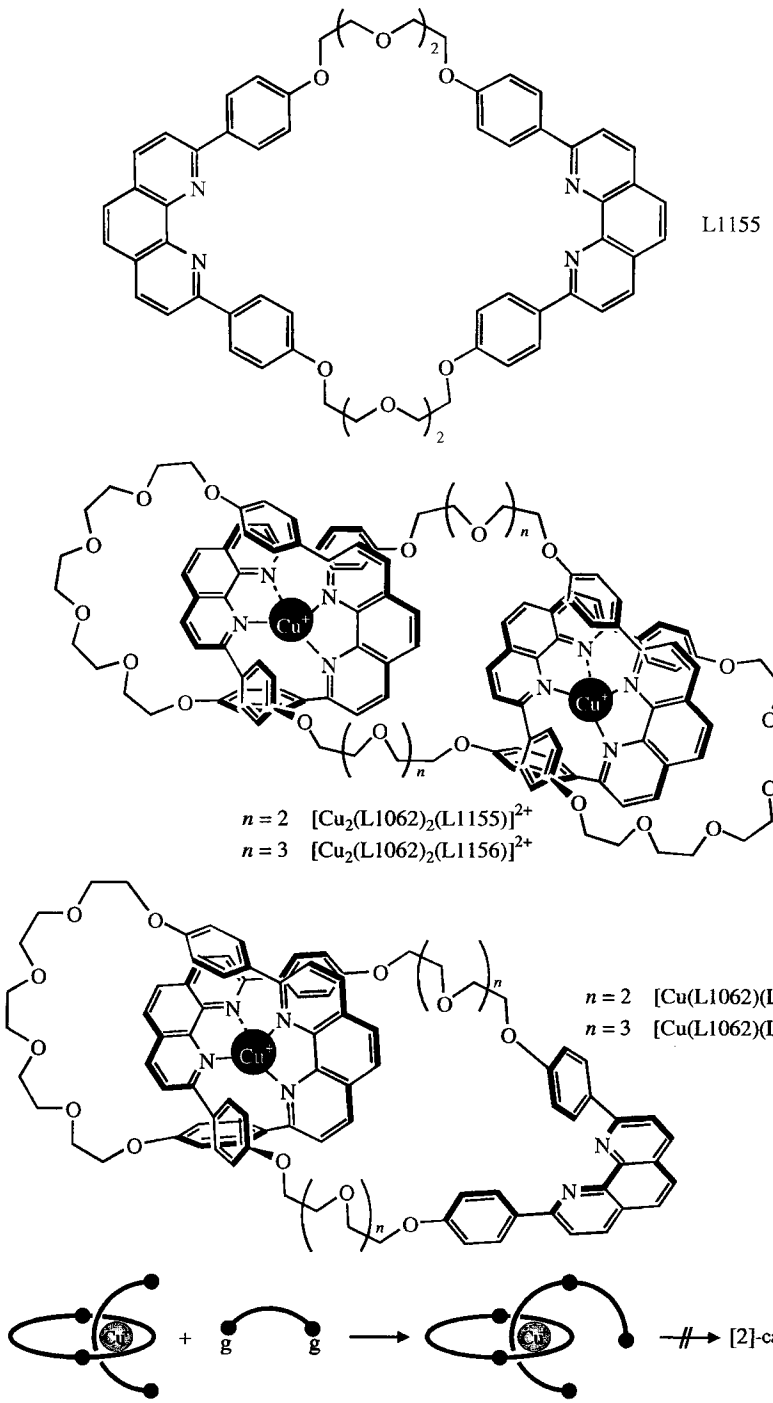
Scheme 4-31. Synthesis of a [2]-catenane containing ruthenium(II) in each ring.



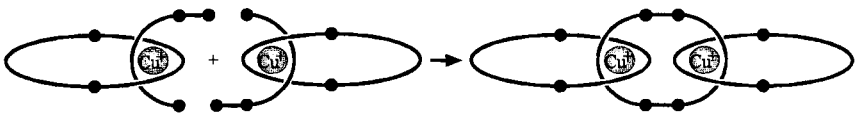
Scheme 4-32. Synthesis of a [2]-catenane containing potassium(I) in each ring.

Multi-ring and polymeric catenanes

The majority of catenane studies deal with [2]-catenanes, but it is possible to link three or more rings together. If a [2]-catenane synthesis is attempted by route B of Scheme 4-20 using an insufficiently long fragment g–g, it is, not surprisingly, unsuccessful (Scheme 4-33). However, a modification of such a synthesis would



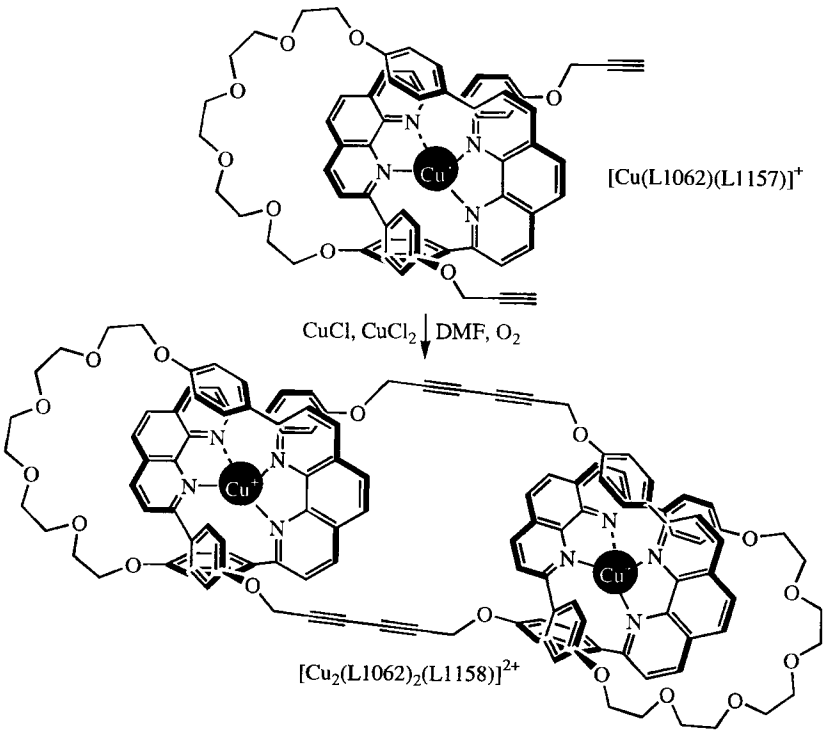
Scheme 4-33. Attempted cyclisation of a precatenane using insufficiently long g–g fragment.



Scheme 4-34. Synthesis of [3]-catenanes.

seem appropriate for the synthesis of [3]-catenanes, as indicated in Scheme 4-34. Specifically, binuclear [3]-catenates $[Cu_2(L1062)_2(L1155)]^{2+}$ and $[Cu_2(L1062)_2(L1156)]^{2+}$ have been obtained, in 6% and 2%, yield respectively, by reacting $[Cu(L1062)(L1119)]^{+}$ with $BrCH_2(CH_2OCH_2)_nCH_2Br$ ($n = 2$ or 3) in DMF at high dilution in the presence of an excess of Cs_2CO_3 [300]. Relatively large quantities of monomacrocyclic compounds result from these reactions. Thus, for instance, in the synthesis of $[Cu_2(L1062)_2(L1155)]^{2+}$ the 48-membered ring L1155 is isolable from the reaction mixture and, in the synthesis of $[Cu_2(L1062)_2(L1156)]^{2+}$, monomacrocycles are also produced. Small quantities of the mixed [2]-catenates $[Cu(L1062)(L1155)]^{+}$ and $[Cu(L1062)(L1156)]^{+}$, 5% and 1%, respectively, are also obtained. The [3]-catenates $[Cu_2(L1062)_2(L1155)]^{2+}$ and $[Cu_2(L1062)_2(L1156)]^{2+}$, as well as the mixed [2]-catenates $[Cu(L1062)(L1155)]^{+}$ and $[Cu(L1062)(L1156)]^{+}$, undergo demetallation in the presence of potassium cyanide to give the corresponding catenands, whose topology has been verified by mass spectrometry [300].

The above strategy for the generation of [3]-catenates is generally characterised by poor yields and tedious procedures. This has led to the exploration of ring closure by oxidative coupling of terminal alkynes (the Glaser reaction) [301]. The open-chain diyne L1157 was prepared in 80% yield from the diphenol L1119 and prop-2-ynyl bromide in DMF in an inert atmosphere in the presence of a large excess of Cs_2CO_3. The complex $[Cu(L1062)(L1157)]^{+}$ is available essentially quantitatively from the reaction of stoichiometric amounts of L1062, $[Cu(MeCN)_4]BF_4$ and L1157. Oxidative coupling is caried out in DMF, using large amounts of CuCl and $CuCl_2$, in the presence of atmospheric oxygen to form $[Cu(L1062)_2(L1158)]^{2+}$ (Scheme 4-35). It is noteworthy that the yield of chromatographically purified product is as high as 58%. Apart from this main product, another copper(I) catenate is produced. Preliminary ^1H NMR spectra suggested this product to be the trinuclear [3]-catenate resulting from cyclotrimerisation of $[Cu(L1062)(L1158)]^{+}$ containing four interlocked rings, namely a central 66-membered hexayne ring and three peripheral L1062 rings. The X-ray structure determination [302] of the main $[Cu_2(L1062)_2(L1158)]^{2+}$ product showed the cation geometry (Figure 4-19) to differ considerably from that suggested in Scheme 4-35. The copper(I) coordination polyhedra are not equivalent: phenanthroline units are arranged symmetrically around Cu1, whereas the phenanthroline fragment C, positioned near Cu2, is displaced in such a way that one of its nitrogens is accommodated on a plane determined by the second phenanthroline unit B′ and the copper atom. The environment of Cu2 is analogous to that of the copper in the [2]-catenate $[Cu(L1062)_2]^{+}$ (see Figure 4-8). As in the case of other catenates, demetallation of $[Cu_2(L1062)_2(L1158)]^{2+}$ was achieved with the aid of potassium cyanide, to give the catenand



Scheme 4-35. Synthesis of the catenate $[Cu_2(L1062)_2(L1158)]^{2+}$.

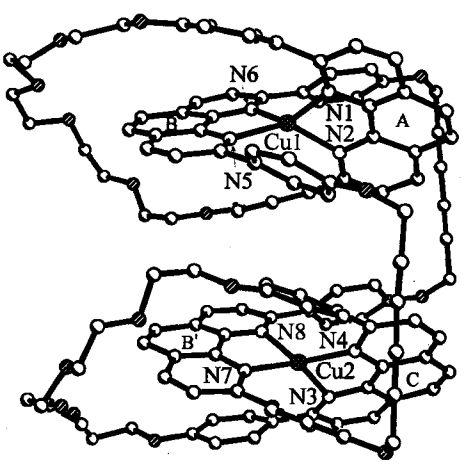
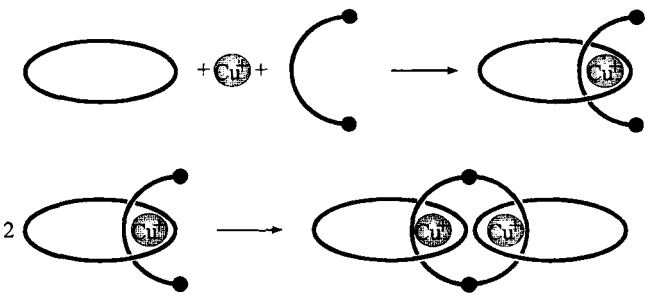
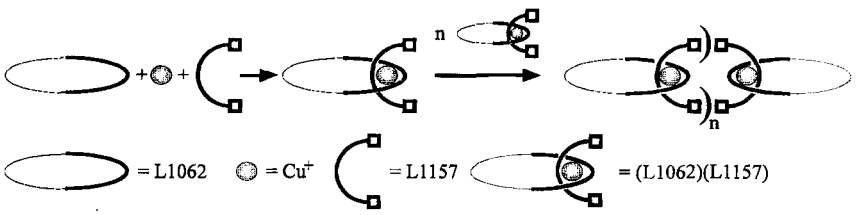


Figure 4-19. The structure of $[Cu_2(L1062)_2(L1158)]^{2+}$.



Scheme 4-36. The strategy for preparing [3]-catenanes by cyclodimerisation.



Scheme 4-37. Synthesis of multi-ring catenanes.

$(L1062)_2(L1158)$, with its 44-membered central ring and two peripheral 30-membered rings in 75% yield. In these preceding cases the strategy for preparing [3]-catenanes corresponds to true cyclodimerisation, involving four reaction centres, as depicted in the general outline shown in Scheme 4-36 [301]. Analogous [3]-catenanes with higher lipophilicity have been prepared from 4,7-di(*n*-hexyl)-substituted phenanthroline precursors [303].

Once prepared, [3]-catenands can be used for preparing novel complexes. Thus by reaction of the appropriate metal salts with the catenand $(L1062)_2(L1158)$, mononuclear $[Cu(L1062)_2(L1158)]^+$, homodinuclear $[Cu_2(L1062)_2(L1158)]^{2+}$, and heteronuclear $[CuAg(L1062)_2(L1158)]^{2+}$, $[CuCo(L1062)_2(L1158)]^{3+}$ and $[CuZn(L1062)_2(L1158)]^{3+}$ were obtained [302, 304]. It is also possible to prepare a formally binuclear [3]-catenate containing one Cu^+ and one H^+ [305]. The photochemistry and photophysics of a number of homo- and hetero-nuclear [3]-catenates of this type have been established [305, 306].

The copper(I) template/Glaser synthetic method has been extended to the preparation of higher cyclooligomers, up to [7]-catenanes, in surprisingly good yields [307]. The synthetic strategy, which can give from one up to six rings interlocked with a large central ring (up to 132 atoms), is illustrated by Scheme 4-37. Here the coordinating fragments are drawn in bold lines, while the squares represent the end functions (–C≡CH) to be dimerized to –C≡C–C≡C–. The systems obtained, namely [3]-catenate^{2+}, [4]-catenate^{3+}, [5]-catenate^{4+}, ... for $n = 1, 2, 3, \ldots$, respectively, consist of $n + 1$ peripheral rings separately interlocked with a central ring built up during the alkynic coupling cyclooligomerisation. The central ring in the

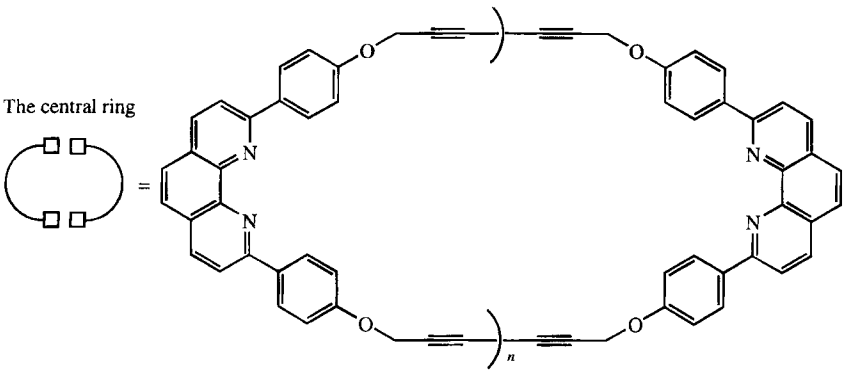


Figure 4-20. The central ring(s) in Glaser syntheses of multi-catenanes.

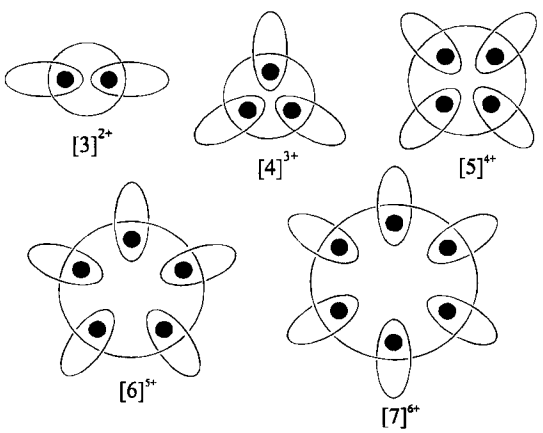


Figure 4-21. Schematic representation of $[3]^{2+}$, $[4]^{3+}$, $[5]^{4+}$, $[6]^{5+}$ and $[7]^{6+}$-catenanes.

case of $n = 1$ (Figure 4-20) corresponds to L1158 in the [3]-catenane $[Cu_2(L1062)_2(L1158)]^{2+}$. In the successive catenates this central ring increases by one half of that in the [3]-catenate. The catenanes prepared are depicted schematically in Figure 4-21. The $[3]^{2+}$-, $[4]^{2+}$-, and $[5]^{4+}$-catenanes were isolated in 23, 23 and 16 % yield, respectively. The yields of the $[6]^{5+}$- and $[7]^{6+}$-catenanes, which were not isolated, in the product mixture were 8% and 5 %. All these multi-ring catenanes were characterised by ESI mass spectrometry.

An alternative way to build up multi-catenanes is to thread rings onto a bicyclic central frame. One, two or three L1062 rings can be threaded onto L1159 (Eq. 4.88); the three-ring-threaded catenane is shown diagrammatically in Figure 4-22 [308]. Polymeric species can be generated by the usual [2]-catenane synthesis on Cu^+ templates. Interlocking 45-membered rings joined by ester linkages are gen-

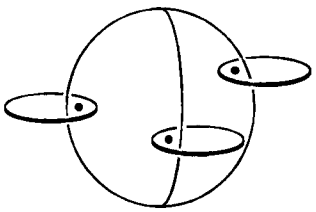
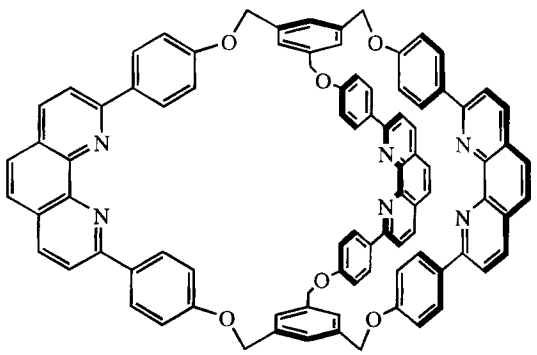


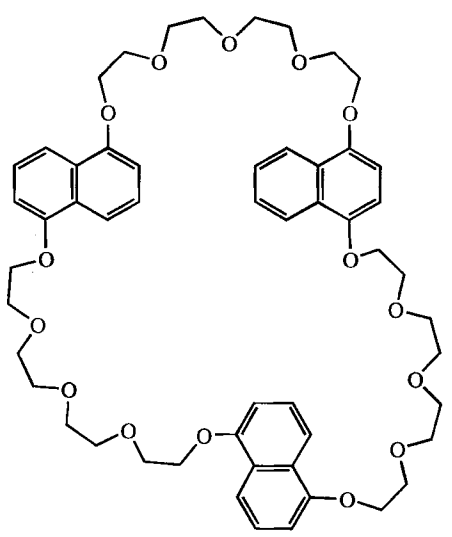
Figure 4-22. A bicyclic multi-catenane.



L1159 (4.88)

erated by condensation of a dicarboxylic acid spacer with hydroxy groups on the catenane rings [309].

Multi-ring catenanes may also be prepared by the cyclophane approach. The polyether L1160 (Eq. 4.89), the trinaphtho-analogue of L1094, is a large ring and



L1160 (4.89)

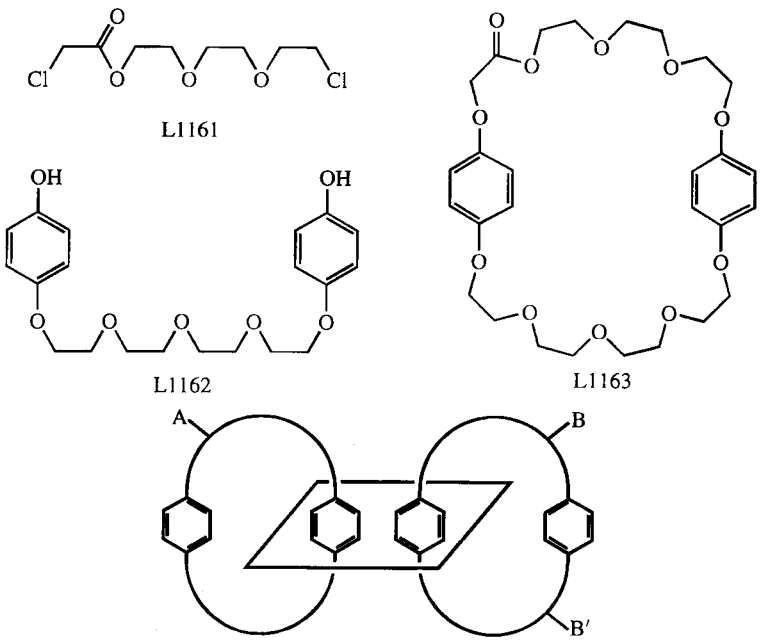
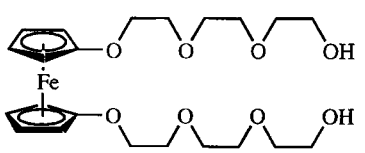


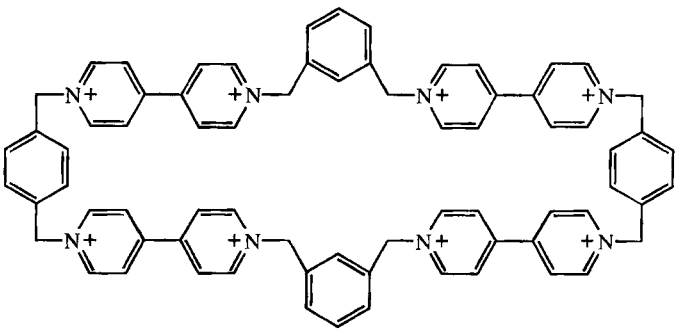
Figure 4-23. Topological isomers of the [3]-catenane (L1079)(L1163)$_2$, in which the isomers have the keto-groups at AB or at AB′.

has three π-electron-rich aromatic centres. One might therefore hope to clip more than one cyclophane ring around it. In practice it is possible to clip two standard L1058 rings around L1160, but it is considerably more difficult to clip two rings to give a [3]-catenane than it is to clip just one cyclophane unit around L1160 to obtain the [2]-catenane (L1160)(L1058). The structure of (L1160)(L1058), established by X-ray diffraction, provides clues as to the reluctance of the [3]-catenane to form [310]. It proves easier to thread two aromatic crown ether rings, such as L1072 or L1094, through L1079, an enlarged version of L1058. Condensing L1161 with L1162 gives a crown ether ring (L1163) with a keto-signpost; the [3]-catenane (L1163)$_2$(L1079) has two topological isomers (Figure 4-23) [208]. L1079 is best prepared using L1164 (Eq. 4.90), or simply ferrocene itself, as tem-

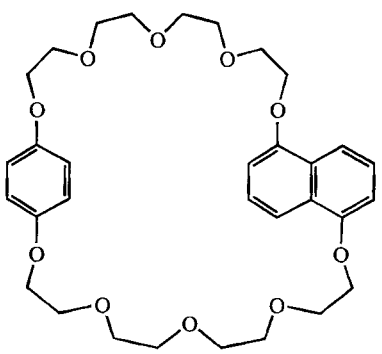


L1164 (4.90)

plate [311]. An alternative enlarged tetra-bipyridinium ring is shown as L1165, which can form a [3]-catenane with, for example L1166 (Eq. 4.91). Both thermodynamic and kinetic template effects are important in this type of [3]-catenane preparation [312].



L1165

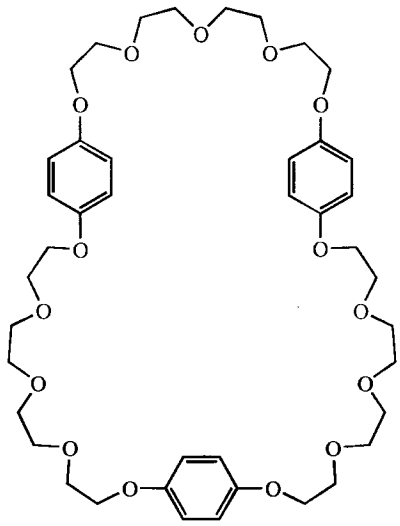


L1166

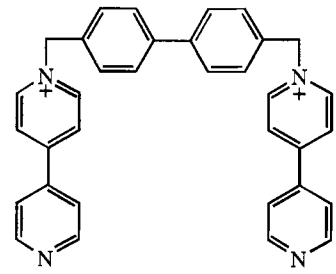
(4.91)

Both [4]- and [5]-catenanes can be prepared by two-step self-assembly. Firstly the [3]-catenane (L1079)(L1167)$_2$ is prepared from L1167, L1168 and L1169 (Eq. 4.92), then one or two additional cyclophane rings can be clipped around one or both of the L1167 rings using the usual reagents L1089 and L1109 [313]. The linearly linked [5]-catenane produced is a candidate for the title of olympiadane, first adumbrated in 1960 and christened from its analogy with the Olympic symbol [314]. A similar strategy has been employed to synthesise a [7]-catenane – a central L1079 ring is threaded with two L1167 rings, which are then each threaded with two L1058 rings [315].

Polymeric catenanes may also be prepared using cyclophane links. Thus two *p*-phenylene bis-bipyridinium units L1089 can be joined by reaction with L1170 to give L1171 (Eq. 4.93), which can be threaded by two L1072 rings. Alternatively

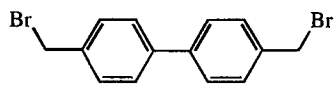


L1167

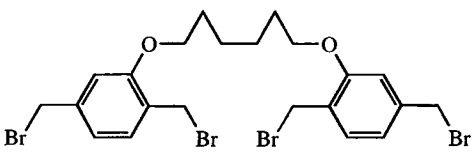


L1168

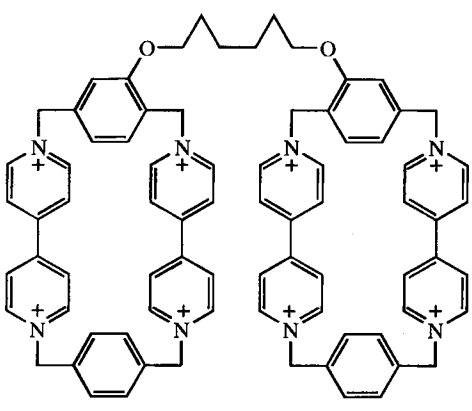
(4.92)



L1169



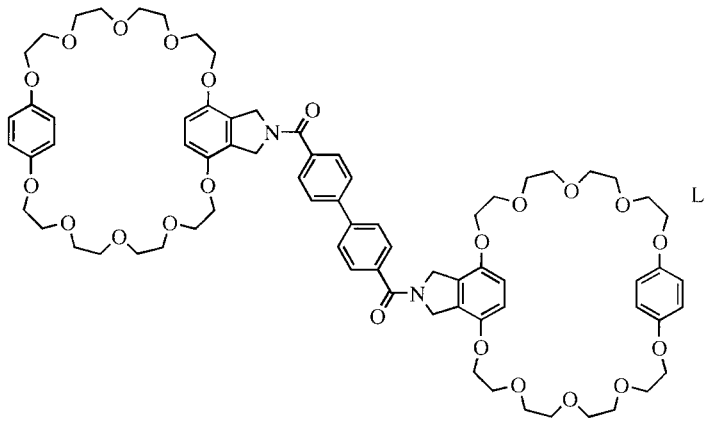
L1170



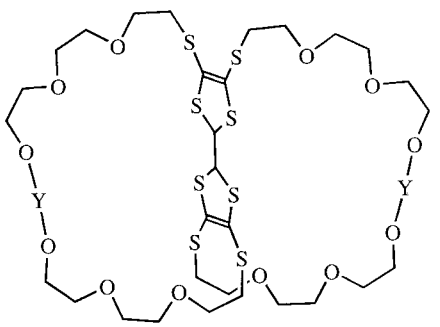
L1171

(4.93)

L1072 rings can be linked as shown in L1172 (Eq. 4.94), threading or clipping L1058 or analogues through each L1072 ring [218]. Polycatenanes may also be generated from diisocyanates [316].



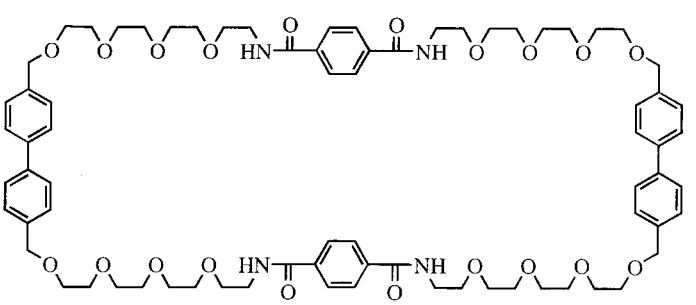
L1172 (4.94)



L1173 (4.95)

A slightly different type of multi-ring system centres on bicyclic tetrathiafulvalenes. These compounds are sometimes referred to as pseudocatenanes, as two of the rings are chemically linked by the bis-tetrathiafulvalene unit L1173 (Eq. 4.95). It is possible to clip the usual L1058 rings either around the central tetrathiafulvalene unit or around phenylene or naphthylene rings (Figure 4-24) [188, 317]. In these, and several of the preceding syntheses, high-pressure methods are often advantageous.

Catenated cyclodextrins are particularly interesting in that they may be assembled in aqueous media. Given a sufficiently large central ring, as in L1174 (Eq. 4.96), [3]-catenanes can be assembled having two terminal cyclodextrin rings. Topological isomers, namely 'head-to-head' and 'tail-to-tail' (Figure 4-25), have been characterised by ^{1}H and ^{13}C NMR [175].



L1174 (4.96)

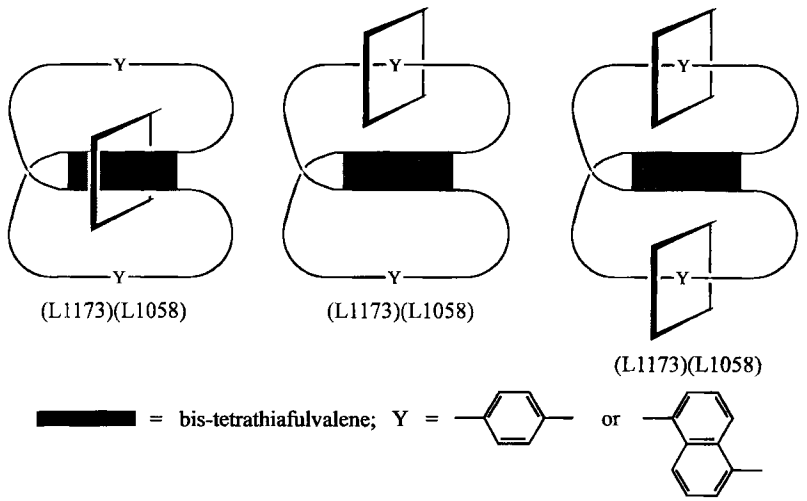


Figure 4-24. Examples of bis-tetrathiafulvalene-cyclophane pseudocatenanes.

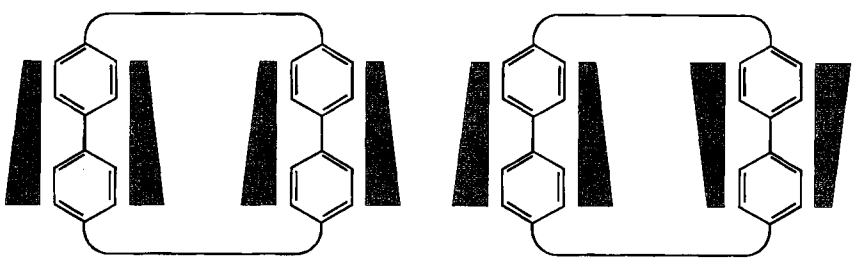
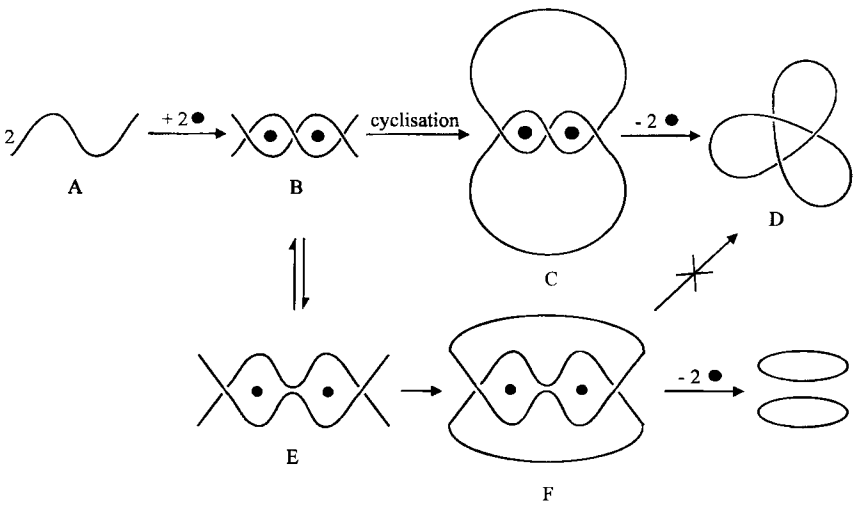


Figure 4-25. The topological isomers of (L1174)(cyclodextrin)$_2$.

4.2.5 Knots

As their name implies, these molecules are characterised by their distinctive topology in which the macrocycle is intertwined to form a knot [170, 171]. The simplest form of knot is the so-called trefoil knot – trefoil as in tracery or heraldry, in turn derived from tripartite leaves, as in clover (which of course is not knotted!). More complex forms are found throughout chemistry and physics [318] and in Nature – in proteins [319], metalloproteins [320] and DNA (both natural [321], and in synthetic derivatives [322]). However not all structures claimed to be knots conform to the strict mathematical definition of a knot (Section 4.2.1).

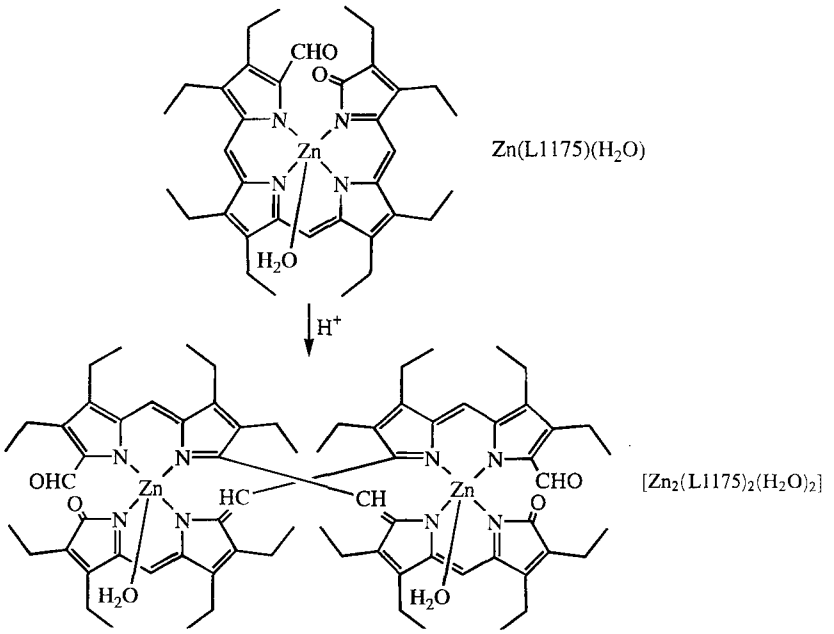
A macrocycle in the form of a knot can be generated by a method analogous to



Scheme 4-38. Cyclisation of a double helix B and its face-to-face isomer E.

that for generating [2]-catenanes (Scheme 4-20). However, whereas building a [2]-catenane requires one transition metal centre, the synthesis of a trefoil knot requires a pair of such centres [323]. As shown in Scheme 4-38, two bis-chelating molecular threads can be interlaced on two metal centres, leading to a double helix B. After cyclisation to C and demetallation, a knotted system D should be obtained. The face-to-face isomer of a double helical complex can also undergo cyclisation, but it would give an unknotted isomer complex which would give two separate rings on demetallation (Scheme 4-38 E to F, but not F to D). An important prerequisite for success is the formation of a helical binuclear complex B, which has to be sufficiently stable to survive the cyclisation conditions used to obtain C. The choice of the chemical link between the two chelating subunits of each fragment A is thus crucial. In addition to chemical stability, steric factors and flexibility have to be considered. In particular, during the reaction of A with the transition metal ion, the formation of B must be favoured over the formation of a polymer or of a mononuclear complex produced by the folding of A around one metal centre.

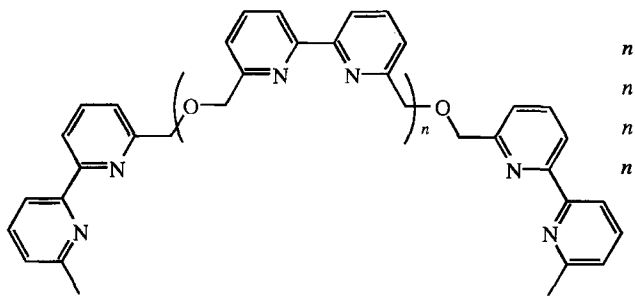
A considerable variety of ligands have been used for the preparation of double-helical coordination compounds by the interaction of bis-bidentate ligands with four-coordinate metal centres. One of the earliest binuclear helical complexes was zinc-based. The complex $[Zn_2(L1175)_2(H_2O)_2]$, identified by X-ray crystallography [324], was obtained by dimerisation of the octaethylformylbiliverdinate complex $Zn(L1175)(H_2O)$ in strongly acidic medium (Scheme 4-39). Various double-stranded helicates have been synthesised from the ether-linked oligo-bipyridine ligands L1176–L1179 and copper(I) (Eq. 4.97). These ligands behave as flexible molecular strands, which coordinate to the copper(I) to give di-, tri-, tetra- or penta-nuclear complexes, respectively (Figure 4-26) [325]. Double helical complexes



$Zn(L1175)(H_2O)$

$[Zn_2(L1175)_2(H_2O)_2]$

Scheme 4-39. Synthesis of the double-helical complex $[Zn_2(L1175)_2(H_2O)_2]$.



$n = 0$ L1176
$n = 1$ L1177
$n = 2$ L1178
$n = 3$ L1179 (4.97)

can also be prepared from terpyridyl and Cu^I [326], from pentapyridyl (L1180) and Co^{II} [327] and Cu^{II} [328], from hexapyridyl (L1181) and Mn^{II}, Fe^{II}, Cu^{II}, Cd^{II}, Cu^I and Ag^I [329], and from L1182 and Ag^I (Eq. 4.98) [330]. All products were binuclear, mainly prepared as their hexafluorophosphate salts $[M_2L_2](PF_6)_n$. Interestingly, it proved possible to prepare a mixed valence copper species $[Cu^ICu^{II}L_2](PF_6)_3$ [331]. The double helical nature of most of these complexes, and of a number of similar species [332], has been demonstrated by X-ray crystallography.

Reaction of stoichiometric amounts of the analogous terpyridyl ligand L1183 (Eq. 4.99) and $Fe(PF_6)_2$ in refluxing ethylene glycol under argon led to an almost

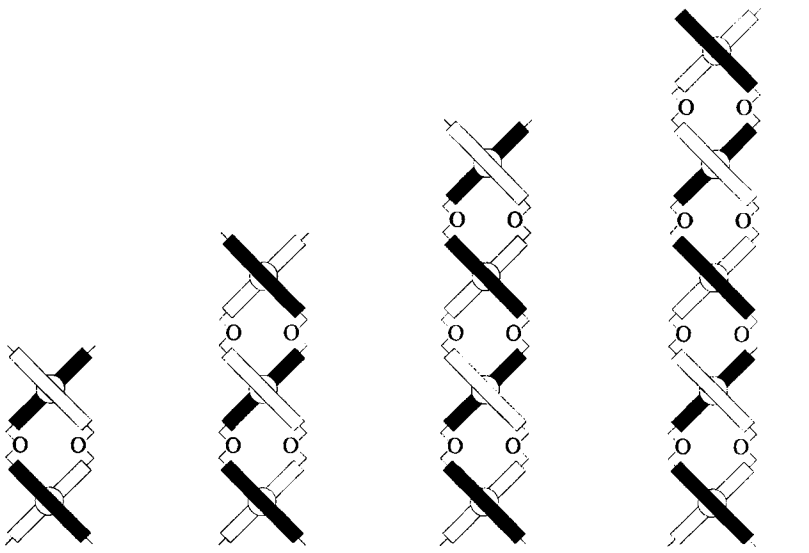
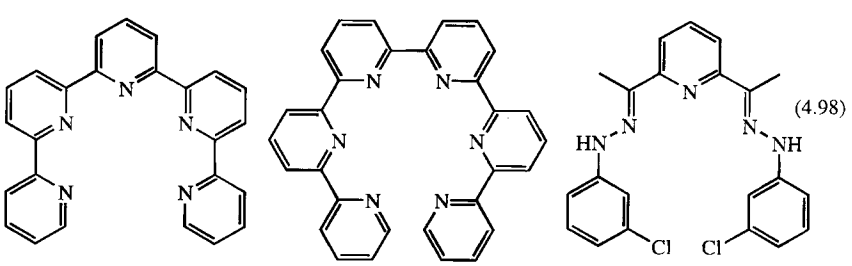
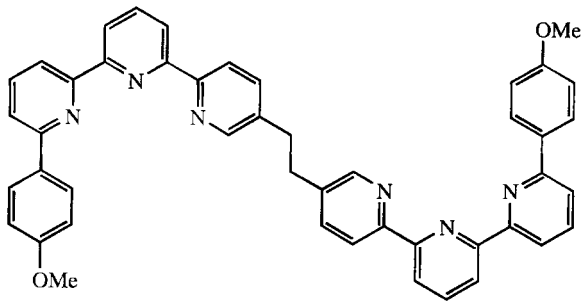


Figure 4-26. A series of double stranded 'helicates' of various lengths obtained from copper(I) and polypyridine ligands.

quantitative yield of the dinuclear compound $[Fe_2(L1183)_2](PF_6)_4$. The ruthenium analogue $[Ru_2(L1183)_2](PF_6)_4$ was prepared similarly from L1183 and $RuCl_3 \cdot 3H_2O$. After anion exchange and then recrystallisation from CH_2Cl_2/CH_3CN, $[Ru_2(L1183)_2](PF_6)_4$ was obtained in 60% yield [333]. X-Ray diffraction revealed the helical nature of $[Ru_2(L1183)_2]^{4+}$ and, by analogy, a similar structure was assumed for $[Fe_2(L1183)_2]^{4+}$. Similar triple helical binuclear iron(II) and related species [334] may also prove valuable in knot generation. These examples are not exhaustive, but merely illustrate the types of helicate systems which can be prepared and which are thus available for conversion into knots by metal-directed self-assembly [335] (Scheme 4-38).

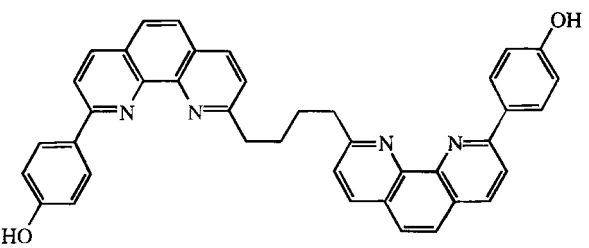
The first synthesis of a trefoil knot compound [336] was based on the synthesis of the bis-phenanthroline derivative L1184 and formation of a mixture of its



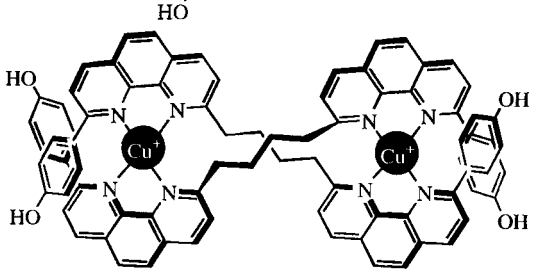


L1183 (4.99)

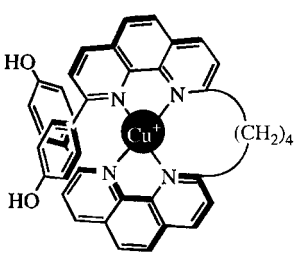
copper(I) complexes $[Cu_2(L1184)_2]^{2+}$ and $[Cu(L1184)]^+$ (Eq. 4.100). This mixture was allowed to react under high-dilution conditions with two equivalents of $ICH_2(CH_2OCH_2)_5CH_2I$ in DMF at 60°C in the presence of a large excess of Cs_2CO_3. After work-up and repeated chromatographic purification the main product, isolated as its BF_4^- salt (in 24% yield), was shown to be mononuclear $[Cu(L1185)]^+$ (Eq. 4.101) formed by ring closure of $[Cu(L1184)]^+$. In addition, a small amount (3%) of the target complex $[Cu_2(L1186)]^{2+}$ was obtained (Eq. 4.102).



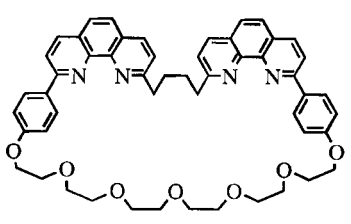
L1184 (4.100)



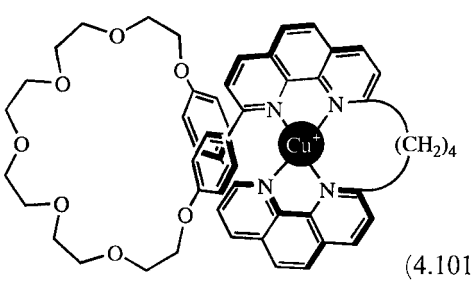
$[Cu_2(L1184)_2]^{2+}$



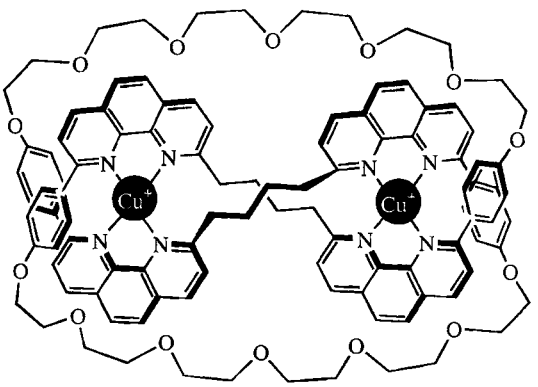
$[Cu(L1184)]^+$



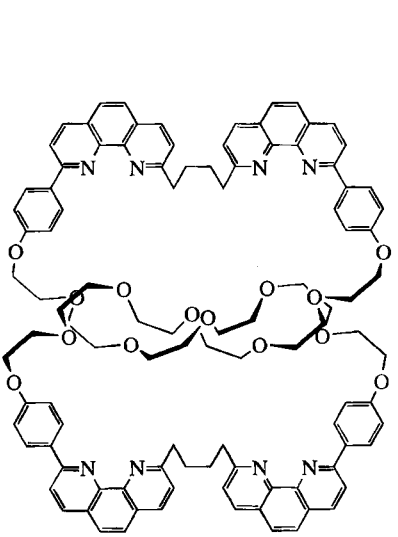
L1185



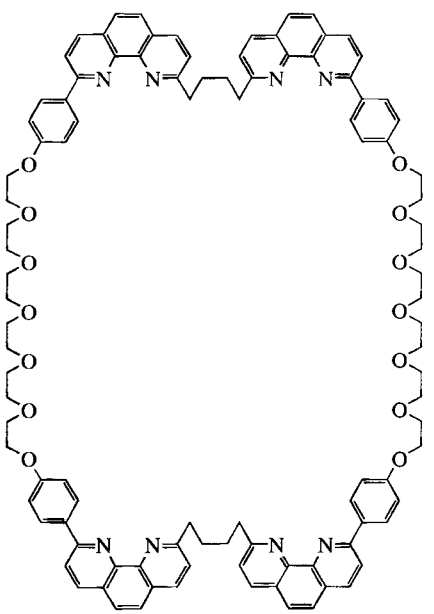
$[Cu(L1185)]^+$ (4.101)



$[Cu_2(L1186)]^{2+}$ (4.102)



L1186



L'1186 (4.103)

Quantitative demetallation of the various copper(I) complexes by aqueous KCN yielded the free ligands L1185 and L1186 (Eq. 4.103). In addition, a very small amount (0.5%) of L'1186, the unravelled topological isomer of L1186, was isolated by further chromatography of the impure fractions from the chromatographic purification of $[Cu_2(L1186)]^{2+}$. An X-ray diffraction study of the benzene solvate $[Cu_2(L1186)](PF_6)_2 \cdot C_6H_6$ confirmed the trefoil knot nature of the complex, shown in Figure 4-27 [337]. The complex cation has effective D_2 symmetry, with three mutually perpendicular pseudo-twofold axes. Of these, one joins the two copper ions, the second passes through the middle of the two $(CH_2)_4$ bridges, and the third passes through the central oxygens of the two polyoxoethylene chains. This sym-

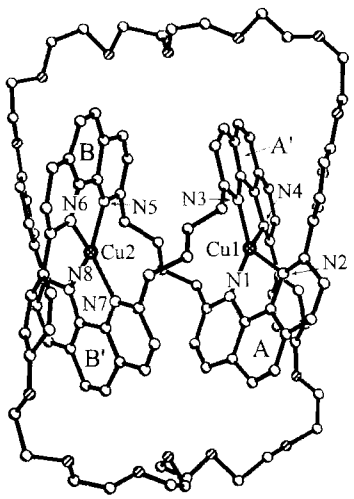
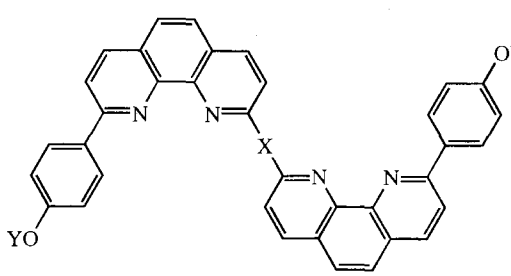


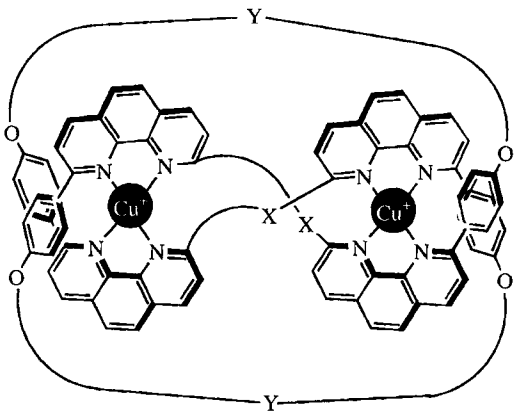
Figure 4-27. The structure of the knotted compound $[Cu_2(L1186)]^{2+}$.

metry places the two complexes around Cu1 and Cu2 with their respective 1,10-phenanthroline rings (Cu1 with phen A and phen A′; Cu2 with phen B and phen B′) superimposed – A over B′ and A′ over B. Starting from phen A, the molecular ribbon goes along the $(CH_2)_4$ bridge joining phen A to phen B, turns around Cu2 with phen B, follows the long oxychain B back to phen A′, turns around Cu1 with phen A′, goes along the second $(CH_2)_4$ bridge to phen B′, and, following the oxychain A, reaches the starting point, phen A [337].

The bis-1,10-phenanthroline ligands L1187 to L1192, with their two phenanthroline moieties linked by polymethylene chains of various lengths, are also precursors for the construction of interlocking rings (Eq. 4.104). Binuclear double-stranded helical complexes such as $[Cu_2(L1190)_2]^{2+}$ and $[Cu_2(L1192)_2]^{2+}$ were obtained in solution by reacting the respective ligands with $[Cu(MeCN)_4](PF_6)$. Cyclisation was achieved using $ICH_2(CH_2OCH_2)_nCH_2I$ (n = 4 or 5) as 'tying reagent', to give knots containing between 80- and 90-membered rings. Yields were low, being 0.5% for $[Cu_2(L1193)]^{2+}$, 0.75% for $[Cu_2(L1194)]^{2+}$, 3% for $[Cu_2(L1195)]^{2+}$, 8% for $[Cu_2(L1196)]^{2+}$ and 2.5% for $[Cu_2(L1197)]^{2+}$ (Eq. 4.105). The knots showed a range of redox behaviour, with the 84-membered ring knot proving the most electrochemically stable [338].



Y = CH_3, X = $(CH_2)_2$	L1187	
Y = CH_3, X = $(CH_2)_4$	L1188	
Y = CH_3, X = $(CH_2)_6$	L1189	(4.104)
Y = H, X = $(CH_2)_2$	L1190	
Y = H, X = $(CH_2)_4$	L1191	
Y = H, X = $(CH_2)_6$	L1192	



(4.105)

$X = (CH_2)_2$, $Y = CH_2(CH_2OCH_2)_5CH_2$ $[Cu_2(L1193)]^{2+}$
$X = (CH_2)_4$, $Y = CH_2(CH_2OCH_2)_4CH_2$ $[Cu_2(L1194)]^{2+}$
$X = (CH_2)_4$, $Y = CH_2(CH_2OCH_2)_5CH_2$ $[Cu_2(L1195)]^{2+}$
$X = (CH_2)_6$, $Y = CH_2(CH_2OCH_2)_4CH_2$ $[Cu_2(L1196)]^{2+}$
$X = (CH_2)_6$, $Y = CH_2(CH_2OCH_2)_5CH_2$ $[Cu_2(L1197)]^{2+}$

Considerably improved yields (up to 30%) were obtained when the polymethylene links between the two phenanthroline moieties in ligands of the L1184, L1187–L1192 type were replaced by a 1,3-phenylene link. Again, copper(I) was used for the template pair, and $ICH_2(CH_2OCH_2)_5CH_2I$ to join the ends of the ligands. A surprisingly strong electronic interaction between the two copper ions was indicated by the cyclic voltammograms – a stable mixed-valence form appears possible [339].

Recent advances in the chemistry of metal-containing knots include the preparation of composite and heteronuclear knots. The composite knots are based on copper templates and phenanthroline ligating moieties, this time linked by alkynic coupling (Glaser) reactions. Despite their complexity, with a minimum of six crossing points in planar representation (Figure 4-28), these species have been fully

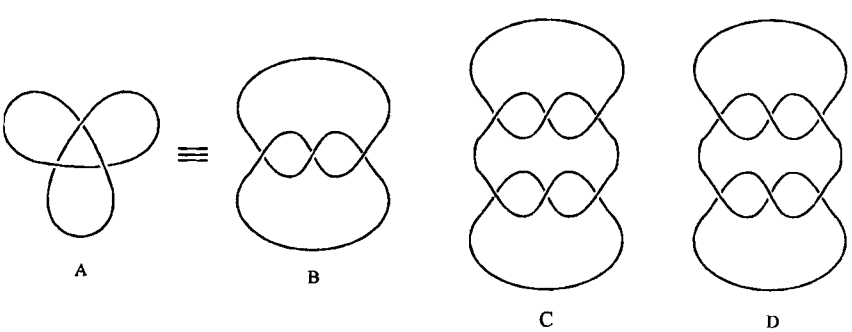
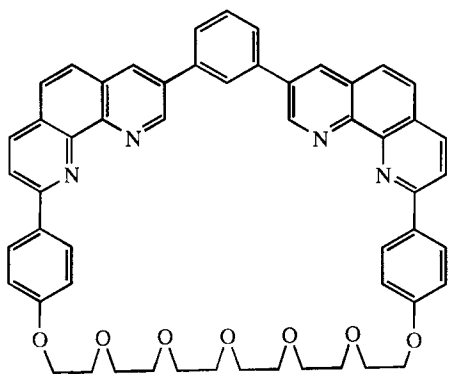


Figure 4-28. Two representations of a trefoil knot (A and B) and two related composite knots (C and D).

characterised, by electrospray-ionisation mass spectrometry (ESI-MS), ^{1}H NMR, and two-dimensional nuclear Overhauser effects spectroscopy (2D; NOESY) [340]. The generation of heterodinuclear knot complexes proved possible thanks to the great stability of the ligand L1198 (Eq. 4.106). The complex $[Cu_2(L1198)]^{2+}$ can be demetallated in two steps, giving $[Cu(L1198)]^+$, then intact metal-free L1198. Reaction of the monocopper(I) complex $[Cu(L1198)]^+$ with such ions as Ag^+ or Zn^{2+} yields the heterodinuclear complexes $[CuAg(L1198)]^{2+}$ and $[CuZn(L1198)]^{3+}$ [341]. The various metal-ion templates mentioned so far have all favoured, or at



L1198 (4.106)

least tolerated, tetrahedral geometry. Currently there is interest in building knots using trefoil geometry associated with (far more commonly occurring) octahedral metal ions, still using diimine chelating units [342].

Trefoil knots, and therefore the molecular knots discussed in this section, are chiral (Figure 4-29). The resolution of a dicopper(I) knot prepared from a helical precursor containing the 1,3-phenylene-linked bis-phenanthroline ligand described above (L1198) has been achieved by crystallisation of the racemic cation with (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl phosphate [343]. As commented by these authors, the preparation of optically pure knot complexes is of great potential interest in relation both to interactions with biological molecules and, where the complexed metal has more than one accessible oxidation state, to enantioselective electron transfer [344].

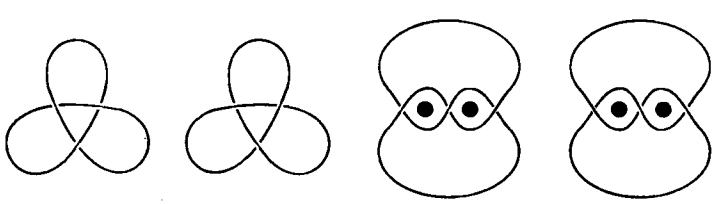


Figure 4-29. Enantiomers of a trefoil knot and of a dicopper knot.

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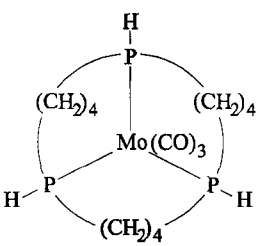
Chapter 5

Phosphorus- and arsenic-containing macrocyclic compounds

5.1 Phosphorus

At present the number of macrocyclic compounds containing phosphorus heteroatoms is not very large in comparison with those containing nitrogen [1]. There are several reasons for this. The main reasons are the relatively limited range of available ligsons and the sometimes quite intricate experimental procedure. Nonetheless, numerous recent studies have yielded new classes of polyphosphine macrocycles and related macrocyclic complexes [2].

The basic pathways for the synthesis of phosphorus-containing macrocyclic substances are high dilution techniques and template reactions. The use of the template route enables the assembly of the triphosphine macrocyclic ligand L8, obtained as its complex with tricarbonylmolybdenum [3]. Cyclooligomerisations of molybdenum-coordinated alkenylphosphines [3] were also investigated [2]. The synthesis of $(CO)_3Mo(L8)$ and $(CO)_3Mo(L1199)$ was carried out in 70–85% yield in a manner similar to that described earlier (Eq. 5.1) [3].



$(CO)_3Mo(L1199)$ (5.1)

The structure of $(CO)_3Mo(L8)$ was established unambigously by single crystal X-ray analysis (Figure 5-1) [3]. It consists of a 12-membered $[HP(CH_2)_3]_3$ ring facially coordinated to the $Mo(CO)_3$ unit. The [12]aneP_3 ring coordination results in the P-H bonds being oriented up and out of the plane defined by the three phosphorus atoms.

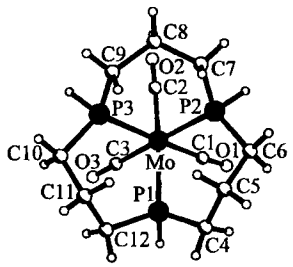
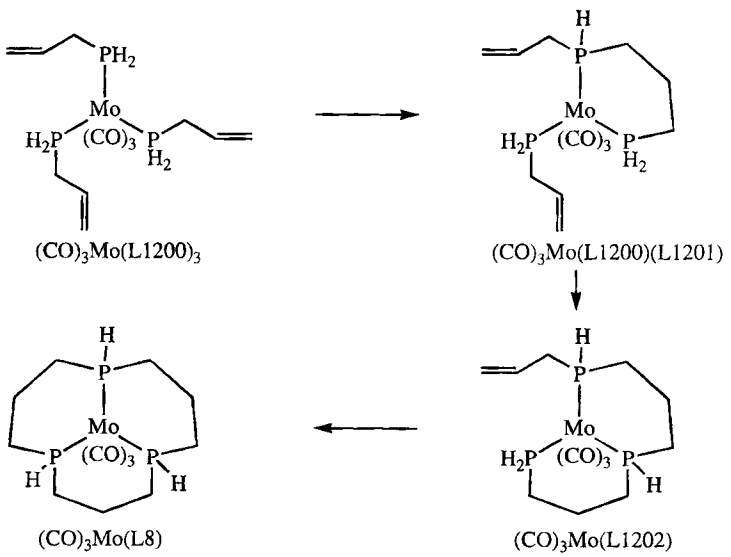


Figure 5-1. Structure and numbering scheme for *fac*-$(CO)_3Mo(L8)$.

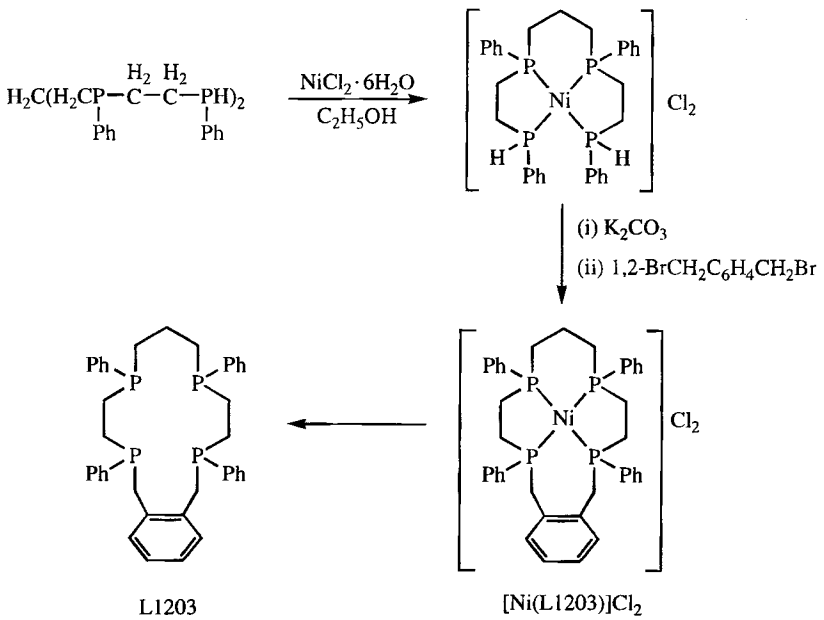


Scheme 5-1. Stepwise template assembly of $(CO)_3Mo(L8)$.

The structural arrangement of coordinated groups around molybdenum is close to octahedral, indicating that the [12]aneP_3 ring fits well without significant distortion of the bond angles at molybdenum. The macrocycle is positioned so that two of the six-membered metallocycles have chair conformations and the third cycle adopts the boat conformation.

The metal-template cyclooligomerisation giving rise to $(CO)_3Mo(L8)$ was examined in greater detail by following the reaction by ^{31}P NMR spectroscopy as a function of time [2]. On the basis of spectral assignments, the sequence of reactions shown in Scheme 5-1 appears to be the major process that occurs. Initial closure of one C_3P_2Mo ring results in $(CO)_3Mo(L1200)(L1201)$, a species containing a single six-membered metallophosphacycle.

Subsequently, after the second cyclisation step the coordinated bicyclic system $(CO)_3Mo(L1202)$ appears. Upon building up the third metallocycle, the final [12]aneP_3 macrocycle is formed as its molybdenum complex *fac*-$(CO)_3Mo(L8)$. The



Scheme 5-2. Ring-forming alkylation involving phosphorus donor atoms.

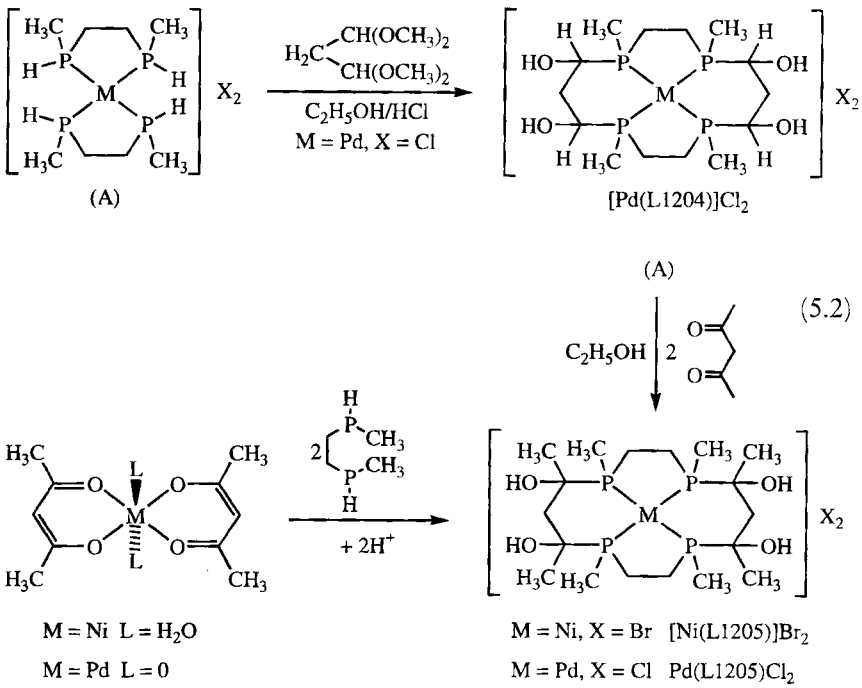
reaction occurs in moderately well-defined steps, the metal template introducing order into the cyclooligomerisation reaction [2].

The alkylation technique successfully explored for linking *cis*-disposed nitrogen and sulphur donor atoms has been extended to phosphorus. The macrocyclic compound benzo-[15]aneP_4, isolated as the complex [Ni(L1203)]Cl_2, was synthesised by the template reaction shown in Scheme 5-2. Note that the terminal coordinated phosphorus donor atoms can be involved in the chelate-forming template reaction only after their deprotonation, which is facilitated by the electron-withdrawing effect of the metal ion and the presence of a base (K_2CO_3).

The metal-free ligand is obtained from [Ni(L1203)]Cl_2 by demetallation with sodium cyanide [4]. The study of $[Ni(L1203)]^{2+}$ in solution in the presence of various anions (Cl^-, NCS^-, BF_4^-) showed that the complex maintains its square-planar diamagnetic state. Five-coordinate $[Ni(L1203)(CN)]^+$ is formed by reaction of KCN with [Ni(L1203)]$(BF_4)_2$ in methanol. These properties may be attributed to the fact that the L1203 cavity is small compared with high-spin nickel(II). As a consequence, the latter prefers to remain in the low-spin configuration in the corresponding complex [5].

Another strategy for the design of phosphorus-containing macrocyclic compounds involves the use of the corresponding bidentate aliphatic PH-type phosphines and β-dicarbonyl compounds as initial ligson pairs [6–8]. One of these ligsons undergoes preliminary binding to form a metal chelate, and addition of the second ligson follows. Compounds L1204 and L1205 are synthesised in this way,

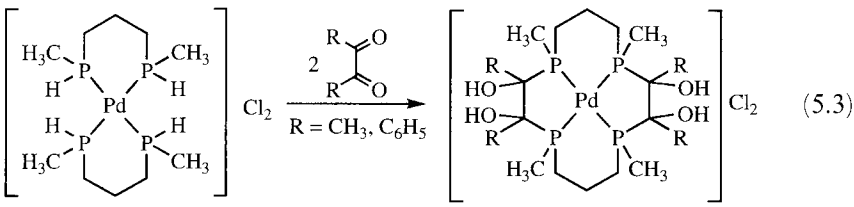
forming coordination compounds with the metals used as templates. Nickel(II) and palladium(II) complexes with L1205 are formed as two isomers, except when starting from $Pd(acac)_2$ when only one isomer is isolated (Eq. 5.2).



Although the terminal coordinated phosphine groups in (A) are effectively quaternary and therefore lack nucleophilic properties, the corresponding reactions with 1,1,3,3-dimethoxypropane and Hacac presumably proceed by partial dissociation of the phosphorus atoms from the metal ion. This is followed by nucleophilic attack of the lone pair of electrons thus generated at the phosphorus atom on the electrophilic carbon centre of malonaldehyde formed by hydrolysis of 1,1,3,3-dimethoxypropane or Hacac. The thermodynamic template effect is likely to be operative in these reactions. In contrast, the coordination of Hacac to the metal ion in the initial step enhances the electrophilicity of the carbonyl groups through ligand polarisation by the metal ion, making them more susceptible to nucleophiles. X-Ray structure determination of the two isomers of $Pd(L1205)Cl_2$ has shown [6, 7] that one has a square-planar geometry, because the donor atoms of the macrocyclic ligand being coordinated in a plane, but that the second isomer has square-pyramidal geometry with one chlorine at the apex.

Attempts to substitute acetylacetone by α-diketones in the reactions considered above were unsuccessful. However, if the number of CH_2 units between the phosphorus atoms is increased by one, the non-coordinated phosphorus donor atoms can be involved in ring-closure reactions by virtue of nucleophilic addition to α-dicarbonyl compounds. This pathway has been illustrated by the synthesis of

Pd(L1206)Cl_2 and Pd(L1207)Cl_2, each again being isolated in the form of two isomers (Eq. 5.3) [6]. The thermodynamic template effect is likely to be operative here. Note that elimination following the addition step does not occur in this case.



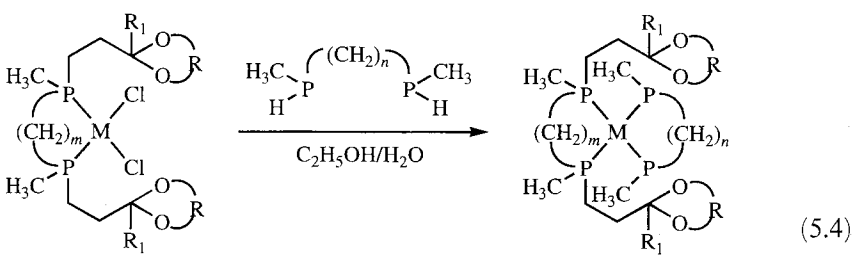
(5.3)

$R = CH_3$ Pd(L1206)Cl_2

$R = C_6H_5$ Pd(L1207)Cl_2

The complexes do not demetallate upon treatment with potassium cyanide, with the exception of square-planar [Pd(L1205)]Cl_2, which releases the metal-free L1205 [6]. In the absence of a metal ion, a redox reaction of $H(CH_3)P(CH_2)_3P(CH_3)H$ with benzil occurs, resulting in benzoin and 1,2-dimethyl-1,2-diphospholane as the main products [6].

The routes shown above are suitable only for the synthesis of symmetric 14-membered macrocyclic systems containing four phosphorus atoms in a cyclic backbone, but a general method for the synthesis of tetraphosphacycloalkanes containing 14–16 units in a ring has been reported [9]. The compounds L1208–L1215 have been synthesised by this technique (Eq. 5.4).



(5.4)

$(RO)_2 = (OC_2H_5)_2$, $R_1 = H$:

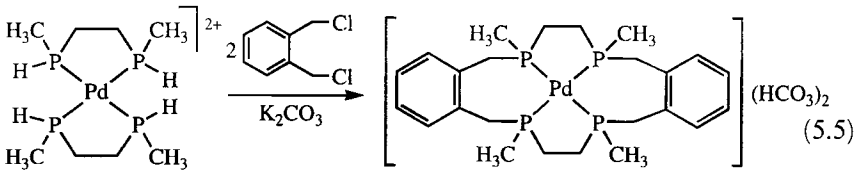
$n = m = 2$, M = Ni	Ni(L1208)Cl_2
$n = 3$, $m = 2$, M = Ni	Ni(L1209)Cl_2
$n = m = 2$, M = Pd	Pd(L1208)Cl_2
$n = 3$, $m = 2$, M = Pd	Pdi(L1209)Cl_2

$(RO)_2 = C_2H_4O_2$, $R_1 = CH_3$:

$n = m = 2$, M = Pd	Pd(L1210)Cl_2
$n = 3$, $m = 2$, M = Pd	Pd(L1211)Cl_2
$n = m = 2$, M = Pt	Pt(L1212)Cl_2
$n = 3$, $m = 2$, M = Pt	Pt(L1213)Cl_2
$n = 2$, $m = 3$, M = Pd	Pd(L1214)Cl_2
$n = m = 3$, M = Pd	Pd(L1215)Cl_2

As shown by ^{1}H and ^{31}P NMR studies, the above coordination compounds were obtained in the form of several (3–6) diastereoisomers depending upon ligand nature (there are six chiral centres in these complexes, namely four phosphorus atoms and two carbons). The possible number of stereoisomers is 20, taking into account the four pairs of enantiomeric arrangements of the (P)CH_3 and (C)OH groups [9]. The complexes are rather stable, both kinetically and thermodynamically. Long heating of aqueous solutions of these complexes with KCN at 80°C does not result in their demetallation [9]. This is not surprising in view of the stability predicted by the HSAB principle.

Alkylation of palladium(II)-coordinated phosphane ligands with 1,2-bis(chloromethyl)benzene gives rise to new chelate rings and coincidentally to the macrocyclic complex [Pd(L1216)]$(HCO_3)_2$ (Eq. 5.5).



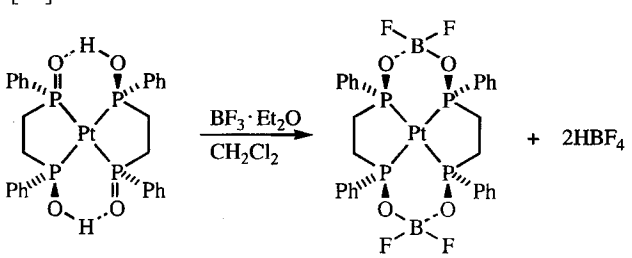
(5.5)

[Pd(L1216)]$(HCO_3)_2$

The generation of nucleophilic phosphorus centres in sufficient concentration to permit the desired coupling to proceed at a reasonable rate is achieved here by deprotonation of terminal phosphorus-containing functions. The bicarbonate salt may be converted into chloride or hexafluorophosphate by metathesis. Metal-free L1216 is obtained by heating [Pd(L1216)]$(HCO_3)_2$ solution with KCN [10]. It was established by ^{1}H and ^{31}P NMR spectroscopy that the complex is a mixture of three diastereoisomers.

The pure *syn*-(*RSRS*)-Pd(L1216)$Cl_2 \cdot CH_3OH$ isomer is obtained by recrystallisation of the chloride from methanol. The structure of this compound was solved by X-ray crystallography and has square-pyramidal geometry with the chlorine atom at the apex, the phosphorus atoms being coordinated in the basal plane. The second chloride anion and the molecule of methanol are not coordinated.

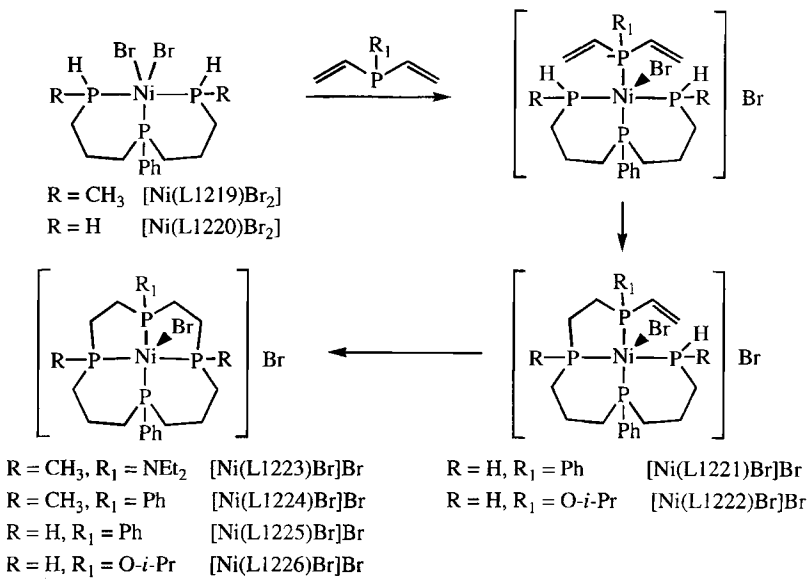
Replacement of the interligand hydrogen bonds in the pseudomacrocyclic complex [Pt(*R,S*-L1217)$_2$] with electrophilic boron-containing bridges affords macrocyclic complexes [Pt(*R,S*-L1218)] similar to those from oxime nickel(II) complexes (Eq. 5.6) [11].



(5.6)

[Pt(*R,S*-L1217)$_2$] [Pt(*R,S*-L1218)]

The reaction is stereoselective due to formation of intramolecular O–H···O



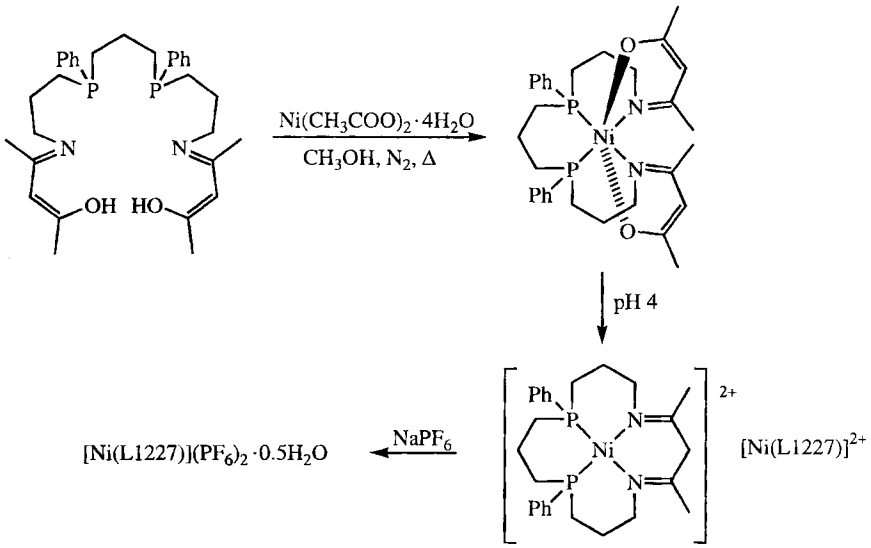
Scheme 5-3. Metal-controlled reaction of triphosphane ligsons with divinylphosphanes.

hydrogen bonds in [Pt(*R,S*-L1217)$_2$], which places all four oxygen atoms in a *syn* arrangement above the coordination plane. It is reasonable that a kinetic template effect in this process can be contributed by the capacity of the platinum(II) ion to bind two (*R,S*)-Ph(O)P(CH$_2$)$_2$P(OH)Ph ligands in a square-planar manner, thereby providing conditions for favourable interligand hydrogen bonding. The structures of both the starting compound and final macrocyclic complex have been determined by X-ray diffraction [11].

Complexes [Ni(L1219)Br$_2$] and [Ni(L1220)Br$_2$] react smoothly with divinylphosphanes R$_1$P(CH=CH$_2$)$_2$ (R$_1$ = Et$_2$N, Ph, O-*iso*-Pr) in CH_2Cl_2 by the addition of terminal P–H bonds of triphosphane coordinated ligands on C=C double bonds, to give, in high yield, macrocyclic complexes [Ni(L1223)Br]Br to [Ni(L1226)Br]Br as a mixture of diastereomers [12, 13]. The ring-closure reaction is facilitated by the kinetic coordination template effect and proceeds stepwise through intermediate species as shown in Scheme 5-3. The intermediate complexes [Ni(L1221)Br]Br and [Ni(L1222)Br]Br have been identified using ^{31}P and ^{1}H NMR spectroscopy.

The complex [Ni(L1223)(CN)]PF_6 was isolated by successive treatment of [Ni(L1223)Br]Br with potassium cyanide and ammonium hexafluorophosphate. The macrocyclic ligand assembled on the nickel(II) matrix is bonded strongly and cannot be removed even on heating [Ni(L1223)X]$^+$ (X = Br, CN) with KCN. The structure of one of the four stereoisomers of the cyanide complex separated by fractional crystallisation has been confirmed by X-ray diffraction [13]. It can be described as a distorted trigonal bipyramid with P–N(C$_2$H$_5$)$_2$ and P–Ph in the apical positions, and CN and the remaining two phosphorus atoms situated in the equatorial plane.

Several examples of the synthesis of N,P-heteroatomic macrocyclic systems on

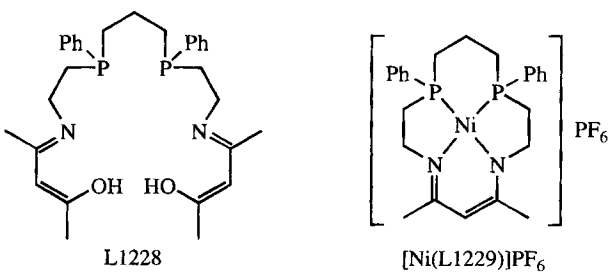


Scheme 5-4. Synthetic metal-controlled pathway to diphosphadiazamacrocycle L1227.

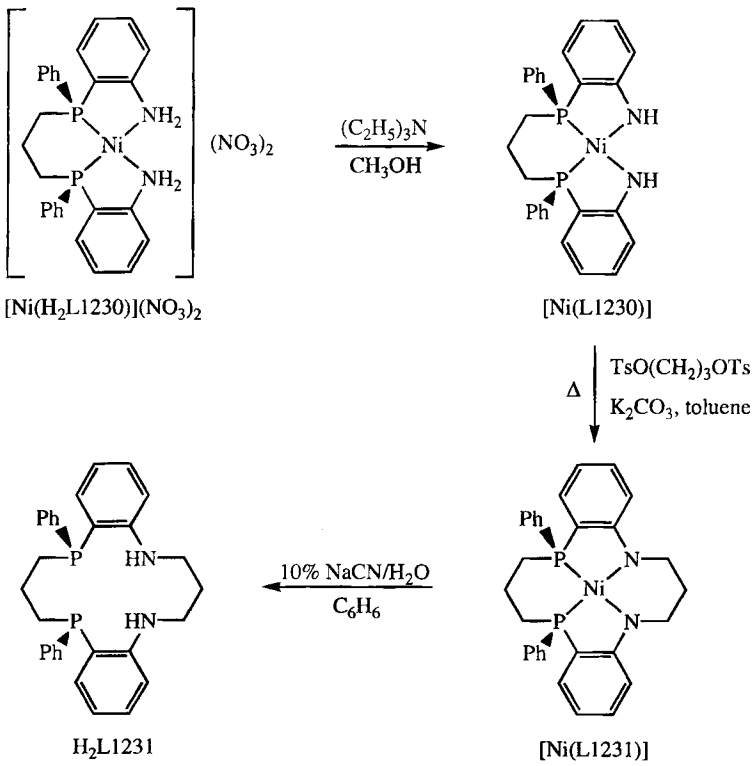
matrices are well documented. In particular, multistep construction of L1227 has been performed (Scheme 5-4) [14, 15].

Thus the assembly of L1227 includes formation of a nickel(II) chelate with a hexadentate open-chain ligand as an intermediate step. Then, after the elimination of the major part of the methanol and addition of the same volume of water, acidification of the solution and heating under reflux releases one molecule of Hacac, and the macrocycle is produced by the remaining acetylacetone moiety due to its involvment in formation of the second azomethine bond accompanied by formation of the final product. The macrocycle was isolated as its nickel(II) complex. The latter is diamagnetic and has a square-planar structure. The donor atoms of the organic ligand (two nitrogen and two phosphorus) are coplanar, and the nickel atom is displaced 0.7 nm out of this plane [14, 15].

Similarly, L1229 is assembled from L1228. This process includes the formation of [Ni(L1228)] followed by the elimination of Hacac and macrocyclisation on the Ni(II) matrix, giving rise to the required product (Eq. 5.7) [Ni(L1229)]PF_6 [15].



(5.7)



Scheme 5-5. Template route to the diphosphadiazamacrocycle H_2L1231.

It is noteworthy that the 14-membered macrocyclic complex is produced in dienate form, but the 16-membered in diene form. An attempt to convert $[Ni(L1229)]^{2+}$ into the diene form by pH variation resulted in decomposition (the opposite conversion of the 16-membered complex has not been carried out) [15].

Synthesis of the P_2N_2 macrocycle H_2L1231 was performed on a nickel(II) matrix by the multistep route shown in Scheme 5-5. The ring closure was achieved by the reaction of 1,3-bis(toluene-*p*-sulphonyloxy)propane, $TsO(CH_2)_3OTs$, with [Ni(L1230)]. The mechanism involves sequential nucleophilic attack on the toluene-*p*-sulphonate substituted carbon atoms of the propane by the lone pair of each of the coordinated amido nitrogen atoms. In the last step the coordination kinetic template effect should be operative. Protons liberated in the course of the reaction are removed by the excess of base.

The X-ray diffraction study of $[Ni(H_2L1230)](NO_3)_2$ (Figure 5-2) indicated [16] that the central chelate ring NiC_3P_2 has a favourable chair conformation, with the amino groups in *cis* positions.

Deprotonation under moderately basic conditions yields [Ni(L1230)], which has the requisite geometric and electronic structure for smooth macrocyclisation with difunctional alkylating agents. This feature predetermines the subsequent

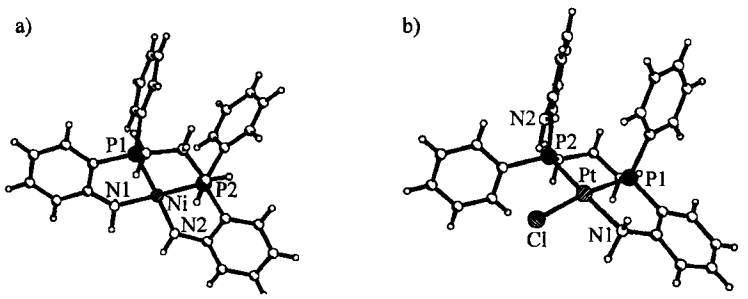
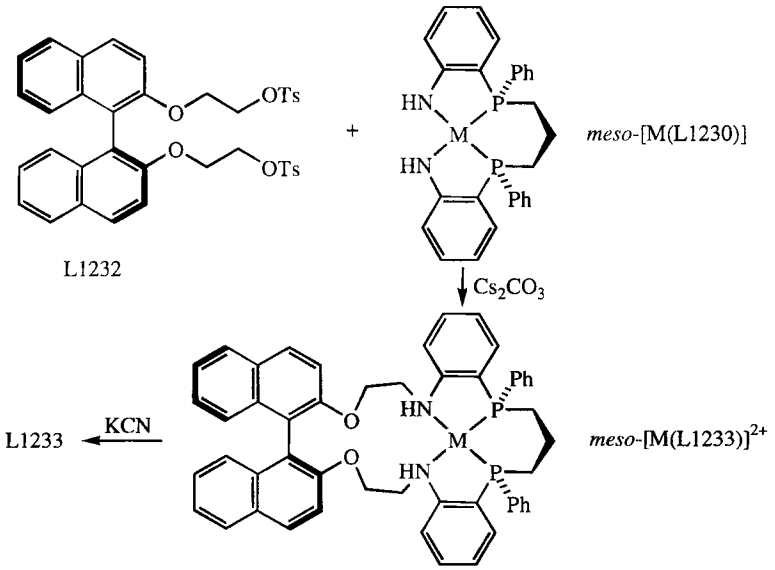


Figure 5-2. The structures of a) $[Ni(H_2L1230)]^{2+}$ and b) $[Pt(H_2L1230)Cl]^{+}$.

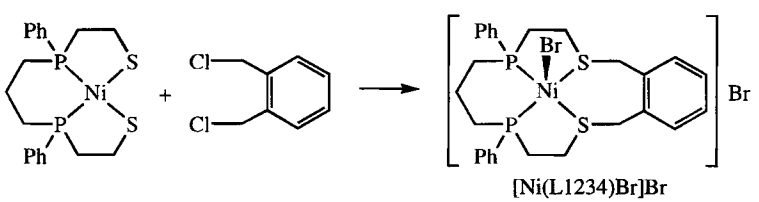
reaction with propane-1,3-ditoluenesulphonate to form [Ni(L1231)]. In contrast to the complex [Ni(L1227)], containing an unsaturated N_2P_2 macrocyclic ligand, [Ni(L1231)], containing a more flexible fully saturated 14-membered macrocycle as ligand, undergoes demetallation readily to yield H_2L1231. The ligand has the *meso* form both in the complex and in the metal-free state. This has been checked crystallographically for [Ni(L1231)] and H_2L1231 [16].

The macrocyclic product H_2L1231 forms coordination compounds with ions larger than nickel(II). In particular, [M(L1231)] (M = Pt, Pd) have been isolated by reaction of $[M(PhCN)_2Cl_2]$ with the free macrocycle in the presence of bases. On treatment with acids they have been converted into $[M(H_2L1231)]X_2$. However *rac*-H_2L1230 does not act as a tetradentate planar ligand, but forms complexes of the type $[M(H_2L1230)X]^{+}$, behaving as a tridentate P_2N ligand without using the second $-NH_2$ group for coordination (Figure 5-2). As a result, this form is not suitable for macrocyclisation [16, 17]. It follows that topological factors dominate in the template synthesis of *meso*-H_2L1231. All this indicates that [M(L1230)] (M = Ni, Pd, Pt) can be used for macrocyclisation reactions as a mixture of *meso* and *rac* stereoisomers without their prior separation. For example, a suspension of a 40:60 mixture of *meso*-[Ni(L1230)], the tosylate L1232, and Cs_2CO_3 (molar ratio 1:1:4) in toluene after prolonged heating, followed by treatment of the filtrate with an aqueous KCN solution, gave the desired macrocycle H_2L1233 in 32% yield (Scheme 5-6) [18]. When starting from pure *meso*-[Ni(L1230)] the yield of the final ligand product was considerably increased (63%), as expected. Less than ideal complementarity between stereoelectronic demands of nickel(II) and the ability of the macrocyclic ligand product (L1233) to meet them by square-planar coordination to the metal ion, makes the resultant macrocyclic complex labile to demetallation with KCN. Direct remetallation reaction with $NiCl_2 \cdot 6H_2O$ yields the complex [Ni(L1233)Cl]Cl [18]. According to the X-ray structure determination, the potentially quadridentate ligand is tridentate, coordinated through two P atoms and only one N atom. The fourth coordination site is occupied by a chloride anion to form a distorted square-planar array.



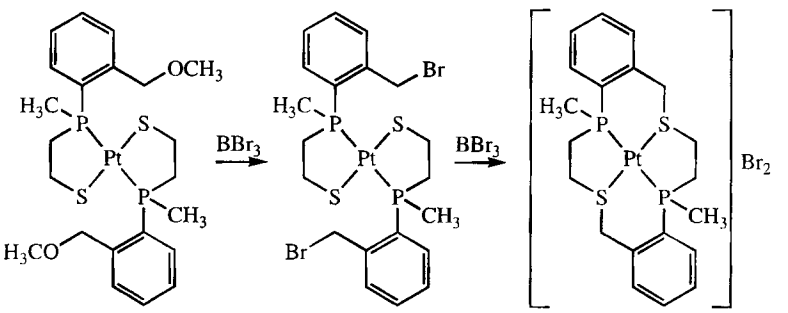
Scheme 5-6. Template synthesis of the 21-membered $O_2N_2P_2$ macrocycle L1233.

The macrocyclic complex [Ni(L1234)Br]Br, containing a P_2S_2 set of donors, was prepared by alkylation of coordinated thiolate (Eq. 5.8). This produces a new chelate ring [19] in a similar way to the synthesis of [Ni(L5)Br_2] [20].



(5.8)

The kinetic template effect has presumably been involved in the formation of *trans*-diphosphadithiamacrocycle L1236 [21]. The dimerisation of the linear bifunctional P,S-ligson L1235 becomes possible by coordination to platinum(II) (Eq. 5.9). The latter approaches the reactive ends of the deprotected ligsons, facilitating the nucleophilic attack of the coordinated mercaptide ion of one ligson at the electrophilic benzylic carbon centre of the adjacent ligson, providing the desired couplings. The free ligand L1236 was isolated by treating the mixture of stereoisomers of the corresponding complex with aqueous hydroxide, followed by

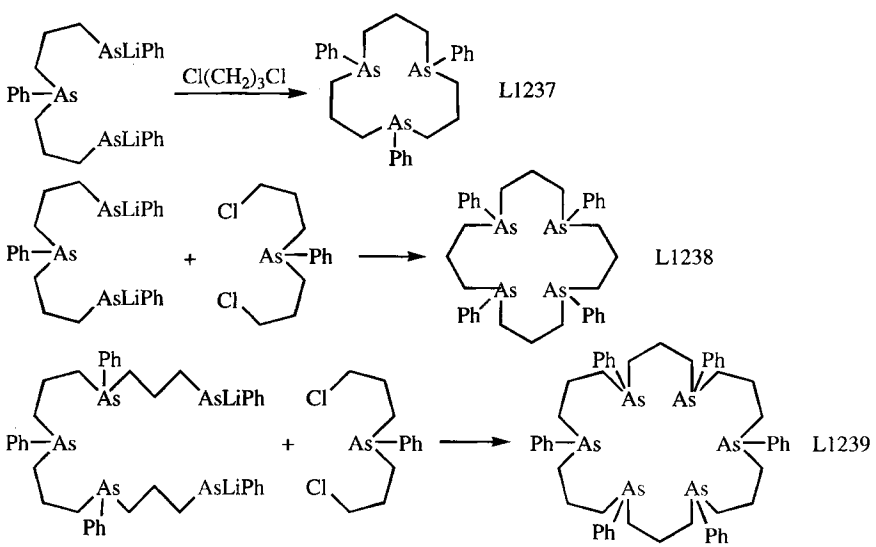


[Pt(L1235)$_2$] [Pt(L1236)]Br$_2$ (5.9)

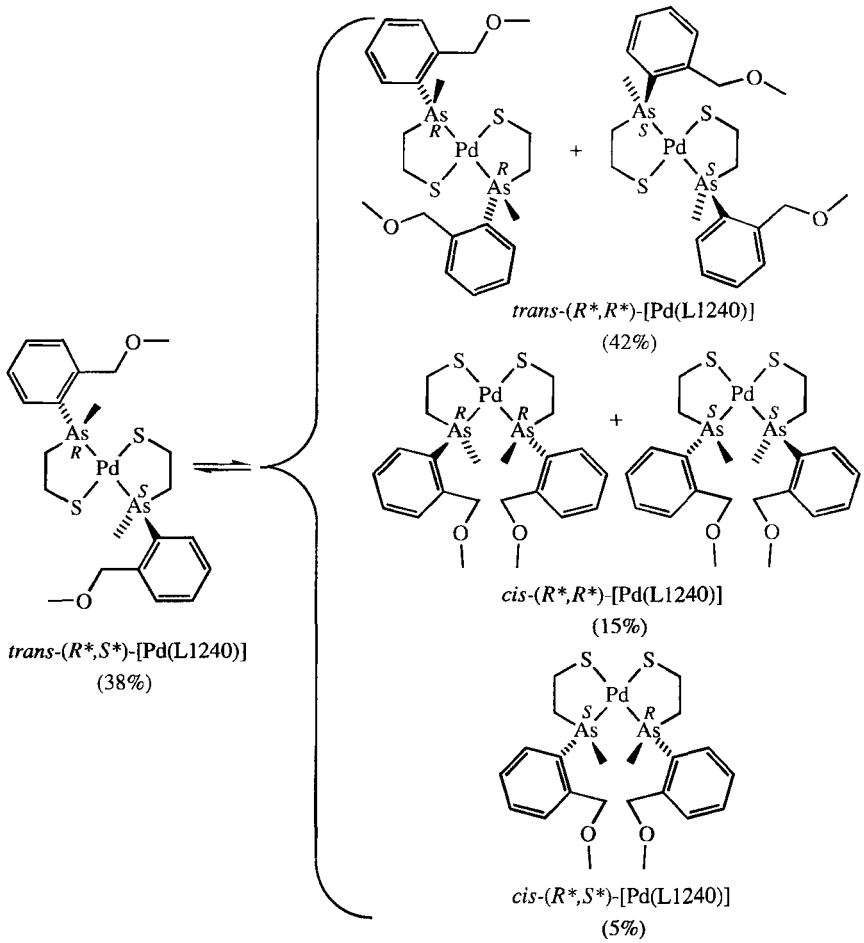
aqueous potassium cyanide, and extracting the aqueous layer with dichloromethane. The stereoisomers of the free ligand were then separated by column chromatography on silica gel with dichloromethane-*n*-hexane as eluent [21].

5.2 Arsenic

Template procedures have not been employed for synthesis of arsenic-containing macrocycles until recently. A number of compounds of this type, including L1237–L1239, were obtained by cyclisation reactions between arsenic-containing compounds and dihalogen derivatives as shown in Scheme 5-7 [22, 23].



Scheme 5-7. Non-template synthesis of polyarsamacrocycles.

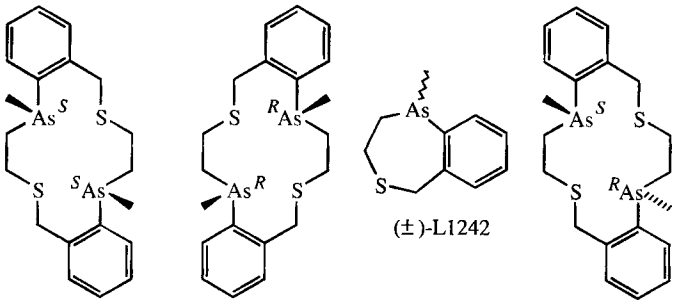


Scheme 5-8. An equilibrium mixture of four identifiable diastereomers originating from *trans*-(R^*, S^*)-[Pd(L1240)] in chloroform.

Palladium(II)-controlled synthesis of *trans*-diarsadithiamacrocycles has also been reported [24, 25]. Thus, the reaction of (±)-L1240 with $Li_2[PdCl_4]$ produces with high yield the complex *meso-trans*-(R^*, S^*)-[Pd(L1240)]. In $CHCl_3$ optically inactive *meso-trans*-(R^*, S^*)-[Pd(L1240)] gives an equilibrium mixture of four identifiable diastereomers (Scheme 5-8) [24].

When treated with boron tribromide in chloroform and subsequently with aqueous sodium hydroxide and potassium cyanide to achieve demetallation, this complex mixture afforded a racemic *trans* As_2S_2 macrocycle (R^*, R^*)-L1241 in 50% yield, together with 38% of (±)-L1242 (Eq. 5.10).

The synthesis is stereospecific. The *meso-trans*-As_2S_2 macrocycle (R^*, S^*)-L1241 was not formed, despite the presence of the corresponding diastereomer *trans*-



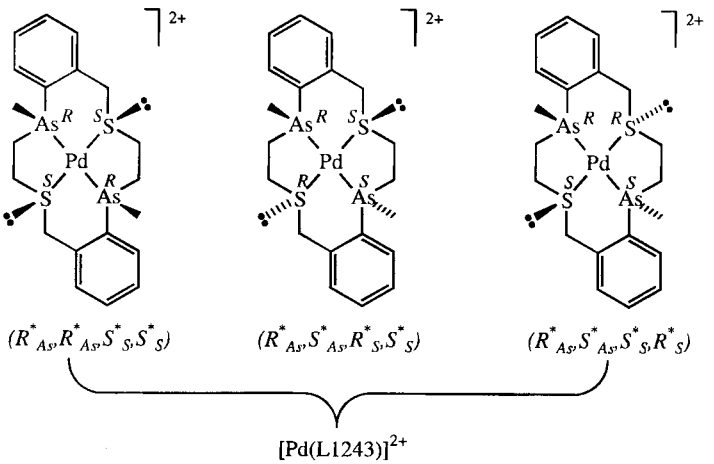
(5.10)

(R^*, S^*)-[Pd(L1240)] in the starting mixture. The structure of this compound, determined by X-ray diffraction, showed [26] the reactive centres to be unfavourably positioned for cyclisation. Generation of the complex containing two As centres of the same chirality, by inversion of one stereogenic centre, would bring the thiolate lone pairs closer to the reactive methylene groups. The only suitable precursor for building up *trans*-(R^*, R^*)-L1241 appears to be *trans*-(R^*, R^*)-[Pd(L1240)]. All other diastereomers present in the starting equilibrium mixture are presumably responsible for the formation of (±)-L1242. The higher yield of the final macrocyclic product (50%) than expected (42%) might be explained by the additional supply of the appropriate precursor, by shifting the equilibrium toward the species consumed in the template reaction. Detailed kinetic studies could clarify this point.

Racemization of *trans*-(R^*, R^*)-L1241, which took place in the presence of halo acids, permitted the isolation of *meso-trans*-(R^*, S^*)-L1241. Thus, a solution of *trans*-(R^*, R^*)-L1241 treated with HCl is converted into an almost equimolar mixture of diastereomers *trans*-(R^*, R^*)-L1241 and *meso-trans*-(R^*, S^*)-L1241. The less soluble *meso* diastereomer is readily separated by crystallisation.

X-Ray crystallographic data for palladium(II) complexes with *trans*-(R^*, R^*)-L1241 and *meso-trans*-(R^*, S^*)-L1241 prepared by direct complexation reactions showed the former complex to contain the $(R^*_{As}, R^*_{As}, S^*_S, S^*_S,)$-$[Pd(L1243)]^{2+}$ cation. However, the latter complex is not stereoselective with respect to the coordination of the prochiral thioether-sulphur donors, and consists of an equimolar mixture of centrosymmetric $(R^*_{As}, S^*_{As}, R^*_S, S^*_S)$-$[Pd(L1243)]^{2+}$ and $(R^*_{As}, S^*_{As}, S^*_S, R^*_S)$-$[Pd(L1243)]^{2+}$ (Eq. 5.11).

It is noteworthy that the arrangement of the methyl substituents and lone pairs on one side of the square plane of the coordinated macrocycle causes the displacement of palladium(II) from this plane of the donor atoms. This enables the palladium atom to assume normal distances to the arsenic atoms (23.9 nm) and to the sulphur atoms (23.1 nm). The corresponding bonds in the centrosymmetric palladium diastereomers are somewhat compressed (Pd–As = 23.6 nm, Pd–S = 22.8 nm) [26], suggesting that template construction of the *meso* macrocycle may be inhibited by the non-ideal fit of the macrocycle cavity to the size of the palladium(II).



(5.11)

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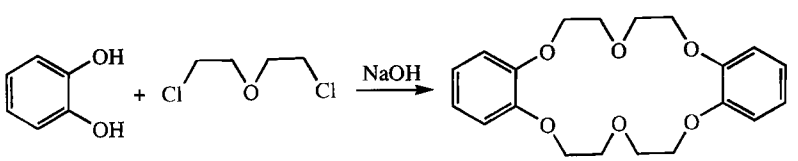
Chapter 6

Crown ethers and related compounds

6.1 Crown ethers

These cyclic polyethers were called crown ethers by their discoverers [1, 2] because of their resemblance to real crowns and their ability to 'crown' cations upon complex formation. They are often prepared by Williamson's reaction, by direct cyclisation of glycols with dialkylating agents under moderate or high dilution conditions to suppress linear polymerisation [3–8]. The serendipitious discovery of crown ethers by Pedersen arose from a manifestation of the template effect by alkali metal ions, although the possible template role of metal ions on the assembly of these macrocyclic substances was not initially apparent. The first crown ether, dibenzo-18-crown-6 (L1244), was isolated by Pedersen as a byproduct of the synthesis of bis[2-(*o*-hydroxyphenoxy)ethyl]ether from bis(2-chloroethyl)ether and the sodium salt of 2-(*o*-hydroxyphenoxy)tetrahydropyran slightly contaminated with catechol [2]. Reaction of pure catechol with bis(2-chloroethyl)ether in the presence of NaOH in 1-butanol gave the dibenzo-18-crown-6 in 44–48% yield (Eq. 6.1) [1].

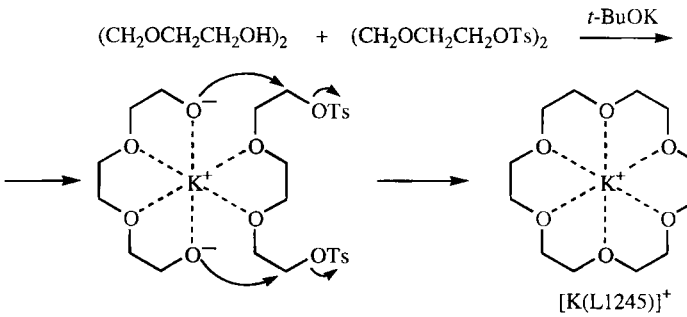


(6.1)

L1244

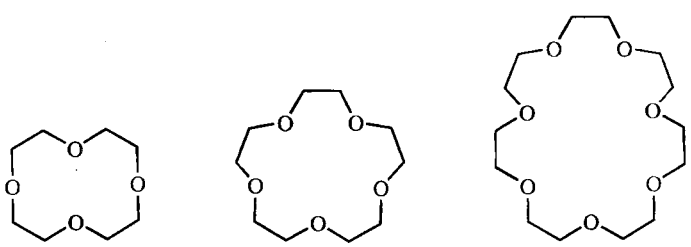
The template properties of the potassium ion are demonstrated in the synthesis of 18-crown-6 (L1245) (yield 75–84%; Eq. 6.2) [9]. In this case the coordinating role of the metal ion is to promote the appropriate orientation of the starting species in such a way that the corresponding functional groups are able to interact favourably with each other yielding a macroring. The isolation of metal-free L1245 was carried out by high vacuum distillation of the reaction products or by column chromatography. Macrocyclisation proceeds only to a small extent in the presence of tetra-*n*-

butylammonium hydroxide, the size of whose cation considerably exceeds the cavity size of L1245; the majority of starting ligsons are converted into polymeric products. A number of subsequent reports [10–53] highlighted the template effect of the other alkali metal ions, as well as of alkaline earth metal ions, in the synthesis of various crown ethers.



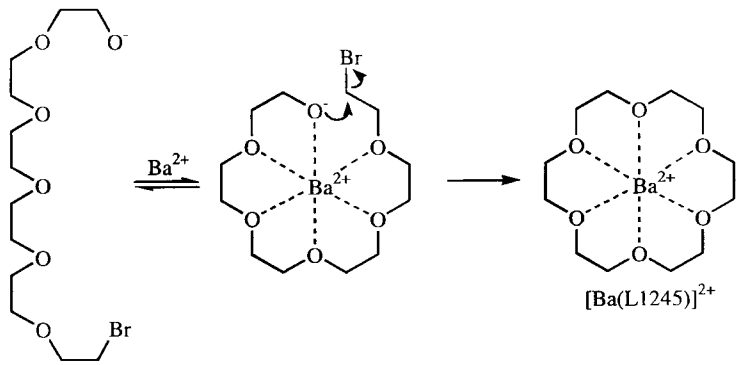
(6.2)

The notable features of the template synthesis of crown ethers are the preparation of target products without using high-dilution techniques and the better yields of macrocycles obtained. The possibility of performing template syntheses of crown ethers in concentrated solutions arises from the presence of the corresponding cations. The course of the reaction is determined by both an increase in cyclisation rate for the starting ligsons and by considerable suppression of polymerisation [10]. There is a strong connection between template ion size and yield of the required cyclic product. The best matrices for the synthesis of 12-crown-4 (L1246), 15-crown-5 (L1247), 18-crown-6 (L1245) and 21-crown-7 (L1248) are lithium(I) [11, 12], sodium(I) [12–14], potassium(I) [9, 12, 14, 15] and caesium(I) [7], respectively. In these cases the sizes of the template and the macrocyclic compound assembled are matched (Eq. 6.3).



(6.3)

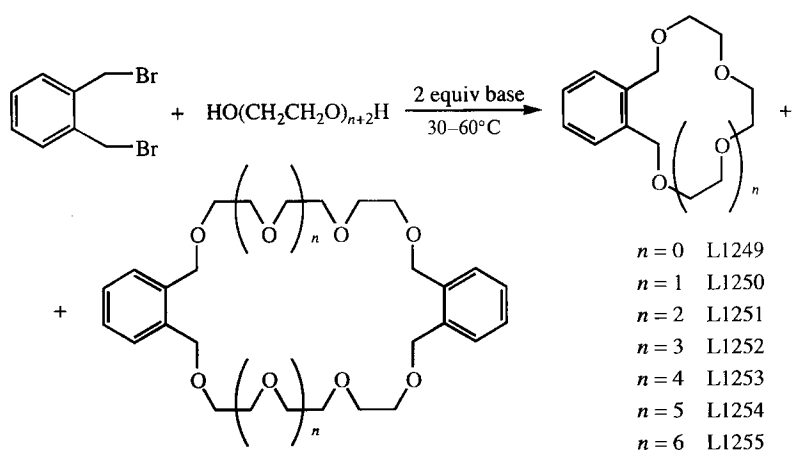
An analogous picture is observed in the case of the alkaline earth metals [7]. For example, Ba^{2+}, of the same radius as K^+, is the most suitable for the synthesis of L1245 (Eq. 6.4) [16].



(6.4)

Ions of diameter significantly smaller than that of the corresponding macrocyclic cavity are not effective for construction of the compounds of interest [12, 17]. However, these products can be synthesised in reasonable yield by using cations larger than the corresponding cavity size [12, 18–20]. The effectiveness of cations in assembling macrocycles is in one to one correspondence with their ability to form complexes with crown ethers, including those with a cavity size smaller than the metal ion diameter.

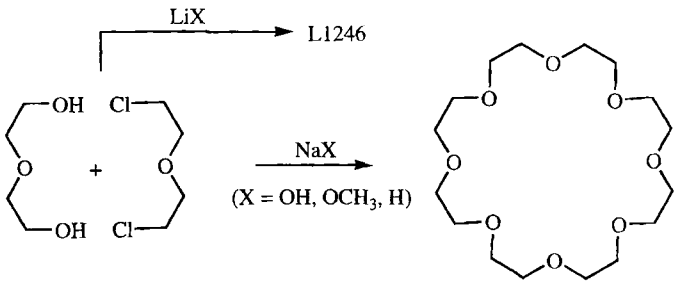
The dependence of yield on template has been established [10, 19–31] by examining benzocrown ethers. In particular, the reaction of 1,2-bis(bromomethyl)benzene with polyethylene glycols proceeds via (1 + 1) or (2 + 2) pathways depending upon the number of CH_2CH_2O units in the *n*-polyethylene glycol chain and the nature of the matrix [19, 21]. (In addition to the main products a small amount of unidentifiable polymers is produced.) For instance, the formation of dimer L1256 is most favourable at $n = 0$, whereas the yield of L1249 is negligible (Eq. 6.5).



(6.5)

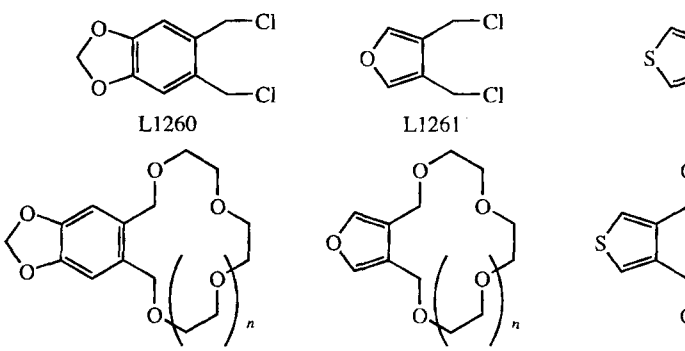
In this case sodium(I) is the most effective for the synthesis of L1251, but potassium(I) provides the highest yield of L1252, L1253, L1256 and L1257.

Lithium(I) is the best template for the synthesis of L1246, and sodium(I) in preparation of 24-crown-8 (L1259) for the reasons discussed above, although the same ligsons are involved as starting building blocks in the reaction (Eq. 6.6) [12].



(6.6)

Reacting L1260, L1261 or L1262 with disodium polyethylene glycolates yielded the corresponding (1 + 1) crown ethers L1263–L1277 and the corresponding (2 + 2) cyclic products in the case of L1261 and L1262 ($n = 0, 1, 2$), similar in composition to L1256–L1258 (Eq. 6.7) [19]. The dependence of the product formed upon the template used is also observed for these compounds. In the template synthesis of crown ethers the polyether ring is able to wrap itself around a metal ion in a folded conformation that can promote the construction of systems of size exceeding the geometrical parameters of the matrix [19].

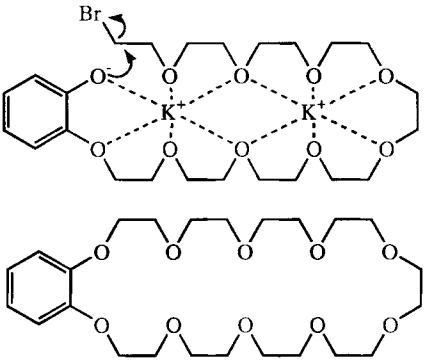


(6.7)

L1260	L1261	L1262
$n = 2$ L1263	$n = 0$ L1265	$n = 0$ L1271
$n = 3$ L1264	$n = 1$ L1266	$n = 1$ L1272
	$n = 2$ L1267	$n = 2$ L1273
	$n = 3$ L1268	$n = 3$ L1274
	$n = 4$ L1269	$n = 4$ L1275
	$n = 5$ L1270	$n = 5$ L1276
		$n = 6$ L1277

When considering the template-macrocycle match it is necessary to consider some unexpected cases, where crown ethers are formed having a cavity size that exceeds

the template size by two or more times. For example, the potassium-promoted synthesis of benzo-30-crown-10 (L1279) [27], starting from the ligson HL1278, can readily be explained by the formation of the macrocyclic compound through a step where a 'premacrocyclic' precursor is assembled topologically by two metal ions (Eq. 6.8).

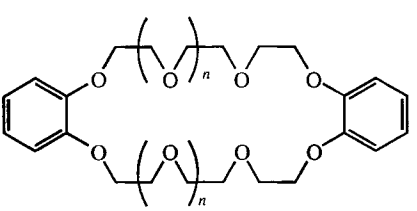


$[K_2L1278]^+$

L1279

(6.8)

The possibility of assembling such an intermediate follows from the fact that complexes of 2:1 composition are known for some crown ethers in solution [32], and the complexes of benzo-30-crown-10 (L1279) and of dibenzo-24-crown-8 (L1067; Eq. 6.9) containing two potassium or sodium atoms have been isolated in the solid state [33–35]. The structure of $[Na_2(L1067)]^{2+}$, showing that the macrocyclic ligand uses four oxygen atoms for coordination to each sodium atom, has been described [35]. The analogous situation arises, for example, when 48-crown-16 is assembled from $1,2\text{-}HOC_6H_4\text{–}(OCH_2CH_2)_{15}Br$ on alkali metal ion matrices [23, 27]. The formation of an open-chain precursor to 24-crown-8, composed of ligsons bonded to two metal ions, cannot be ignored in the synthesis of L1259 on a sodium ion matrix [12]. Evidence exists [32] for such an assumption in that NMR spectroscopy has shown that dibenzo-30-crown-10 (L1068), containing only two oxygens more than L1259, forms the complexes $Na(L1068)^+$ and $Na_2(L1068)^{2+}$ in solution. In the solid state, dinuclear species $Na_2(L1068)I_2$ and $Na_2(L1068)(NCS)_2$ were isolated.

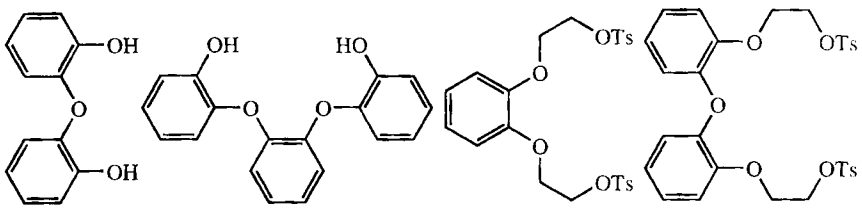


$n = 1$ L1067
$n = 2$ L1068

(6.9)

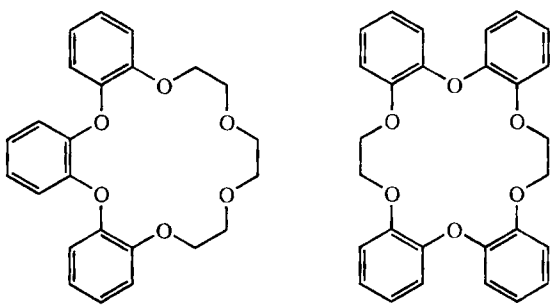
Using Cs_2CO_3 as the template source permitted the assembly of L1284 from L1281 and L1282, as well as of L1285 from L1280 and L1283 (Eq. 6.10) [29].

As a rule, equimolar quantities of ligsons are used in the synthesis of crown ethers. However, it has been shown [19, 21, 36] (in the case of L1286) that varia-



L1280 L1281 L1282 L1283

(6.10)

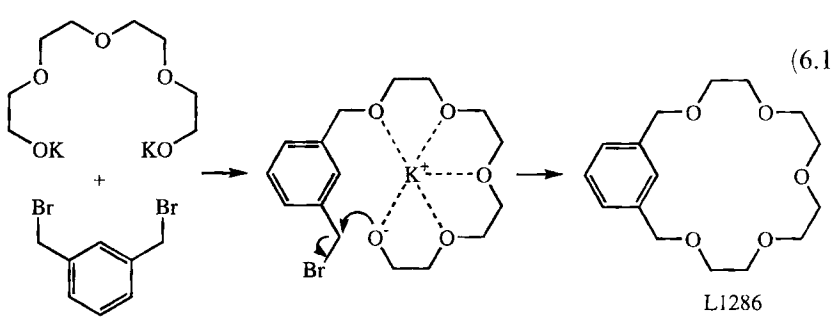


L1284 L1285

tions over a wide range in the period of addition of dibromide to potassium tetraethylene glycolate have no significant effect on the yield of L1286. This suggests that in the second step of the reaction intramolecular substitution of the second bromine atom, resulting in ring closure, goes much faster than the competing intermolecular substitution leading to polymerisation. The difference between the rates of the two competing types of solvolysis must be determined by a greater entropy contribution to the intermediate state for the intramolecular process which, in turn, must result from the formation of a more developed conformation in the first step of the synthesis due to the coordination of the polyether chain to the potassium ion. However, the reduction of nucleophilic ability attributable to the terminal alkoxide group of the polyethylene glycol, due to the formation of a charge-separated ion pair in an intermediate complex, provides an opposing effect resulting in inhibition of the reaction (Eq. 6.11) [10, 25, 26].

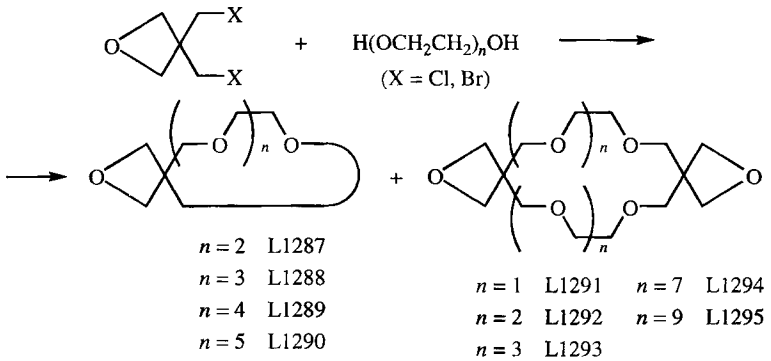
The use of 3,3′-bis(chloro- or bromomethyl)oxetane and polyethylene glycols as ligsons allows the assembling of crown ethers containing spirooxetane units on

(6.11)



L1286

sodium(I) and potassium(I) matrices. The synthesis results in 1 + 1 (L1287–L1290) and 2 + 2 (L1291–L1295) macrocyclic products (Eq. 6.12) [37].



(6.12)

$n = 2$ L1287
$n = 3$ L1288
$n = 4$ L1289
$n = 5$ L1290

$n = 1$ L1291 $n = 7$ L1294
$n = 2$ L1292 $n = 9$ L1295
$n = 3$ L1293

The nature of the template has an effect on the yield of final products. For example, the yield of L1289 is higher when NaOH is used, and potassium *tert*-butoxide proves to be effective for the production of L1290, as it is in the synthesis of L1292. Apart from the compounds indicated, L1294 and L1295 are also produced using potassium *tert*-butoxide for the matrix. Yields fall along the series L1290, L1294 and L1295 as 60%, 35% and 24% [37].

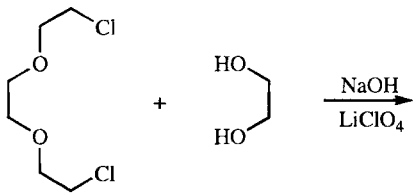
A number of reports [10, 17, 22, 25–27] suggest that, in the case of condensation between aromatic diols and polyethylene glycols, the nature of the template exerts an influence on the rate of macrocyclisation. The templates form various series depending on the size of the synthesised crown ether, but lithium ion is an inhibitor in all cases. This must be attributed to the fact that Li^+ forms the most stable ion pair with phenolate and simultaneously gives the least stable complexes with benzo crown ethers. It should be noted that alkaline earth metal ions, even in small concentrations, promote these reaction more effectively than alkali metal ions. In addition, it has been emphasised [12] that there is a definite correlation between the basicity of the substance used in the template synthesis of macrocyclic polyethers and the yield of final product.

A number of authors have established [12, 17, 21, 26, 38–41] that the caesium cation is exceptionally effective in the synthesis of crown ethers in such solvents as tetrahydrofuran, dimethylformamide and acetonitrile. Caesium(I) is not only suited to make products of various ring sizes, but also gives good yields (80–90%). These properties follow from the fact that Cs^+ has the largest size, the lowest surface charge density, and the highest polarisability in the series of alkali metal ions, and that the caesium compounds used in these reactions (carbonates, fluorides) have the highest solubility. These features must result in a high template concentration in solution, a higher state of dissociation into solvated cations and 'free' anions, which in turn must possess maximum reactivity and result in a higher yield [38].

The effectiveness of template ions under otherwise equal conditions depends on the solubility of the compound containing the template, which determines the concentration of the template in the reaction mixture. The synthesis of crown ethers is generally carried out in water, primary alcohols, dimethyl sulphoxide, dioxan, acetonitrile or toluene, which dissolve the hydroxides, *tert*-butoxides and hydrides used

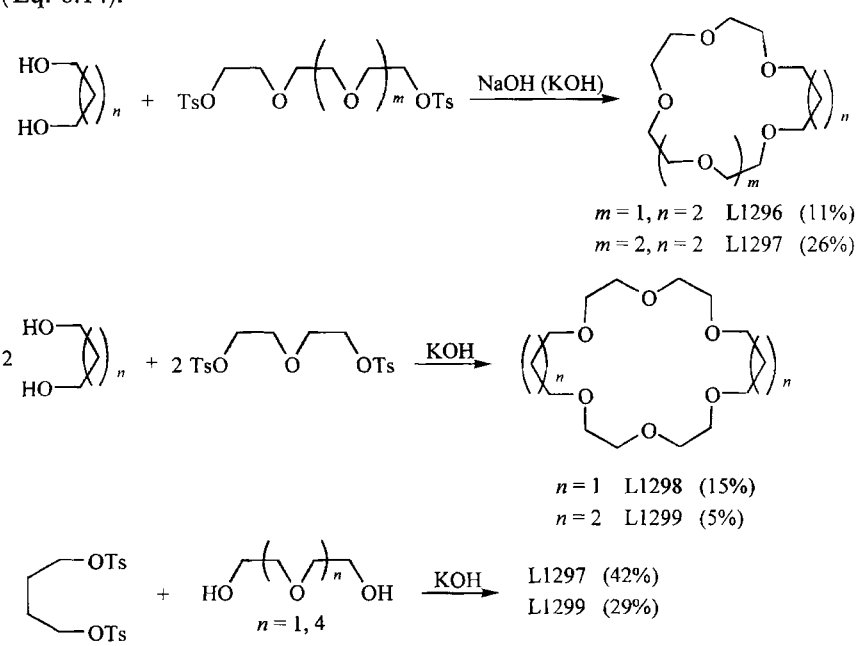
as matrix sources. If it is necessary to increase the solubility of a given reagent, phase-transfer catalysis can be applied in a number of cases by using a series of crown ethers as phase-transfer agents [42, 43].

The solvent plays a definite role in the synthesis of crown ethers [12, 26, 44]. In particular, synthesis of L1246 involving ethylene glycol and 1,8-dichloro-3,6-dioxaoctane occurs smoothly in DMSO and fails in THF (Eq. 6.13). In the case of polar solvents solvation processes must be of great importance. These processes are responsible for at least the enthalpy contribution to the total template effect [26].

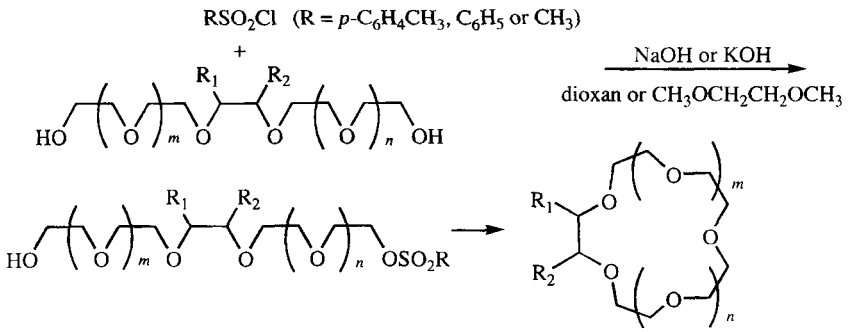


(6.13)

The yield of crown ether depends to a great extent upon the nature of the ligson and nature of its functionalities. For example, the use of tosylates of polyethylene glycols commonly gives higher yields than the use of the corresponding chlorides as starting reagents [26, 27, 45]. This can be attributed to the weaker nucleophilic ability of tosyl groups than of chloride ions, and their facile elimination in the course of cyclisation. In addition, tosylates stabilise premacrocyclic complexes better [5]. The yield of macrocyclic compound may be influenced even by the nature of the reagent involved in the form of the corresponding derivative [19, 46]. Crown ethers L1296 to L1299 can be synthesised in low yield by reaction of α, ω-glycols with polyethylene glycol ditosylates in THF in the presence of NaOH or KOH (Eq. 6.14).



(6.14)

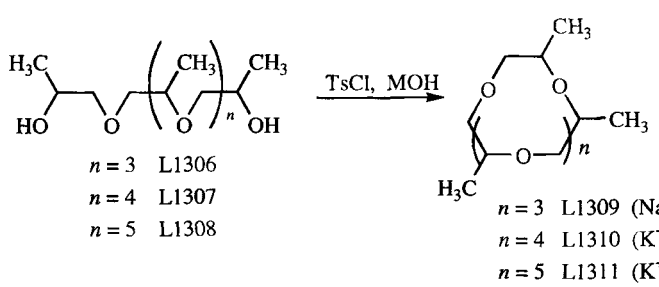


Scheme 6-1. Template synthesis of crown ethers L1300–L1305.

Yields become much better if the α, ω-glycols are added as their ditosylates. A variety of crown ethers (symmetrical and less symmetrical) can be synthesised by changing the number of methylene units between two adjacent oxygen atoms of the ligsons involved in the template reaction [46, 47].

Substituted and unsubstituted crown ethers L1300–L1305 were prepared in good yields by treating the corresponding polyethylene glycols with sulphonyl chlorides in the presence of alkali metal hydroxides (NaOH, KOH), the metal ion acting as the template [48] (Scheme 6-1).

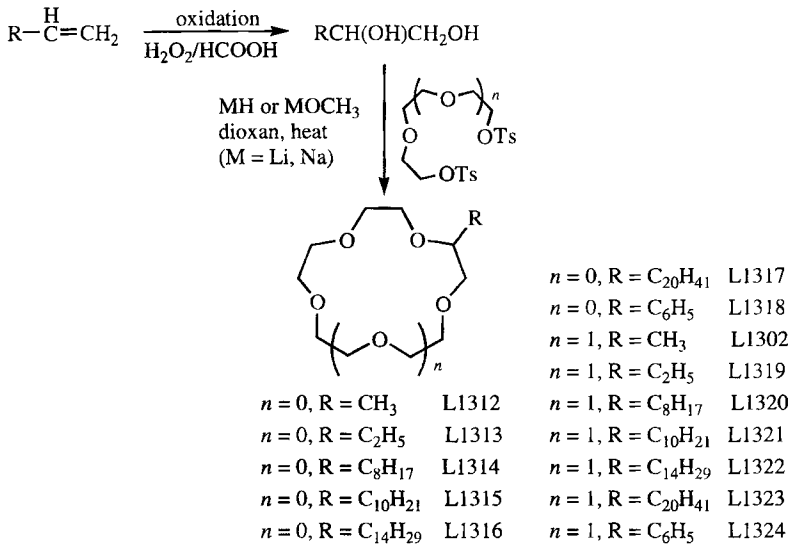
Potassium(I) is the best template for constructing L1301 and L1303. The crown ether L1304 is a macrocycle with a pendant arm. Analogously L1309–L1311 were prepared from L1306–L1308, respectively, as starting ligsons (Eq. 6.15) [49].



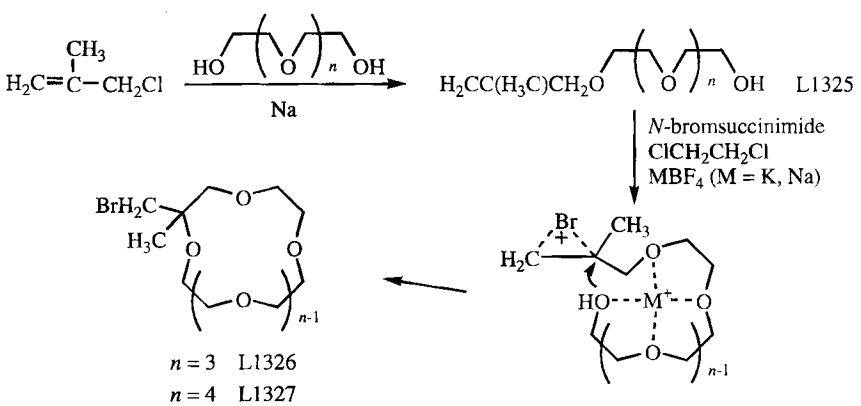
(6.15)

Crown ethers L1302 and L1312 to L1324 have been synthesised according to Scheme 6-2 [50].

Substituted 12-crown-4 and 15-crown-5 ethers were obtained by using Li^+ and Na^+ as templates, respectively.



Scheme 6-2. Synthesis of substituted crown ethers L1302 and L1312–L1324.



Scheme 6-3. Template synthesis of 2-bromomethyl-2-methyl crown ethers.

The synthesis of the crown ethers L1326 and L1327 was performed by intramolecular bromoalkoxylation of the oligoethylene glycol mono-2-methylallyl ether L1325 (Scheme 6-3) [51]. It should be noted that temperature control is paramount for the success of this reaction. If it is higher than 50°C substantial amounts of side products are formed, whereas at lower temperatures the reaction is slow. The presence of a template ion is also necessary for good results. Potassium(I) proved

superior to sodium(I) in the synthesis of L1326, whereas L1327 is isolated when using Na^+ as template [51].

Through the heterogenous reaction of polyethylene glycols with tosyl chloride and KOH in dioxan, not only can the coronands from 12-crown-4 to 24-crown-8 be obtained but also some higher homologues up to about 60-crown-20. A systematic investigation has shown that:

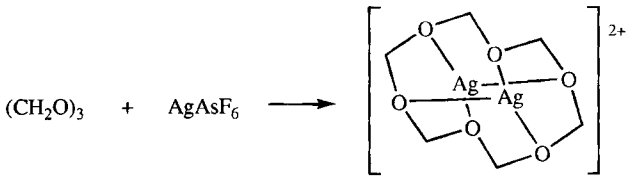
- 27-crown-9 and 30-crown-10 can be formed from nona- and deca-ethylene glycol, respectively, and isolated in pure form;
- the whole series of polyethylene glycols from tri- to deca-ethylene glycol yields not only the corresponding crown ethers but also higher cyclooligomers – in particular, 36-crown-12 and 48-crown-16 were obtained from tetraethylene glycol [52].

For the formation of relatively small rings K^+ is assumed to act as template, whereas for higher oligomers it is probable that more than one cation enters the cavity of the cyclic transition state [52]. Supporting kinetic evidence has been reported [53], where the formation of 21- to 30-membered benzo crown ethers has been monitored at varying concentrations of $KClO_4$ in dioxan:DMSO 2:1 as solvent. Further evidence has been obtained from the analysis of the yields of unsubstituted crown ethers prepared under very similar conditions from polyethylene glycols and *p*-toluenesulphonyl chloride in the presence of NaOH, KOH or CsOH. It suggests that the template effect of two cations depends on spatial fit requirements and favours the formation of 27-crown-9 and 30-crown-10 in the presence of K^+, and of 24-crown-8 in the presence of Na^+ [53].

Apart from the ligsons listed above, simpler building blocks, for example ethylene oxide [15] or paraformaldehyde [54], can be used as starting materials for obtaining crown ethers. Thus L1246–L1248 are produced by using ethylene oxide and various template agents [15]. The course of the reaction is directed by using alkali, alkaline earth and other metal (Ag, Hg, Ni, Cu, Zn) fluoroborates, fluorophosphates and fluoroantimonates in the presence of BF_3 as a catalyst. The process is carried out in dioxan, benzene or methylene chloride. Crown ethers are obtained as the corresponding salts and can be isolated in the metal-free state by pyrolysis under low pressure. Some dioxan (the product of dimerisation of ethylene oxide) is formed among other byproducts.

The cation template effect includes both the promotion of the assembly of the growing chain around the template before cyclisation and protection against degradation to dioxan. The positive charge on the cation prevents the formation of the oxonium salt which is the precursor for dioxan formation. Experiments on deuterated dioxan showed involvement of the latter in the formation of the assembled chain; consequently the equilibrium was effectively shifted to formation of complexed rings [15].

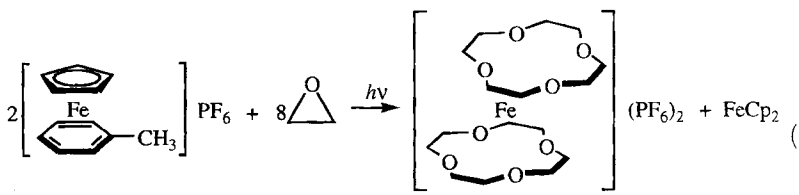
Product L1328 has been built by condensation of $(CH_2O)_3$ on a silver(I) matrix provided by $AgAsF_6$. X-Ray diffraction of the complex $[Ag_2(L1328)](AsF_6)_2$ showed that each of two silver ions is bound to three of the six oxygens of the macrocyclic ligand in an alternating manner (Eq. 6.16) [54].



(6.16)

$[Ag_2(L1328)]^{2+}$

Light-induced polymerisation of ethylene oxide in the presence of organometallic derivatives of iron(II) yielded 12-crown-4 in the form of an iron(II) complex (Eq. 6.17) [55].

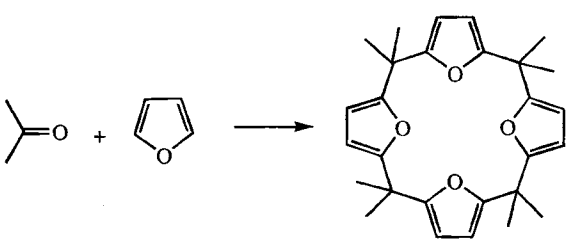


(6.17)

$[Fe(L1246)_2](PF_6)_2$

Demetallation is easily achieved by addition of 2,2′-bipyridine (bipy) to the solution of the complex produced to give the chelate $[Fe(bipy)_3](PF_6)_2$ with the liberation of metal-free crown ether. Note that a small amount of 15-crown-5 has also been detected. An X-ray diffraction study of $[Fe(L1246)_2]^{2+}$ showed a sandwich arrangement of crown ether ligand products about the metal ion. The coordination polyhedron of iron(II) approximates to a cube, with oxygen atoms being positioned at its corners.

The use of acetone and furan as building blocks permits the template synthesis of L1329 (Eq. 6.18) [56–59].

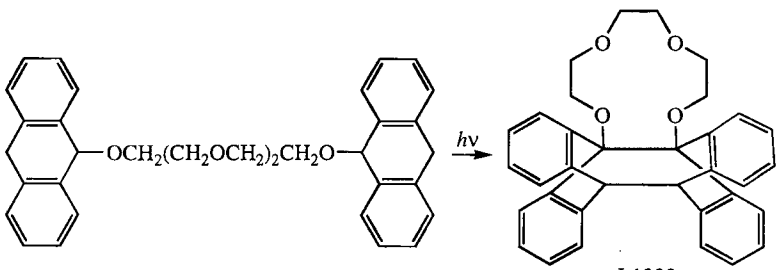


(6.18)

This cyclic polyether is formed in low yield by reaction of the corresponding ligsons in acidic medium, together with polymeric materials (main product of the reaction). However, the yield of L1329 is higher in the presence of alkali and other metal ions. The relationship between yield and pH has also been studied. It has been found [56] that, in the absence of metal ions, 35% yield of L1329 is possible by optimising the acid concentration. This yield is equivalent to the best obtainable on a cation when, for instance, $LiClO_4$ is employed. In addition, several transi-

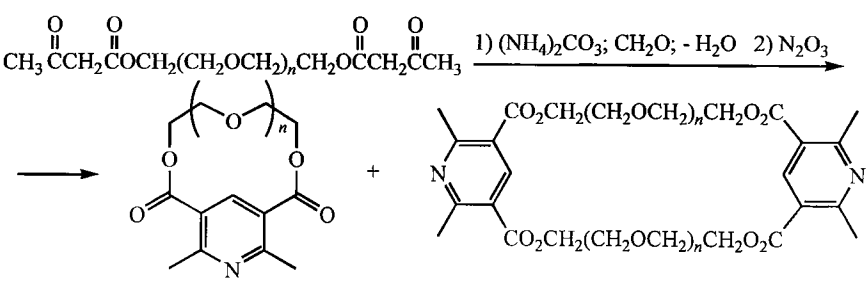
tion metal (Cr, Mn, Co, Ni, Cu) salts, which are known to have greater affinity for nitrogen-containing ligands, are more effective in L1329 synthesis than alkali metal cations, except Li^+ [56, 59]. All these data indicate that the role of metal ions in promotion of this synthesis is not as simple as seemed initially. In particular, it can be assumed that an increase in pH must favour the protonation of the acetone carbonyl group and increase its reactivity [56]. Tetramers analogous to L1329 are also obtained on condensation of furan with other ketones (butan-2-one, pentan-2-one, pentan-3-one, octan-2-one, nonan-2-one, undecan-2-one). The reactions are carried out in acidic medium. In the presence of $LiClO_4$, the yield appears to be 4–18 times higher [56].

An unusual reaction results from photochemical macrocyclisation of bis-anthracene linked by a polyether chain on a lithium cation matrix to form L1330 (Eq. 6.19). Ring closure is probably successful as the final conformation appears to be locked by the cation [60].



L1330 (6.19)

The examples reported above indicate that alkali and alkaline earth metal ions are usually the most effective in the synthesis of crown ethers. However, in some cases transition metal [15, 54, 56, 58], thallium(I) [12, 13] or ammonium [61–63] ions are suitable templates. In particular, assembly of the crown ethers L1331 and L1332 has been carried out by reaction in water of the corresponding bis(acetoacetic esters) $CH_3COCH_2CO_2CH_2(CH_2OCH_2)_nCH_2O_2CCH_2COCH_3$ with formaldehyde and a large excess of $(NH_4)_2CO_3$ as ammonia source, buffer and template agent, followed by oxidation with N_2O_3 (Eq. 6.20) [62, 63].



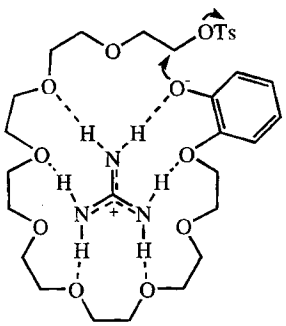
(6.20)

$n = 2$ L1331
$n = 3$ L1332

$n = 0$ L1333 $n = 2$ L1335
$n = 1$ L1334 $n = 3$ L1336

Several L1331 and L1332-type crown ether bis-lactones have also been synthesised by the Williamson reaction starting from 3,5-pyridinedicarboxylic acid and the corresponding dibromopolyoxaethylenes on a caesium(I) matrix [64]. It is of note that (1 + 1) condensation products are not formed for $n = 0$ or 1, probably because small sizes are extremely difficult to construct at the relatively large NH_4^+ ion. The synthesis of crown ethers produced by (2 + 2) ligson reactions is carried out not only for L1335 ($n = 2$) and L1336 ($n = 3$), but for L1333 ($n = 0$) and L1334 ($n = 1$) due to the effectiveness of the template in the favourable arrangement of acetoacetic fragments required for intramolecular ring closure [62].

The use of the guanidinium ion $[C(NH_2)_3]^+$ (HGu^+) as a template in the synthesis of benzo-27-crown-9 was mentioned in Chapter 1 [65]. In this case the topological functions of the template centre arise from an appropriate geometry, namely an open-chain precursor of the crown ether product being accommodated around the matrix in a position suitable for ring closure by hydrogen-bond formation (Eq. 6-21).



(6.21)

X-Ray crystallography [66] of the supramolecular associate of L25 with the guanidinium cation clearly established the template functions of the latter by showing that the organic cation was fully entrapped in the macrocyclic polyether cavity, and that all HGu^+ hydrogens were involved in hydrogen-bonding with oxygens of the host molecule (Figure 6-1). The N–H···O bond angle ranges from 148° to 177°. Besides the hydrogen-bonding stabilisation of the supramolecular complex, there

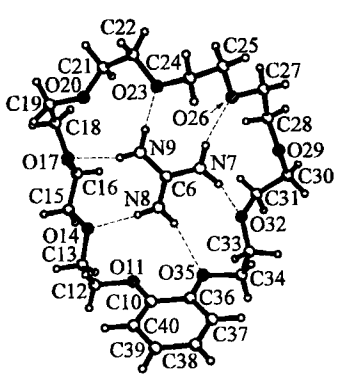


Figure 6-1. A view of one of the benzo-27-crown-9 molecules with its associated guanidinium cation.

Table 6-1. Crown ether yield as a function of template used.

Template	Glycol ditosylate	Crown ether yield (%)			
		L25	L1337	L1244	L1338
t-BuOK	octaethylene-	59			
$HN{=}C(NH_2)_2$	octaethylene-	23			
$HN{=}C\{N(CH_3)_2\}_2$	octaethylene-	2			
t-BuOK	diethylene-		5	44	20
$HN{=}C(NH_2)_2$	diethylene-		4	25	11
$HN{=}C\{N(CH_3)_2\}_2$	diethylene-		11	6	0
$[(n\text{-}Bu)_4N]OH$	diethylene-		15	23	5.5

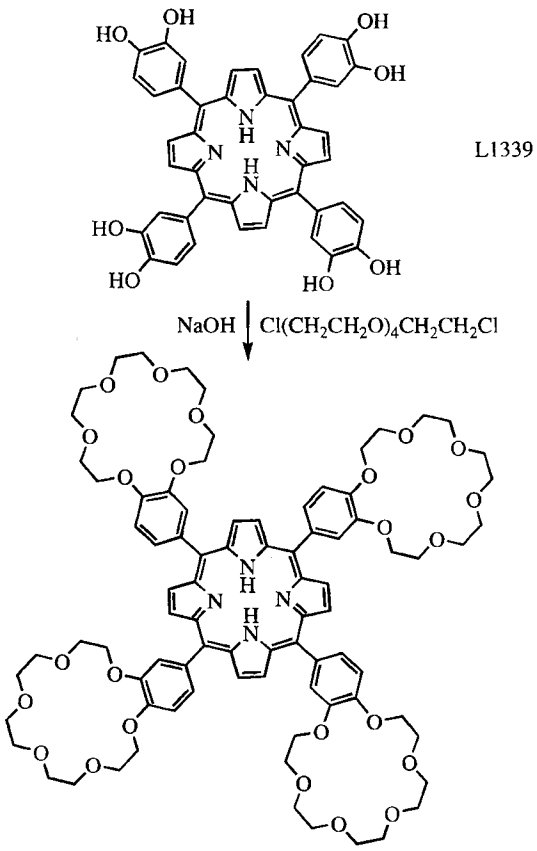
seems to be an electrostatic contribution from the three non-hydrogen-bonded crown ether oxygen atoms with the nitrogen atoms (N···O distances 29.9–31.4 nm) [66].

The results of comparative studies of the ability of guanidine, tetramethylguanidine, tetrabutylammonium hydroxide and *t*-BuOK to promote the synthesis of L25, benzo-9-crown-3 (L1337), dibenzo-18-crown-6 (L1244) and tribenzo-27-crown-9 (L1338), starting from catechol and the corresponding polyethylene glycol ditosylate, are summarised in Table 6-1. The results show that methylation of aminoguanidine makes the yield of L25 ten times lower. No doubt this must be attributed to the suppression of the template ability to form hydrogen-bonds. The guanidinium ion, and K^+, do not favour the formation of the small-ring crown ether L1337. As for the compounds L1244 and L1338, the ability of the agents used in the synthesis of the corresponding products decreases in the order K^+ > aminoguanidinium > $(n\text{-}Bu)_4N^+$ > tetramethylguanidinium. This verifies the fact that GuH^+ is preferred as a matrix for building up larger-ring-size cyclic backbones within this series of macrocyclic products. The data reported [65–67] unambiguously indicate that K^+ is more effective than GuH^+, as the former is a stronger base.

These data suggest that the range of matrices suitable for the production of macrocyclic polyethers may be much wider than that known at present, thanks to the involvement of organic-type cations.

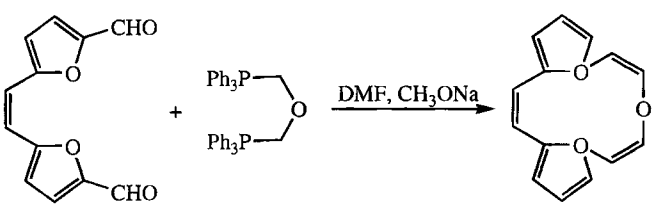
Many publications have dealt with the template synthesis of crown ethers. It has been said [68] that the matrix effect was widely revealed in the synthesis of various crown ethers, and also that the principle of matrix synthesis was extremely fruitful in crown ether chemistry and played a major role in the development of methods for the synthesis of these compounds. However, many authors have not stressed the role played by metal ions [76–80]. In our opinion, the most attractive preparation of L1340 [78] is by reaction of L1339 with $Cl(CH_2CH_2O)_4CH_2CH_2Cl$ in *n*-butanol, in the presence of NaOH (Eq. 6.22). The pentacompartmental species L1340, containing polyether and porphyrin rings, must possess a range of properties due to the different character of its macrocycles. In particular this compound forms complexes

with transition metals and with metals from Groups I and II of the Periodic Table [78].



(6.22)

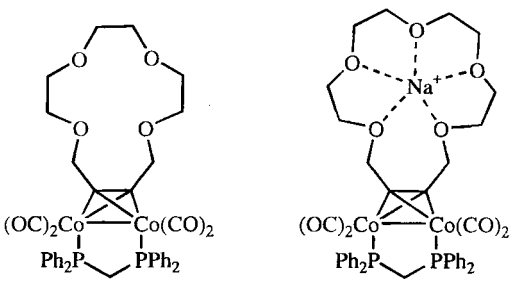
A convenient method of obtaining 18-crown-6 involves reaction of triethylene glycol and *p*-toluenesulfonyl chloride (in the molar ratio 1.0:1.0:1.1) with a mixture of potassium hydroxide and barium oxide (or potassium carbonate) [79]. The potassium complex of L1245 is produced in the reaction and then thermolysed under reduced pressure. The required product is collected in 36–46% yield. The synthesis of L1341 has been carried out on a sodium(I) matrix by the Wittig reaction (Eq. 6.23) [81, 82].



(6.23)

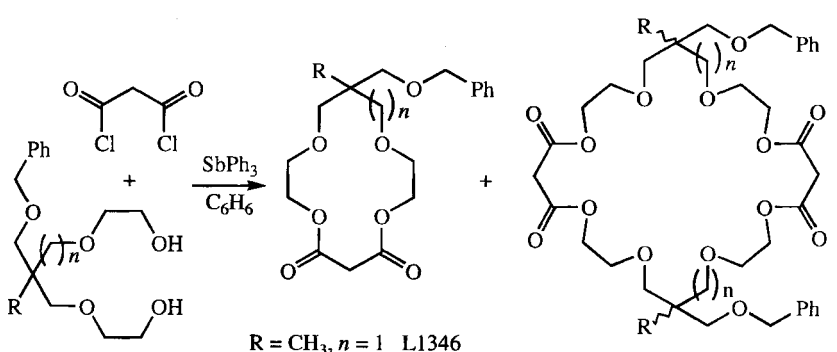
Crown ethers are excellent ligands for alkali and alkaline earth metals. As a rule, they form the most stable coordination compounds with those cations that are the best template agents for the assembly of the corresponding macrocycles.

Alkali-metal-free dicobalt complexed alkynic crown ether L1342 (Eq. 6.24) has been prepared in high yield by treatment of $[Co_2(\mu\text{-}HOCH_2C{\equiv}CCH_2OH)(\mu\text{-}Ph_2PCH_2PPh_2)(CO)_4]$ with triethylene glycol and $NaBF_4$ as template salt in the presence of $HBF_4{\cdot}Et_2O$ as catalyst in methylene chloride [83]. The analogous reaction with tetraethylene glycol yields the complex $[Na(L1343)]BF_4$. The sodium template can easily be removed by washing $[Na(L1343)]BF_4$ with deionised water.



L1342 [Na(L1343)]$^+$ (6.24)

The specific ability of antimony and bismuth compounds to interact with ether oxygen atoms [84–87] has been successfully exploited for template assembly of crown ether esters [88, 89]. Triphenyl antimony ($SbPh_3$) proved to be a suitable template for construction of (benzyloxy)methyl-substituted crown ether esters [88] as it is highly soluble in low polarity solvents, stable in water and air, and easily recoverable. Starting from the diol L1344 and malonyl chloride both 1 + 1 and 2 + 2 macrocyclic species L1346 and L1348 have been prepared in 40% and 15% yield, respectively. The diol L1345 in the same conditions gave only the 1 + 1 crown ether ester L1347 in 54% yield [88]. Compounds L1346–L1348 have also been synthesised with comparable yields under high dilution conditions (Eq. 6.25) [88].

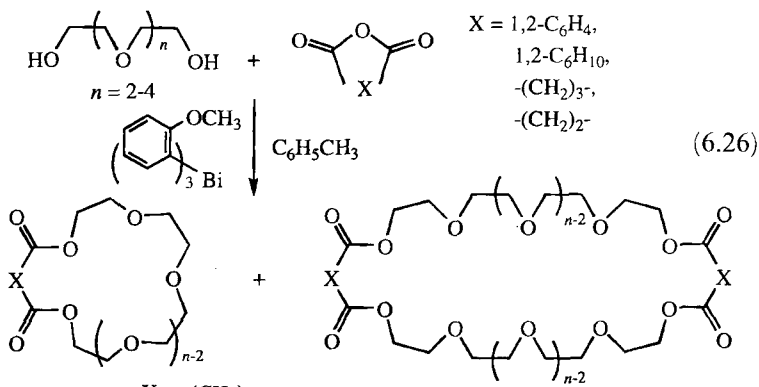


R = CH_3, n = 1 L1344
R = H, n = 0 L1345

R = CH_3, n = 1 L1346
R = H, n = 0 L1347

R = CH_3, n = 1 L1348 (6.25)

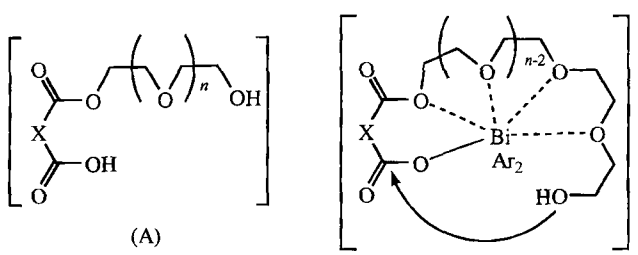
Another organometallic compound, tris(2-methoxyphenyl)-bismuthane, is a mild dehydrating agent and a good template for building up crown ether esters. Prolonged heating of the corresponding diacid anhydride with a glycol in the presence of tris(2-methoxyphenyl)-bismuthane in toluene results in the corresponding macrocyclic 1 + 1 diester (L1349–L1359) in 13–83% yield, together with a small amount of a macrocyclic 2 + 2 tetraester (L1360–L1363) (Eq. 6.26) [89].



(6.26)

	X = $-(CH_2)_3-$:	
X = 1,2-C_6H_4:	n = 2, L1354 (20%)	X = 1,2-C_6H_4:
n = 2, L1349 (18%)	n = 3, L1355 (47%)	n = 2, L1360 (13%)
n = 3, L1350 (61%)	n = 4, L1356 (83%)	n = 3, L1361 (3%)
n = 4, L1351 (13%)	X = $-(CH_2)_2-$:	X = $-(CH_2)_3-$:
X = 1,2-C_6H_{10}:	n = 2, L1357 (17%)	n = 2, L1362 (9%)
n = 3, L1352 (60%)	n = 3, L1358 (48%)	X = $-(CH_2)_2-$:
n = 4, L1353 (56%)	n = 4, L1359 (65%)	n = 2, L1363 (8%)

It is supposed that the first step is a normal reaction between diacid anhydride and glycol to form a monoester (A), which then reacts with the organobismuth compound (template) to give the complex (B), in which the terminal reactive functionalities are held in close proximity for their effective interaction (Eq. 6.27).



(A) (B)

(6.27)

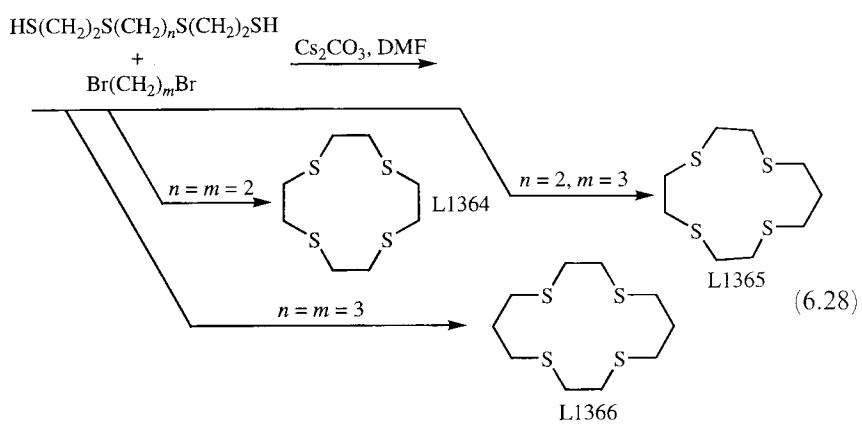
The coupling is also facilitated by organobismuth compound-mediated dehydra-

tion, which proceeds intramolecularly producing the corresponding macrocyclic diester. X-Ray crystal structures of L1354 and L1360 are available [89].

6.2 Thiacrown ethers

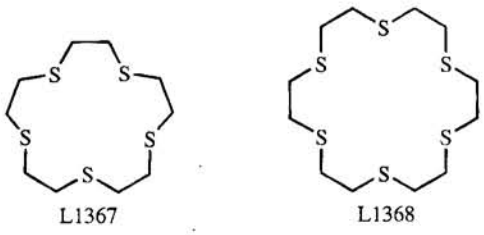
Macrocyclic compounds designed in an analogous way but containing sulphur atoms instead of oxygens form a class of substances related to crown ethers. Whereas the template effect of alkali and alkaline earth metals brings about relatively high yields of crown ethers due to their coordination to oxygen atoms of ligsons, the synthesis of thioanalogues of the latter on matrices of these elements is very much less successful or even non-effective on account of weak metal–sulphur interaction. For this reason the preparation of many thioanalogues of crown ethers has been carried out under high dilution conditions which make cyclisation favourable kinetically [90–92]. It has been also shown [61, 93–95] that a wide range of macrocyclic thioethers can be successfully prepared if caesium salts are employed.

In particular, the macrocyclic tetrathia-crown ethers L1364–L1366 have been built according to Equation (6.28) [94]. Yields of these substances obtained in the presence of Cs_2CO_3 in DMF amount to 88, 72 and 76%, respectively, and exceed those achieved by the alternative synthetic route in the presence of Na^+ by 5–10 times [96, 97].



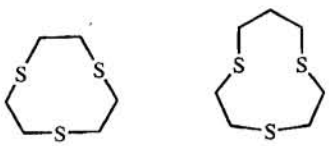
(6.28)

In a similar [94] way L1367 (yield 52%) [98] and L1368 (yield 89%) [99] were prepared in DMF through the caesium ion-assisted reaction of 2-mercaptoethyl sulphide with 3,6-dithiaoctane-1,8-diyl bis(methanesulphonate) and 1,11-dichloro-3,6,9-trithiaundecane with 3-thiapentane-1,5-dithiol, respectively (Eq. 6.29).



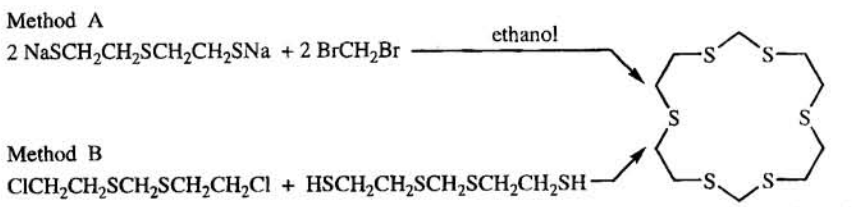
L1367 L1368 (6.29)

The simplest representative of the thiacrown ethers, 1,4,7-trithiacyclononane, L1369, was prepared by using the high-dilution technique [100], or the influx procedure, reaction of 2-mercaptoethyl sulphide with 1,2-dichloroethane in the presence of Cs_2CO_3 in DMF (yield 50%) [101]. Employing the same procedure and starting from bis(2-mercaptoethyl) sulphide and 1,3-dichloropropane L1370 (the closest analogue of L1369) was obtained in 17.7% yield (Eq. 6.30) [102].



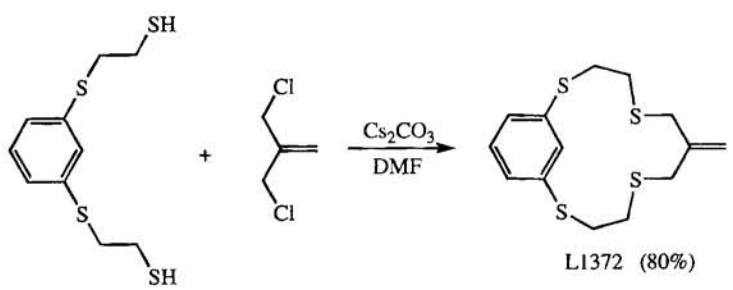
L1369 L1370 (6.30)

The thiacrown ether L1371 was synthesised (A) by the high dilution technique and (B) by using the Cs^+-assisted reaction between the corresponding ligsons in 8.4% and 62% yield, respectively (Eq. 6.31) [103].



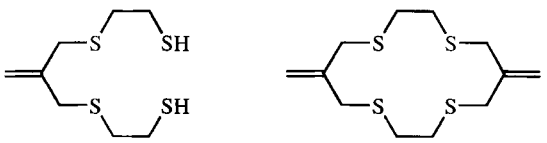
L1371 (6.31)

A further example is the synthesis of the thiacrown ether L1372, containing an isobutenyl unit in the periphery (Eq. 6.32) [104].



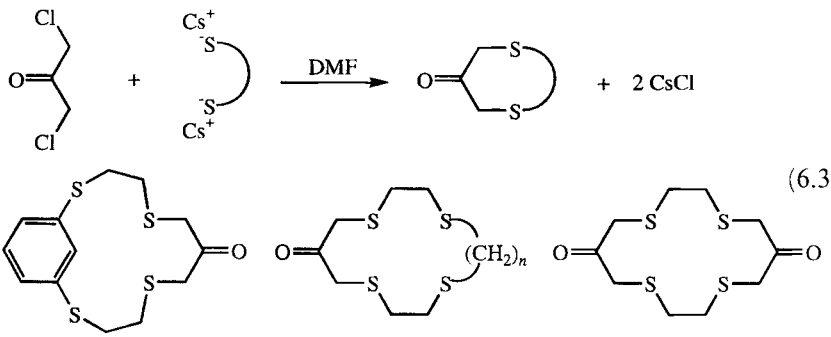
L1372 (80%) (6.32)

Analogously, starting from 1,3-dichloro-2-methylenepropane and L1373 the tetrathiacrown ether L1374 was assembled in 70% yield (Eq. 6.33) [104].

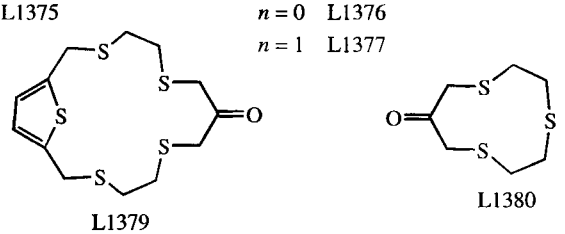


L1373 L1374 (6.33)

Thiacrown ethers L1375–L1380, containing ketone functionalities derived from 1,3-dichloroacetone and long-chain dithiolates, have been prepared in 70–80% yields (Eq. 6.34) [105].

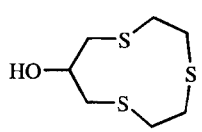


L1375 $n = 0$ L1376 $n = 1$ L1377 L1378 (6.34)



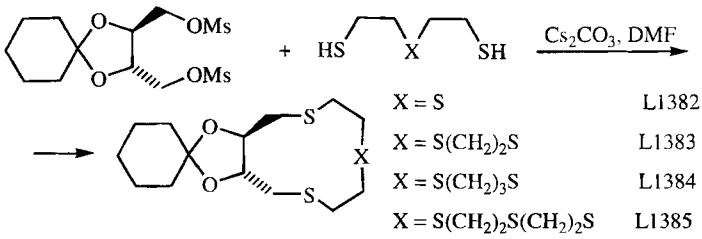
L1379 L1380

The Cs_2CO_3/DMF approach proved to be suitable for the synthesis of the functionalised thiamacrocyclic compound L1381 [106]. Bis(2-mercaptoethyl)sulphide and 1,3-dichloro-2-propanol were used as ligsons to construct L1381 (Eq. 6.35).



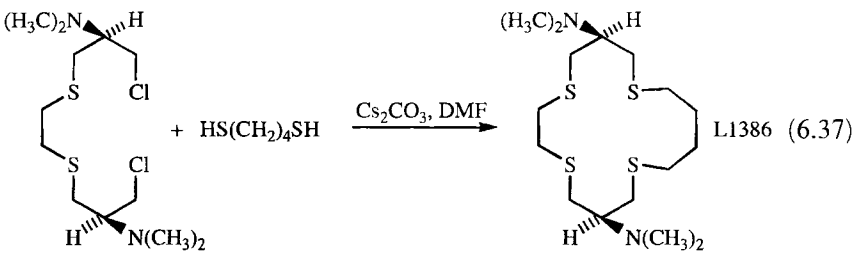
L1381 (6.35)

The synthesis of chiral thiacrown ethers L1382–L1385 in the presence of caesium carbonate in DMF has been reported (Eq. 6.36) [95].



(6.36)

Using the same base-solvent combination the chiral bis-dimethylamino-tetrathiamacrocycle L1386 has been prepared [95]. The yield of final product mixture (including the *meso* epimer L1386) is low (8%), mainly because of the lability of the starting ligson.

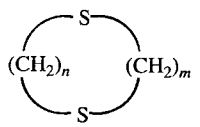


(6.37)

The usefulness of the Cs_2CO_3/DMF procedure (based on a good base-solvent combination) in the synthesis of thiacrown ethers [93–99, 101–106], *N*-tosyldiaza-cycloalkanes [107], polyazamacrocycles [108–110], macrobicyclic compounds [111, 112], crown ethers [29, 113, 114], lactones [115] and cyclophanes [107, 116, 117] is clear. The product yields are higher (often significantly) compared to reactions carried out in the presence of K_2CO_3 or Na_2CO_3, or in the absence of alkali metal ions. It should be noted, however, that this method, now widely exploited for the synthesis of various macrocyclic compounds, was firstly used for the preparation of Merrifield resins through S_N2 esterification of caesium salts of *N*-protected amino-acids with chloromethylated polystyrene [118]. The success of this approach for the synthesis of macrocyclic species focuses attention on the role of caesium salts in the promotion of these reactions.

A template role for the caesium ion cannot be ruled out in the synthesis of crown ethers [64, 119], as a polyoxyethylene chain capable of coordination to alkali metal ion was involved in ring-closure reaction. The low affinity of sulphur for alkali metal ions, however, makes the manifestation of a template effect of these metal ions in the synthesis of thiacrown compounds very much less probable, or even impossible. It has been shown, for example, that even ligsons which do not contain potential donor atoms or groups for coordination to caesium ion in their chain react effectively, yielding 1 + 1 cyclic products. For example, the reaction of $HS(CH_2)_nSH$ with $Br(CH_2)_mBr$ in the presence of Cs_2CO_3 in DMF produces thio-ethers L1387–L1390 (Eq. 6.38) [93, 94], which do not strictly fall into the category of macrocyclic compounds (from the point of view of some coordination chemists

[3]), in 63, 45, 90 and 80% yield, respectively. This result rules out any template effect of Cs^+ in these processes.



$m = n = 5$	L1387
$m = 3, n = 4$	L1388
$m = 5, n = 10$	L1389
$m = n = 10$	L1390

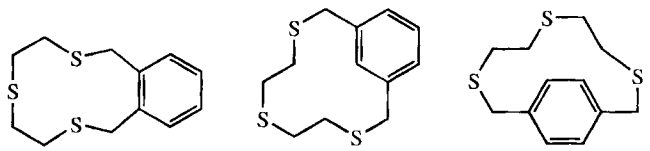
(6.38)

The use of other alkali metal carbonates is less effective. For example, yields of L1389 are 84, 48, 33 or 0% when Rb_2CO_3, K_2CO_3, Na_2CO_3 or Li_2CO_3 are used instead of Cs_2CO_3.

Different explanations of the role of the caesium ion in the synthesis of macrocyclic compounds are available [38, 120–125] and the interpretation of this phenomenon is still under discussion. Some authors [38, 120–122] are searching for the answer in the special properties of the caesium ion – the caesium ion effect – and believe that caesium promotes intramolecular versus intermolecular couplings. Another point of view [126] regards the behaviour of the caesium ion as 'a simple manifestation of well-understood physico-chemical effects' within the alkali metal family. Caesium-133 NMR evidence of weak ion-pairing of caesium propanoate in the range of concentrations from 1.5×10^{-2} to 1.0×10^{-3} mol/l in DMF has been reported [38]. The 'decrease of the extent of ion-pairing, in going from Li^+ to Cs^+, makes the reactivity of the nucleophile gradually to approach the limiting reactivity of the free ion' [126]. The higher solubility of Cs_2CO_3 compared to other alkali metal carbonates ensures a higher amount of base in solution necessary to generate the anion nucleophiles from the original acid. Both these properties contribute to a more efficient conversion of initial ligsons into final products. Kinetic investigations [127, 128] of the effect of ion pairing upon intra- and intermolecular reactions of $Br(CH_2)_{14}CO_2^-$ in DMF demonstrated that both processes are influenced equally by ion pairing. The ratio k_{intra}/k_{inter}, known as the effective molarity (EM), and has the dimensions of concentration, proved to be independent of the nature of the counterion (Et_4N^+, Cs^+ or Na^+) [127, 128]. (The EM is the ligson concentration at which the intramolecular cyclisation and intermolecular coupling (oligomerisation) proceed with equal reaction rates.) Some authors believe [126] these results to negate the opinion [38, 122] about the capacity of the caesium ion to favour intramolecular rather than intermolecular coupling. The main requirement for an intramolecular cyclisation to be favoured is a low concentration of the ligson (or ligsons). The lower the EM, the more strict is this reqiurement. The higher the EM, the more easily the cyclisation takes place [126]. A more detailed discussion of the role of caesium salts in these syntheses is available [126, 129].

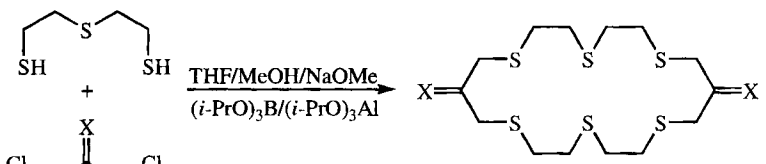
A promising route for the preparation of thiacrown ethers which are labile under the more basic conditions created by Cs_2CO_3 in DMF has recently been discovered [130, 131]. It is based on the use of boron derivatives as promoting agents in ring-closure reactions. For example, the reaction of 3-thia-1,5-pentanedithiol with 1,2-, 1,3- or 1,4-bis(bromomethyl)benzene in the presence of $B(OH)_3$ and NaOMe in methanol yielded 1 + 1 S_3-cyclophanes (L1391–L1393) in high yield (50–85%) (Eq.

6-39) [130]. The template role of $B(OMe)_3$ has been claimed [130], although the mechanism of the reaction has not been revealed.



L1391 L1392 L1393 (6.39)

In addition to high yields, this procedure can be used in the presence of functional groups such as C=O or C=C [131]. Thus 3-thia-1,5-pentanedithiol reacts with 1,3-dichloroacetone and 3-chloro-2-(chloromethyl)propene in the presence of a 5:1 $(i\text{-PrO})_3B/(i\text{-PrO})_3Al$ couple affording mainly 2 + 2 macrocyclic products L1394 and L1395 in 42% and 67% yield (Eq. 6.40) [131]; only small amounts of 1 + 1 species could be identified. The X-ray crystal structure of L1394 is available [131].

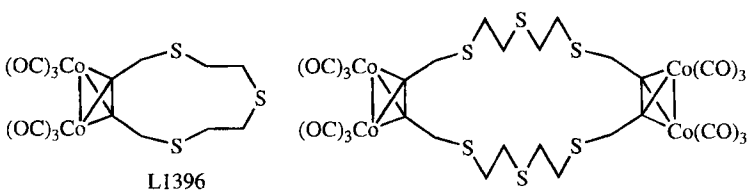


X = O, CH_2 (6.40)

X = O, L1394
X = CH_2, L1395

All the thiacrown ethers described so far are synthesised by stoichiometric reactions between the corresponding ligsons. However, a few examples of catalytic formation of polythiamacrocycles are well documented. It has also been reported that, in the presence of the Lewis acid $BF_3 \cdot Et_2O$, 1,4-dihydro-2,3-benzodithiin reacts with alkenes to give mixtures of 2 + 2 and 1 + 1 macrocyclic tetrathiacrown ethers [132]. In the presence of a catalytic amount of Lewis acid the 1 + 1 macrocycle is the only product isolated (68% yield).

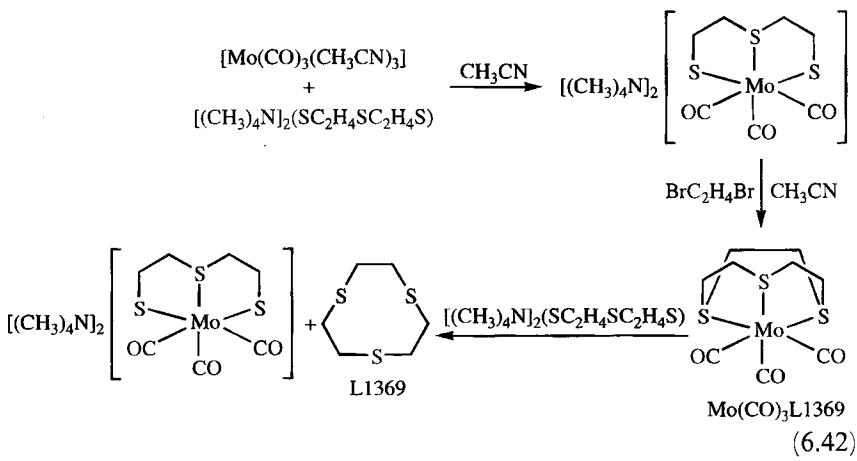
Dicobalt-complexed thiacycloalkyne L1396 and its dimeric counterpart L1397 have been prepared by $HBF_4 \cdot Et_2O$-catalysed reaction of $[Co_2(\mu\text{-}HOCH_2C{\equiv}CCH_2OH(CO)_6]$ with $HSCH_2CH_2SCH_2CH_2SH$ in CH_2Cl_2 (Eq. 6.41) [133].



L1396 L1397 (6.41)

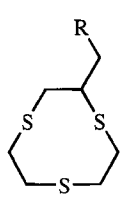
Symmetric polythiamacrocycles [12]ane-3, [16]ane-4 and [24]ane-6 have been prepared by catalytic cyclooligomerisation of thietanes [134]. The process is facilitated by the coordination and activation of thietane by trirhenium cluster complexes.

Template methodology often competes favourably with high-dilution methods, Cs_2CO_3/DMF and Lewis acid-promoted procedures explored for synthesis of thiacrown ethers. It has been demonstrated [135–139] that metal carbonyls are quite suitable for the template synthesis of crown ether thiaanalogues. An example is the multistep pathway for assembling and isolating 1,4,7-trithiacyclononane L1369 (Eq. 6.42) [135].



(6.42)

Prepared this way L1369 is formed in 60% yield, whereas the routes explored before to produce this compound based on the high-dilution method gave only 0.04–4.4% [136, 137]. In addition, this route is distinguished by its simplicity and reproducibility. The procedure can also be carried out in the presence of a catalytic amount of $Mo(CO)_3$-based template. Analogously, reaction of the appropriate electrophilic 1,2-dibromide with 3-thia-1,5-pentanedithiol in the presence of a molybdenum tricarbonyl template in acetonitrile produced *C*-functionalised 1,4,7-trithiacyclononanes L1398–L1404 (Eq. 6.43) [138].



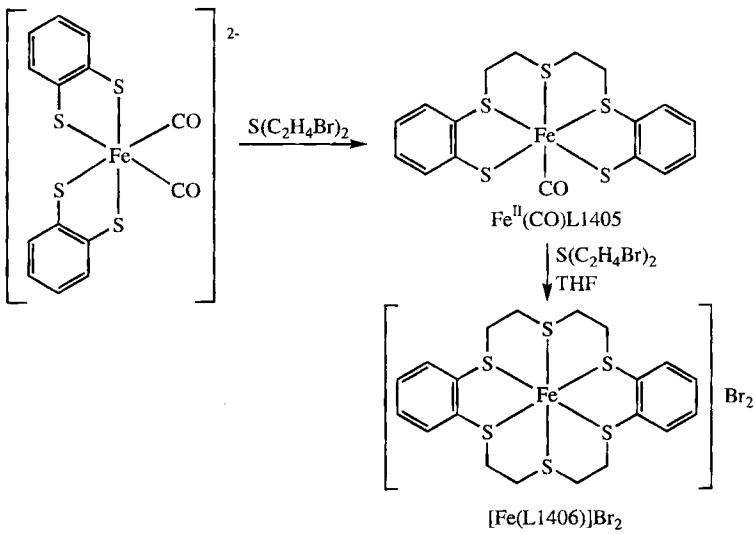
R = H	L1398
R = OH	L1399
R = OBz	L1400
R = $OCH_2C_6H_4Br$-*p*	L1401
R = $OCH_2C_6H_4Br$-*m*	L1402
R = $OCH_2C_6H_4COOH$-*p*	L1403
R = $OCH_2C_6H_4CN$-*p*	L1404

(6.43)

Some of these compounds have also been prepared by a high-dilution technique.

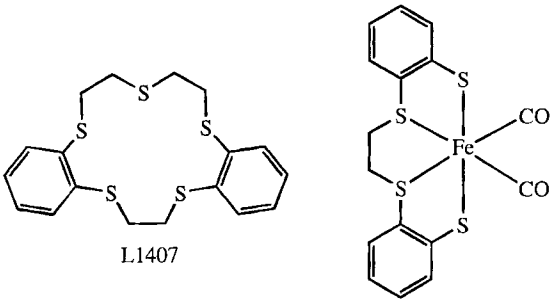
The template method was found to give significantly higher yields. For example, L1398 was produced in 25% yield using the template method, whereas the high-dilution technique proved to be unsuitable – a polymeric material was the only product. It should be mentioned that the yields were commonly lower compared to analogous preparations of 1,4,7-trithiacyclononane itself [135].

The iron(II) complex with the thia-analogue of dibenzo-18-crown-6 (L1406) resulted from a stepwise alkylation (Eq. 6.44).



(6.44)

Treatment of Fe(CO)L1405 with $BrCH_2CH_2Br$ gives $[Fe(L1407)]Br_2$ [139]. The same compound has been obtained by alkylation of $Fe(CO)_2L1408$ with $S(C_2H_4Br)_2$ (Eq. 6.45) [139].



(6.45)

Metal-free macrocycles L1406 and L1407 were obtained by demetallation of $[Fe(L1406)]Br_2$ and $[Fe(L1407)]Br_2$ on refluxing with hydrogen chloride in THF [139, 140].

A number of X-ray diffraction studies have been carried out on thiacrown ethers

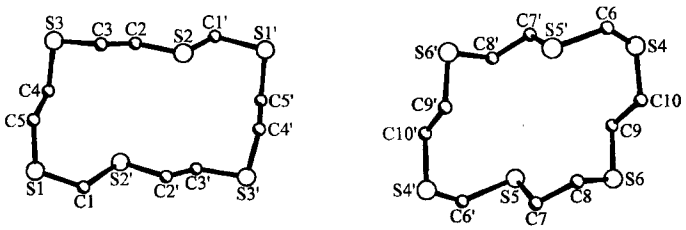


Figure 6-2. A perspective drawing of L1371, molecule 1 (left) and molecule 2 (right), showing the atom numbering scheme.

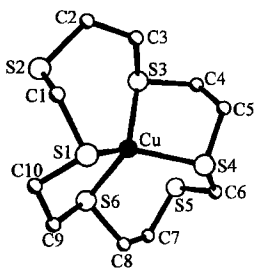


Figure 6-3. A perspective drawing of the $[Cu(L1371)]^+$ cation, showing the atom numbering scheme.

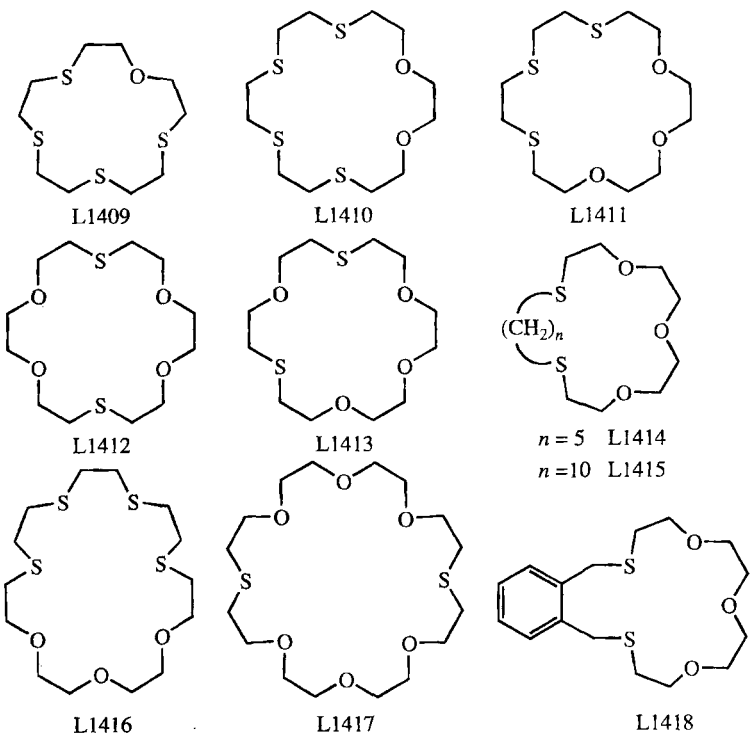
[102–105, 140–147]. These revealed that only trithia-9-crown-3 has all three S atoms endodentate. For the remaining ones either all (tetrathia-12-crown-4 and pentathia-15-crown-5) or some (hexathia-18-crown-6) of the S atoms are exodentate. Thiacrown ethers are flexible enough to adapt to the stereochemical demands of the central ion. Thus, hexathia-18-crown-6, uses all its donor atoms in its nickel complex, giving octahedral coordination at the central atom [141]. The structures of L1371 and (tetrahedral) $[Cu(L1371)]ClO_4$, taken as examples, are given in Figures 6-2 and 6-3 [103].

In the case of the metal-free ligand the unit cell contains discrete molecules of L1371 such that the asymmetric unit contains two independent halves of a molecule, each on a crystallographic centre of inversion. Perspective views of the crystallographically independent molecules of L1371 are shown in Figure 6-2. In both molecules four of the sulphur atoms are exodentate and two of the S atoms are endodentate to the 16-membered ring. The Cu atom in $[Cu(L1371)]^+$ (Figure 6-3) is in a tetrahedral environment bonded to four of the six S atoms of the ligand (Cu–S distances are 23.05(3), 22.99(3), 23.06(3) and 22.91(3) nm for S1, S3, S4 and S6, respectively). The remaining two S atoms are oriented towards the Cu atom at non-bonding distances of 35.55(3) nm for S2 and 34.13(3) nm for S5.

6.3 Heterocrown ethers

In this group, macrocyclic polyethers contain such elements as sulphur, nitrogen or phosphorus as well as oxygen in their cyclic skeleton.

Synthesis of macrocyclic compounds L1409–L1418 (Eq. 6.46) containing both oxygen and sulphur atoms has been carried out in high yield (73–80%) by reaction of the corresponding caesium dithiolate and dibromide derivative [93, 94].



(6.46)

For example, L1414 and L1415 are obtained according to the reactions:

$$HS(CH_2)_5SH + BrCH_2(CH_2OCH_2)_3CH_2Br \xrightarrow{Cs_2CO_3,DMF} L1414$$

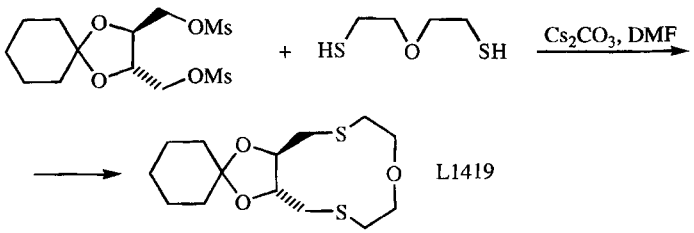
$$HSCH_2(CH_2OCH_2)_3CH_2SH + Br(CH_2)_{10}Br \xrightarrow{Cs_2CO_3,DMF} L1415$$

The compound L1417 is synthesised starting from two glycols containing the terminal functional groups required for cyclisation:

$$HSCH_2(CH_2OCH_2)_3CH_2SH + BrCH_2(CH_2OCH_2)_3CH_2Br \xrightarrow{Cs_2CO_3,DMF} L1417$$

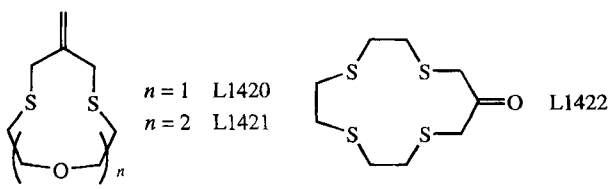
The compound L1418 resulted from the reaction of 3,6,9-trioxaundecane-1,11-dithiol with 1,2-bis(bromomethyl)benzene, by analogy with the reactions shown above.

In addition, the synthesis of the chiral thiacrown ether L1419 has been carried out according to Equation (6.47) for L1382–L1385 [95], using the Cs_2CO_3/DMF procedure.



L1419 (6.47)

A caesium-promoted synthesis of L1420, L1421 [104] and L1422 [105] was realised following the procedures employed in the case of the homoleptic thiacrown ethers (Eq. 6.48).

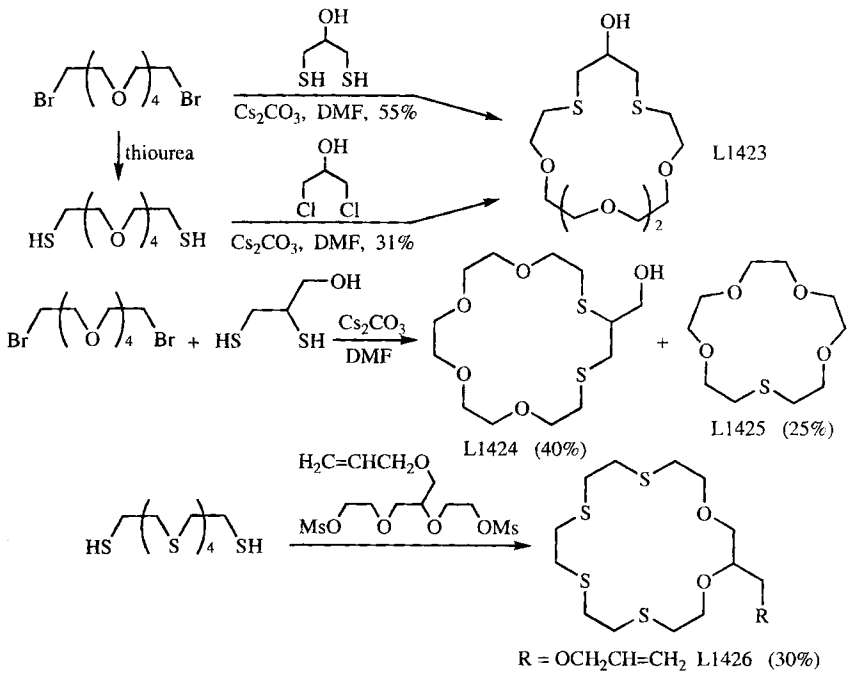


(6.48)

The compounds L1423 to L1426 were prepared using the reactions depicted in Scheme 6-4 [148].

Formation of L1423, L1424 and L1426 is not unexpected, but isolation of L1425 requires that a part of the starting SH-containing ligson (see Scheme 6-4) loses a mercaptide ion which reacts with the 1,14-dibromo-3,6,9,12-tetraoxatetradecane to form the macrocycle L1425 [148]. The fact that L1425 was originally prepared from the corresponding dichloride ligson and sodium sulphide [149] supports this assumption. It should be noted that the template role of Cs^+ cannot be neglected in these syntheses, taking into account that the number of oxygen atoms able to interact with the caesium ion is two or more.

There is a great variety of macrocyclic compounds containing both oxygen and nitrogen atoms as donors [5, 6, 8, 69, 150–168]. Partial substitution of nitrogens for oxygens in a crown ether ring leads to noticeable changes in almost all parameters of significance. This is because nitrogen is an excellent electron donor and, as a consequence of its valency of three and its reactivity, subsequent transformations and modifications of compounds containing such atoms are enabled. As a result,



Scheme 6-4. Synthesis of macrocycles L1423–L1426.

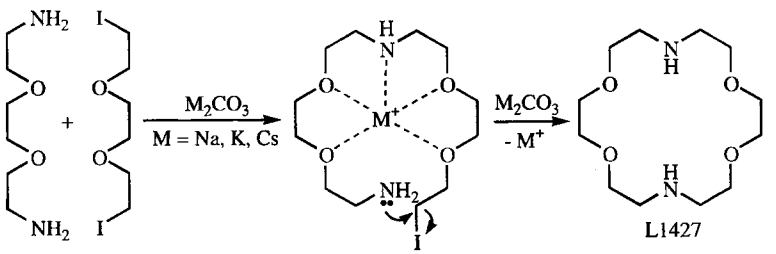
the possibility arises for incorporation of additional functions into azapolyether compounds and to provide peripheral donor centres. The latter results in enhanced ligand-cation interaction, and may change the cation selectivity of a ligand, assisting the formation of ion-selective reagents, active biological substances, bicyclic derivatives and polymeric reagents, all with a common set of donor centres [5, 6, 8, 69, 143, 150].

Cyclisation with the formation of azacrown ethers can be carried out starting from ligsons containing various substituents near either nitrogen or carbon or both. Both aliphatic and aromatic amines can be used as nitrogen-containing units. A huge variety of compounds containing nitrogen atoms incorporated into polyether rings means that studies on this ligand class are more advanced than on many other representatives of the crown ether series [6, 69].

However, the presence of nitrogen atoms in the starting materials required for assembling azacrown ethers leads to some synthetic difficulties which are not encountered in the case of purely oxygen-containing macrocyclic polyethers. One of the difficulties is the necessity to protect nitrogens of secondary amino groups in the starting ligsons before their use in the preparation of the macrocyclic products. This is often achieved by tosylation of these groups, although sometimes other techniques are employed. The second obstacle to the template pathway for producing azacrown ethers is less frequently encountered. In view of the less pronounced

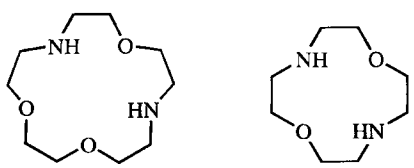
complexing ability of nitrogen towards alkali and alkaline earth metal ions, used as matrices in the synthesis of crown ethers, the assembly of the required components on such templates often becomes marginal. Nevertheless, retaining sufficient oxygen atoms in the compound of interest maintains the possibility of using the cations mentioned for producing at least some azacrown ethers. This may explain why the template synthesis of a wide range of azacrown substances has indeed been carried out. Several characteristic examples are presented below.

The template synthesis of 1,10-diaza-18-crown-6 (L1427) has been realised (Eq. 6.49) [156] in a process carried out in a number of organic solvents (methanol, dioxan, 1,2-dimethoxyethane, acetonitrile). In general, the yield was most effective with Na_2CO_3 (44% yield of L1427), followed by K_2CO_3 (27%), Cs_2CO_3 (15%) and Li_2CO_3 (6%) – cation solvation decreases in the same direction. Kinetic measurements [157] showed that the function of the promoting ion is to form a complex with the macrocyclic precursors to increase the ring-closure probability. (This conclusion is supported by the observation that when an excess of dicyclohexyl-18-crown-6, which binds the metal ions, is added to the reaction mixture, the formation of L1427 is inhibited – in the case of K_2CO_3 the yield falls from 27% to 4%.) Under otherwise identical conditions the yield of final product depends upon rate constants and metal ion concentration. Thus the mechanism of formation of L1427 is controlled by both kinetic and thermodynamic factors [156, 157].



(6.49)

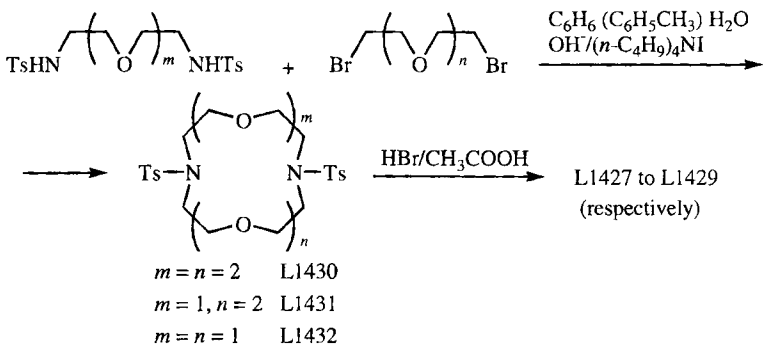
The diazacrown ethers L1428 and L1429 are obtained from the corresponding ligsons on an Na^+ matrix in an analogous way (Eq. 6.50) [156].



(6.50)

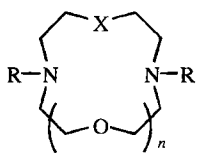
A convenient route to L1427–L1429 is template synthesis using diaza-crown ethers L1430–L1432 tosylated at the nitrogen atoms (Eq. 6.51) [150].

The macrocycles L1430–L1432 are obtained in good yield (54–82%) according to the above reaction in two-phase systems consisting of benzene or toluene, aqueous alkali hydroxide, and tetra-*n*-butylammonium iodide employed as a phase-transfer catalyst. The yield depends upon the MOH used – NaOH is the most effective in the synthesis of L1430 and L1431, and LiOH in the formation of L1432.



(6.51)

The compounds L1433–L1446 (Eq. 6.52) are produced [159] in a manner analogous to that reported in Reference 150.



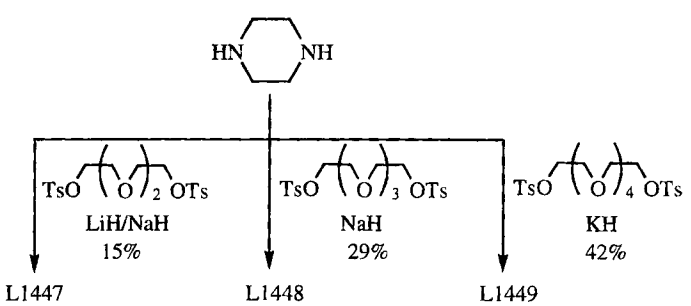
X = O, n = 3, R = Ts L1433
X = O, n = 3, R = H L1434
X = NR, n = 1, R = Ts L1435
X = NR, n = 1, R = H L1436

(6.52)

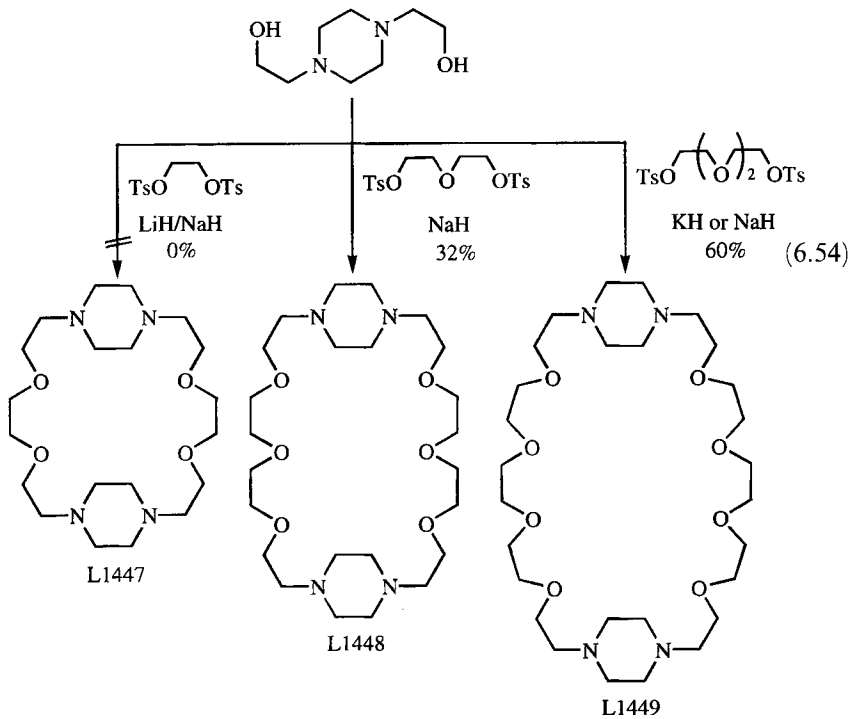
X = NR, n = 2, R = Ts	L1437	X = NR, n = 2, R = H	L1442
X = NR, n = 3, R = Ts	L1438	X = NR, n = 3, R = H	L1443
X = $RN(CH_2)_2NR$, n = 1, R = Ts	L1439	X = $RN(CH_2)_2NR$, n = 1, R = H	L1444
X = $RN(CH_2)_2NR$, n = 2 , R = Ts	L1440	X = $RN(CH_2)_2NR$, n = 2 , R = H	L1445
X = $RN(CH_2)_2NR$, n = 3, R = Ts	L1441	X = $RN(CH_2)_2NR$, n = 3, R = H	L1446

Template construction of L1447–L1449 was performed in two ways [158]:

- by reacting piperazine with the corresponding ditosylates in the presence of alkali metal hydrides (Eq. 6.53);
- by using *N*,*N*′-bis(2-hydroxyethyl)piperazine as starting ligson instead of piperazine (the synthesis of L1447 by this route was unsuccessful) (Eq. 6.54).

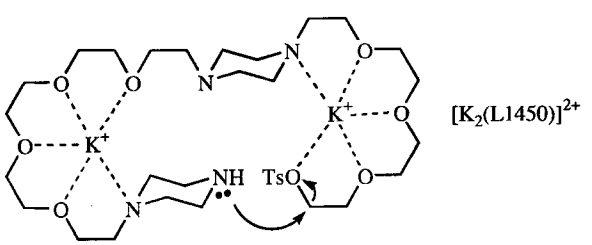


(6.53)



(6.54)

The synthesis of 24-, 30- and 36-membered macrocycles in good yield is presumably facilitated by a two-centre (double) template effect as illustrated schematically by formation of the complex with ring precursor $[K_2(L1450)]^{2+}$ (Eq. 6.55).



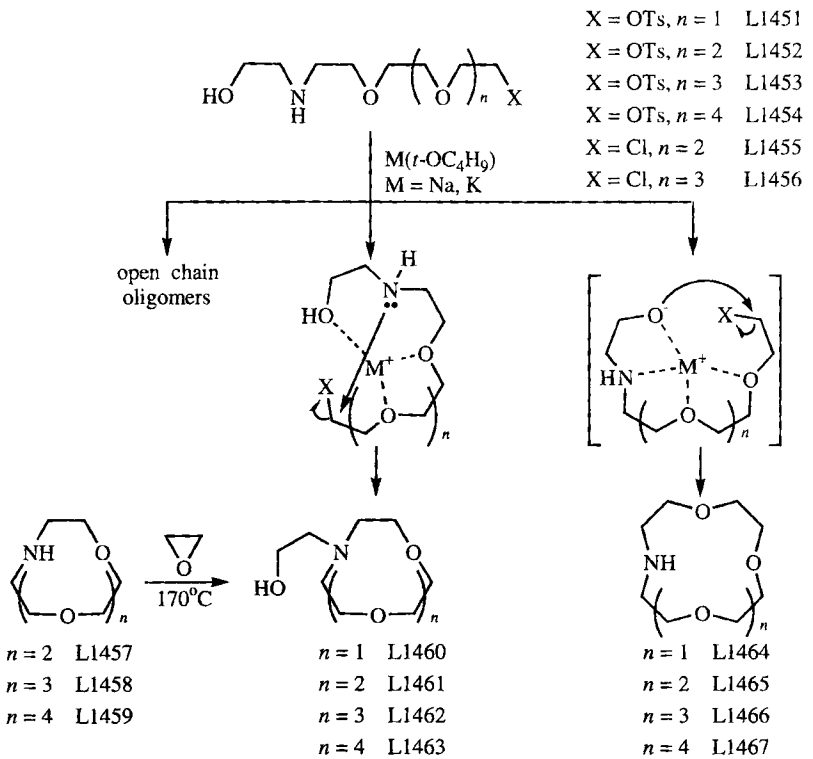
$[K_2(L1450)]^{2+}$

(6.55)

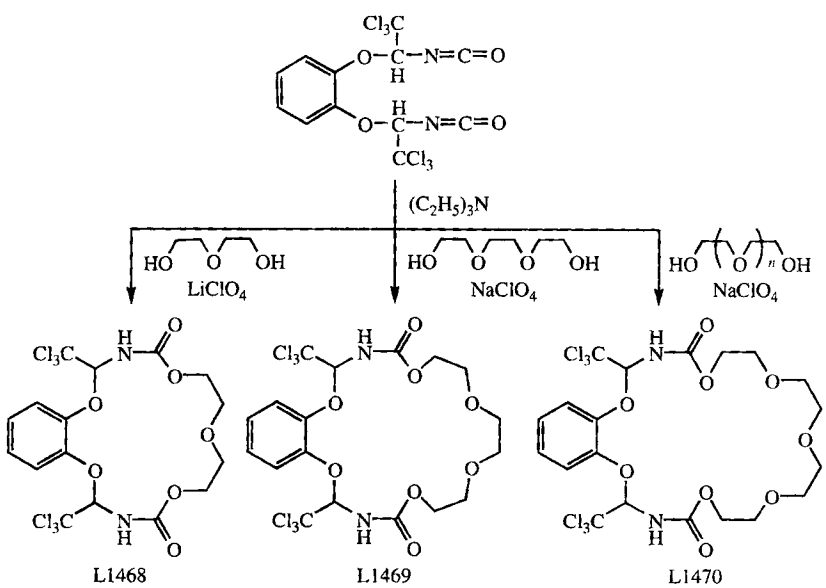
A general synthesis for monoazacrown ethers has been described. The compounds L1460–L1467 were obtained according to Scheme 6-5 [169].

Sodium(I) is a superior template to potassium(I) in the synthesis of monoaza-15-crown-5. However sodium and potassium *tert*-butoxide gave almost the same yield of monoaza-18-crown-6 [169].

Template synthesis (alkali metal cations) of crown ethers containing a urethane group L1468–L1470 has been reported (Eq. 6.56) [160, 161].

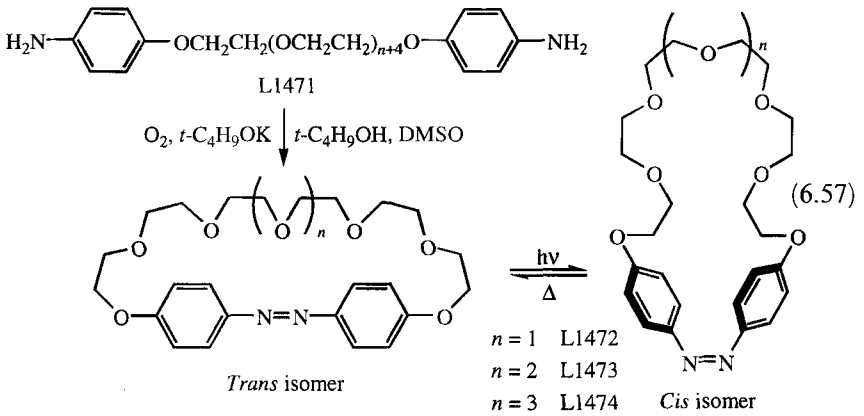


Scheme 6-5. Synthesis of monoazacrown ethers L1460–L1467.



(6.56)

Azacrown ethers L1472–L1474 are synthesised by an oxidising ring-closure reaction involving L1471 on a potassium cation matrix. These three substances are formed as the *trans* isomers and can then be converted into the *cis* isomers by exposure to ultraviolet radiation (Eq. 6.57) [162].



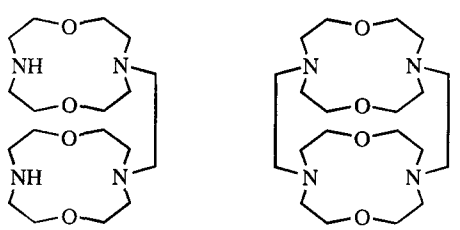
(6.57)

Azacrown ethers containing formazan moieties are obtained by reaction of bis(2-azoaryl)-oligooxoalkanes with compounds containing activated methylene or methine groups, namely malonic, acetoacetic, cyanoacetic, phenylmalonic, or 4-nitrophenylacetic acids in alkaline medium with the addition of pyridine on copper(II), zinc(II) or nickel(II) matrices [152, 163–165]. For instance, crown formazans L1475 to L1484 are built up in this way (Scheme 6-6).

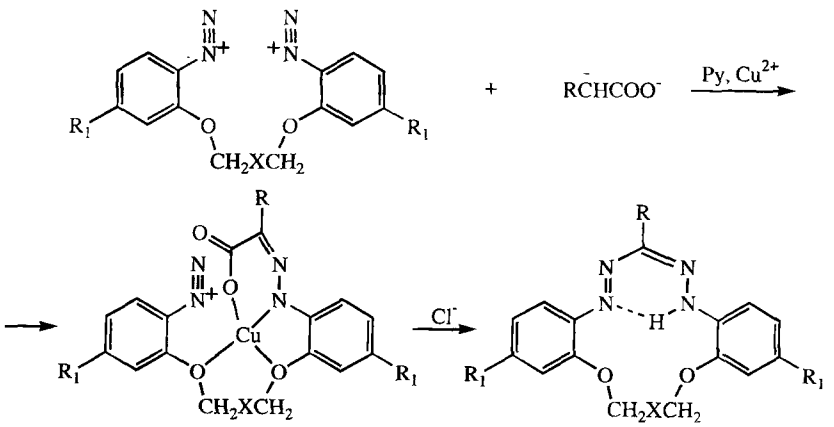
A template synthesis for the bicyclic azacrown ether L1485 (a cryptand, see Section 4.1) is given in Scheme 6-7 [166].

Demetallation of the complex occurs when an acidified aqueous solution of [Na(L1485)]I is passed first through a cation exchange, then through an anion-exchange resin, to give metal-free L1485.

The preparation of the tricyclic cryptand L1487 is carried out by a multi-step synthesis. The reaction of the bis(azacrown) L1486 with ethane-1,2-bis(toluene-*p*-sulphonate) on an Li^+ matrix forms the last step of this synthesis (Eq. 6.58) [167].

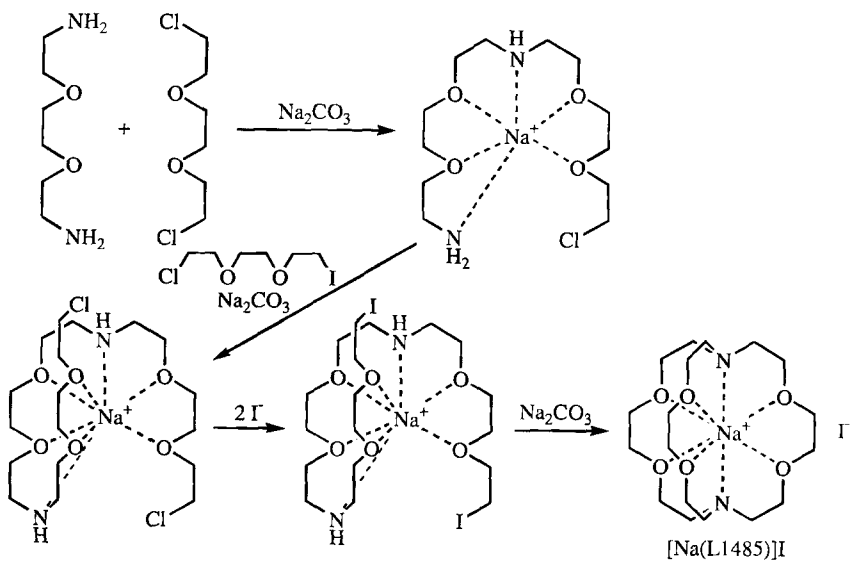


(6.58)

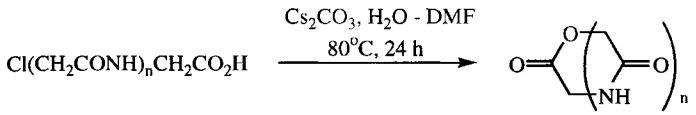


$X = (CH_2)_3$, $R = H$, $R_1 = NO_2$	L1475
$X = CH_2OCH_2$, $R = R_1 = H$	L1476
$X = CH_2OCH_2$, $R = CN$, $R_1 = H$	L1477
$X = CH_2OCH_2$, $R = COCH_3$, $R_1 = H$	L1478
$X = CH_2O(CH_2)_2OCH_2$, $R = R_1 = H$	L1479
$X = CH_2O(CH_2)_2OCH_2$, $R = H$, $R_1 = NO_2$	L1480
$X = CH_2O(CH_2)_2OCH_2$, $R = CN$, $R_1 = NO_2$	L1481
$X = CH_2O(CH_2)_2OCH_2$, $R = CN$, $R_1 = H$	L1482
$X = CH_2O(CH_2)_2OCH_2$, $R = COCH_3$, $R_1 = H$	L1483
$X = CH_2O(CH_2)_2OCH_2$, $R = COCH_3$, $R_1 = NO_2$	L1484

Scheme 6-6. The synthesis of crown formazans L1475–L1484.

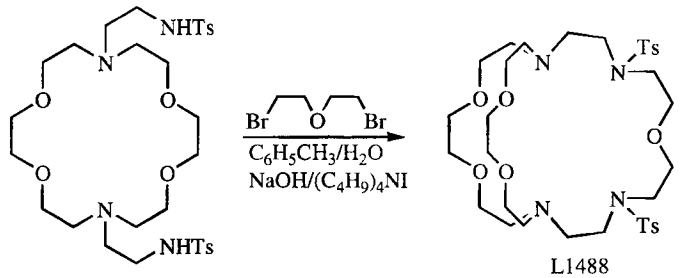


Scheme 6-7. The proposed mechanism for the formation of cryptand $[Na(L1485)]^+$.



Scheme 6-8. Conversion of dipeptides and tetrapeptides into macrocyclic azacrown species.

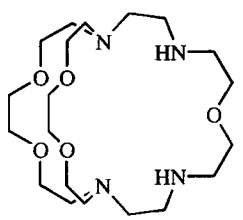
Template synthesis of the cryptand L1488 is carried out under phase-transfer catalysis conditions, using tetrabutylammonium iodide (Eq. 6.59) [168].



L1488

(6.59)

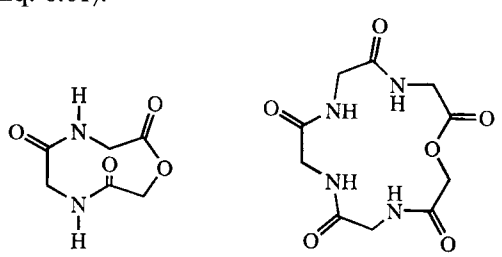
Compound L1489 is obtained by detosylation of L1488 with hydrobromic acid in CH_3COOH (Eq. 6.60) [168].



L1489

(6.60)

Conversion of dipeptides and tetrapeptides into macrocyclic functionalised azacrown compounds by means of caesium-assisted ring closure of *N*-2-chloroacetyl derivatives was carried out according to Scheme 6-8 [170], to obtain L1490 and L1491 (Eq. 6.61).



n = 2 L1490 *n* = 4 L1491

(6.61)

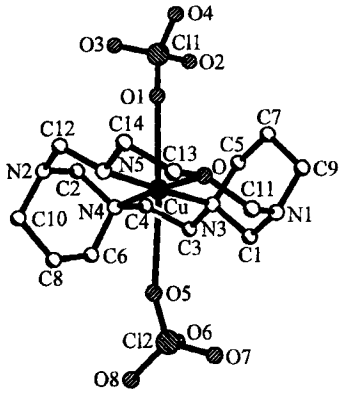
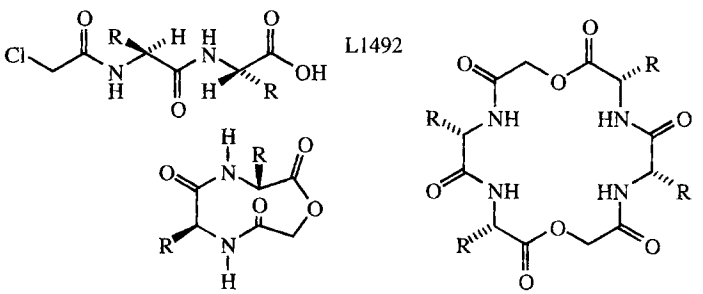


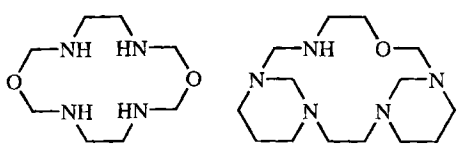
Figure 6-4. The structure of $[Cu(L1496)](ClO_4)_2$.

The monomer L1493 and dimer L1494 were similarly prepared from L1492 (Eq. 6.62). The yield of L1491 was 50%, of L1490, L1493 and L1494 85–90% [170].



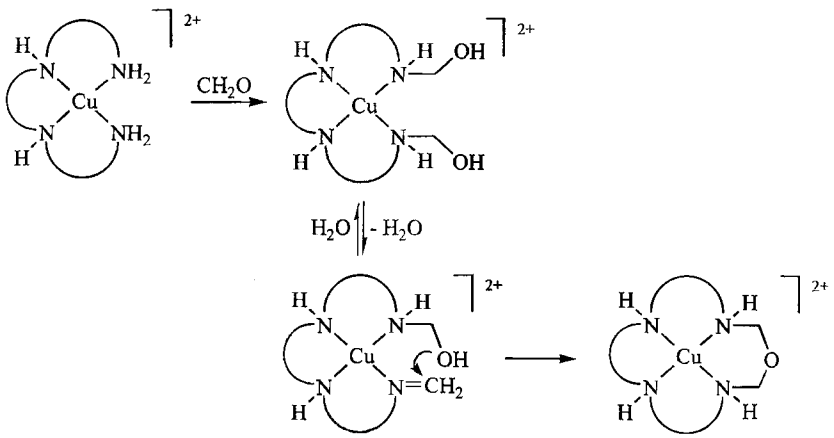
(6.62)

Condensation of formaldehyde with glycinato-bis(ethane-1,2-diamine)cobalt(III), $[Co(en)_2(gly)]^{2+}$, in aqueous solution saturated with Li_2CO_3 yields several products including the macrocycle L1495 (Eq. 6.63) isolated as its cobalt(III) complex [171], whose X-ray diffraction structure is also available.



(6.63)

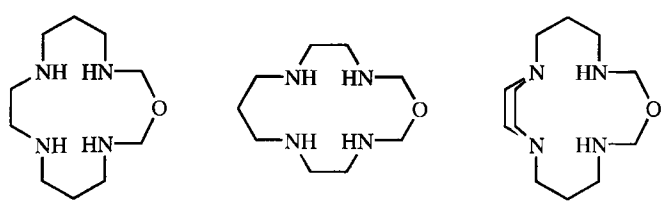
Reaction of formaldehyde, ethanolamine and 1,10-diamino-4,7-diazadecane in the presence of Cu^{II} readily leads to the formation of $[Cu(L1496)](ClO_4)_2 \cdot \frac{1}{2}H_2O$, in which the macrocyclic ligand contains one ring-oxygen atom [172, 173]. An X-ray diffraction study established that this ether oxygen atom participates in coordination to the central atom (Figure 6-4).



Scheme 6-9. The proposed mechanism of formation of oxatetraazamacrocyclic compounds.

This example provides a relatively rare case of coordination of an ether oxygen atom to a d metal ion in this type of complex.

Oxatetraazamacrocyclic compounds L1497–L1499 (Eq. 6.64) were prepared by reaction of paraformaldehyde with the copper(II) complexes of appropriate tetramines in acetonitrile in the presence of triethylamine. The reaction is thought to proceed by the mechanism illustrated in Scheme 6-9 [173].

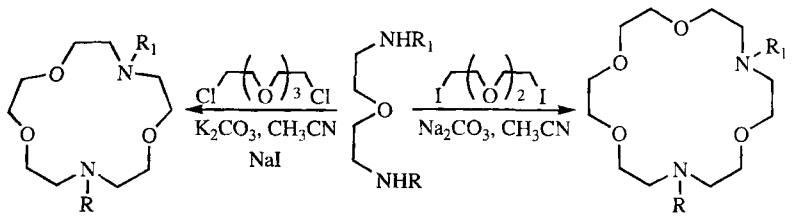


L1497 L1498 L1499 (6.64)

Nitrogen-substituted diazacrown ethers derived from 15-crown-5, L1500–L1508, and from 18-crown-6, L1509–L1517, have been prepared according to Scheme 6-10 [174].

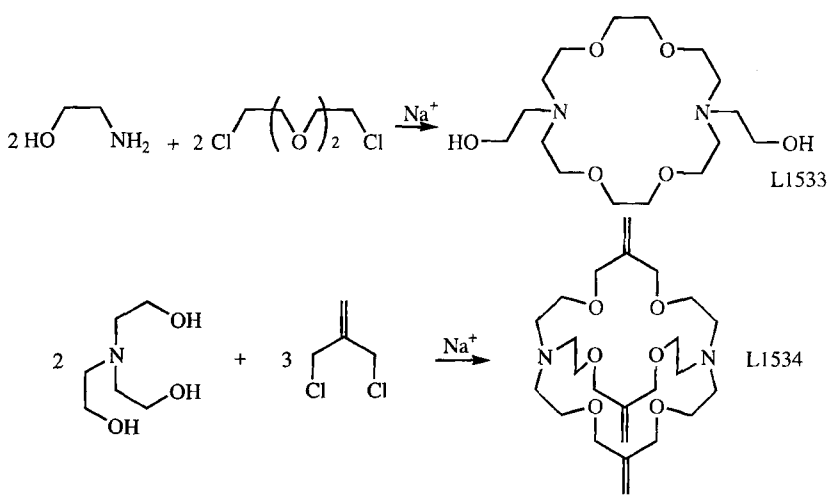
Sodium, potassium and caesium have been used as the metal cation templates for the preparation of the bis(2-hydroxyethyl)diazacrown ethers L1518–L1520 and the macrobicyclic polyethers L1521–L1532 [175, 176], following the transformations depicted in Scheme 6-11.

A very attractive one-pot synthesis of symmetrical macrocycles of various sizes can be performed by simple condensation of two starting materials in a 2:2 ratio for a crown ether (L1533) or a 3:2 ratio for a cryptand (L1534), using Na^+ as the template (Eq. 6.65) [177].



$R = C_2H_5$, $R_1 = (CH_2)_3N(C_2H_5)_2$	L1500	$R = C_2H_5$, $R_1 = (CH_2)_3N(C_2H_5)_2$	L1509
$R = C_2H_5$, $R_1 = (CH_2)_2N(C_2H_5)_2$	L1501	$R = C_2H_5$, $R_1 = (CH_2)_2N(C_2H_5)_2$	L1510
$R = C_2H_5$, $R_1 = (CH_2)_3N(CH_3)_2$	L1502	$R = C_2H_5$, $R_1 = (CH_2)_3N(CH_3)_2$	L1511
$R = C_2H_5$, $R_1 = (CH_2)_2N(CH_3)_2$	L1503	$R = C_2H_5$, $R_1 = (CH_2)_2N(CH_3)_2$	L1512
$R = C_2H_5$, $R_1 = (CH_2)_2OH$	L1504	$R = C_2H_5$, $R_1 = (CH_2)_2OH$	L1513
$R = C_2H_5$, $R_1 = (CH_2)_2O(CH_2)_2OH$	L1505	$R = C_2H_5$, $R_1 = (CH_2)_2O(CH_2)_2OH$	L1514
$R = C_2H_5$, $R_1 = CH_2C_6H_5$	L1506	$R = C_2H_5$, $R_1 = CH_2C_6H_5$	L1515
$R = C_2H_5$, $R_1 = (CH_2)_2$morpholine	L1507	$R = C_2H_5$, $R_1 = (CH_2)_2$morpholine	L1516
$R = CH_2C_6H_5$, $R_1 = (CH_2)_3N(C_2H_5)_2$	L1508	$R = CH_2C_6H_5$, $R_1 = (CH_2)_3N(C_2H_5)_2$	L1517

Scheme 6-10. Synthesis of nitrogen-substituted diazacrown ethers.

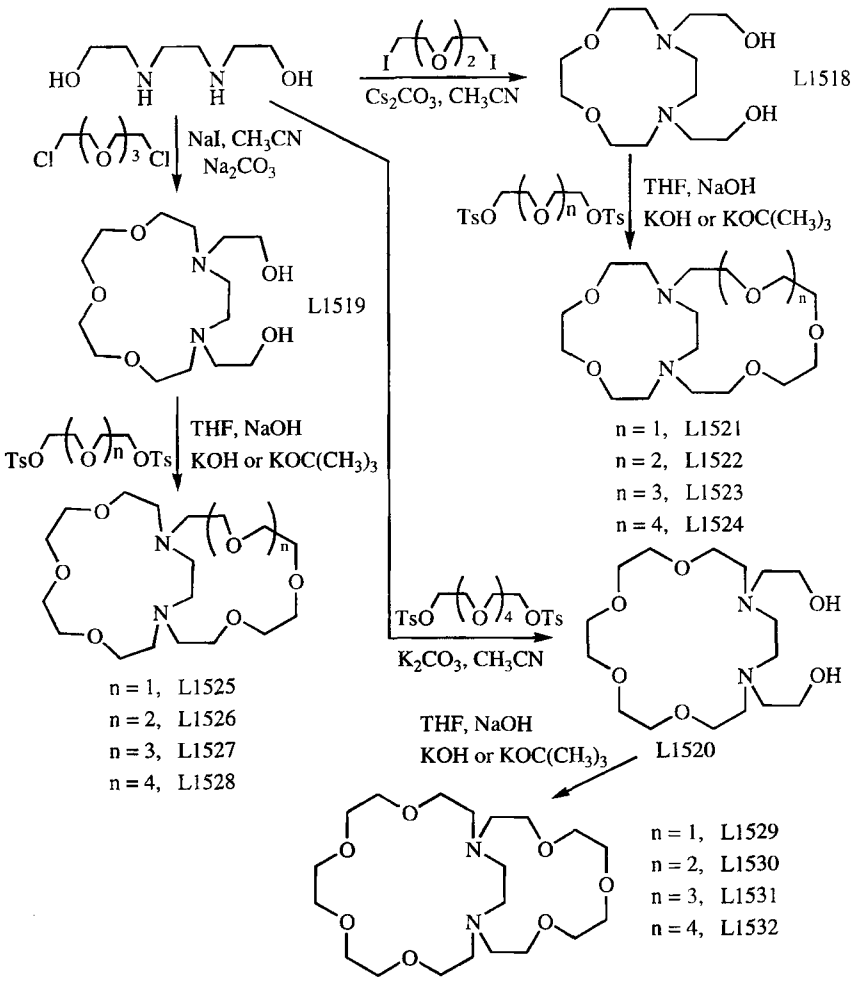


(6.65)

The macrocyclic species shown in Scheme 6-12 were obtained employing the template cations stated in Table 6-2 [178].

Azacrown ethers L1543–L1545, containing a hydrazine fragment in the cyclic backbone, were obtained in the presence of Na^+ or K^+ following Scheme 6-13 [179, 180].

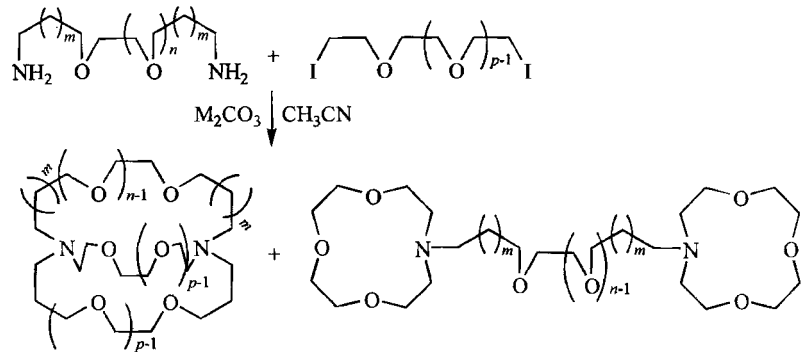
A few macrocyclic polyethers containing a ring phosphorus atom are known. As a rule, the synthesis of such substances is not carried out by template processes. However, the assembly of crown ethers possessing ring phosphonyl groups has been achieved on alkali metal ion (lithium, sodium, potassium) matrices [181–184]. The product L1546 is synthesised in an inert atmosphere (Eq. 6.66).



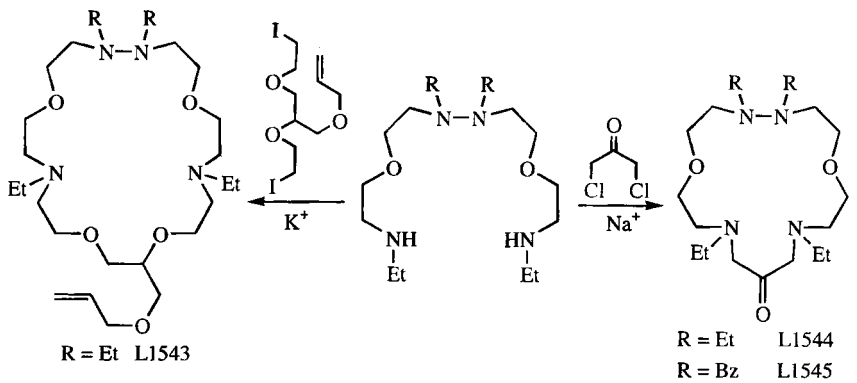
Scheme 6-11. Template synthesis of crown ethers L1518–L1520 and macrobicyclic polyethers L1521–L1532.

Table 6-2. Compounds prepared following Scheme 6-12, using the stated templates [178].

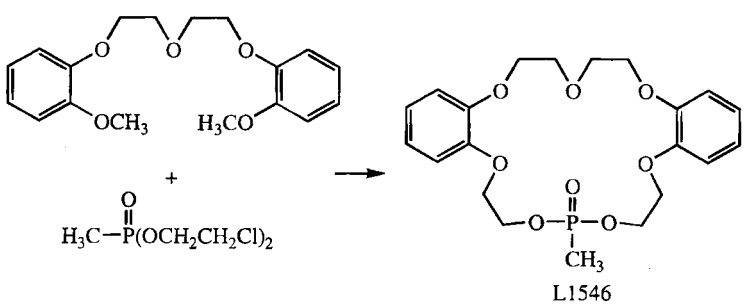
Structure *m n p*	Template cation	Cryptand, yield (%)	Bis(azacrown), yield (%)
0 2 3	K^+	L1535, 40	L1540, 17
1 2 2	Na^+	L1536, 31	not detected
1 2 3	K^+	L1537, 19	L1541, 16
1 3 2	Na^+	L1538, 34	not detected
1 3 3	Cs^+	L1539, 8	L1542, 26



Scheme 6-12. Synthesis of cryptands and bis(azacrowns).

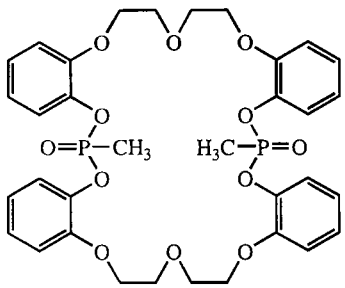


Scheme 6-13. Synthesis of hydrazino-crown ethers L1543–L1545.



(6.66)

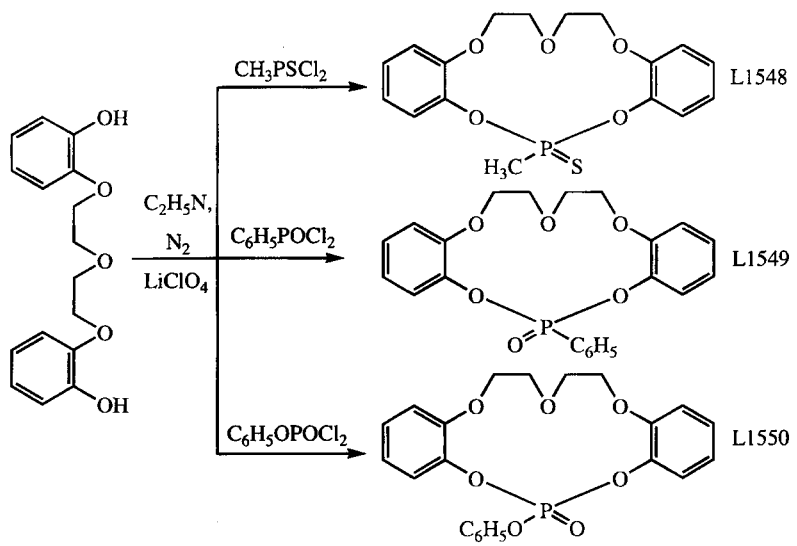
The Na^+ ion is the most suitable template, giving a 40% yield. The yield of L1546 by non-template reaction is only 9% [185]. The macrocyclic product L1547 is synthesised utilising the same component, bis-[2-(*o*-hydroxyphenoxy)ethyl] ether (Eq. 6.67).



L1547 (6.67)

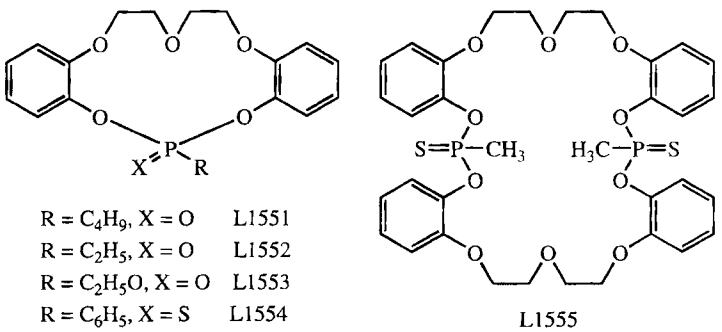
It has been reported [181, 182] that L1547 is obtained as mixture of three isomers of different melting points and complexing ability. Isomerism of L1547 can be attributed to the different orientation of the phosphonyl group relative to the crown ether polyether ring [182], as shown by NMR spectroscopy using lanthanide shift reagents [186].

Macrocycles L1548–L1550 are obtained by using lithium perchlorate as template agent (Eq. 6.68) [182].



(6.68)

The macrocyclic compound L1550 is isolated as mixture of two isomers which, as for L1547, probably differ in spatial orientation of the phosphonyl group [182]. Template syntheses of the macrocycles L1551–L1555 have also been reported (Eq. 6.69) [184]. L1554 is obtained by condensation of the phosphorus-containing ligson $C_6H_5PSCl_2$ with 2,2′-(oxydiethyleneoxy)diphenol on a sodium cation matrix. The

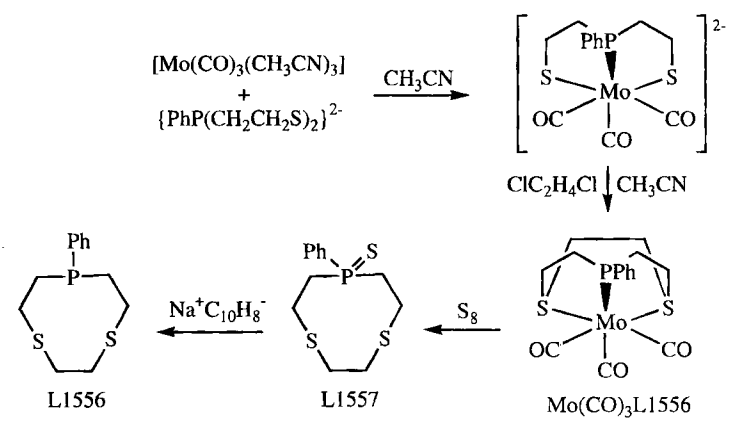


(6.69)

larger potassium cation facilitates the (2 + 2) synthesis of the condensation product L1555.

There are two ways of varying the assembly of monomeric and dimeric macrocycles, by using a suitable template and by selection of solvent. Reaction in polar solvents favours production of 28-membered compounds, whereas in solvents of relatively low dielectric constant 14-membered compounds are favoured. Yields of polyethers are influenced to a greater extent by the template effect than by the solvent nature [184].

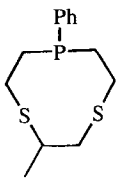
Starting from $PhP(CH_2CH_2SH)_2$ and $Mo(CO)_6$ and following the scheme used for building up 1,4,7-trithiacyclononane led to efficient ring closure yielding the complex $[Mo(CO)_3(L1556)]$ (Eq. 6.70) [187].



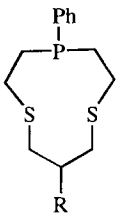
(6.70)

As expected, replacement of one sulphur atom by a phosphine donor led to an increase in stability over the corresponding molybdenum(0) complex with the 9-thiacrown-3. Complexes $[Mo(CO)_3(L1558)]$, $[Mo(CO)_3(L1559)]$ and $[Mo(CO)_3(L1560)]$, containing nine- and ten-membered phosphadithiamacrocycles, have been similarly prepared (Eq. 6.71). The structure of $[Mo(CO)_3(L1556)]$ has been confirmed by an X-ray diffraction study [188]. The $Mo(CO)_3$-template can be removed by reacting $[Mo(CO)_3(L1556)]$ with sulphur in refluxing toluene. On

demetallation the metal-free ligand L1556 undergoes oxidation giving L1557, which can easily be reduced to L1556 by treating with sodium naphthalenide [188].



L1558



R = H L1559
R = OH L1560

(6.71)

6.4 References

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Chapter 7

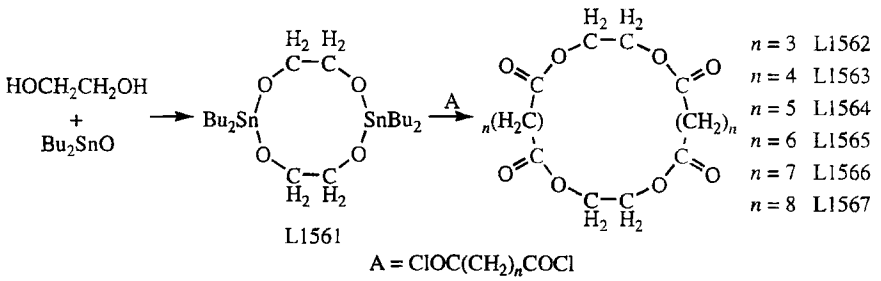
Covalent template synthesis

A unique approach to the controlled design of such systems as macrocyclic polylactones, polylactams and related compounds has been developed [1]. The synthesis of these substances, called biomimetic macrocyclic molecules by reason of their resemblance to naturally occuring ionophores (such as valinomycin, nonactin, enniatin and enterobactin [2–5]), is carried out by a covalent-template method. This description arises from the use of elements forming covalent bonds (tin, silicon, antimony, boron) as matrices.

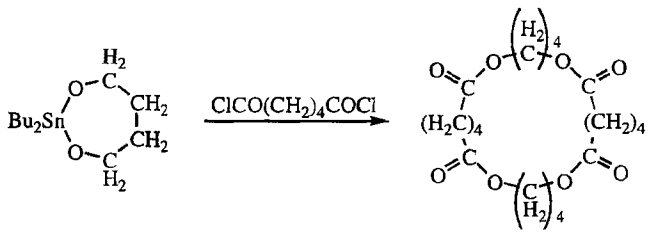
The technique is applied to link non-cyclic ligsons together to form macrocyclic systems. The ligson heteroatoms have weak donor properties, so that centres such as transition and rare earth element, alkali, and alkaline metal ions are not able to play a template role in synthesis from the relevant species. The metalloids are able to form covalent bonds to weak donors and are thus suitable for the realisation of the required reactions. Organo-element compounds of appropriate metals are used for covalent-template synthesis. These combine the coordination ability of metals and the substitution ability of organic moieties, and therefore facilitate the wide range of chemical conversions involved in template processes. The basic feature of the reactions considered here is the weakness of bonds between matrix and ligsons, so that the synthesis of the free macrocyclic compound may be completed by release of the template.

7.1 Macrocyclic polylactones, polylactams and related compounds

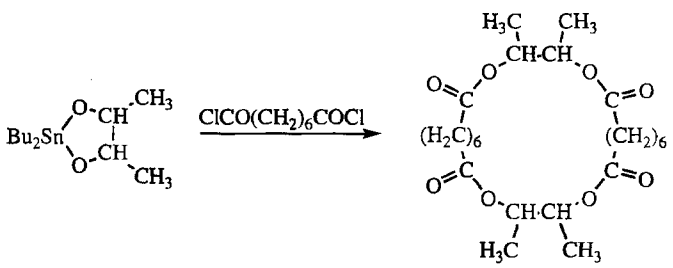
Until now most covalent-template syntheses have been carried out to form macrocyclic polylactones [1, 6–16]. The synthesis of tetralactones L1562–L1567 represented in Scheme 7-1 has been achieved in 30–85% yield [7, 10]. Other cyclic stannoxanes are also suitable for covalent-template synthesis of macrocyclic tetralactones, for example L1568 (Eq. 7.1) [10]. Tetralactones L1569 (Eq. 7.2) and L1570 (Eq. 7.3) are synthesised in an analogous way [10].



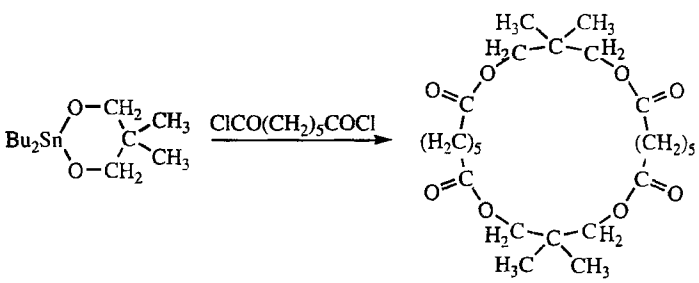
Scheme 7-1. The synthesis of tetralactones L1562–L1567.



(7.1)

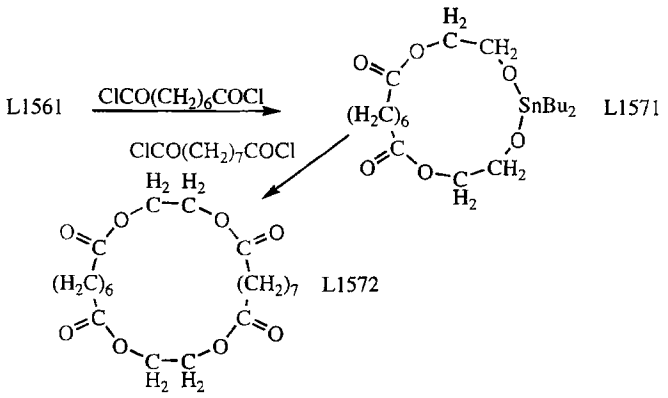


(7.2)



(7.3)

The tin-containing compounds involved in the above processes exercise their template function by controlling the conversion of non-cyclic diols to cyclic stannoxanes. This activates the corresponding oxygen atoms, thus facilitating interaction of diacyl dihalides with the latter, to give macrocyclic tetralactones as the only

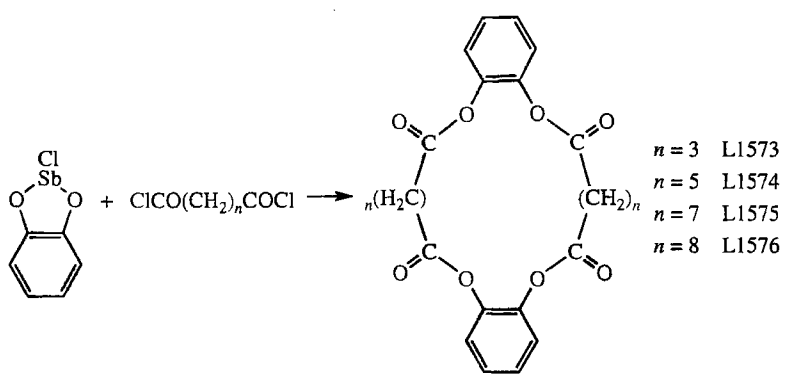


Scheme 7-2. The synthesis of asymmetric lactone L1572.

ring-closed products. Naturally, both ring closure of the initial diols to form cyclic stannoxanes and formation of the final tetralactones must be stepwise reactions. Evidence in favour of this conclusion, at least at the stage of conversion of stannoxanes to macrocyclic tetralactones, resulted from the stepwise synthesis of the asymmetric product L1572 [10] (Scheme 7-2).

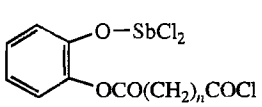
X-Ray studies of L1562, L1563 and L1566 verifying the formation of the respective tetralactones have been performed [10].

Macrocycles L1562–L1570 and L1572 have reflection planes, so may be called reflectolactones or reflactones for short [7, 12]. The reflactones L1573–L1576 have been synthesised by a covalent-template pathway by using antimony(III) as template (Eq. 7.4) [15].



(7.4)

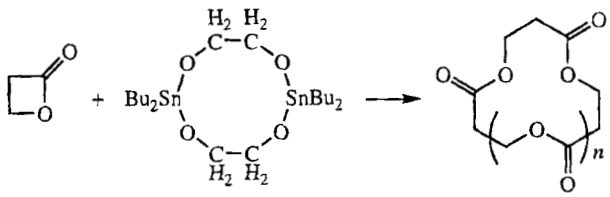
It is supposed [15] that the reaction proceeds stepwise via formation of a 1:1 open-chain intermediate (Eq. 7.5).



(7.5)

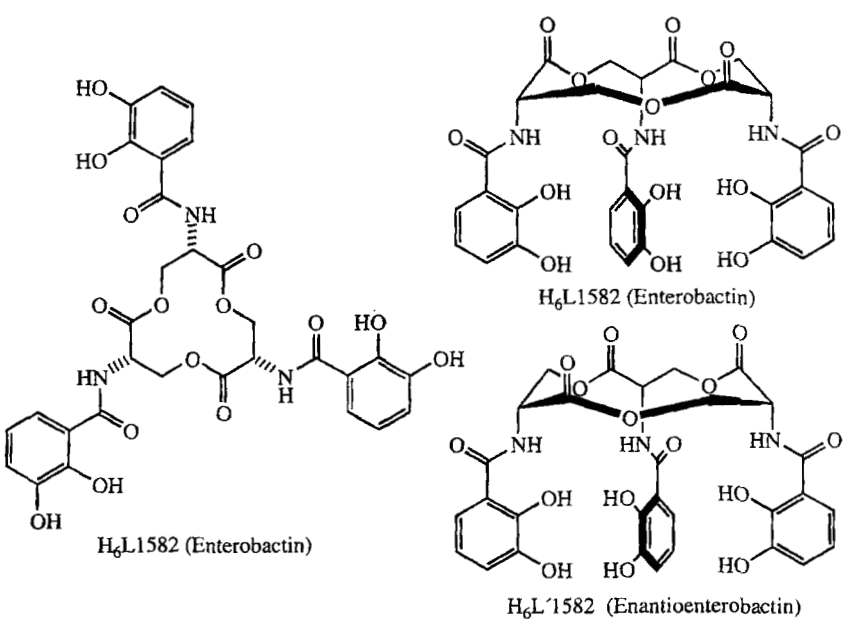
Macrocyclic tetraesters with aliphatic substituents (alkane or cycloalkane) have been synthesised analogously using both the 1,3,2-dioxastannolanic and the corresponding stibolanic derivatives as templates [16]. The greater reactivity of stibolanic derivatives toward diacyl chlorides reduces considerably the reaction times and makes their use preferable.

Macrocyclic polylactones L1577–L1581, possessing rotational symmetry and therefore called rotolactones [12], are obtained by reaction of distannoxanes with propiolactone in up to 80% yields (Eq. 7.6) [6, 9].

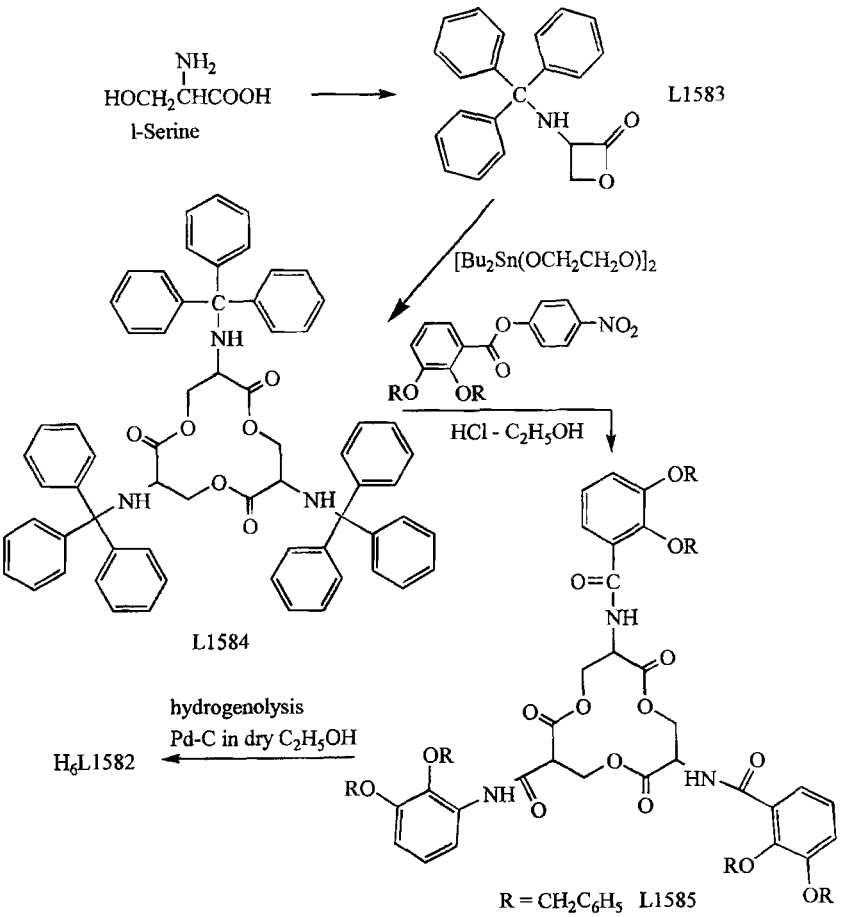


(7.6)

It is noteworthy that the linear stannoxane dibutyltin diethoxide, in contrast to cyclic stannoxanes, did not give any macrocyclic compounds. Instead open-chain hydroxyesters were produced [9]. X-Ray studies of L1577 and L1578 [6, 9] established the structures of these compounds. The trilactone L1577 has a crown conformation with carbonyl groups arranged on the same side of the macroring plane. This *syn* arrangement of CO groups is analogous to that of many synthetic and natural polycarbonyl compounds, including the iron ionophore enterobactin H_6L1582 and its synthetic antipode enantioenterobactin ($H_6L'1582$) derived from d-serine [5, 6, 9], whose macrocyclic skeleton is identical to that of L1577 (Eq. 7.7).



(7.7)



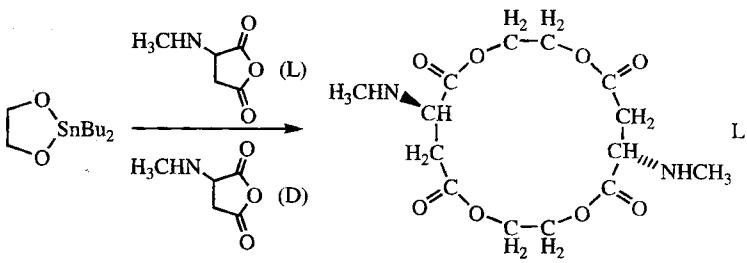
Scheme 7-3. Total synthesis of enterobactin.

The tetralactone L1578 has a different conformation, characterised by an alternating arrangement of carbonyl groups above and below the plane of the ring and by formation of an internal cavity of tetrahedral geometry [6] in a way analogous to that of many natural ionophores, such as nonactin [17] and related compounds. The application of the covalent-template technique made possible the synthesis of the corresponding naturally occuring compounds. Complete synthesis of enterobactin H_6L1582 by using l-serine as a initial ligson has been reported [18] (Scheme 7-3).

The crucial step in the total synthesis of enterobactin is the cyclisation of the β-lactone L1583, produced from tritylated l-serine, to the enterobactin trilactone backbone in the presence of the $[Bu_2Sn(OCH_2CH_2O)]_2$ as template, which is likely to proceed by multiple insertions of L1583 into the dimeric tin species followed by liberation of the desired macrocycle and recovery of the template. Even more effective procedures for producing the triserine lactone backbone have since been discovered [19, 20], although the latter generally follow the route developed earlier

[18]. For example, commercially available methyl-*N*-trityl-l-serinate undergoes cyclooligomerisation to l-serine trilactone in the presence of 2,2-dibutyl-1,3,2-dioxastannolane as template in 81% yield [20], compared to 26% of template trimerisation of l-*N*-tritylserine to the desired lactone (Scheme 7-3) [18].

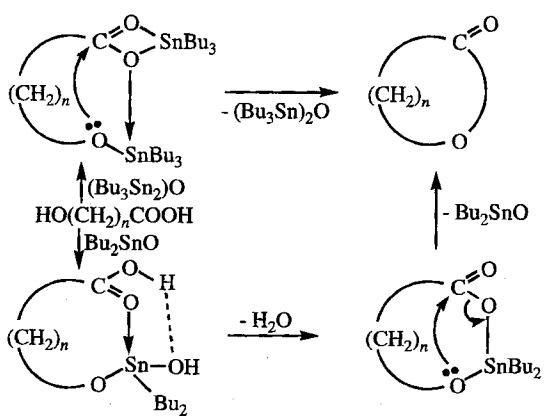
In addition, template synthesis of diastereoisomeric and chiral macrocyclic polylactones can be carried out using covalent-template pathways on tin-containing compound matrices by using the corresponding building blocks [1, 8, 11, 13]. In particular, heterochiral L1586 in the *anti* configuration containing one residue of l- and one of d-aspartic acid can be synthesised by stepwise reaction of 1 mole of stannoxane with 0.5 mole of l- and then d-aspartic anhydride (Eq. 7.8) [1, 11].



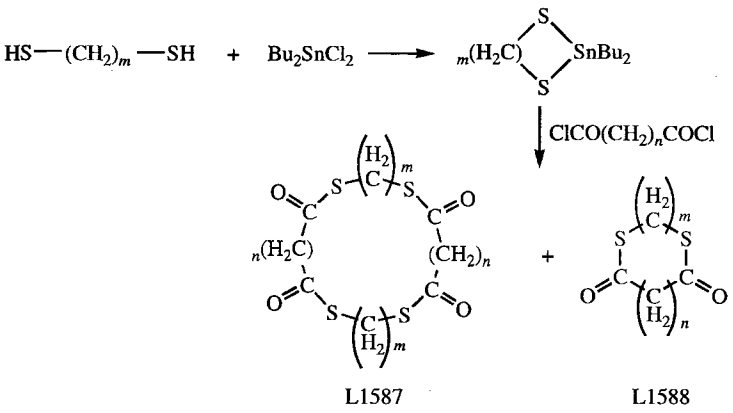
(7.8)

It has been supposed [8] that the formation of tetralactones such as L1586 proceeds through electrophilic attack of the anhydride carbonyl at stannoxane oxygen, followed by extrusion of dibutyltin oxide and liberation of the macrocyclic ligand product.

The covalent-template approach has been used to carry out intramolecular esterification of ω-hydroxy carboxylic acids in the presence of catalytic amounts of stannoxanes to form monomacrolactones, including natural macrolide antibiotics such as nodusmicin, pyrenophorin, vermiculine and ingramycin. The course of the synthetic reaction is shown in Scheme 7-4 [21–23].



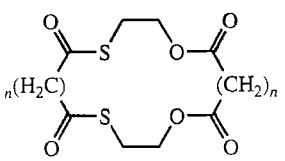
Scheme 7-4. Synthesis of monomacrolactones.



Scheme 7-5. Synthesis of polythialactones L1587 and L1588.

Organotin compounds have also been used for the covalent-template construction of macrocyclic polythia- and poly-S, O-lactones [24, 25]. For example, L1587 and L1588 resulted from reaction of the corresponding dithiols and diacid dichloroanhydrides with dibutyltin dichloride used as the matrix (Scheme 7-5). L1587 is formed mainly when $m = 2$ and $n = 3$, and L1588 when $m = 3$ and $n = 5$ [24].

Similarly, the macrocyclic products L1589–L1592 have been synthesised by reacting the templated 2-mercaptoethanol with the corresponding diacyl dihalides (Eq. 7.9).

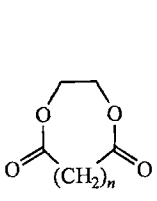


$n = 4$ L1589
$n = 5$ L1590
$n = 6$ L1591
$n = 7$ L1592

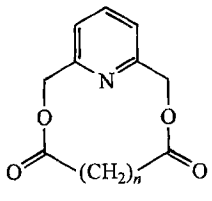
(7.9)

In addition to L1589–L1592 as the main products, small amounts of mono-, tri- and tetra-meric cyclic deivatives, separable by chromatography, result from these template reaction [25]. An X-ray diffraction study of L1591 showed [25] that its structure is similar to that of the all-oxygen tetralactone [6, 10].

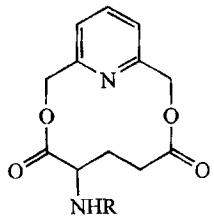
Macrocyclic dilactones such as L1593–L1598 (Eq. 7.10; containing exclusively nitrogen and/or oxygen donors in the macrocycle), L1599–L1602 (Eq. 7.11; incorporating one ring sulphur atom or one sulphoxide functionality), and L1603–L1610 (Eq. 7.12; with an S–S linkage in the cyclic backbone), are assembled by successive reactions of the corresponding diol with $(SnR_3)_2O$ ($R = C_6H_5$, n-C_4H_9) or other organotin derivative, then with diacid fluorides [26, 27].



$n = 4$ L1593
$n = 6$ L1594

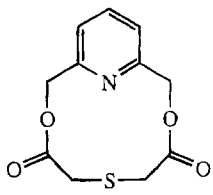


$n = 3$ L1595
$n = 6$ L1596

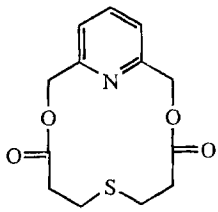


R = H L1597
R = $COOCH_2C_6H_5$ L1598

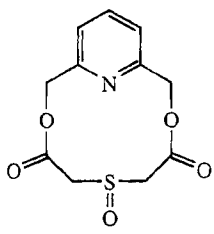
(7.10)



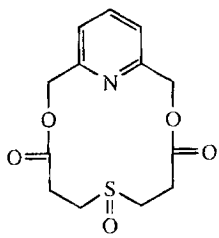
L1599



L1600

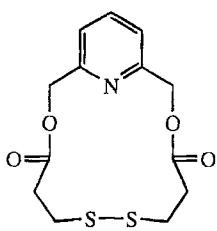


L1601

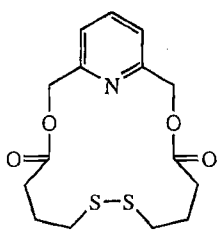


L1602

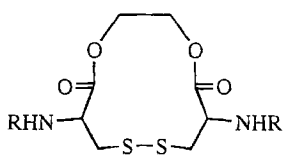
(7.11)



L1603

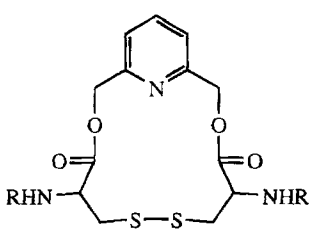


L1604

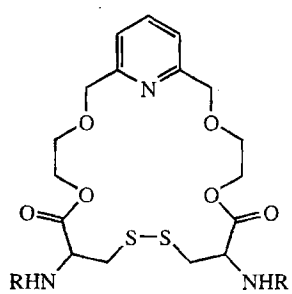


L1605

(7.12)

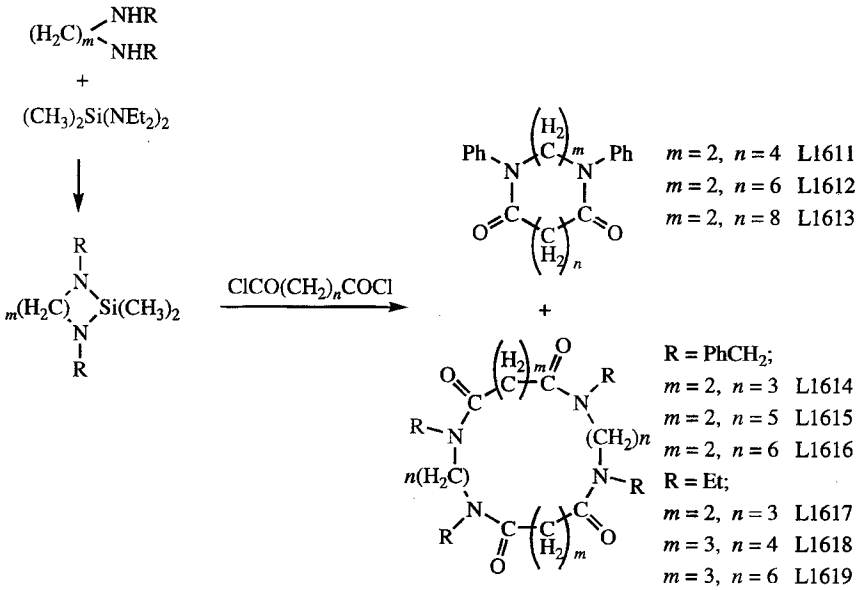


R = $COOCH_2C_6H_5$ L1606
R = $COOCH_2C_6H_4NO_2$-*p* L1607
R = H L1608



R = H L1609
R = $COOCH_2C_6H_5$ L1610

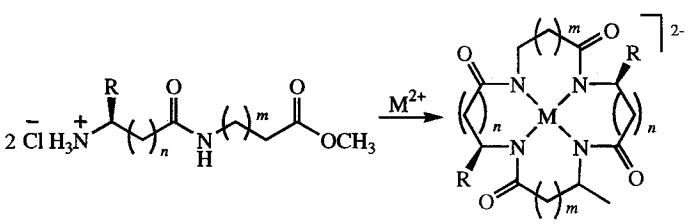
Organosilicon derivatives can be used for the covalent-template synthesis of macrocyclic polylactams [28, 29]. The method includes conversion of acyclic dia-



Scheme 7-6. Synthesis of macrocyclic di- and tetralactams.

mines to cyclic diazasilolidines and reaction of the latter with diacids, their chlorides or esters to form ring-closed polylactams, followed by elimination of the silicon(IV) used as template. The ligson nature predetermines the type of product isolated: if the initial open-chain diamines and diacid units permit the construction of macrocyclic dilactams having an even number of links, the reaction proceeds with their formation, otherwise tetralactams are the sole reaction products. This is shown in Scheme 7-6 for the generation of L1611–L1619.

The synthesis of the 12-, 14-, 16- and 18-membered cyclic tetrapeptides L1620–L1623 has been performed by reacting linear dipeptide esters (or tetrapeptide esters) with non-covalent metal-templates Ni^{II}, Pd^{II} or Cu^{II}-salts in the presence of $NaOCH_3$ as a base in methanol (Eq. 7.13) [30].

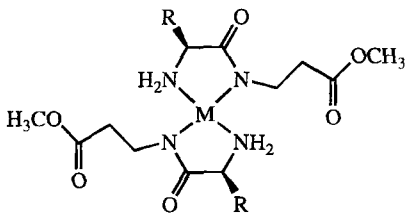


(7.13)

M = Ni, Pd, Cu

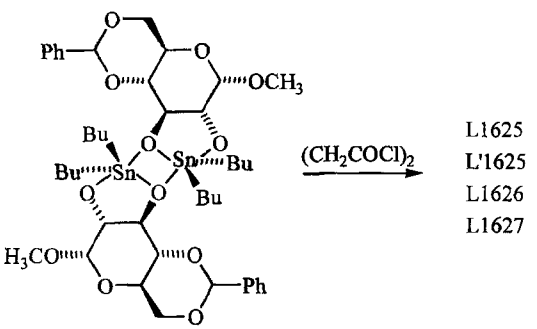
$n = m = 0$; R = CH_3	[Ni(L1620)]
$n = 0$, $m = 1$; R = H, CH_3, $CH(CH_3)_2$, CH_2OH	[M(L1621)]
$n = 0$, $m = 2$; R = H	[Pd(L1622)]
$n = 0$, $m = 3$; R = H	[Pd(L1623)]

The conformation of the dipeptide diester ligson is controlled by its coordination to the metal centre. The generation of the *trans*-bis(dipeptidediester)metal(II) complex shown (Eq. 7.14) is presumably the crucial step preceding macrocyclisation. A concerted cyclisation mechanism cannot be excluded. The pathway involving deprotonation of the coordinated terminal amino group under strongly basic conditions and generation of nucleophilic amido intermediates in concentration, permitting the cyclisation reaction to proceed at a reasonable rate, is likely to be operative. The structure of $[Ph_3PNPPh_3]_2[Pd(L1621)]\cdot 8H_2O\cdot 3CH_3CN$, where R = H, has been confirmed by X-ray diffraction. By treating the corresponding nickel(II) complex with methanol saturated with HCl, metal-free H_4L1621 has been obtained in quantitative yield [30].



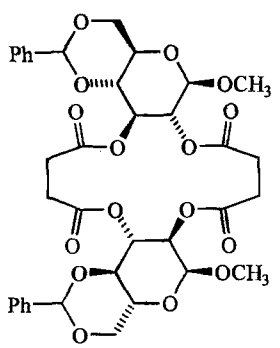
(7.14)

The addition of one equivalent of succinyl chloride at room temperature to a solution of $[Bu_2Sn(L1624)]_2$ in toluene yielded a mixture of four macrocyclic lactones (L1625, L'1625, L1626 and L1627) in 69% overall yield (Eqs. 7.15 and 7.16). These were separated by chromatography [31].

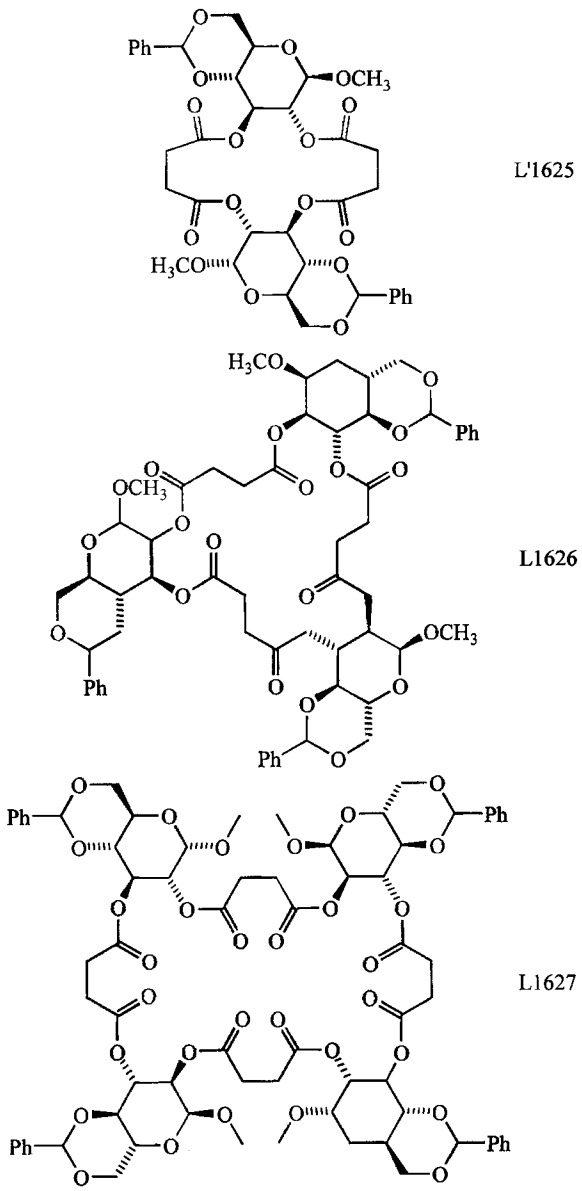


$[Bu_2Sn(L1624)]_2$

(7.15)



L1625



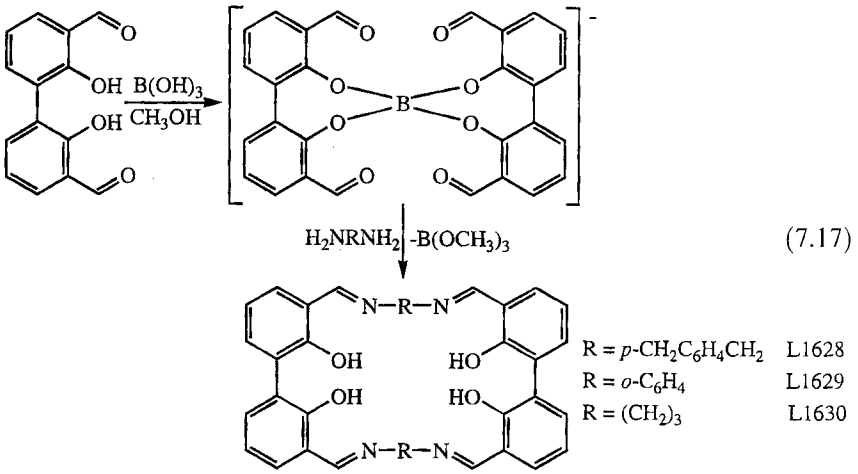
L'1625

L1626

L1627

(7.16)

Other classes of macrocyclic compounds have been also obtained by the covalent-template method, such as the synthesis of L1628–L1630 on a boron(III) matrix (Eq. 7.17) [32, 33].



(7.17)

Attempts to carry out cyclisation of the corresponding ligsons under high-dilution conditions or by using a barium salt as a matrix always resulted in the formation of polymeric products [32].

7.2 References

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Chapter 8

Polynucleating macrocyclic compounds

One of the remarkable features of template processes is the possibility of using them for the design of macrocyclic compounds, and open-chain analogues, potentially able to coordinate two or more identical or different metal ions. The conditions required for the formation of such compounds are the presence of suitable ligsons, selection of the correct matrix, reaction conditions, ratio of reagents and choice of appropriate solvent. A number of binucleating macrocyclic compounds are presented in the previous chapters, alongside their related mononucleating systems. This chapter covers systems specifically designed for polynucleation.

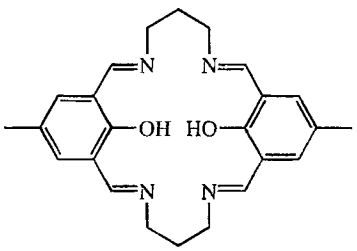
The study of systems containing two or more metal atoms simultaneously complexed by one ligand is of great importance to such fields as: homogeneous catalysis, processes of magnetic exchange between paramagnetic centres, electrical conductivity and bioinorganic chemistry [1–5].

In order to assemble binucleating ligands, dialdehydes that contain carbonyl groups separated by donor atom(s) suitably disposed for chelation are most frequently used. Compounds containing terminal amino groups separated by not less than two CH_2 links are the partners in this case. Such ligsons can also contain additional functional groups, but this condition is not obligatory.

8.1 Binucleating systems based on 4-substituted 2,6-dicarbonylphenol derivatives and simple diamines

The first binucleating macrocyclic compound produced by a template pathway was H_2L1631 (Eq. 8.1), formed by reaction of 1,3-diaminopropane with 2,6-diformyl-4-methylphenol in the presence of various metal salts and isolated as complexes with the respective cations [6]. The compounds Cu_2(L1631)$(ClO_4)_2 \cdot 2H_2O$, M_2(L1631)$Cl_2 \cdot 2H_2O$ (M = Mn, Ni, Zn), M_2(L1631)$Cl_2 \cdot 2CH_3OH$ (M = Co, Fe),

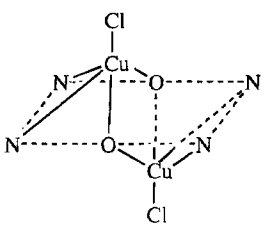
$Cu_2(L1631)Cl_2 \cdot 6H_2O$ and $Ni(H_2L1631)(ClO_4)_2 \cdot H_2O$ were obtained in this way [6].



H_2L1631 (8.1)

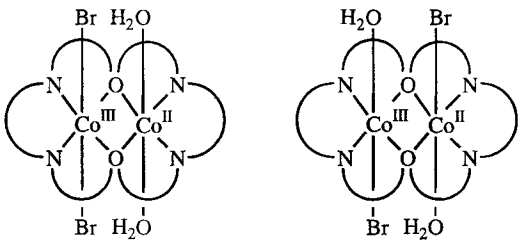
In the absence of metal ions, in the presence of a labile first-row transition metal or in the presence of d^{10} metal ions such as Ni^{II}, Cu^{II} or Zn^{II}, cyclisation does not proceed cleanly [7]. Resin-like polymeric products, which were not identified due to their complete insolubility in common solvents and their involatility, were commonly isolated [6, 8].

An X-ray diffraction study has revealed the structure of $Cu_2(L1631)Cl_2 \cdot 6H_2O$ (Eq. 8.2). The copper atoms of this complex are each in a square-pyramidal environment, with donor atoms of the organic ligand in the plane and chlorine atoms at the opposite vertices of the two di-μ-oxo-linked polyhedra. The binuclear cobalt complexes $Co_2(L1631)Cl_2 \cdot 2CH_3OH$ and $Co_2(L1631)Br_2 \cdot CH_3OH$ have analogous structures [9, 10]. The difference between the structures of $Cu_2(L1631)Cl_2 \cdot 6H_2O$ and $Co_2(L1631)Br_2 \cdot CH_3OH$ is that, whereas the environment of each copper atom in $Cu_2(L1631)Cl_2 \cdot 6H_2O$ is truly square-pyramidal, the environment of the cobalt in $Co_2(L1631)Br_2 \cdot CH_3OH$ is pseudo-square pyramidal. In addition, the cobalt(II) ions are displaced further out of the $(L1631)^{2-}$ ligand plane (3.0 nm) than are the copper(II) ions (2.1 nm) [8, 9].



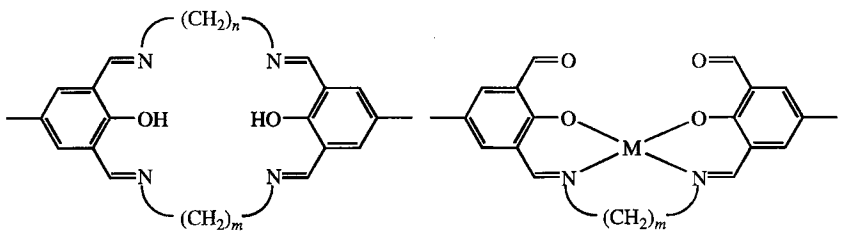
(8.2)

Oxidation of $Co_2(L1631)Br_2 \cdot CH_3OH$ with molecular bromine yielded a number of products depending on the reaction conditions. A compound of stoichiometry $Co_2(L1631)Br_3 \cdot 2H_2O$ was obtained as two isomers (A and B; Eq. 8.3) from a methanolic solution of $Co_2(L1631)Br_2 \cdot CH_3OH$ and bromine in equimolar ratio [10]. X-Ray diffraction studies of these isomers showed that both were binuclear with an octahedral environment around each cobalt ion. They differ in the arrangement of the axial ligands [10, 11].



Isomer A Isomer B (8.3)

Macrocycles H_2L1632 and H_2L1633 have been synthesised as the following coordination compounds: $Ni_2(L1632)Cl_2 \cdot 3H_2O$, $Cu_2(L1632)Cl_2 \cdot C_2H_5OH \cdot 2H_2O$ and $M_2(L1633)Cl_2 \cdot 2H_2O$ (M = Ni, Cu). All these complexes were obtained by the action of a stoichiometric amount of metal salt on [M(L1632)] or [M(L1633)] which, in turn, were synthesised by reaction of the corresponding diamine with [M(L1639)] or [M(L1640)] (Eq. 8.4) [12, 13].



$n = m = 2$ H_2L1632
$n = 2, m = 3$ H_2L1633
$n = m = 4$ H_2L1634
$n = 4, m = 2$ H_2L1635
$n = 5, m = 2$ H_2L1636
$n = 4, m = 3$ H_2L1637
$n = 5, m = 3$ H_2L1638

$m = 2$ [M(L1639)]
$m = 3$ [M(L1640)] (8.4)

The copper(II) complex with H_2L1634 has also been synthesised by the template technique [14]. The structure of $[Cu_2(L1634)Cl_2][Cu_2(L1634)(H_2O)_2]Cl(ClO_4) \cdot 5.5H_2O$, prepared from $[Cu_2(L1634)](ClO_4)_2$, is available [15].

Tetrafluoroborate salts of cobalt(II), nickel(II) and iron(II) complexes with H_2L1631, including $[Fe_2(L1631)(imid)_4](BF_4)_2$ (imid = imidazole), have been reported [16]. The iron complex consists of separate cations $[Fe_2(L1631)(imid)_4]^{2+}$ and anions BF_4^-. Four donor atoms (N_2O_2) of the macrocyclic ligand are coordinated to each iron atom in the plane (phenolic oxygens play the role of μ-oxobridges) and two imidazole molecules in axial positions. Heterobinuclear complexes with H_2L1631 containing bivalent manganese, iron, cobalt, nickel and zinc as the second metal ion are synthesised by the action of the corresponding salts on mononuclear [Cu(L1631)] in methanol [17].

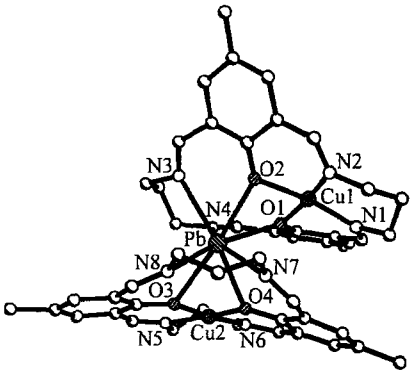


Figure 8-1. The structure of the complex cation in $[PbCu_2(L1631)_2](ClO_4)_2 \cdot DMF$.

Study of the electrochemical behaviour of homo (Cu_2) and hetero (CuM) binuclear coordination compounds with H_2L1631 shows that these substances undergo reversible or quasireversible Cu^{II}–Cu^{I} reduction. If CO is passed through the system simultaneously, it is captured by coordination to the forming copper(I). The reduction of the Cu_2 complex proceeds in a stepwise fashion with final conversion to $Cu^{I}Cu^{I}$. The complex $Cu^{I}Cu^{I}(L1631)(CO)_2$ is formed in contact with carbon monoxide [17–19].

By adding 1,3-diaminopropane to a water-acetonitrile solution containing 2,6-diformyl-4-methylphenol, NaOH and $Pb(ClO_4)_2 \cdot 3H_2O$, the complex $Pb_2(L1631)(ClO_4)_2$ has been obtained, whose structure has been established by X-ray diffraction [20]. These results [20] revealed that the lead(II) ion can act as a template to afford the binucleating macrocycle H_2L1631 in spite of the mismatch between the size of the N_2O_2 coordinating cavity and the radius of the metal ion.

The heterobinuclear complex $Co^{II}Cu^{II}(L1631)Cl_2$ was obtained by interaction of [Co(L1640)] with copper(II) chloride and 1,3-diaminopropane [21]. Controlled oxidation of $[Co^{II}Cu^{II}(L1631)]^{2+}$ with chlorine in methanol afforded the new complex $[Co^{III}Cu^{II}(L1631)Cl_3]$. Unusual polynuclear complexes of the composition $PbM_2L_2X_2$ (L = L1632–L1638 with M = Ni or Cu and X = ClO_4, PF_6, BPh_4 or BF_4) have been obtained by reaction of [M(L1639)] or [M(L1640)] with $H_2N(CH_2)_nNH_2$ ($n = 2$–5) in the presence of lead(II) salts as template sources [22].

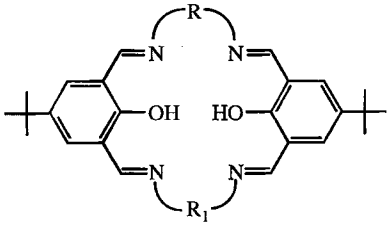
An X-ray diffraction study of $[PbCu_2(L1631)_2](ClO_4)_2 \cdot DMF$ confirmed that it is trinuclear. The compound consists of the cation $[Pb^{II}Cu_2^{II}(L1631)_2]^{2+}$, two perchlorate ions, and a DMF molecule. The perchlorate ions and the DMF molecule are not coordinated. The two [Cu(L1631)] entities (Figure 8-1) in the cation are structurally similar to each other, the copper ion being bound at one of the N_2O_2 sites. The Cu–N and Cu–O bond distances fall in the range 19.1(1)–19.9(1) nm and are slightly shorter than those in $Cu_2(L1631)Cl_2$ (Cu–N 19.78, Cu–O 19.81 nm) [6]. The other N_2O_2 site is coordinated to the lead(II) ion. The latter is sandwiched between two quadridentate [Cu(L1631)] molecules, giving eight-coordinate lead. The configuration around the Pb^{II} is approximately a square antiprism. The Cu1···Pb and Cu2···Pb separations are 34.42(2) and 34.24(2) nm, respectively. The Pb–N and Pb–O distances fall in the range 24.9(1)–27.1(1) nm and are longer than

those in $Pb_2(L1631)^{2+}$ (23.6–24.8 nm) [23], probably because of the strong coordination of the phenolic oxygen to the copper(II) ion [22]. The $[PbCu_2L_2]^{2+}$ species can be used for the preparation of heterodinuclear complexes. For example, reaction of $[PbCu_2(L1635)_2](ClO_4)_2$ with one equivalent of $NiSO_4 \cdot 6H_2O$ and one equivalent of $Ni(ClO_4)_2 \cdot 6H_2O$ in acetonitrile gave $[CuNi(L1635)(ClO_4)(H_2O)]ClO_4$ [24]. Binuclear $CuZn(L1635)(ClO_4)_2 \cdot H_2O$ has been synthesised analogously. According to the X-ray crystal structure determination of the dimethylformamide adduct $CuNi(L1635)(ClO_4)_2 \cdot H_2O \cdot 2DMF$ [24], the complex cation has the composition $[CuNi(L1635)(H_2O)(DMF)]^{2+}$. Square-planar copper(II) (by coordination of the macrocycle via the N_2O_2 site of the ethylene lateral chain) and pseudo-octahedral nickel(II) (by coordination of the macrocycle *via* the N_2O_2 site of the tetramethylene lateral chain, together with DMF and water molecules at the axial sites) are present in this complex.

Condensation of 1,3-diaminopropane and 2,6-diformyl-4-methylphenol in methanol in the presence of H^+ as template affords the protonated 2 + 2 macrocyclic product $[H_4L1631]^{2+}$, which has been isolated as its hexafluorophosphate or tetrafluoroborate salt [25]. The X-ray diffraction structure of $[H_4L1631](PF_6)_2 \cdot CH_3NO_2$ revealed a folded conformation of the protonated macrocycle (the dihedral angle between phenyl rings being 14°) with four protons being involved in intramolecular hydrogen-bonding of the N–H···O type. This unusual conformation is stabilised by inter- and intra-molecular π–π interactions. Both salts are useful starting materials for the synthesis of complexes with inert metal ions such as Pt and Pd [25].

It is noteworthy that sodium 2,6-diformyl-4-methylphenolate reacts easily with 1,3-diaminopropane, leading to a 2 + 2 macrocyclic Schiff base isolated as its disodium complex [26]. The latter undergoes transmetallation by transition metals to yield dinuclear macrocyclic complexes [27].

The syntheses of ligands H_2L1641 to H_2L1647, isolated as dicopper(II) fluoroborate complexes, have been carried out on a copper(II) matrix (Eq. 8.5) [28].



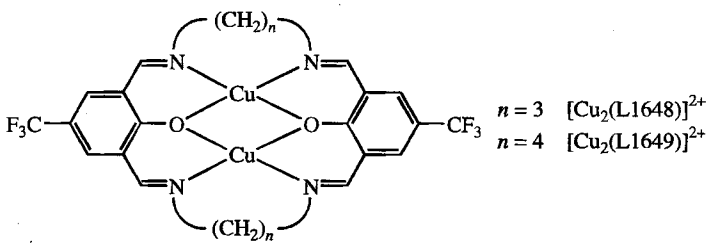
$R = R_1 = (CH_2)_3$	H_2L1641
$R = R_1 = CH_2C(CH_3)CH_2$	H_2L1642
$R = R_1 = (CH_2)_4$	H_2L1643
$R = R_1 = CH_2C(C_6H_5)_2CH_2$	H_2L1644
$R = (CH_2)_3$, $R_1 = CH_2C(CH_3)_2CH_2$	H_2L1645
$R = (CH_2)_3$, R_1 = 2, 2-biphenylene	H_2L1646
$R = (CH_2)_3$, $R_1 = (CH_2)_4$	H_2L1647

(8.5)

Coordination compounds of copper(II) with H_2L1641–H_2L1644 are obtained in one step by reaction of stoichiometric amounts of reagents. The assembly of products containing the latter three ligands ($R \neq R_1$) is carried out in two steps. In the first step mononuclear products containing binucleating ligands of the same geometry as H_2L1639 and H_2L1640 (see Eq. 8.4) are synthesised by reaction of dialdehyde with one of the diamines and a copper(II) salt in the ratio 2:1:1. The substances produced in this way form the final binuclear complexes by

reaction with the second amine and the copper(II) salt [28]. The compounds $Cu^{II}Cu^{II}(L1641)(BF_4)_2$ to $Cu^{II}Cu^{II}(L1647)(BF_4)_2$ are reduced by sodium dithionite to $Cu^{II}Cu^{I}(L1641)BF_4$ to $Cu^{II}Cu^{I}(L1647)BF_4$, respectively [28]. This is one of the relatively rare examples of production of binuclear mixed-valence complexes of macrocyclic ligands without use of electrochemical reduction.

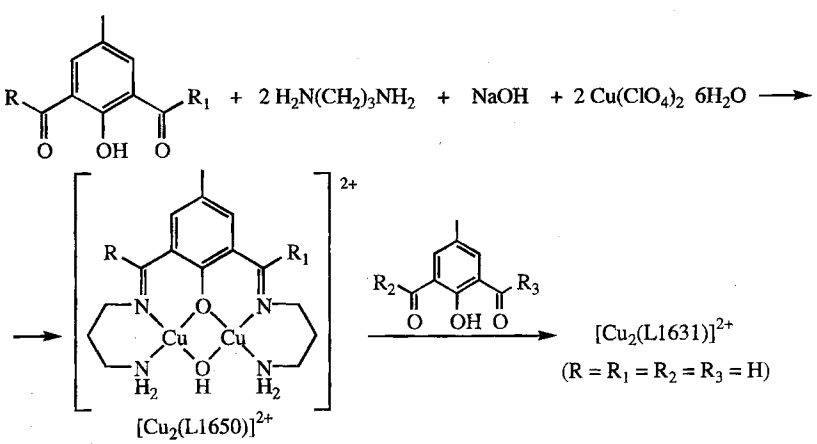
Upon reaction of the corresponding ligsons in the presence of copper(II) as template the products $[Cu_2(L1648)](ClO_4)_2$ and $[Cu_2(L1649)](ClO_4)_2$ were produced (Eq. 8.6). Their binuclear structure was confirmed by an X-ray diffraction study of the former complex [29]. Using $tcnq^-$ (tetracyanoquinodimethane) as the counter anion a complex with the unusual stoichiometry $[Cu_2(L1648)](tcnq)_3$ has been isolated, in which both copper ions are formally in the 2+ oxidation state and one $tcnq^-$ is in fact reduced to $tcnq^0$ [30].



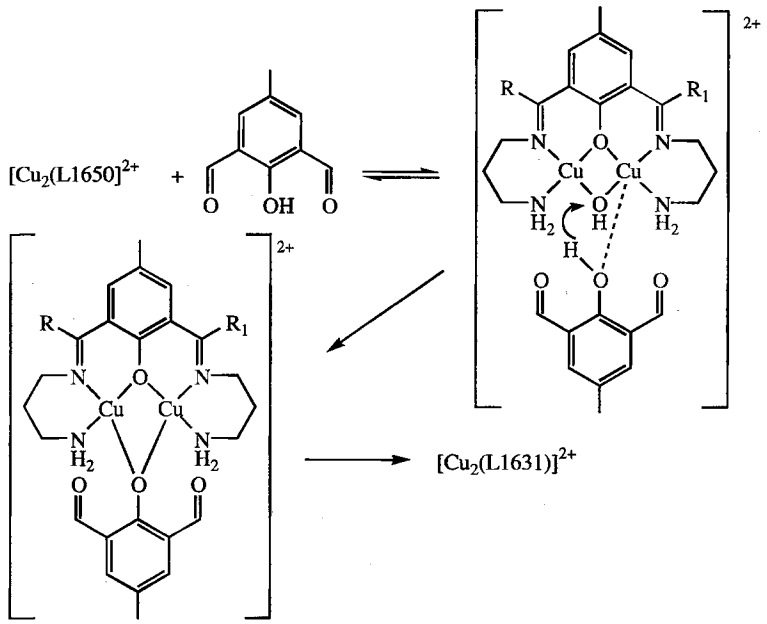
$n = 3$ $[Cu_2(L1648)]^{2+}$
$n = 4$ $[Cu_2(L1649)]^{2+}$ (8.6)

In addition to the methods for assembling the binucleating systems discussed above, the somewhat different route shown in Scheme 8-1 has been proposed for the case of H_2L1631 [31–33].

Variation of substituents R, R_1, R_2 and R_3 in the phenolaldehydes employed as ligsons gives a series of binuclear copper(II) complexes with the following binucleating ligands, which are H_2L1631 derivatives: H_2L1651 ($R = R_1 = R_2 =$



Scheme 8-1. An alternative template route to binucleating macrocyclic ligands.



Scheme 8-2. Suggested mechanism of formation of $[Cu_2(L1631)]^{2+}$.

$R_3 = CH_3$), H_2L1652 ($R = R_1 = R_2 = R_3 = n - C_3H_7$), H_2L1653 ($R = R_1 = R_2 = R_3 = C_6H_5$), H_2L1654 ($R = R_1 = CH_3$, $R_2 = R_3 = C_6H_5$), H_2L1655 ($R = R_1 = H$, $R_2 = R_3 = CH_3$), H_2L1656 ($R = R_1 = H$, $R_2 = CH_3$, $R_3 = C_6H_5$), H_2L1657 ($R = R_1 = R_2 = CH_3$, $R_3 = C_6H_5$), H_2L1658 ($R = R_1 = CH_3$, $R_2 = R_3 = C_6H_5$) [32, 33]. Electrochemical reduction of these compounds proceeds in two steps, in quasireversible fashion, to form complexes of the type $[Cu^{II}Cu^{I}L]^{+}$ and $[Cu^{I}Cu^{I}L]$.

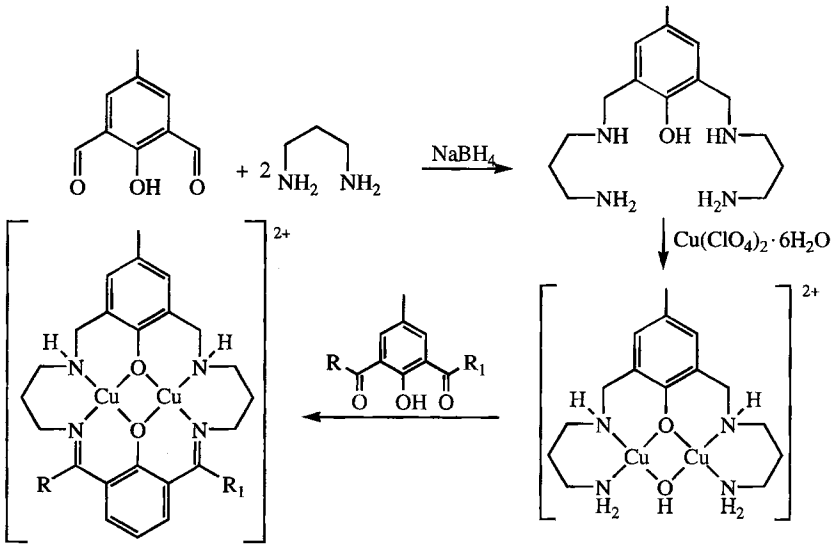
Kinetic studies [32] suggested the mechanism for the formation of the final product from $[Cu_2(L1650)]^{2+}$ to be as shown in Scheme 8-2.

The construction of macrocyclic binucleating compounds formed by the same N_4O_2 donor set but with only two azomethine bonds in the ring has been described [32, 33]. The multistep synthesis of these compounds is shown in Scheme 8-3.

A voltammetric study of $[Cu_2(L1659)](ClO_4)_2 \cdot 2H_2O$ and its L1660 and L1661 analogues demonstrated that these, like the complexes containing four azomethine bonds, were reduced in a two-step quasireversible manner. Comparison of half-wave potentials for the two types of compound for the transition

$$Cu^{II}Cu^{II} \rightleftharpoons Cu^{II}Cu^{I}$$

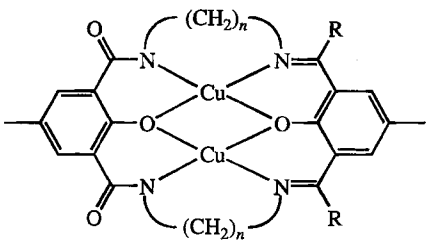
indicates that this step proceeds at more negative potentials for the partially saturated compounds than for those having four C=N bonds. This can be explained by the fact that secondary amine nitrogens in $[Cu_2(L1659)]^{2+}$ to $[Cu_2(L1661)]^{2+}$ act



Scheme 8-3. Template synthesis of partially reduced macrocyclic binucleating systems contained two azomethine bonds.

as stronger donors to copper(II), as compared with the C=N nitrogens, thus stabilising $Cu^{II}Cu^{II}$ to a greater extent [33].

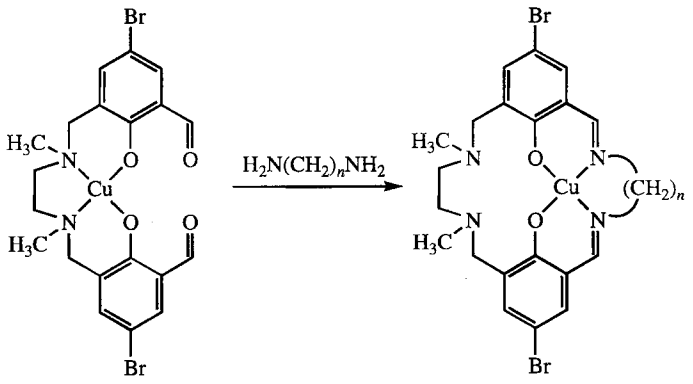
Neutral binuclear macrocyclic copper(II) complexes $[Cu_2(L1662)]$ and $[Cu_2(L1663)]$, involving asymmetric ligands with two deprotonated amides, two azomethine nitrogens, and two phenolic donors, have also been synthesised on templates (Eq. 8.7) [34]. Their structures have been confirmed by X-ray diffraction.



$n = 2$, R = n-C_3H_7 $[Cu_2(L1662)]$
$n = 3$, R = C_6H_5 $[Cu_2(L1663)]$ (8.7)

Starting from [Cu(L1664)] and 1,2-diaminoethane or 1,3-diaminopropane in DMF and methanol, the corresponding macrocyclic complexes [Cu(L1665)] and [Cu(L1666)] have been synthesised (Eq. 8.8) [35]. The acyclic precursor H_2L1664, needed for the synthesis of the corresponding copper(II) complex, can be prepared

by a Mannich reaction of 5-bromosalicylaldehyde, *N*,*N*′-dimethylethylenediamine and paraformaldehyde in refluxing ethanol.

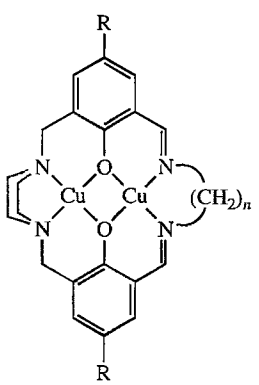


[Cu(L1664)] $n = 2$ [Cu(L1665)] $n = 3$ [Cu(L1666)] (8.8)

The macrocyclic ligands H_2L1665 and H_2L1666 have the same number of azomethine bonds as H_2L1659–H_2L1661. Their arrangement, in contrast, differs and makes the N_2O_2 metal binding sites dissimilar. According to an X-ray diffraction study of [Cu(L1666)]·2*n*-C_3H_7OH [35], the copper(II) ion prefers the $N_{(imine)2}O_2$ environment and shifts from the $N_{(amine)2}O_2$ site in $(L1664)^{2-}$ to the $N_{(imine)2}O_2$ site in $(L1665)^{2-}$ through cyclisation.

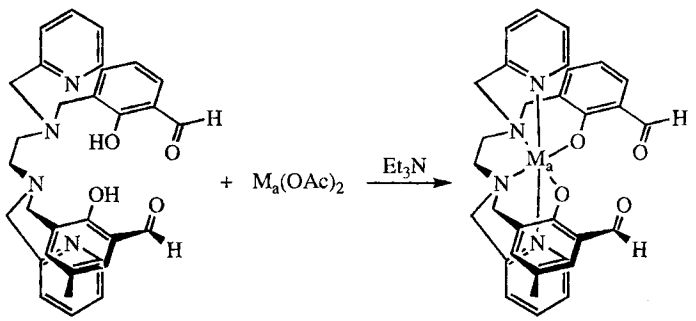
The mononuclear copper(II) complexes of H_2L1665 and H_2L1666 can incorporate a second metal ion giving homo- or hetero-dinuclear complexes [CuM(L1665)]X_2 and [CuM(L1666)]X_2 with M = Cu, Pb, Mn, Co, Ni or Zn and X = Cl or ClO_4 [35, 36]. The structures of [CuPb(L1666)(C_6H_5COO)(DMF)]ClO_4 and [CuZn(L1666)(CH_3COO)]ClO_4 have been reported [36].

Binuclear copper(II) complexes $[Cu_2(L1667)]^{2+}$ to $[Cu_2(L1673)]^{2+}$ have been synthesised [37] following the route successfully exploited to produce H_2L1665 and H_2L1666 and their dicopper(II) complexes (Eq. 8.9) [35, 36].



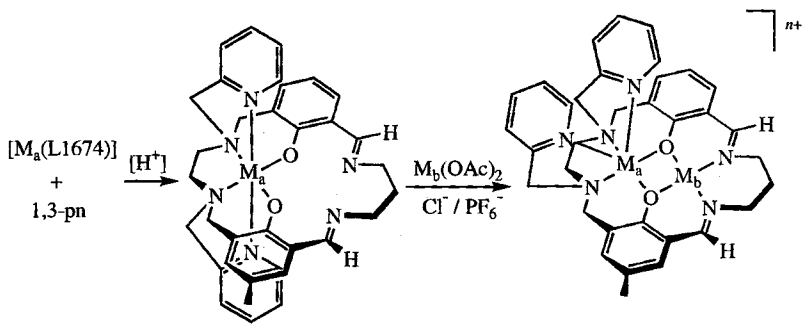
R = CH_3, $n = 2$ $[Cu_2(L1667)]^{2+}$
R = Cl, $n = 2$ $[Cu_2(L1668)]^{2+}$
R = CH_3, $n = 3$ $[Cu_2(L1669)]^{2+}$
R = Cl, $n = 3$ $[Cu_2(L1670)]^{2+}$
R = CH_3, $n = 4$ $[Cu_2(L1671)]^{2+}$
R = Cl, $n = 4$ $[Cu_2(L1672)]^{2+}$
R = CH_3, $n = 6$ $[Cu_2(L1673)]^{2+}$ (8.9)

The more elaborate open-chain precursor H_2L1674 has also been prepared and used for the construction of binucleating macrocyclic ligands [38, 39]. Similar to H_2L1664, the compound H_2L1674 readily forms monometallic complexes by reacting with metal acetate and triethylamine in alcohol solvents (Eq. 8.10).



H_2L1674 $[M_a(L1674)]$ (8.10)

Substitution of the methyl groups in H_2L1664 by 2-methylenepyridyl arms (H_2L1674) provides conditions for full encapsulation of the metal ions, making these kinetically and thermodynamically more stable. Further condensation of the monometallic dialdehyde complex $[M_a(L1674)]$ with 1,3-diaminopropane (1,3-pn) in the presence of H^+ affords the macrocyclic product [M(L1675)] (Eq. 8.11).

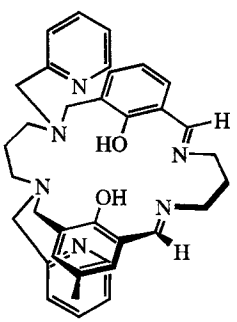


$[M_a(L1675)]$ $[M_a(L1675)M_b]^{n+}$ (8.11)

As expected, no metal shift from the six-coordinate binding site to the four-coordinate $N_{(imine)2}O_2$ binding site was observed during the cyclisation reaction (as was the case for H_2L1664). The second metal added to $[M_a(L1675)]$ led to homo- or hetero-bimetallic species. X-Ray diffraction studies of $[Mn(L1675)MnCl]PF_6$, $[Co(L1675)CoCl]PF_6$, $[Co(L1675)Co](PF_6)_2$ and $[Mn(L1675)(\mu\text{-}Cl)MnCl]PF_6$ revealed all these complexes, in contrast to $[Zn(L1674)]$ and $[Co(L1674)]^+$ to have an unsymmetrical arrangement of ligands at the six-coordinate binding site where

both pyridyl ligands lie on the same side of the macrocycle mean plane. Such an arrangement is impelled by steric demands specific to H_2L1675. The six-coordinate metal binding site in these compounds approaches a trigonal-prismatic geometry, with the $N_{(imine)_2}O_2$ binding site providing a square-planar environment. The coordination number of the metal ion accommodated in the $N_{(imine)_2}O_2$ binding site can be increased to five or even to six by monodentate ligands, as is the case for $[Mn(L1675)MnCl]PF_6$, $[Co(L1675)CoCl]PF_6$ and the mixed valence complex $[Mn(L1675)(\mu\text{-}Cl)MnCl]PF_6$, respectively.

It has been supposed [40] that the symmetrical stereochemistry of the six-coordinate metal binding site in mono- and bimetallic species can be achieved if the ethylenediamine chelate ring is expanded by one aliphatic carbon atom. Indeed, the X-ray structure determination for $[Zn(H_2L1676)](PF_6)_2$ and $[Zn(L1676)Zn(CH_3COO)]PF_6 \cdot CH_3OH$ revealed essentially C_2 symmetric structures with *trans*-coordinated pyridyl ligands (8.12) [40].



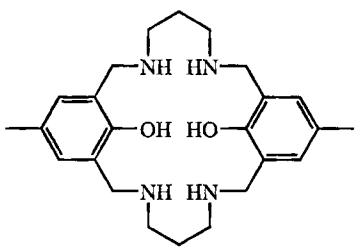
H_2L1676 (8.12)

The monometallic imine complexes of the macrocyclic ligands H_2L1675 and H_2L1676 containing six- and four-coordinate metal binding sites can be reduced by BH_4^- to the corresponding amine complexes [41]. The second metal ion can be introduced into the four-coordinate $N_{(amine)_2}O_2$ site under mild conditions.

Template methodology also enables the synthesis of chiral binucleating macrocyclic ligand systems containing six-coordinate and four-coordinate metal binding sites [42, 43].

The complex $Pb_2(L1631)(NO_3)_2 \cdot 4H_2O$ can be synthesised by addition of a mixture of $Pb(CH_3COO)_2 \cdot 3H_2O$ and $Pb(NO_3)_2$ dissolved in hot DMF to a boiling methanolic solution of 4-methyl-2,6-diformylphenol, followed by immediate addition of 1,3-diaminopropane in methanol and further prolonged heating under reflux (the reagents are taken in the molar ratio 1:1:2) [6]. It is easily reduced by $NaBH_4$ to the lead(II) complex with H_2L1677 (Eq. 8.13). This, when treated with the calculated amount of cold H_2SO_4 solution, generates the metal-free macrocycle, which contains no azomethine bonds in the ring. The complex $Cu_2(L1677)(ClO_4)_2$ is obtained on reaction of H_2L1677 with $Cu(ClO_4)_2 \cdot 6H_2O$

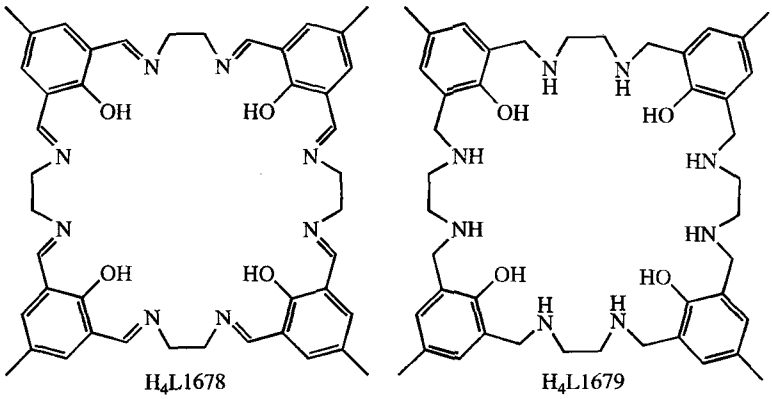
and NaOH in stoichiometric ratio [44]. The two copper atoms bridged by the phenol oxygens are each coordinated to two nitrogen atoms to form a distorted CuN_2O_2 plane. Perchlorate groups play the role of axial bridging ligands and bring the coordination number of the central atom up to six. The most remarkable property of $[Cu_2(L1677)](ClO_4)_2$ is its ability to undergo electrochemical two-step oxidation and two-step reduction to form Cu^{III}-Cu^{III}, Cu^{I}-Cu^{I}, as well as intermediate Cu^{III}-Cu^{II} and Cu^{II}-Cu^{I} species [44]. The first step in reduction of $[Cu_2(L1677)]^{2+}$ proceeds at a more negative potential [32] than that of the complexes $[Cu_2(L1659)]^{2+}$ to $[Cu_2(L1661)]^{2+}$ [33]. Thus on decreasing the number of azomethine bonds in the macrocyclic binucleating ligands the tendency of $[Cu^{II}Cu^{II}L]^{2+}$ systems to reduction is decreased; complexes containing no azomethine bonds can be oxidised to copper(III) products [44]. Related saturated macrocycles differing in the number of methylene units in the lateral chains have been produced analogously. These have been converted into the dinickel(II) species by direct complexation reactions [45].



H_2L1677 (8.13)

A cyclic voltammetric study of binuclear copper(II) compounds of macrocyclic ligands [16, 31–33] showed that reduction of metal cations was complete before there was any reduction of C=N bonds. The reagent $NaBH_4$ reduces C=N bonds, but processes such as the oligomerisation of phenol groups, the hydrolysis of azomethine bonds and the reduction of copper(II) also occur. It is thus clear that, in order to produce systems containing no azomethine bonds, a cation must be used for template assembling of a macrocyclic ligand that has a more negative reduction potential than that of the C=N bond and that can simultaneously form a complex with the final ligand product. The construction of H_2L1631 to H_2L1634 has been reported to occur in the presence of $Mg(NO_3)_2$ or a 1:1 mixture of $Mg(NO_3)_2{\cdot}6H_2O$ and $Mg(CH_3COO)_2{\cdot}4H_2O$ [46, 47]. Complexes of the type $[Mg_2L](NO_3)_2$, resulting from the template reaction, are reduced with $NaBH_4$ after isolation from solution. The solution of the product is then treated with Na_2H_2EDTA, and the metal-free ligand containing no azomethine bonds is generated. It has subsequently been found that the reaction of 4-methyl-2,6-diformylphenol and 1,2-diaminoethane in the presence of magnesium acetate and nitrate, in 2:2:1:1 ratio, affords a 4 + 4 tetraprotonated 36-membered macrocyclic ligand product, isolated as its magnesium(II) complex $[Mg_2(H_4L1678)(NO_3)_2]$-

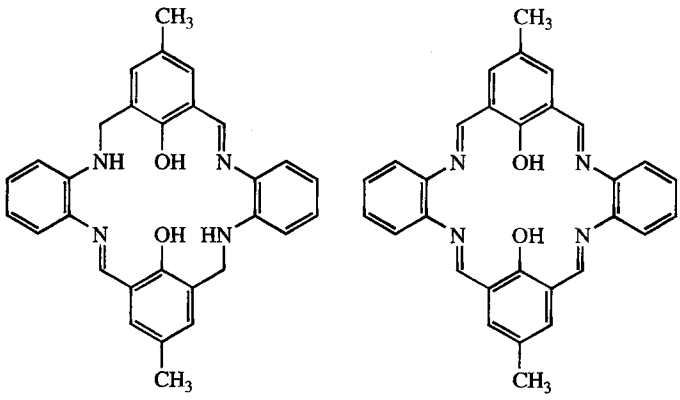
$(NO_3)_2{\cdot}6H_2O$ in 70% yield. Reduction of the latter with $NaBH_4$, followed by demetallation with Na_2H_2EDTA yielded the octaminotetraphenol macrocyclic ligand H_4L1679 in 70% yield (Eq. 8.14) [48, 49].



H_4L1678 H_4L1679 (8.14)

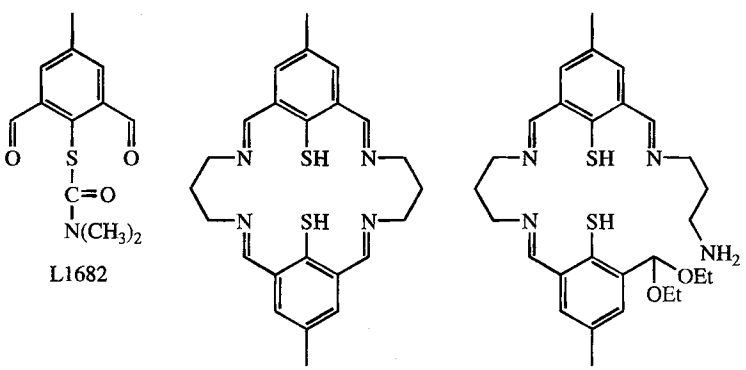
This ligand gives tetranuclear complexes $[Cu_4(L1679)(H_2O)_4](ClO_4)_4$ [50] and $[Ni_4(L1679)(\mu_3\text{-}OH)(\mu_2\text{-}H_2O)(ClO_4)](ClO_4)_2{\cdot}2CH_3COCH_3{\cdot}2H_2O$ [48] on reaction with the perchlorate salts of copper(II) and nickel(II) in the presence of triethylamine. The structure of the latter has been established by X-ray diffraction study [48]. All these chemical transformations confirm the formation of 4 + 4 octaiminotetraphenol macrocycles on magnesium(II) matrices. It is noteworthy that $[Mg_2(H_4L1678)(NO_3)_2](NO_3)_2{\cdot}6H_2O$ on transmetallation with $Cu(ClO_4)_2{\cdot}6H_2O$ produces the dicopper(II) complex $[Cu_2(L1632)(ClO_4)_2]$. The 2 + 2 stoichiometry of the macrocycle produced on transmetallation was confirmed by single-crystal structure determination of $[Cu_2(L1632)(ClO_4)_2]$ [49]. The conversion of H_2L1678 into H_2L1632 is presumably induced by copper(II) ions and requires hydrolytic cleavage of the 4 + 4 macrocycle with subsequent recondensation of the fragments generated to give the 2 + 2 macrocyclic ligand product.

If 1,2-diaminobenzene is employed as ligson instead of 1,2-diaminoethane, condensation with 2,6-diformyl-4-methylphenol in a 1:1 molar ratio in methanol yields the 18-membered diimine–diamine macrocycle H_2L1680 of 2 + 2 stoichiometry (Eq. 8.15), even in the absence of a template metal ion [51]. The macrocyclic nature of H_2L1680 is confirmed by its FAB mass spectrum, in which the peak at m/z 477 corresponding to the molecular ion $[P + H]^+$ is observed. Attempts to perform complexation reactions with lanthanide(III) and yttrium(III) metal ions in a number of solvents failed. When the condensation reaction is carried out in the presence of hydrated lanthanide(III) nitrate in refluxing ethanol only the metal-free macrocycle H_2L1680 is formed. In acetonitrile, however, monometallic complexes with the tetraimine macrocycle H_2L1681 result in good yield [51].



H_2L1680 H_2L1681 (8.15)

The availability of *S*-(2,6-diformyl-4-methylphenyl)dimethylthiocarbamate (L1682) [7, 52], a valuable precursor of 2,6-diformyl-4-methylbenzenethiol, enabled the development of the synthesis of the dithiolate macrocycle H_2L1683, the analogue of H_2L1631 (Eq. 8.16).



L1682 H_2L1683 H_2L1684 (8.16)

The 2 + 2 condensation of the corresponding ligsons can be performed in the presence of redox-inert template metal ions such as Ni^{II} and Zn^{II} [7, 52, 53]. Note that the solvent markedly influences the course of this template process. For example, condensation carried out in acetonitrile in the presence of metal acetate afforded the bimetallic complexes $[Ni_2(L1683)]^{2+}$ and $[Zn_2(L1683)CH_3COO]^+$ in low yield [7, 53]. When isopropanol was used as solvent the reaction in the presence of nickel(II) perchlorate or zinc(II) trifluoromethanesulphonate produced $[Ni_2(L1683)](ClO_4)_2$ and $[Zn_2(L1683)(H_2O)_2](CF_3SO_3)_2 \cdot H_2O$ in 40% and 43% yield, respectively [52]. In ethanol in the presence of nickel(II) the formation of the 2 + 2 macrocycle H_2L1683 has not been achieved. Instead, the acyclic ligand product H_2L1684 in the form of its trinickel complex $[Ni_3(L1684)_2](ClO_4)_2 \cdot H_2O$ has been isolated in 50% yield. Copper(II) proved to be an unsuitable template

for building up H_2L1683 [7]. Redox side-reactions are supposed to accompany the template process. Access to copper(II) complexes has been achieved by transmetallation of $[Zn_2(L1683)(CH_3COO)]^+$ with copper(II) nitrate to give $[Cu_2(L1683)(CH_3OH)_2(NO_3)]^+$ in high yield (75–80%). The structures of $[Ni_2(L1683)](PF_6)_2$ [7, 53], $[Ni_2(L1683)](ClO_4)_2$ [52], $[Zn_2(L1683)(H_2O)_2](CF_3SO_3)_2 \cdot H_2O$ [52], $[Ni_3(L1684)_2](ClO_4)_2 \cdot H_2O$ [52] and $[Cu_2(L1683)(CH_3OH)_2NO_3]PF_6$ [7] have been reported.

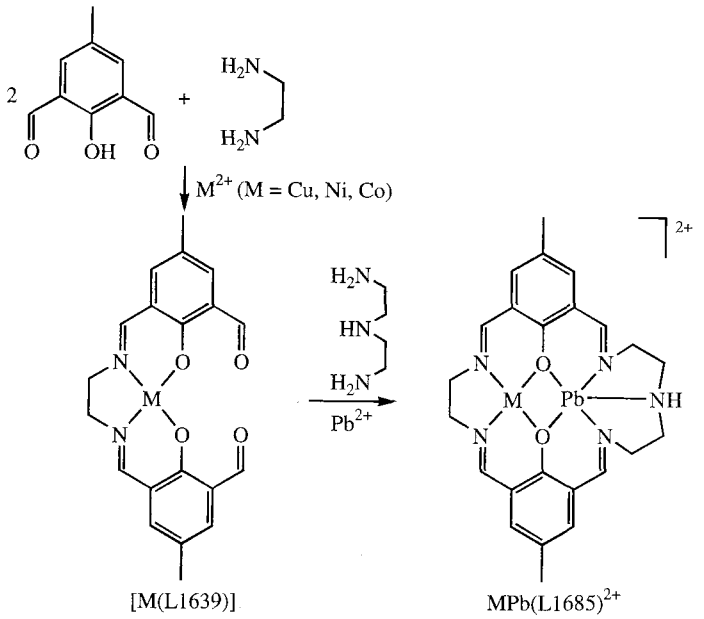
8.2 Binucleating systems based on 4-substituted 2,6-dicarbonylphenol derivatives and diamines containing additional donor atoms or groups

As shown in Section 8.1, template methodology can be successfully exploited to build up dinucleating macrocyclic ligands with similar and dissimilar metal binding sites.

An interesting approach based on stepwise template reactions has been developed for construction of heterodinucleating macrocycles. In addition to two diamine ligsons, differing in their ligating ability or in the number of atoms separating the terminal amino groups, this approach requires two kinds of template metal ions involved successively at the different steps in the cyclisation reaction. For example, using Cu^{II} and Pb^{II} [54], Ni^{II} and Pb^{II} [55] or Co^{II} and Pb^{II} [56] as templates at the different steps of cyclisation and involving three different ligsons – 2,6-diformyl-4-methylphenol, ethylenediamine and diethylenetriamine – the synthesis of the macrocyclic ligand product H_2L1685 containing four- and five-coordinate metal binding sites, has been performed in high yield (Scheme 8-4).

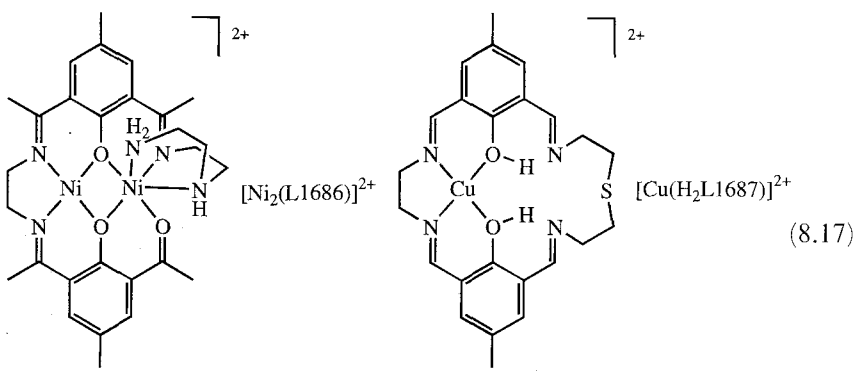
The X-ray structures of $[CuPb(L1685)(CH_3COO)]BPh_4 \cdot DMF$ [54] and $[CoPb(L1685)(CH_3OH)](ClO_4)_2 \cdot CH_3OH$ [56] showed the copper(II) and cobalt(II) ions to be located at the four-coordinate N_2O_2 binding site of the macrocycle, giving a square-planar geometry for copper(II) and a square-pyramidal geometry (with an axial methanol molecule) for cobalt(II). The lead(II) resides at the five-coordinate N_3O_2 site, being additionally bonded to three oxygen atoms of two bridging acetate anions. The lead(II) ion can readily be replaced by a number of divalent transition metal ions (Mn, Fe, Co, Ni, Cu, Zn), by reacting dinuclear $Cu^{II}Pb^{II}$, $Ni^{II}Pb^{II}$ or $Co^{II}Pb^{II}$ complexes of H_2L1685 with metal(II) sulphate in stoichiometric amounts in an appropriate solvent [54–57]. The structures of $[CuMn(L1685)(CH_3COO)]BPh_4$, $[CoM(L1685)(CH_3COO)]ClO_4$ with M = Mn, Fe or Co and $[CoM(L1685)(NCS)]ClO_4$ with M = Mn, Fe or Co are available [54, 57].

It is noteworthy that employment of the same template metal ion, as for example nickel(II), at the second step of cyclisation involving 2,6-diacetyl-4-methylphenol, ethylenediamine and diethylenetriamine inhibited the full cyclisation. As a result the dinickel(II) complex $[Ni_2(L1686)](ClO_4)_2$, containing the open-chain ligand product H_2L1686, has been isolated in 35% yield [58]. According to the X-ray diffraction



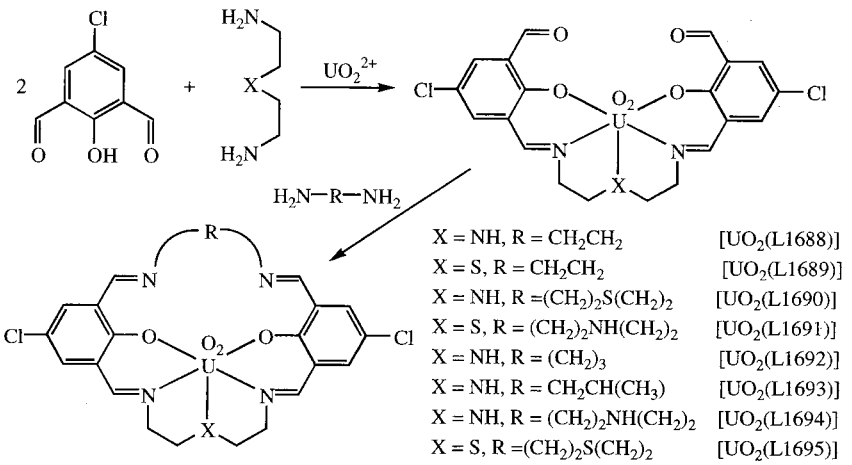
Scheme 8-4. Stepwise template assembly of H_2L1685.

study the complex consists of two dissimilar nickel(II) ions, one square-planar and the other octahedral. The octahedral coordination of the second nickel(II) ion is achieved through coordination of two bridging phenolate oxygens, imine and secondary amine nitrogen donors, unreacted primary amine nitrogen and acetyl oxygen atoms (Eq. 8.17).



(8.17)

The phenol-based dinuclear macrocycle H_2L1687 with N_2O_2 and N_2O_2S metal binding sites has been obtained as the mononuclear copper(II) complex $[Cu(H_2L1687)](ClO_4)_2$ by following Scheme 8-4 but using 3-thiapentane-1,5-diamine instead of diethylenetriamine [59]. Despite the lack of Pb^{II} in the final



Scheme 8-5. Uranyl-promoted synthesis of asymmetric and symmetric dinucleating macrocycles.

product, its employment in the second step is crucial for successful cyclisation. Non-template reaction yielded impure material.

Binucleating asymmetric and symmetric macrocyclic systems have been assembled by using UO_2^{2+} as matrix [60–62]; the synthesis may be carried out following Scheme 8-5.

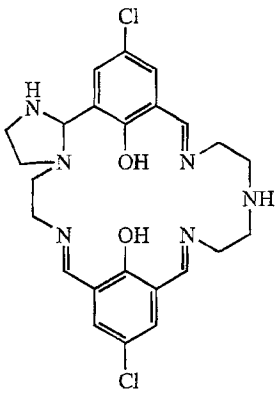
The bulky uranyl ion forms only monometallic products with the ligands listed. However, heterodinuclear complexes $[UO_2M(L1694)]^{2+}$ and $[UO_2M(L1695)]^{2+}$ (M = Ni, Cu) may be prepared by the action of salts of smaller cations (Ni^{2+}, Cu^{2+}) on the monouranyl complex [60–62].

The homodinuclear nickel(II) and copper(II) complexes formed by symmetric ligands H_2L1694 and H_2L1695 are obtained by reacting stoichiometric amounts of starting compounds in one step. Those of asymmetric ligands H_2L1688 to H_2L1693 are assembled stepwise via intermediate (2 + 1) open-chain ligands followed by addition of the second diamine [60–62]. In the latter case homo- and hetero-dinuclear 3d metal complexes can be prepared. Note that products H_2L1690 and H_2L1691 are the same ligand, but different metal-binding sites of the ligand are involved in coordination in the two mononuclear macrocyclic complexes with UO_2^{2+}.

An X-ray diffraction study of $[UO_2(L1695)]$ showed that the organic ligand used only one metal-binding site (N_2O_2S) for coordination to UO_2^{2+} (see Scheme 8-5). Being an uncharged complex, it volatilises without decomposition when heated in vacuum. The presence of the parent peak in the mass spectrum of this complex indicates that its macrocyclic structure remained intact in the gaseous phase [63].

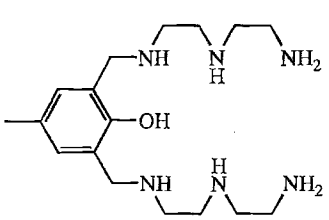
The macrocyclic binucleating ligand H_2L1695 may also be synthesised on lanthanide(III) matrices and isolated as mononuclear complexes with the corresponding cations. The template pathway involves an open-chain intermediate which consists of two dialdehyde and one diamine residues (the first step) and ring closure by addition of a further diamine ligson. The complexes $M(L1695)(NO_3)\cdot nH_2O$ (M = La, n = 4; M = Dy, n = 2) have been isolated in this way [64].

Condensation of equimolar amounts of 2,6-diformyl-4-chlorophenol and diethylenetriamine in the presence of $Ln(NO_3)_3 \cdot 6H_2O$ (Ln = Y^{3+}, La^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Ho^{3+}, Yb^{3+}, Lu^{3+}) in methanol affords complexes isolated in the solid state as $[Ln(H_2L1696)(NO_3)_2]NO_3$ [64–66]. Powder diagrams showed all complexes to be isostructural. An X-ray diffraction study of $[Ln(H_2L1696)(NO_3)_2]NO_3$ with Ln = Tb [64], Eu [65] or Y [66] confirmed the contracted 18-membered structure of the macrocyclic ligand product. The nine-coordinate lanthanide(III) resides at the binding site associated with the expanded lateral chain. The coordination polyhedron of the metal(III) approaches a distorted tricapped trigonal prism where, in addition to five donor atoms of H_2L1696, two nitrate groups are coordinated as bidentate ligands (Eq. 8.18).

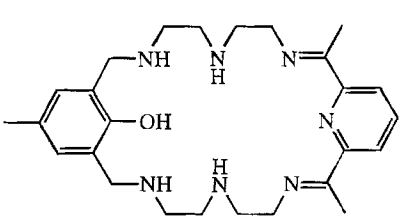


H_2L1696 (8.18)

The unsymmetrical trinucleating macrocycle HL1698 (Eq. 8.19) containing both phenolic and pyridine head units was prepared in the form of its complex $[Pb_2(L1698)(Cl)](ClO_4)_2$ in 54% yield from the reaction of HL1697·6HCl, 2,6-diacetylpyridine, KOH and lead(II) perchlorate in refluxing methanol [67]. The single crystal X-ray analysis showed that all donor atoms of the macrocycle are involved in binding to both lead(II) ions, which have similar coordination environments. Each lead(II) ion is six-coordinate. The dilead macrocyclic units form an infinite chain via a bridging chloride anion. The lead ions can be replaced by transition metal ions. Transmetallation reaction of $[Pb_2(L1698)(Cl)](ClO_4)_2$ with copper(II) perchlorate results in a tricopper(II) complex $Cu_3(L1698)(OH)(ClO_4)_4(H_2O)$ [67]. The formation of this trinuclear complex is confirmed by its FAB mass spectrum, in which a peak corresponding to $[Cu_3(L1698)(OH)(ClO_4)_3]^+$ was present.



HL1697

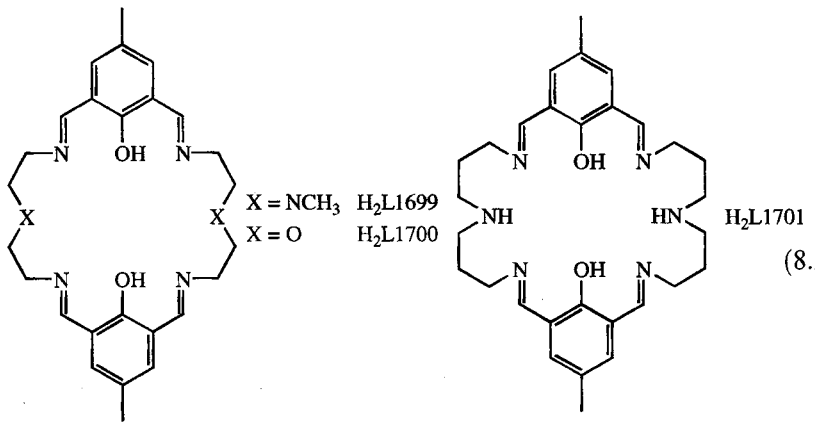


HL1698

(8.19)

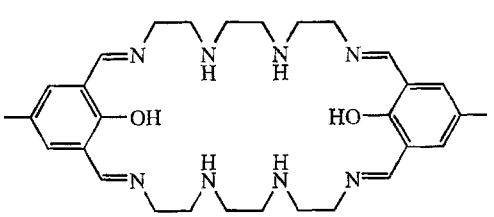
Lanthanide(III) and yttrium(III) ions have been reported to promote 2 + 2 condensation of 2,6-diformyl-4-methylphenol and a rigid 2,6-diaminopyridine ligson [68]. Decreasing the metal ion radii of the lanthanide(III) cations diminishes the yield of the final product, whereas their potential ability to act as a template remains intact.

Manganese(II) and sodium(I) proved to be suitable templates for construction of the symmetrical dinucleating systems H_2L1699, H_2L1700 and H_2L1701 (Eq. 8.20) [69–71].



(8.20)

The product H_2L1702 (Eq. 8.21) is formed on template condensation of 2,6-diformyl-4-methylphenol with triethylenetetramine in alcohol in the presence of lanthanide salts. It is isolated in the form of binuclear products $Ln_2(L1702)(NO_3)_4 \cdot nH_2O$ (Ln = La, Pr, Nd, Ce; $n = 0$. Ln = Pr, Nd, Sm, Eu, Gd, Tm, Yb, Lu; $n = 2$), $Ln_2(L1702)(NO_3)_3(OH)$ (Ln = Eu, Gd, Tb, Dy, Ho, Er), $Gd_2(L1702)X_4$ (X = NO_3, ClO_4), $Nd_2(L1702)(ClO_4)_3(OH)$ and $Gd_2(L1702)(ClO_4)_2(OH)_2$, depending upon conditions (type of alcohol used as solvent, reagent concentrations, nature of anion and cation, temperature) [72–75]. The binuclear character of these complexes was established on the basis of FAB mass spectra [72, 73].

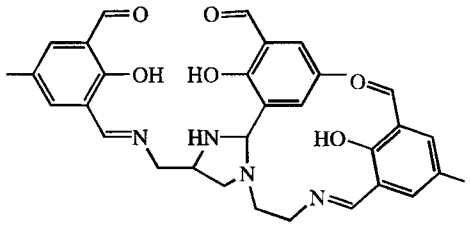


(8.21)

Thus the lengthening of the amine-containing building block by one more $-CH_2CH_2NH-$ unit in H_2L1702, in comparison with H_2L1694, results in the situation that rare earth element cations are suitable for the construction of the corresponding (2 + 2) systems, and are able to form binuclear complexes with this macrocyclic ligand.

However, binuclear coordination compounds of lanthanides with H_2L1702 are

unstable in solution and eliminate one of the two lanthanide ions. This process is followed by hydrolysis of one of the azomethine bonds and condensation of a carbonyl group with a neighbouring secondary (>NH) amino group, as well as by addition of the 2,6-diformyl-4-methylphenol ligson formed in solution and production of mononuclear complexes with a new tripod ligand H_3L1703 (Eq. 8.22) [75].

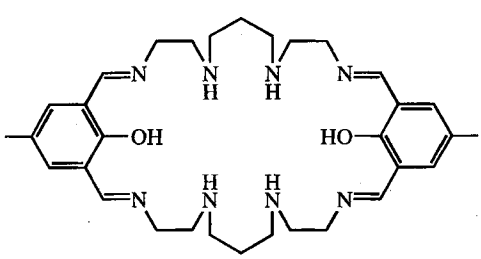


H_3L1703 (8.22)

The formation of such products has been checked by X-ray crystallography of $[Pr(H_3L1703)(NO_3)(OH)]_2(ClO_4)_2 \cdot NaNO_3 \cdot 2H_2O$ and $[Nd(H_3L1703)(NO_3)(H_2O)](NO_3)_2$. The ligand H_3L1703 has also been synthesised on a neodymium(III) matrix, from the corresponding ligsons in stoichiometric ratio [75]. Condensation of an aldehyde group, accompanied by involvement of secondary amino groups upon the assembly of H_3L1703, is likely to be the first example of such a reaction directed by a metal ion. This possibility should be taken into consideration in future syntheses of related ligands [75].

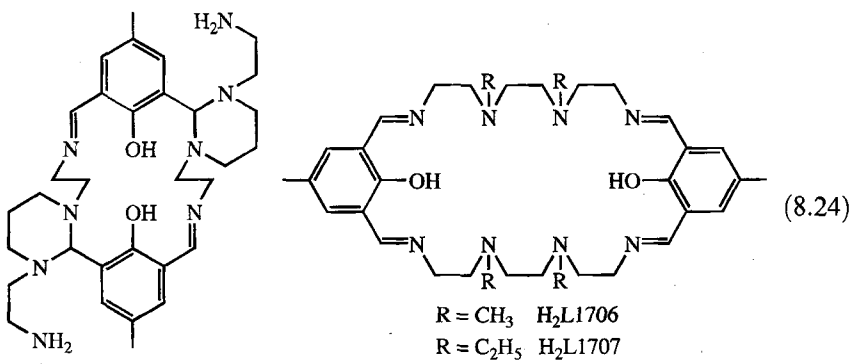
Moving from ligands such as H_2L1694 to species like H_2L1702 enables lanthanides to form mono- and di-nuclear complexes. The 3d elements, with smaller ionic radii, can form dinuclear and even tetranuclear complexes. For instance, the reaction of 2,6-diformyl-4-methylphenol, triethylenetetramine and a copper(II) salt in 2:2:4 molar ratio gives the macrocyclic tetracopper(II) complex $[Cu_4(L1702)(OH)_2](ClO_4)_4$ [76] or $[Cu_4(L1702)(OH)_2](CH_3COO)_2(PF_6)_2 \cdot CH_3OH$ [77]. The tetranuclear structure of the latter has been confirmed by X-ray diffraction, having the composition $[Cu_4(L1702)(OH)_2](CH_3COO)_2(PF_6)_2 \cdot 4CH_3CN \cdot 2Pr^iOH$ when grown from acetonitrile/propan-2-ol [77].

Attempts to synthesise a tetranuclear copper(II) complex of H_2L1704 (Eq. 8.23) failed [78], although this ligand differs from H_2L1702 only in one CH_2 link in each tetramine unit. This minor difference seems to result in some moving apart of NH groups in H_2L1704 as compared with H_2L1702, preventing the OH groups from acting as bridging groups upon complex formation.



H_2L1704 (8.23)

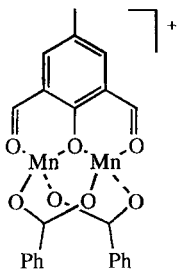
Using lead(II) as template for 2 + 2 condensation of 2,6-diformyl-4-methylphenol and 1,9-diamino-3,7-diazanonane does not result in formation of the corresponding metal complex of H_2L1704. Instead the binuclear complex $Pb_2(H_2L1705)(DMF)_4(ClO_4)_4$ is formed [78]. Thus, as a result of this reaction, the particularly unusual ligand H_2L1705 was assembled (Eq. 8.24). Its construction was directed by metal ion template requirements and was accompanied by significant contraction of the macrocycle. This occurred because the tetramine condenses through a primary amino group with a formyl group of one 2,6-diformyl-4-methylphenol to form a C=N linkage, and through two secondary amino groups with a formyl group of another 2,6-diformyl-4-methylphenol molecule to form a six-membered hexahydropyrimidine ring. One of the primary amino groups of the tetramine remains intact. Formation of this ligand product was confirmed by X-ray analysis of $Pb_2(H_2L1705)(DMF)_4(ClO_4)_4$ [78]. According to the X-ray crystallographic data the phenol oxygens are deprotonated and the corresponding protons are attached to the imino nitrogens.



(8.24)

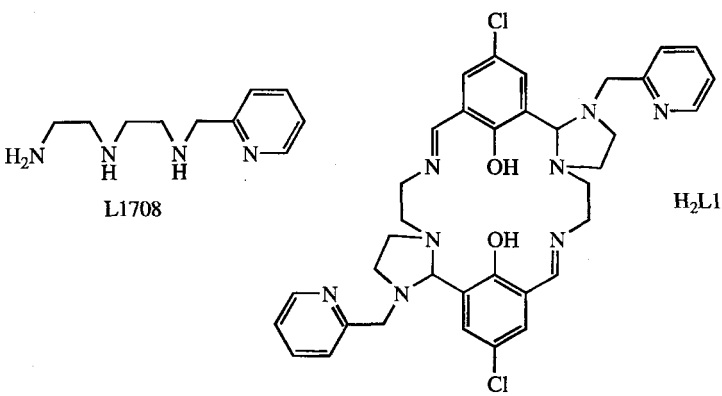
H_2L1705

On using the 3,6-dimethyl-protected derivative of 1,8-diamino-3,6-diazaoctane as ligson for condensation with 2,6-diformyl-4-methylphenol in the presence of lead(II) in DMF, the above kind of contraction of the forming macrocycle cannot take place. As a result the binuclear lead(II) complex $[Pb_2(H_2L1706)(DMF)_4(ClO_4)_2]$ was prepared [79]. Manganese(II) also proved to be suitable for promoting 2 + 2 condensation of 1,8-diamino-3,6-dialkyl-3,6-diazaoctane (alkyl = methyl, ethyl) with 2,6-diformyl-4-methylphenol. As a result tetranuclear manganese(II) complexes $[Mn_4(L1706)(C_6H_5COO)_6]$ and $[Mn_4(L1707)(C_6H_5COO)_6]$ were produced [80]. The formation of the macrocycle H_2L1707 and its ability to bind four manganese(II) ions was confirmed by single-crystal X-ray diffraction of $[Mn_4(L1707)(C_6H_5COO)_6(Pr^iOH)_2]\cdot 2CH_2Cl_2$. It should be noted that the complexes are formed when the corresponding polyamine is added to the mixture of manganese(II) benzoate dihydrate and 2,6-diformyl-4-methylphenol in methanol. Other operating conditions preclude the formation of the tetranuclear macrocyclic species. The formation of the μ-phenoxo-bis(μ-benzoato)dimanganese(II) precursor seems to be crucial for the success of template synthesis (Eq. 8.25).



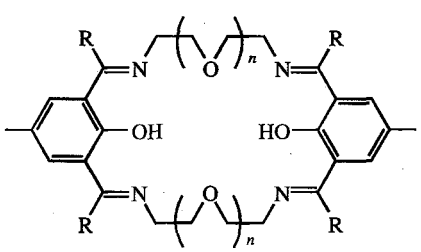
(8.25)

Condensation involving unprotected secondary amino groups also occurs upon reaction of L1708 with 2,6-diformyl-4-chlorophenol in the presence of barium(II) as template, leading to the corresponding complex of H_2L1709 (Eq. 8.26) [81].



L1708 H_2L1709 (8.26)

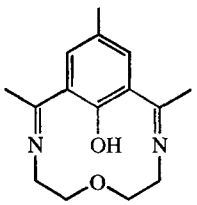
Binucleating macrocyclic compounds H_2L1710 and H_2L1711 are obtained as the corresponding complexes by template condensation of phenoldicarbonyl ligsons with 1,5-diamino-3-oxapentane containing an ether oxygen in its chain (Eq. 8.27) [82].



R = H, n = 1 H_2L1710
R = CH_3, n = 1 H_2L1711
R = H, n = 2 H_2L1712 (8.27)

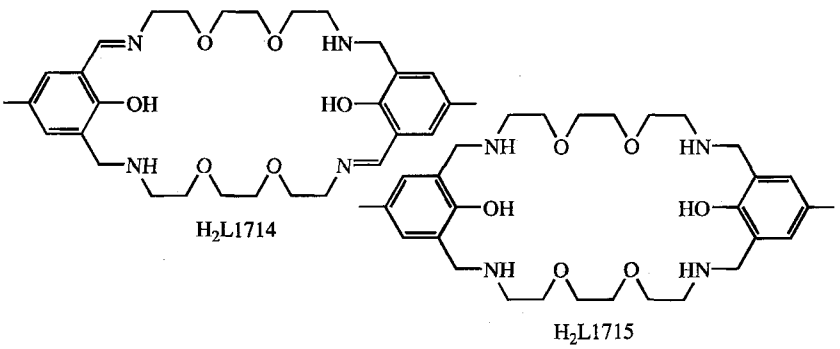
The complexes $M_2(L1710)(CH_3COO)_2 \cdot nH_2O$ (M = Ni; n = 5. M = Cu; n = 4, 5. M = UO_2; n = 0) and $Cu_2(L1711)X_2 \cdot nH_2O$(X = ClO_4, n = 0; X = BF_4, n = 2) have been isolated. It is of note that, in the case of H_2L1710, a diuranyl complex is produced. This is in contrast to the case of structurally similar binucleating ligands containing NH or S in the diamine fragment instead of oxygen [60–62]. Reaction

of the corresponding ligsons in the absence of matrices results in formation of a viscous oil showing a mass spectrum with a peak assigned to the 1 + 1 condensation product HL1713 (Eq. 8.28) [82].



HL1713 (8.28)

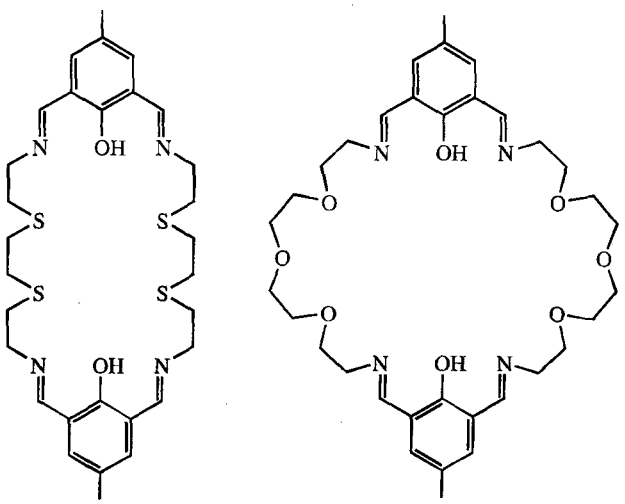
Complexes $Ln_2(L1712)(NO_3)_4 \cdot H_2O$ (Ln = La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb) were prepared [83] in a manner similar to the above-mentioned barium(II) complex of H_2L1709 [81]. An X-ray diffraction study of the gadolinium complex confirmed the encapsulation of a lanthanide cation pair in the macrocycle [83, 84]; the luminescence of the Eu^{3+} complex indicates Eu–Eu interactions [84]. Heteronuclear dilanthanide complexes of H_2L1712 prepared by template synthesis have also been reported [85]. 3,6-Dioxa-1,8-octanediamine reacts with 2,6-diformyl-4-methylphenol with formation of the 2 + 2 macrocycle H_2L1712, even in the absence of a template metal ion [86]. Further reduction of H_2L1712 with $NaBH_4$ in methanol, followed by addition of $Ln(NO_3)_3 \cdot nH_2O$ (Ln = La, Pr, Nd, Eu, Tb), results in dinuclear complexes of H_2L1714 (Eq. 8.29) in which only two imine groups have been reduced to amine functions. In contrast reduction of the dilanthanide(III) imine complexes of H_2L1712 assembled via the template route with $NaBH_4$ in methanol yields the corresponding dilanthanide(III) amine species $Ln_2(L1715)(NO_3)_4$ [86]. The imine–amine macrocycle H_2L1714 can also be obtained in the presence of $Ln(NO_3)_3 \cdot nH_2O$, if $NaBH_3CN$ is employed as reductant [87].



(8.29)

Like H_2L1702, the thiaanalogue H_2L1716 (Eq. 8.30) has been synthesised from 3,6-dithia-1,8-octanediamine and 2,6-diformyl-4-methylphenol in the presence of copper(II) ions and isolated as the tetracopper(II) complex $[Cu_4(L1716)(OH)_2](ClO_4)_4 \cdot H_2O$ [77]. The latter was converted into $[Cu_4(L1716)(OH)_2(CH_3CN)_4]$-

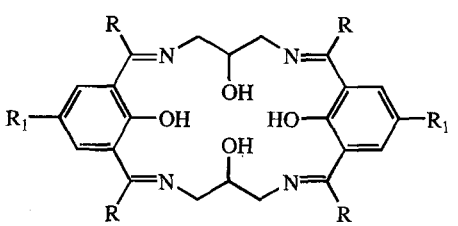
$(PF_6)_4 \cdot 4H_2O$ the structure of which was confirmed by X-ray diffraction methods [77].



H_2L1716 H_2L1717 (8.30)

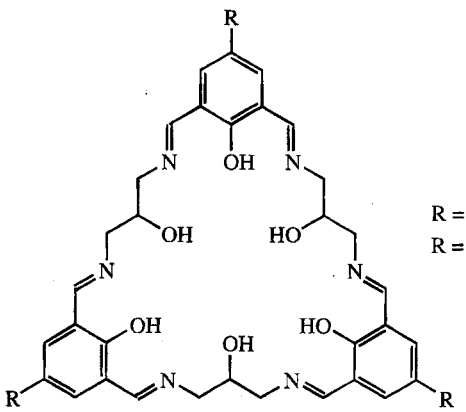
The 2 + 2 condensation of 1,11-diamino-3,6,9-trioxaundecane with 2,6-diformyl-4-methylphenol has been shown to be promoted by zinc(II) as template [88]. The reaction of the corresponding ligsons with zinc(II) acetate, followed by addition of $NaClO_4$ as a counter anion supplier, afforded the tetranuclear zinc(II) complex $[Zn_4(L1717)(\mu\text{-}O_2CCH_3)_4](ClO_4)_2$. The structure of the dichloromethane adduct of the latter, established by X-ray diffraction, showed a centrosymmetric cation containing two pairs of zinc(II) ions bridged by a phenolic oxygen and two acetate ligands. Treatment of this product with $NaBH_4$ in methanol yielded the dizinc(II) complex with the phenol–amine macrocycle, which is a fully reduced form of H_2L1717.

1,3-Diamino-2-hydroxypropane and 2,6-diformyl- or 2,6-diacetyl-4-methylphenol are suitable ligsons for template construction of binucleating macrocyclic systems [82, 89, 90]. In particular, H_4L1718 and H_4L1719, isolated as complexes with the cations used for their assembly, result from reaction of the required ligsons in the presence of the corresponding template. The complexes $Cu_2(H_2L1718)(ClO_4)_2$, $[Ni_2(H_2L1718)(H_2O)_2Cl_2] \cdot 2H_2O$, $[Mn_2(H_2L1718)(CH_3COO)_2] \cdot 2CH_3OH$, $M_2(H_2L1719)(CH_3COO)_2 \cdot nH_2O$ (M = Ni; $n = 5$. M = Cu; $n = 4, 6$. M = UO_2; $n = 4$) and $Cu_2(H_2L1719)(ClO_4)_2$, containing bridging phenolate donors, are synthesised in this way (Eq. 8.31).



R = H, R_1 = CH_3 H_4L1718
R = R_1 = CH_3 H_4L1719
R = H, R_1 = $C(CH_3)_3$ H_4L1720 (8.31)

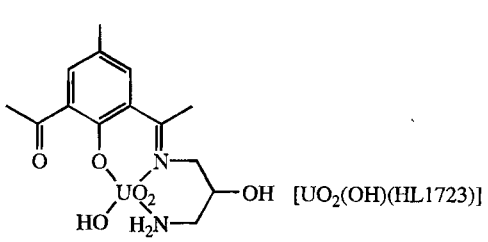
As X-ray crystallographic data for $[Ni_2(H_2L1718)(H_2O)_2Cl_2]\cdot 2H_2O$ and $[Mn_2(H_2L1718)(CH_3COO)_2]\cdot 2CH_3OH$ showed, the potentially octadentate ligand uses only six donors for coordination to the Ni^{II} and Mn^{II} ions. The two alcohol functions of the macrocycle remain protonated and do not coordinate to metal ions [90]. In other words 1,3-diamino-2-hydroxypropane behaves like 1,3-diaminopropane in this template condensation. In order to encourage the participation of alkoxide groups in coordination by their deprotonation, a reaction between 2,6-diformyl-4-methylphenol, 1,3-diamino-2-hydroxypropane and copper(II) or nickel(II) salt (nitrate or perchlorate) was carried out in the presence of triethylamine. Instead of the 2 + 2 stoichiometry expected for this condensation reaction, 3 + 3 cyclisation occured. As a result, hexanuclear macrocyclic complexes of H_6L1721 have been produced (Eq. 8.32) [91].



$R = CH_3$ H_6L1721
$R = C(CH_3)_3$ H_6L1722 (8.32)

Copper(II)-promoted condensation of 2,6-diformyl-4-*tert*-butylphenol with 1,3-diamino-2-hydroxypropane under analogous conditions results in a mixture of 3 + 3 and 2 + 2 macrocyclic complexes $[Cu_6(L1722)(\mu_2\text{-}OH)_3](ClO_4)_3\cdot 4H_2O$ and $[Cu_2(H_2L1720)(NCS)_2]$ [91].

Like H_2L1710 considered above, the ligand H_2L1718 is able to form binuclear species not only with 3d metal cations, but also with the much larger UO_2^{2+} ion. The 1 + 1 open-chain condensation product in the form of the complex $UO_2(OH)(HL1723)$ (Eq. 8.33) has been isolated from reaction of the ligsons on a uranyl matrix in the presence of LiOH [82]. A similar species is likely to be the first intermediate on the way to construction of the final macrocyclic compound H_2L1718.

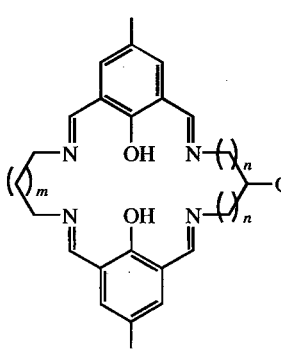


$[UO_2(OH)(HL1723)]$ (8.33)

Barium(II) is an effective template for the synthesis of H_4L1718 and H_4L1719, although they form mononuclear coordination compounds $[Ba(H_4L1718)(NCS)_2]\cdot 2H_2O$ and $[Ba(H_4L1719)(ClO_4)_2]$ [89, 92]. An X-ray diffraction study of $[Ba(H_4L1719)(ClO_4)_2]$ showed the barium ion to be eight-coordinate with four protonated OH groups, two nitrogen donors of the ligand positioned diagonally, and two perchlorate oxygens [89]. In this connection it should be noted that strontium(II) is also suited to the synthesis of H_4L1719, but forms a binuclear complex with this ligand. This difference from barium(II) may be attributed to the fact that the cation radii (11.3 nm for Sr^{2+} and 12.9 nm for Ba^{2+}) are close to the values that promote the formation of mono- or binuclear products with ligands of this type.

Reaction of ligsons in the presence of $Pb(ClO_4)_2\cdot 6H_2O$ in methanol yielded three products, which have been characterised as mononuclear $Pb(H_4L1718)(ClO_4)_2$, binuclear $Pb_2(H_2L1718)(ClO_4)_2$, and a salt of the protonated ligand $(H_6L1718)(H_2O)_2(ClO_4)_2$. The X-ray crystal structure of each of these compounds has been determined [92]. The initial product of the reaction is the binuclear complex. However, if the reaction mixture is allowed to stand for several days the mononuclear complex and ligand salt are obtained, the amount of the latter increasing with time. Pure samples of $Pb(H_4L1719)(ClO_4)_2$ and $Pb_2(H_2L1719)(ClO_4)_2$ are quite stable and remain unchanged even after 48 h refluxing in methanol. It seems therefore that loss of a metal ion from these complexes requires the presence of acid in solution in order for the accompanying protonation step to occur. The compound $(H_6L1718)(H_2O)_2(ClO_4)_2$ can also be prepared directly, by reaction of ligsons in the presence of perchloric acid [92]. Use of $Pb(NCS)_2$ in the template reaction resulted in the formation of only one complex, $Pb(H_4L1718)(NCS)_2\cdot 2H_2O$, under all conditions tried [92].

Binuclear coordination compounds $[Mn_2(HL1724)X_2]$ (X = Cl, Br) and $[Mn_2(HL1724)(CH_3COO)]ClO_4$ were obtained by the template reaction of the manganese(II) complex of H_2L1640 with 1,3-diamino-2-hydroxypropane in methanol. Boiling the latter with CH_3ONa in methanol gives rise to $Mn_2(L1724)ClO_4$, in which both phenol and alcohol ligand protons are substituted by the metal. The X-ray diffraction study of $[Mn_2(HL1724)(CH_3COO)]ClO_4$ revealed a structure with binuclear units joined together by bridging acetate groups to form an infinite chain (Eq. 8.34) [93].

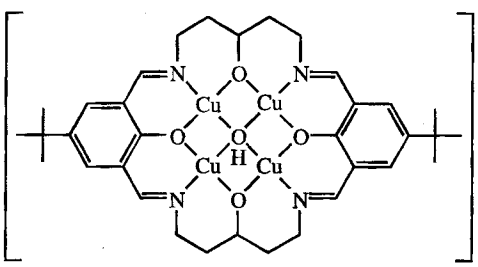


$m = n = 1$ H_3L1724
$m = 0, n = 1$ H_3L1725
$m = 0, n = 2$ H_3L1726 (8.34)

Heterodinuclear complexes $CuPb(HL1724)(ClO_4)_2\cdot DMF\cdot CH_3CN$,

$CuPb(HL1725)(ClO_4)_2 \cdot 2A$ (A = DMF, H_2O), $CuPb(L1724)ClO_4 \cdot \frac{1}{2}H_2O$, $CuPb(L1725)ClO_4 \cdot 2H_2O$ and $CuPb(L1726)Cl \cdot H_2O$ were synthesised by addition of a methanolic solution of 1,3-diaminopropan-2-ol or 1,5-diaminopentan-3-ol dihydrochloride together with sodium methoxide or hydroxide to a mixture of [Cu(L1639)] or [Cu(L1640)] and $Pb(ClO_4)_2 \cdot 3H_2O$ in DMF. The complex $[CuPb(HL1724)(ClO_4)(DMF)](ClO_4)$ has been structurally characterised by single crystal X-ray analysis. The Cu^{II} is bound to the four (N_2O_2) coordination sites of the macrocyclic ligand in a planar configuration. The Pb^{II} is bound to the five-donor N_2O_3 set (including the lateral chain alcohol oxygen atom in protonated form) and assumes a seven-coordinate geometry with a monodentate perchlorate ion and a DMF molecule [94].

Template synthesis of the ligand H_4L1727, isolated as $[Cu_4(L1727)(OH)](NO_3)_3 \cdot 3H_2O$, is carried out by boiling a methanol–ethanol solution of 2,6-diformyl-4-*tert*-butylphenol, 1,5-diamino-3-hydroxypentane and copper(II) nitrate in the molar ratio 1:1:2 (Eq. 8.35) [95].

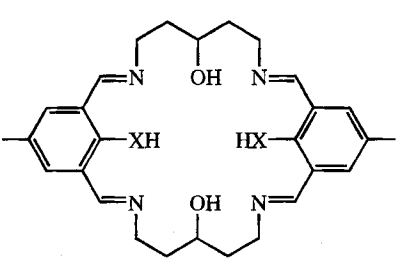


(8.35)

$[Cu_4(L1727)(OH)](NO_3)_3 \cdot 3H_2O$

Thus only a slight symmetric lengthening of the chain, by two methylene groups on going from 1,3-diamino-2-hydroxypropane to 1,5-diamino-3-hydroxypentane, leads to the surprising transition from binucleating (H_4L1718 and H_4L1719 [82]) to tetranucleating systems (H_4L1727) [95]. The structure of $[Cu_4(L1727)(OH)](NO_3)_3 \cdot 3H_2O$ has been established by X-ray diffraction; the square-planar coordination of the oxygen of a μ_4-OH group, to the copper(II) ions in this complex, is an unusual feature [95].

The tetranuclear mixed-valence manganese complex $[Mn_2^{II}Mn_2^{III}(L1728)\text{-}O(CH_3COO)_3Cl(CH_3OH)] \cdot 3CH_3OH$ was obtained from the reaction of 2,6-diformyl-4-methylphenol with 1,5-diamino-3-hydroxypentane in the presence of manganese(II) acetate, in a methanol–ethanol mixture (Eq. 8.36) [96].



X = O H_4L1728
X = S H_4L1729

(8.36)

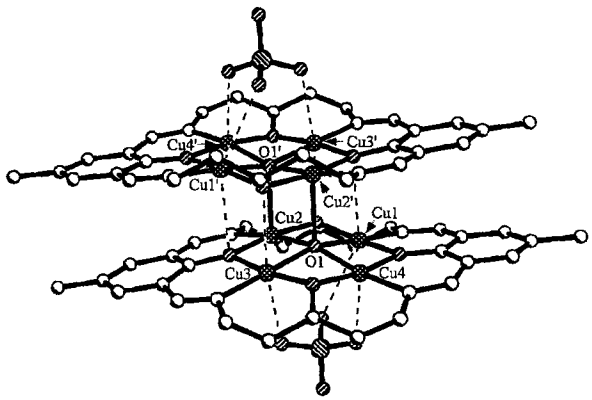


Figure 8-2. The structure of the $[Cu_4(L1728)O(ClO_4)]_2^{2+}$ cation.

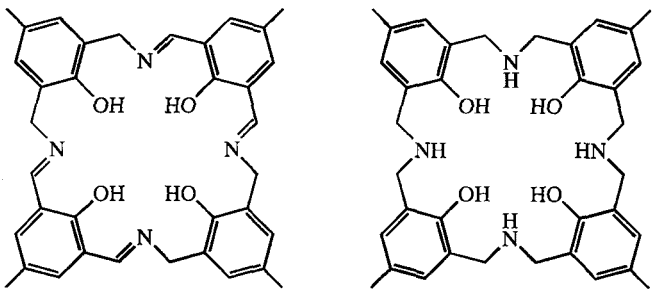
An X-ray structural study of this complex showed that, in contrast to $[Cu_4(L1727)(OH)](NO_3)_3 \cdot 3H_2O$ [95], the macrocycle is not planar. The mean planes of the two phenol rings are inclined to each other at an angle of 38.5°. The alcohol and phenol groups of the macrocycle are all deprotonated and each bridges two manganese ions, so that the ligand is octadentate. The coordination spheres of the metal ions are completed by a central oxoanion (bound to each manganese ion), three bridging acetate groups, a chloride ion and a methanol molecule. As a result each metal ion is six-coordinate and approximately octahedral [96].

The structure of $[Cu_4(L1728)O(ClO_4)]_2(ClO_4)_2 \cdot 2H_2O$ also turned out to be very unusual (Figure 8-2) [97]. The packing of this compound in the crystal is such that two tetranuclear near-planar macrocyclic complexes form dimeric units $[Cu_4(L1728)O(ClO_4)]_2^{2+}$. In each macrocycle the arrangement is similar to that reported for $[Cu_4(L1727)OH]^{2+}$. The four copper atoms are coplanar, and each is coordinated to an imine nitrogen atom, to bridging phenoxide and alkoxide donors, and to a central oxygen donor. In $[Cu_4(L1727)OH]^{2+}$ the central species is a hydroxo group located in the plane of the four copper atoms [95]. In the present complex the central moiety is a five-coordinate oxoanion, which is displaced by 2.9 nm from the mean plane of the four copper ions. The coordination sphere of O1 is completed by Cu2′, a copper atom from a second macrocyclic unit. This bond and the symmetry-related Cu2–O1′ linkage hold the two macrocyclic units together in a centrosymmetric dimer. In addition, there are weaker interactions involving Cu1 and Cu3. The outer faces of the dimer are blocked by perchlorate ions which are bound, in tripod fashion, to the Cu_4 array. It seems that this may have been the first structurally characterised example of perchlorate binding as a tripodal (μ_3-) ligand [97].

Employment of 2,6-diformyl-4-methylthiophene instead of the corresponding phenol ligson does not preclude the template formation of a 2 + 2 macrocycle upon condensation with 1,5-diamino-3-hydroxypentane. The tetranickel(II) complex $[Ni_4(L1729)(OH)(CH_3CO_2)_3(CH_3CO_2H)] \cdot CH_3OH$ was prepared from reaction of $Ni(CH_3COO)_2 \cdot 4H_2O$ and 2,6-diformyl-4-methylthiophenol, followed by dropwise addition of 1,5-diamino-3-hydroxypentane in a methanol-isopropyl alcohol mixture under an inert atmosphere [98]. The tetranuclear structure of the nickel(II)

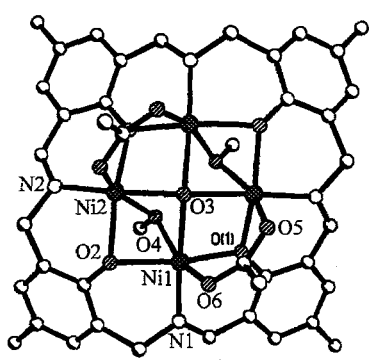
complex of the 2 + 2 macrocyclic ligand product H_4L1729 was confirmed by X-ray diffraction.

Like diamino alcohols, diaminophenols (aromatic analogues of 1,5-diamino-3-hydroxypentane) turned out to be extremely useful counterparts in template condensation with 2,6-diformyl-4-substituted phenols. Tetranuclear nickel and zinc complexes of the macrocyclic Schiff base H_4L1730 formed by 2 + 2 condensation of 2,6-diformyl-4-methylphenol and 2,6-bis(aminomethyl)-4-methylphenol in methanol, have been prepared (Eq. 8.37) [99].

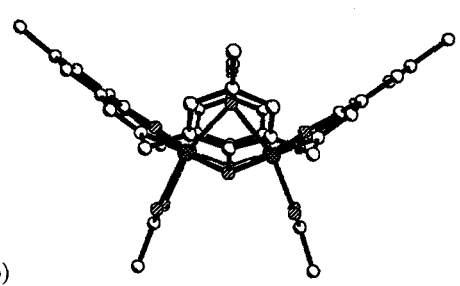


H_4L1730 H_4L1731 (8.37)

X-Ray diffraction studies of $Ni_4(L1730)(CH_3COO)_2(OH)(CH_3O{\cdot}H{\cdot}OCH_3){\cdot}4CH_3OH$ and $Zn_4(L1731)(CH_3COO)_3(OH){\cdot}2.64CH_3OH{\cdot}2.5H_2O$ confirmed the tetranuclear structure of both complexes (Figures 8-3 and 8-4) [99]. In the Ni_4



(a)



(b)

Figure 8-3. (a) Structure of $Ni_4(L1730)(CH_3COO)_2(OH)(CH_3O{\cdot}H{\cdot}OCH_3)$ in the tetramethanolate complex – view down the two-fold axis. (b) Structure of $Ni_4(L1730)(CH_3COO)_2(OH)(CH_3O{\cdot}H{\cdot}OCH_3)$ in the tetramethanolate complex – view approximately perpendicular to the two-fold axis.

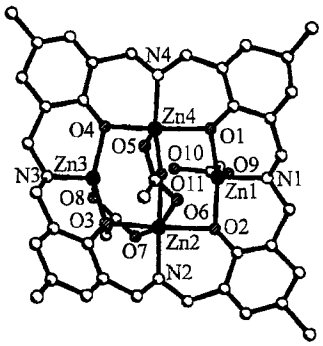


Figure 8-4. Structure of $Zn_4(L1730)(CH_3COO)_3(OH)$ in its hydrate/methanol solvate.

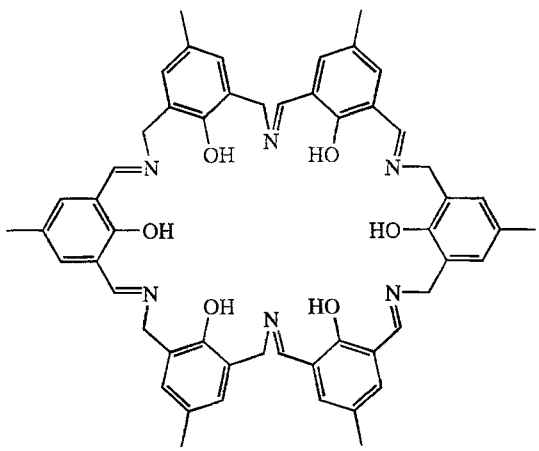
compound the four nickel(II) ions are located at the corners of a rectangle with edges 27.88(1) and 29.36(1) nm. An unusual μ_4-hydroxo group is located with its oxygen atom about 6.0 nm above midpoint of the Ni_4 cluster; formally the oxygen should be able to donate only three electron pairs to form donor-acceptor bonds. An unusual, strongly hydrogen-bonded $[CH_3O{\cdot}H{\cdot}OCH_3]^-$ unit with a short O···O separation of 25.09(7) nm bridges the face of the Ni_4 group on the side opposite to the μ_4-hydroxo group, each methoxo oxygen being equally attached to two nickels. The arrangement of the macrocyclic ligand resembles a bowl, with the Ni_4 group in the bottom. The $[CH_3O{\cdot}H{\cdot}OCH_3]^-$ unit is inside the bowl. Two acetate units bridge edges of the Ni_4 group on the outside of the bowl. A similar but less symmetrical bowl-like ligand arrangement is present in $Zn_4(L1730)(CH_3COO)_3(OH){\cdot}2.64CH_3OH{\cdot}2.5H_2O$; the Zn_4 group is markedly distorted from a square, being no longer planar and having a short (36.32(7) nm) diagonal and a long (47.42(7) nm) diagonal. A hydroxo group bridges the short diagonal with normal Zn–O bonds of length 19.7(3) and 20.6(3) nm, but it also interacts less strongly with the other two zincs at distances 21.7(2) and 26.0(2) nm. One acetate bridges the short diagonal on the side opposite to the hydroxo group and on the inside of the bowl. A second acetate bridges an edge of the Zn_4 cluster and the third acetate is monodentate but hydrogen-bonded to the hydroxo group. One zinc is intermediate between four- and five-coordinate, two are five-coordinate, and the fourth is six-coordinate.

Like nickel(II) and zinc(II), manganese(II) is able to control the 2 + 2 condensation between 2,6-diformyl-4-methylphenol and 2,6-bis(aminomethyl)-4-methylphenol. In contrast, however, the final ligand product H_4L1730 is able to accommodate only two manganese ions within the macrocyclic cavity. An X-ray diffraction study of the complex $[Mn_2(H_2L1730)(\mu\text{-}O_2CCH_3)(\mu\text{-}OH)(CH_3OH)_2]^{2+}$, obtained by reaction of manganese(II) acetate with the corresponding ligsons in the presence of $LiCH_3COO$ and $NaClO_4$, revealed its dinuclear structure with both manganese centres being six-coordinate in oxidation state +3 [100]. Attempts to isolate Mn_4 complexes of H_4L1730 failed.

The Zn_4 complex underwent demetallation when treated with HBF_4. The metal-free 2 + 2 macrocycle was isolated in its diprotonated form as $H_6L1730(BF_4)_2$ [100]. The chloride salt $(H_6L1730)Cl_2$ is formed on reaction of the corresponding

ligsons in the presence of H^+ as template. The template role of H^+ was deduced from the X-ray diffraction study of $(H_6L1730)Cl_2$, which revealed both protons to be involved in intramolecular hydrogen-bonding [100]. Reduction of $(H_6L1730)Cl_2$ with $NaBH_4$ in ethanol produces the tetramino macrocycle H_4L1731 [101]. Direct complexation reaction of the latter with zinc(II) acetate in methanol in the presence of tetraethylammonium hydroxide gives rise to a tetrazinc complex, whereas cobalt(II) acetate in analogous conditions produces a trinuclear cobalt(III) complex with one metal-binding site provided by H_4L1731 remaining vacant [101].

Template condensation of 2,6-bis(aminomethyl)-4-methylphenol monohydrochloride with 2,6-diformyl-4-methylphenol in the presence of copper(II) acetate monohydrate and tetrabutylammonium tetrafluoroborate (1:1:2:excess) in boiling methanol proceeds via the (3 + 3) pathway giving the product $[Cu_6(L1732)(CH_3COO)_2(OH)_2(CH_3OH)_2(H_2O)](BF_4)_2 \cdot 4.4CH_3OH$, where H_6L1732 is the macrocyclic hexaphenolic ligand shown (Eq. 8.38) [102].



H_6L1732 (8.38)

X-Ray examination revealed this complex to consist of hexanuclear cations $[Cu_6(L1732)(CH_3COO)_2(OH)_2(CH_3OH)_2(H_2O)]^{2+}$ with BF_4^- ions and lattice methanol. The general view of the complex cation is shown in Figure 8-5.

This is a rare example of a complex in which a single macrocyclic ligand binds six copper(II) atoms in close proximity. This hexanuclear complex and related species may provide the opportunity for devising and studying previously unobserved types of molecular trapping and of multimetal-promoted processes within the macrocyclic cavity; the associated redox chemistry will clearly be rich and interesting [102].

The Schiff-base macrocycle H_2L1733 (Eq. 8.39) with increased coordination capacity has been assembled in the presence of lanthanum(III) acetate from 6,6′-bis(aminomethyl)-2,2′-bipyridyl and 2,6-diformyl-4-methylphenol and isolated as the homodinuclear complex $[La_2(L1733)(O_2CCH_3)_4] \cdot 4CH_3CN \cdot 3H_2O$ [103]. X-Ray crystallographic study of the latter showed that all ten donor atoms of the macrocycle are involved in coordination to two identical La^{III} centres. A coordination number of 10 for each La^{III} is completed by two bidentate acetate anions. Reduc-

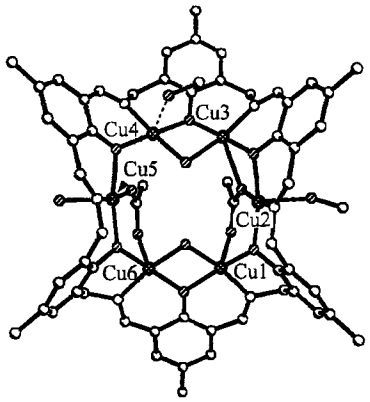
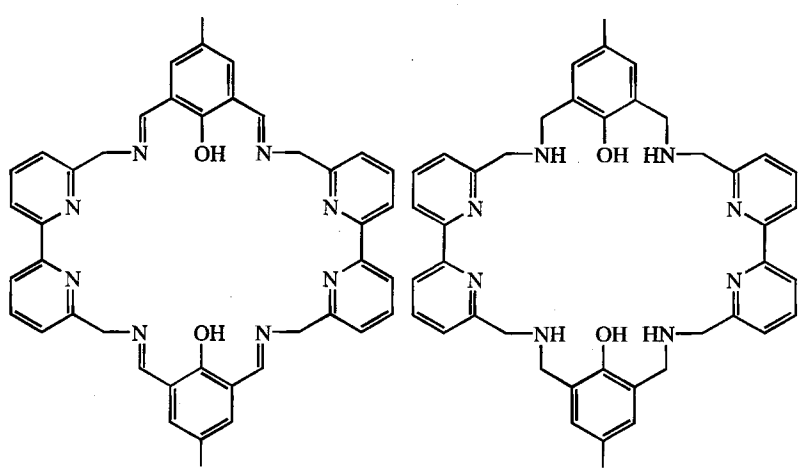


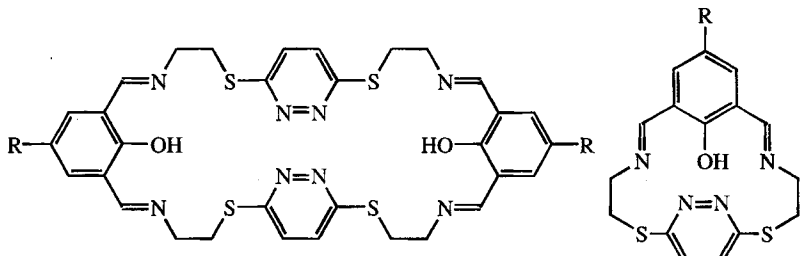
Figure 8-5. The structure of the $[Cu_6(L1732)(CH_3COO)_2(OH)_2(CH_3OH)_2(H_2O)]^{2+}$ cation.

tion of the dilanthanum(III) complex of H_2L1733 with $NaBH_4/NaBH_3CN$ (2:1) in methanol, followed by demetallation with diethylenetriamine pentaacetic acid, led to metal-free tetramino macrocycle H_2L1734 isolated as its hydrochloride salt in 56% yield [103].



H_2L1733 H_2L1734 (8.39)

Copper(II) has been shown to control intramolecular *versus* intermolecular condensation of 2,6-diformyl-4-(*R*)-phenols with 3,6-bis-((aminoethyl)thio)pyridazine. When copper(II) salts involving weakly coordinating or non-coordinating anions such as ClO_4^- and BF_4^- were employed as template source, 2 + 2 condensation of the corresponding ligsons occured with the formation of dinuclear copper(II) complexes of the 34-membered macrocyclic ligands H_2L1735 and H_2L1736 (8.40) [104].



$R = CH_3$ H_2L1735
$R = C(CH_3)_3$ H_2L1736

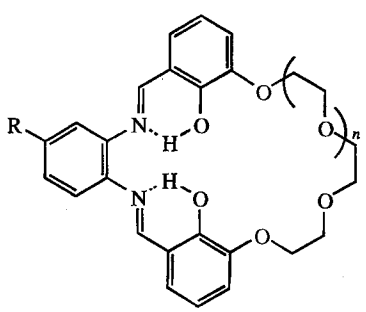
$R = CH_3$ HL1737

(8.40)

In contrast, the 1 + 1 macrocyclic product HL1737, able to coordinate two copper ions, is produced in the presence of copper(II) salts of anions with higher coordinating abilities (NO_3^-, $CF_3SO_3^-$) [105]. Note that only phenoxide oxygen atoms and imine nitrogens of both types of macrocycle are involved in coordination to copper(II) ions.

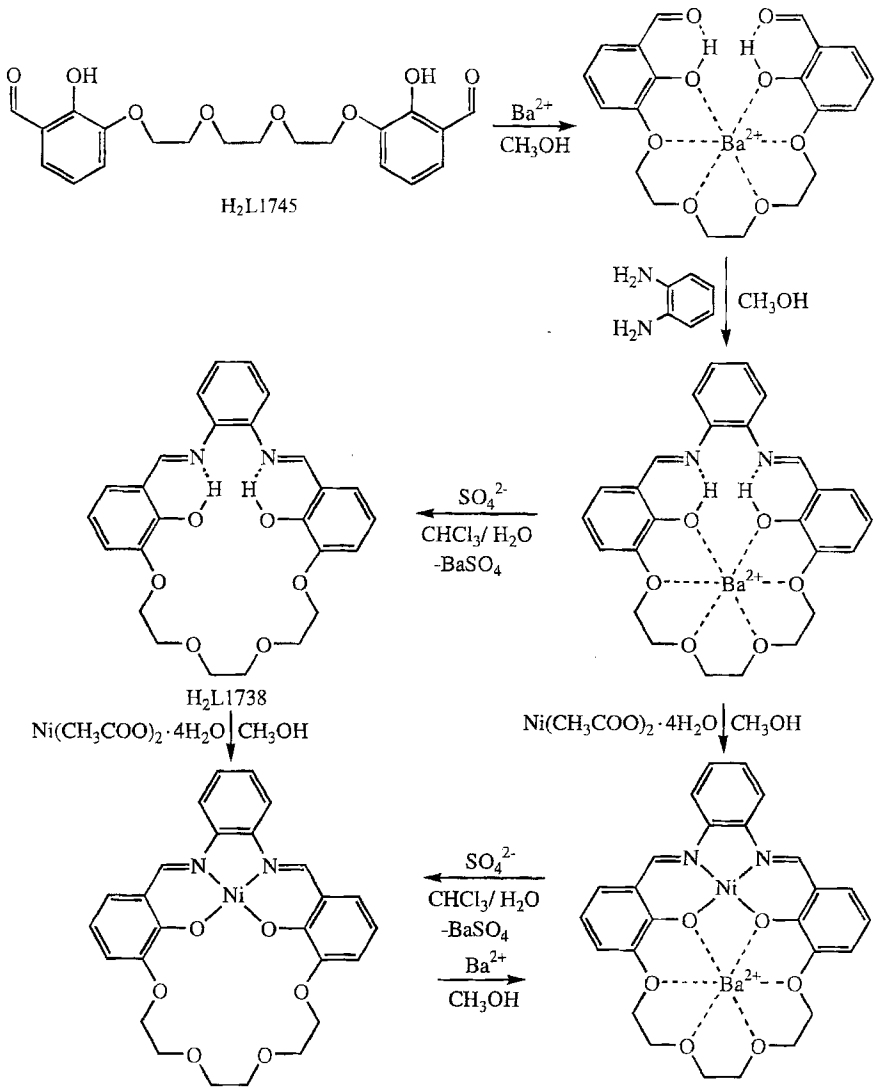
8.3 Polynucleating macrocycles bearing soft and hard metal-binding sites

Like the cyclic molecules considered in the previous two sections, the macrocycles of interest here possess several metal-binding sites within the same ring backbone. However, the nature of the metal-binding sites in these systems is so different that soft transition metal ions and hard alkali, alkaline-earth or lanthanide metal cations can be complexed simultaneously and located in close proximity within the same macrocycle. The relative simplicity of the general approach to their development [106, 107] has permitted the building up of a large number of such systems, systematically modifying the structure of each binding site. Generally, these polynucleating ligands are assembled in the presence of a metal ion template and consist of hard crown-ether and softer salen-type (N_2O_2) cavities situated in close proximity. Barium(II) has turned out to be the most suitable template for the synthesis of heteronuclear macrocycles H_2L1738 to H_2L1744 (Eq. 8.41) from the appropriately selected building blocks [108–110], as illustrated for H_2L1738 in Scheme 8-6.



R = H, n = 1	H_2L1738
R = H, n = 2	H_2L1739
R = H, n = 3	H_2L1740
R = H, n = 4	H_2L1741
R = H, n = 5	H_2L1742
$R = CH_3$, n = 1	H_2L1743
$R = COC_6H_5$, n = 1	H_2L1744

(8.41)



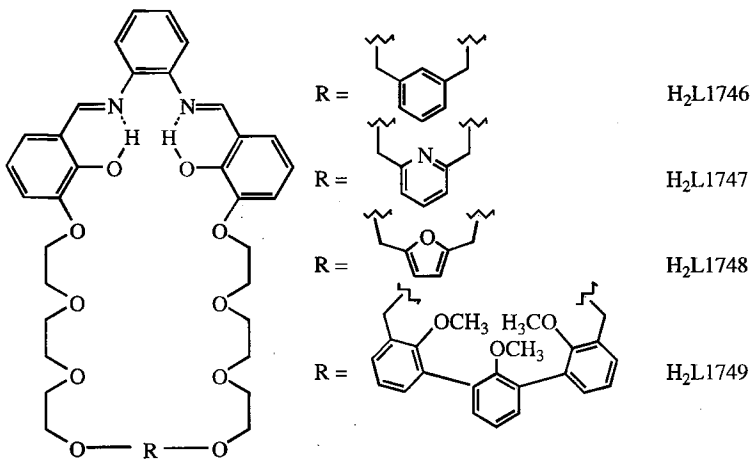
Scheme 8-6. Synthetic pathway to the heteronuclear salen-crown ether macrocycle H_2L1738.

This behaviour is not very surprising as the Ba^{2+} cation has been used successfully in the synthesis of a series of crown ethers [111]. The template role of barium(II) is predominantly conformational. By coordination of the polyoxyethylene-containing ligson to barium(II) the terminal aldehyde groups are held in close proximity. Under such circumstances the cyclisation of the 1 + 1 open-chain condensation product occurring inevitably at the next step of the template process, is favoured over intermolecular pathways leading to polymerisation. The assembly of the above binucleating products in the absence of a template yields only small

amounts of product. An attempt to use nickel(II) as the template resulted in very poor yields, the required product being detected only by mass spectrometry. Alkali metal (sodium, potassium, caesium) ions are also unsuitable as matrices [110].

By making use of the availability of the metal-free macrocycle H_2L1743 the direct reaction with manganese(II) produced the complex $[Mn^{II}(L1743)]$. Oxidation of the latter with dioxygen in acetonitrile afforded the $Mn^{III}Mn^{III}$ μ-oxo dimer $[Mn_2(L1743)]_2(\mu\text{-}O)$ [112].

Template synthesis of analogous compartmental ligands H_2L1746–H_2L1749 has also been performed (Eq. 8.42) [113].



H_2L1746

H_2L1747

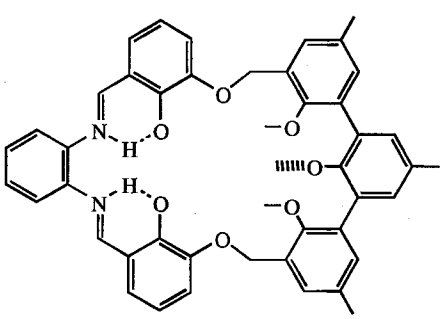
H_2L1748

H_2L1749

(8.42)

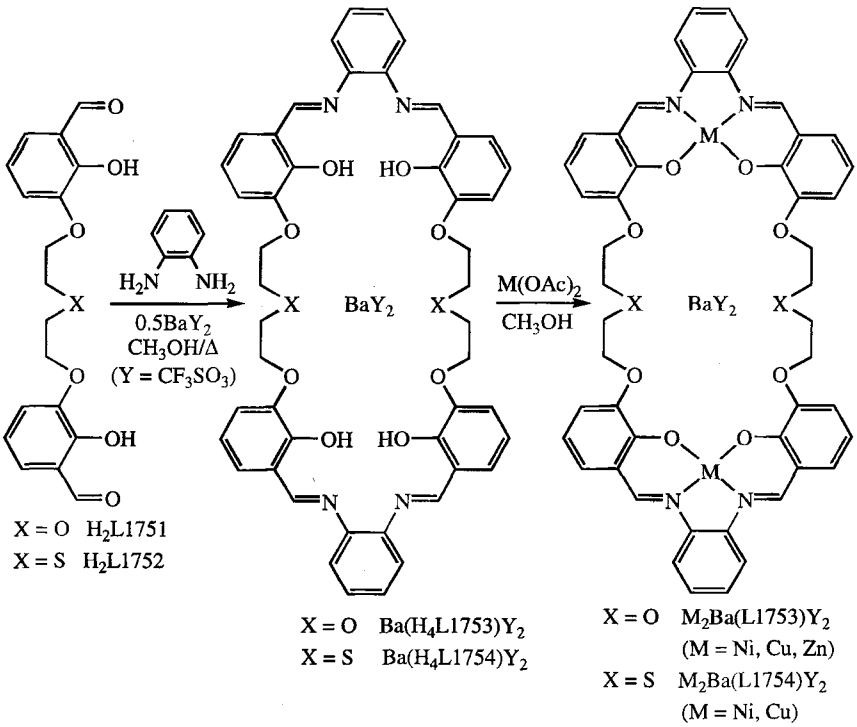
Treating the barium(II) complexes of H_2L1746–H_2L1749 with uranyl acetate results in the formation of UO_2L1746 to UO_2L1749.

The synthesis of H_2L1750 as its barium complex was carried out by slow addition of a solution of the corresponding ligsons to a refluxing solution of $Ba(CF_3SO_3)_2$, acting as a template salt, in methanol [114]. Reaction of $Ba(H_2L1750)(CF_3SO_3)_2$ with one equivalent of nickel(II), copper(II), or zinc(II) acetates afforded the dinuclear complexes $MBa(L1750)(CF_3SO_3)_2$ (M = Ni, Cu, Zn) (Eq. 8.43) [114].



H_2L1750

(8.43)



Scheme 8-7. Synthetic pathway to heterotriniclear M_2Ba (M = Ni, Cu, Zn) complexes.

The X-ray structure of $UO_2(L1747)\cdot 4H_2O$ shows that the uranyl cation is complexed in the salophen moiety. The cavity is filled with four water molecules, one of which is coordinated at the fifth position of the complexed uranyl cation [113]. X-Ray crystallography of mononuclear barium complexes of H_2L1739 and H_2L1740 showed that the macrocyclic ligand used all oxygens to coordinate to the central atom.

Shortening the ligson polyoxyethylene chain separating the terminal benzaldehyde functionalities by one oxyethylene unit makes the use of barium(II) as template for construction of 1 + 1 macrocycles non-effective. The lack of complementarity between metal template and the final 1 + 1 macrocyclic ligand product is presumably responsible. Under such conditions, however, barium(II) controls the 2 + 2 condensation of the dialdehyde H_2L1751 as well as H_2L1752 with 1,2-diaminobenzene giving complexes $Ba(H_4L1753)(CF_3SO_3)_2$ and $Ba(H_4L1754)(CF_3SO_3)_2$ in high yield. The mononuclear complexes can easily be converted into the heteronuclear complexes $M_2Ba(L1753)(CF_3SO_3)_2$ (M = Ni, Cu, Zn) and $M_2Ba(L1754)(CF_3SO_3)_2$ (M = Ni, Cu) by reaction with two equivalents of nickel(II), copper(II), or zinc(II) acetate (Scheme 8-7) [115, 116]. By using caesium(I) as the template $Cs(H_4L1753)CF_3SO_3$ and $M_2Cs(L1754)CF_3SO_3$ have been obtained [116].

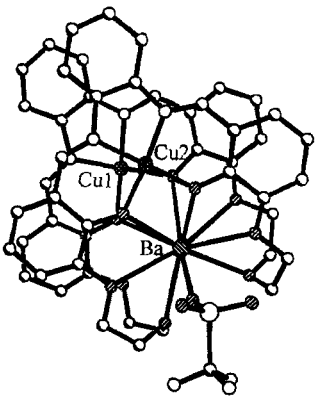
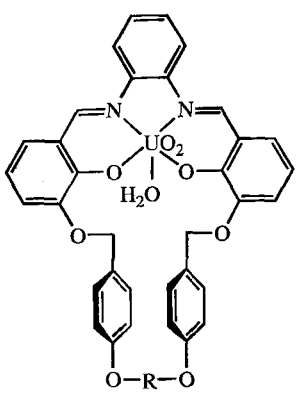


Figure 8-6. The structure of the $[Cu_2Ba(L1753)CF_3SO_3(H_2O)]^+$ cation.

The complexes $Ba(H_4L1753)(CF_3SO_3)_2$, $Cu_2Ba(L1753)(CF_3SO_3)_2{\cdot}2H_2O$ and $Ni_2Ba(L1753)(CF_3SO_3)_2$ have been analysed by X-ray diffraction. In all three crystal structures the O_{10} ring is folded around the barium cation. The copper-copper distance in the heteronuclear complex is 35.0 nm, the nickel–nickel distance 34.2 nm. The structure of the cation in $Cu_2Ba(L1753)(CF_3SO_3)_2{\cdot}2H_2O$ is given in Figure 8-6 [115, 116]. The coordination capacity of the trinuclear ligand is fully used in these heterometallic complexes. The coordination number of barium(II) is made up to 12 by coordination of one triflate anion and a water molecule.

The uranyl cation, UO_2^{2+}, turned out to be an effective template for constructing binuclear macrocyclic systems related to those described above [108–110, 112–116]. Thus, metallomacrocycles $UO_2(L1755)(H_2O)$ to $UO_2(L1757)(H_2O)$ were synthesised from 1,2-benzenediamine and the corresponding aldehydes in the presence of $UO_2(CH_3COO)_2{\cdot}2H_2O$ in methanol/dichloromethane (Eq. 8.44) [117].

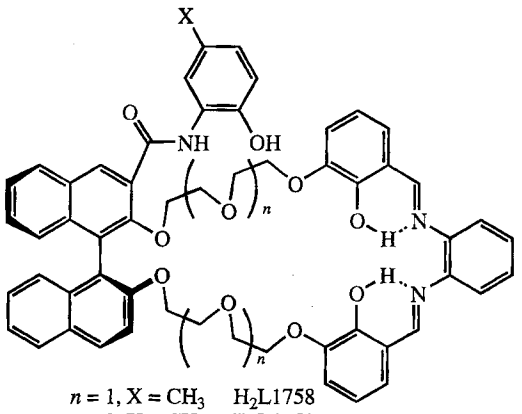


$R = (CH_2)_3$	$UO_2(L1755)(H_2O)]$
$R = (CH_2)_4$	$UO_2(L1756)(H_2O)]$
$R = (CH_2)_2O(CH_2)_2$	$UO_2(L1757)(H_2O)]$

(8.44)

Replacing one ethylene glycol unit in (2-hydroxybenzaldehyde-3-yl)-O-$(CH_2CH_2O)_n$-(3-yl-2-hydroxybenzaldehyde), with $n = 5$ or 7, by a 1,1′-binaphthol

moiety enables the construction of functionalised binaphthyl salophen heterocyclic systems H_2L1758 to H_2L1761 (Eq. 8.45) via Ba(II)-templated cyclisation [118]. Addition of $UO_2(CH_3COO)_2$ produces the corresponding uranyl complexes.



$n = 1, X = CH_3$ H_2L1758
$n = 2, X = CH_3$ H_2L1759
$n = 1, X = Cl$ H_2L1760
$n = 2, X = Cl$ H_2L1761

(8.45)

Aromatic diamines, isothiosemicarbazides, cyclic and aliphatic diamines, 1,2-bis(aminooxy)ethane etc. can all serve as closing agents, providing the formation of softer metal-binding sites by incorporation of imine nitrogens into the macrocycle formed.

Insertion of the isothiosemicarbazide moiety into the macrocyclic backbone was generally achieved by following the route shown in Scheme 8-6. As isothiosemicarbazides, $H_2N{-}N{=}C(SR){-}NH_2{\cdot}HX$ (X = acid counterion), do not normally undergo condensation reactions with aldehydes or ketones through a terminal thioamide group, under typical conditions for metal-free reactions, the presence of a metal ion template is required. Thus, the linear dialdehyde (2-hydroxybenzaldehyde-3-yl)-O-$(CH_2CH_2O)_n$-(3-yl-2-hydroxybenzaldehyde), with $n = 3$, reacts with *S*-methylisothiosemicarbazide hydroiodide (or hydrochloride) in the presence of $Ba(CF_3SO_3)_2$ and $M(CH_3COO)_2{\cdot}nH_2O$ (M = Ni, Cu, Zn) or $VOCl_2$ to give metal(II)/barium complexes $[MBa(L1762)(CF_3SO_3)_2]_2$ (M = Ni, Cu), $[ZnBa(L1762)I(CF_3SO_3)(CH_3OH)]_2{\cdot}0.5H_2O$, $[VOBa(L1762)(CF_3SO_3)_2]_2$ and $[VOBa(L1762)(I_3)I(CH_3OH)]_2$ in reasonable yields (Eq. 8.46) [119–121]. The formation of dimeric structures for the products isolated was proved by X-ray diffraction. A centrosymmetric dimeric complex $[NiBa(L1762)(CF_3SO_3)_2]_2$, which is bridged by two $CF_3SO_3^-$ ligands, is shown in Figure 8-7.

Each barium atom carries an additional $CF_3SO_3^-$ ligand. The bridging triflate anions are disordered over two positions. The barium ion is coordinated by all six oxygen atoms of the macrocycle, giving a total coordination number for the Ba^{2+}

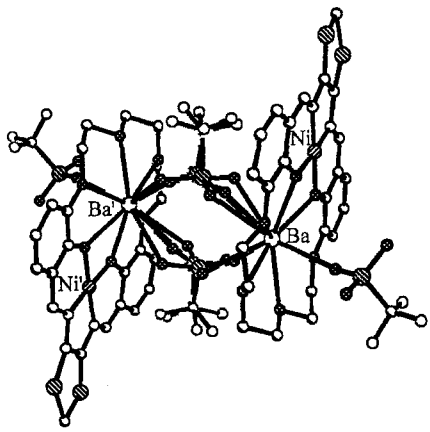
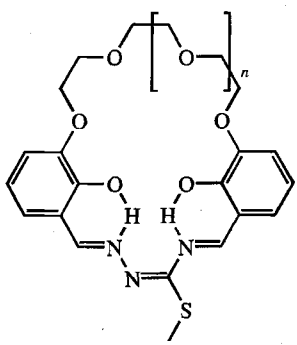


Figure 8-7. Centrosymmetric dimeric structure of $[NiBa(L1762)(CF_3SO_3)_2]_2$.



$n = 1$ H_2L1762
$n = 2$ H_2L1763 (8.46)

cation of 10. The Ni atom has square-planar coordination, and the Ni···Ba distance is 36.64(5) nm, similar to the 3d metal···Ba distances in related salen and salophen complexes (36–37 nm) [114, 122, 123]. A related dimeric structure with $CF_3SO_3^-$ ligands bridging the Ba atoms was revealed for the Zn/Ba complex [120]. Each barium atom is coordinated by 10 oxygen atoms, three from the bridging triflate anions, six from the macrocycle and one due to an additional methanol molecule. The coordination polyhedron of the Zn atom is a distorted square pyramid. The metal ion deviates from the mean plane of the coordinated N_2O_2 donors of the macrocycle by 6 nm towards the apical I^-. The intramolecular Zn···Ba distance is 37.36(1) nm.

The monomeric complexes $[VOBa(L1762)(I_3)I(CH_3OH)]$ are associated in a dimer (Figure 8-8) by two symmetry related oxovanadium oxygen atoms [121]. The distance between the planes of the macrocyclic rings is 36.4 nm. The coordination number of the barium atom is made up to 10 by six oxygen atoms of the macrocycle, iodide and triiodide anions, a molecule of methanol and the oxovanadium oxygen atom of the adjacent counterpart. The intramolecular V···Ba distance is 38.75(1) nm.

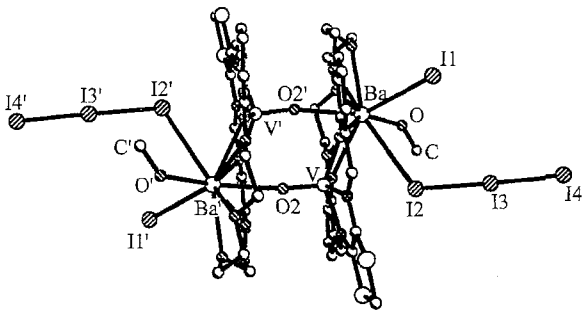


Figure 8-8. Dimeric structure of $[VOBa(L1762)(I_3)I(CH_3OH)]_2$.

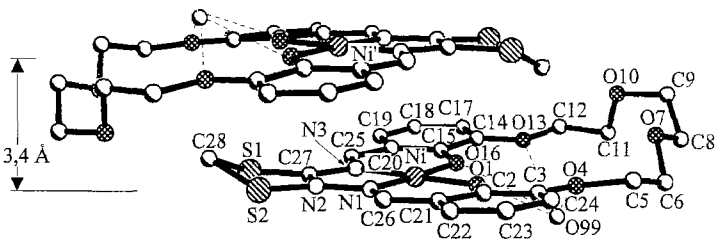


Figure 8-9. Fragment of the crystal structure of $[Ni(L1762)]\cdot H_2O$.

The barium-free mononuclear complexes $[M(L1762)]\cdot nH_2O$ (M = Ni, Cu) are easily prepared in high yields using a standard procedure [119, 120] by stirring a suspension of the corresponding metal(II)/barium complex in chloroform with an excess of a solution of guanidinium sulphate in water. The structure of one of the complexes isolated, $[Ni(L1762)]\cdot H_2O$, is shown in Figure 8-9.

The specific feature of $[Ni(L1762)]\cdot H_2O$ is the coordination of a water molecule by a polyether fragment of the macrocycle. The oxygen atom of the water molecule is situated 18 nm below the mean plane of the polyether O atoms and has four short contacts of 30.81(6), 30.42(6), 30.29(7) and 30.44(6) nm, with O1, O4, O13 and O16, respectively. The water molecule thus appears to form two bifurcated hydrogen-bonds. Note that by making use of hydrogen-bonding interactions, bimetallic inclusion complexes $[M(L1738)\cdot Fe(\eta^5\text{-}C_5H_5)(CO)_2(NH_3)]PF_6$ (M = Ni, Cu) have been prepared [124] using organometallic complexes as guest molecules and nickel(II)- and copper(II)-containing crown ethers [M(L1738)] as hosts. The molecules of $[Ni(L1762)]\cdot H_2O$ are packed in pairs (Figure 8-9) about the centres of symmetry, with the coordination planes of the Ni atoms lying parallel to one another and separated by 34 nm. Favourable π–π interactions are presumably responsible for association of molecules in pairs.

Insertion of an additional oxygen donor atom in the starting dialdehyde ligson does not preclude macrocycle formation in the presence of $Ba(CF_3SO_3)_2$ followed by adding $Ni(CH_3COO)_2\cdot 4H_2O$. However, in this case no dimeric species were isolated. According to an X-ray diffraction study [119] the resulting complex has the composition $[NiBa(L1763)(CH_3OH)_3](I_3)I$ (Figure 8-10). As with $[NiBa(L1762)(CF_3SO_3)_2]_2$, the coordination number of the barium(II) is 10 (seven

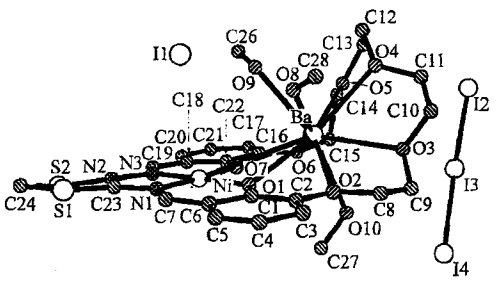


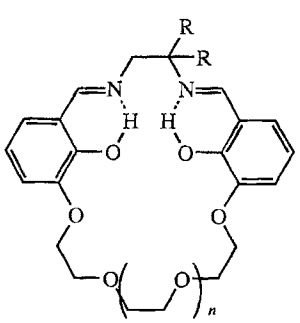
Figure 8-10. The structure of $[NiBa(L1763)(CH_3OH)_3](I_3)I$.

oxygen atoms from the macrocycle and three methanol molecules), and the polyether chain adopts a locally non-planar conformation to ensure that all its oxygen atoms are bonded to the cation. This conformation enables the two metal ions to approach one another. The resulting Ba···Ni distance is 37.23(3) nm and is not significantly different from that in $[NiBa(L1763)(CF_3SO_3)_2]$ (36.64(5) nm).

Note the remarkable coordination ability of polyoxyethylene dialdehyde ligsons toward Ba(II), which predetermines the success of ring-coupling reaction with isothiosemicarbazides. Reaction of the dialdehyde (2-hydroxybenzaldehyde-3-yl)-O-$(CH_2CH_2O)_3$-(3-yl-2-hydroxybenzaldehyde) with *S*-methylisothiosemicarbazide hydroiodide in the presence of barium(II) triflate afforded the desired macrocyclic complex $Ba(H_2L1762)(CF_3SO_3)_2$ in 20% yield [120]. The macrocyclic nature of the ligand product formed is confirmed by the EI mass spectrum, which shows an intense peak at *m/z* 459 ($P^{+\cdot}$). It is also noteworthy that, by adding a 3d metal(II) salt to the reaction mixture containing barium(II) triflate, the yield of the final macrocycle can be markedly increased. This suggests a sequestering and stabilising role for 3d metal ions in the formation of the corresponding M/Ba complexes.

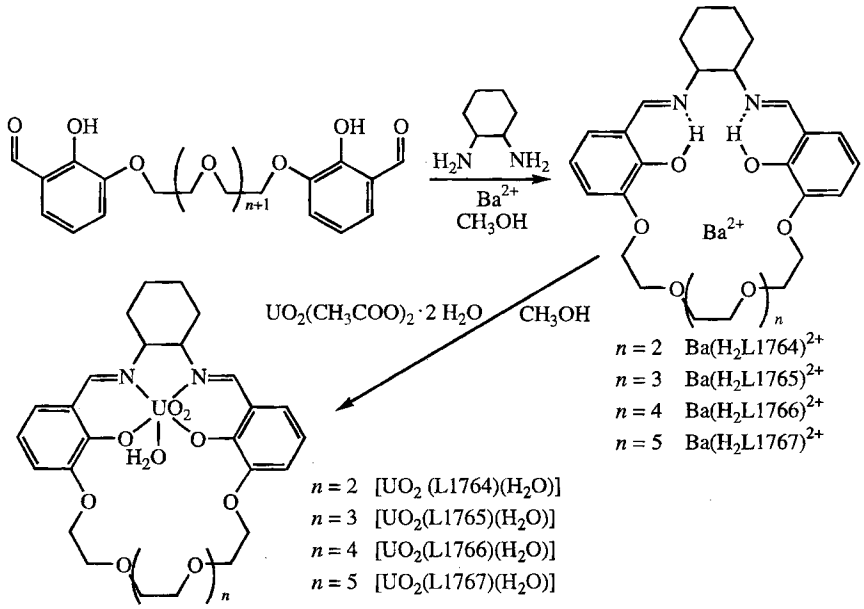
Compartmental macrocyclic ligands and their barium and uranyl complexes were also prepared by reaction of the corresponding dialdehydes and *cis*-1,2-cyclohexanediamine according to Scheme 8-8 [122].

Ligands H_2L1768 and H_2L1769 may be obtained from dialdehydes shown in scheme 8-8 ($n = 1, 2$) and 2-methyl-1,2-propanediamine (Eq. 8.47). To synthesise these compounds a somewhat modified method was chosen, employing $Ba(CF_3SO_3)_2$ as the matrix source, and the reaction was carried out under high dilution conditions [110, 114].



R = CH_3:
$n = 1$ H_2L1768
$n = 2$ H_2L1769
R = H:
$n = 1$ H_2L1770

(8.47)

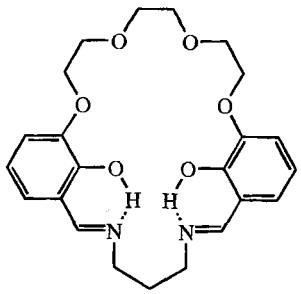


Scheme 8-8. Synthesis of $[UO_2(1764)(H_2O)] - [UO_2(1767)(H_2O)]$.

The resulting barium complex was not isolated, but one equivalent of nickel(II) or copper(II) acetate was added, which afforded the solid dinuclear complexes $MBa(L1768)(CF_3SO_3)_2$ and $MBa(L1769)(CF_3SO_3)_2$ (M = Ni, Cu) [118].

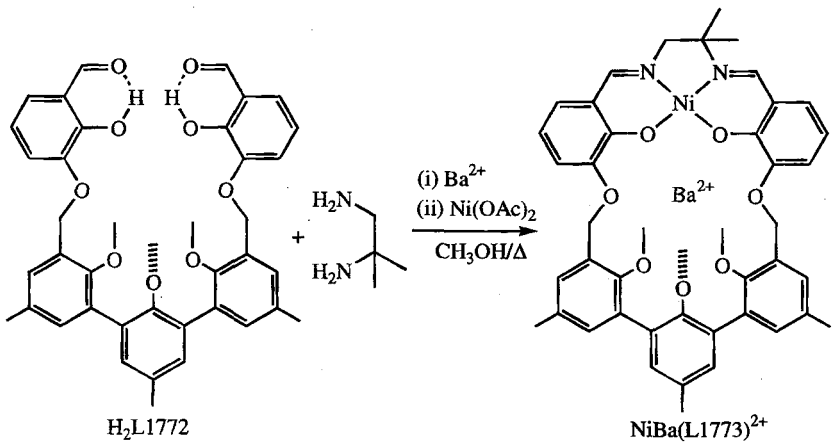
A non-template synthesis of the 1 + 1 macrocycle H_2L1770 derived from condensation of the (2-hydroxybenzaldehyde-3-yl)-O-$(CH_2CH_2O)_3$-(3-yl-2-hydroxybenzaldehyde) and 1,2-diaminoethane in acetonitrile has been reported and its structure confirmed by X-ray diffraction [125]. Direct complexation with $LaCl_3 \cdot 7H_2O$ in methanol yields $[La(H_2L1770)(H_2O)_4]Cl_3$. Single crystal X-ray analysis revealed that lanthanum is 10-coordinated, like barium in the complexes shown in Figures 8-7, 8-8 and 8-10. It should be mentioned that lanthanide(III) ions have not been employed so far as templates for the construction of related macrocycles, in which a softer donor site is combined with a hard polyether binding site.

Reaction of (2-hydroxybenzaldehyde-3-yl)-O-$(CH_2CH_2O)_3$-(3-yl-2-hydroxybenzaldehyde) with 1,3-diaminopropane in the presence of $Ba(CF_3SO_3)_2$ in CH_3OH/THF followed by addition of $Mn(CH_3COO)_2 \cdot 4H_2O$ under an inert atmosphere afforded impure $[Mn^{II}(L1771)]$ (Eq. 8.48) [126]. Oxidation of the latter by dioxygen in the presence of NH_4PF_6 as counter anion supplier gave $[Mn^{III}(L1771)]PF_6$. Reduction of this manganese(III) complex by Cp_2Co in acetonitrile and reoxidation of the pure $[Mn^{II}(L1771)]$ with dioxygen in acetonitrile resulted in formation of the $Mn^{IV}Mn^{IV}$ bis(μ-oxo)dimer $[Mn^{IV}(L1771)(\mu\text{-}O)_2]_2$ [126]. Note that the metal-free ligand was not isolated because of its instability.



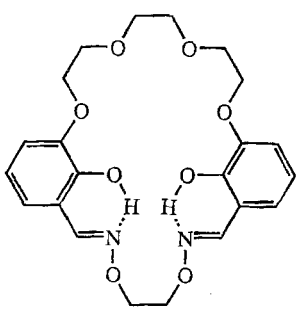
H_2L1771 (8.48)

The aliphatic ligson 2-methyl-1,2-propanediamine was used for macrocyclisation with the dialdehyde H_2L1772, and the resulting dinuclear complex NiBa(L1773)-$(CF_3SO_3)_2$ was isolated (Eq. 8.49) [114].



H_2L1772 $NiBa(L1773)^{2+}$ (8.49)

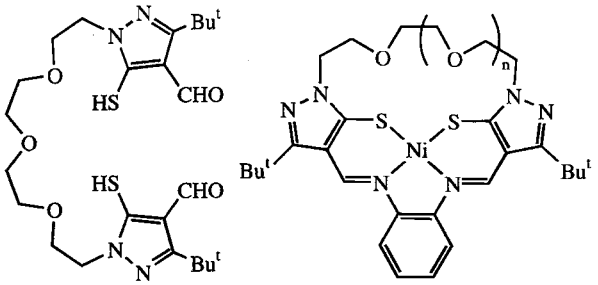
Following a published procedure [108–110, 114–117] the complexes $Ba(H_2L1774)(CF_3SO_3)_2$ and $MBa(L1774)(CF_3SO_3)_2$ (M = Ni, Cu, Zn) were synthesised from the corresponding ligsons (Eq. 8.50) [123].



H_2L1774 (8.50)

The structures of the barium complex and of the nickel(II)barium(II) dinuclear compound were established by X-ray crystallography [123].

Thiolato functions have also been incorporated as binding units in heterotopic macrocycles. For example, reaction of the dithiodialdehyde H_2L1775 (Eq. 8.51) with 1,2-diaminobenzene in the presence of $Ba(ClO_4)_2$ as template source under high dilution conditions, followed by addition of nickel(II) acetate, gave a dark brown residue. The latter in chloroform when treated with aqueous guanidinium sulphate afforded the mononuclear nickel(II) complex [Ni(L1776)] [127].



H_2L1775

$n = 2$ [Ni(L1776)]
$n = 1$ [Ni(L1777)]
$n = 3$ [Ni(L1778)]
$n = 4$ [Ni(L1779)]
$n = 5$ [Ni(L1780)]

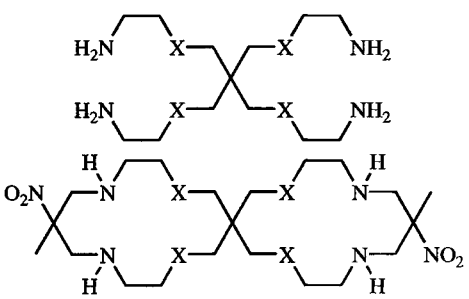
(8.51)

The ^1H NMR spectrum and the presence of the molecular ion peak in its FAB mass spectrum are in agreement with the structure proposed. Note that attempts to use Ni^{II} as template led to the formation of an almost black precipitate of unidentifiable composition. A number of other derivatives, [Ni(L1777)]–[Ni(L1780)], differing by the number of oxyethylene units, are available [127].

8.4 Polynucleating systems with space-separated metal-binding sites

In this section the discussion is limited to polynucleating systems containing several substrate- or metal-binding sites which do not reside within the same macrocyclic framework.

The ligands L1783 and L1784 were synthesised by a metal-directed condensation, around two copper(II) centres, of L1781 and L1782 with nitroethane and formaldehyde (Eq. 8.52) [128, 129].

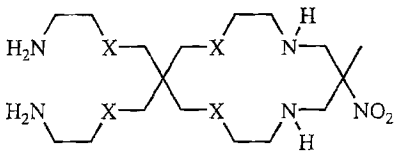


X = NH L1781
X = S L1782

X = NH L1783
X = S L1784

(8.52)

The ligands L1785 and L1786, half macrocyclic and half acyclic, are the byproducts of this synthesis. The dicopper(II) complexes of L1785 and L1786 (Eq. 8.53) possess three distinctly different electroactive groups when the pendant nitro group is considered in addition to the two non-equivalent metal centres [128].

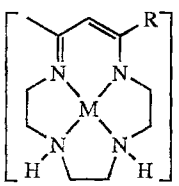


X = NH L1785
X = S L1786

(8.53)

Selectivity in reduction with the hydrated electron and oxidation with the hydroxyl radical have been shown to occur in redox reactions of dicopper(II) complexes with different ligand fields. The stronger field tetraazacomplexes exhibit $Cu^{2+/+}$ and $Cu^{3+/2+}$ couples at significantly more negative potentials than their $Cu^{II}N_2S_2$ analogues. The result of this is a preferential reduction of the copper(II) centre instead of the nitro groups in the $Cu^{II}N_2S_2$ complexes, whereas the reduction of the pendant nitro groups in the $Cu^{II}N_4$ complexes led to nitro radical anions. Oxidation of the $Cu^{II}N_4$ complexes with ·OH was metal centred, in contrast to the $Cu^{II}N_2S_2$ complexes, where oxidation involved hydrogen abstraction [129].

The mononuclear complexes [M(L1787)]X and [M(L1788)]X were obtained by condensation of triethylenetetramine with β-diketones on nickel(II) [130, 131] and copper(II) [132] templates (Eq. 8.54).

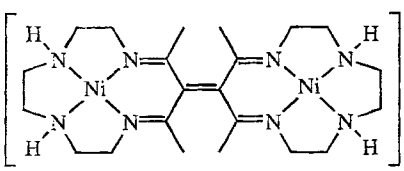


X

R = CH_3 [M(L1787)]X (M = Ni, Cu)
R = CF_3 [M(L1788)]X (M = Ni, Cu)
X = Br, I, NCS, NO_3, PF_6, BF_4, ClO_4

(8.54)

Upon prolonged standing of an aqueous solution of [Ni(L1787)]I at 5°C and pH 1, the dimer $[Ni_2(L1789)]I_4$ precipitates, resulting from oxidative dehydrogenation at methine carbon atoms and coupling through a localised double bond [133]. The structure of this binuclear complex was established by X-ray diffraction (Eq. 8.55) [133].

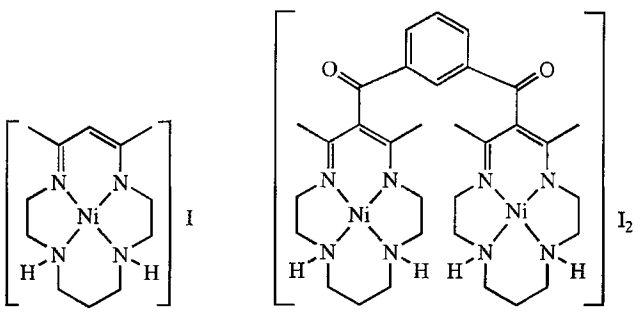


I_4 $[Ni_2(L1789)]I_4$

(8.55)

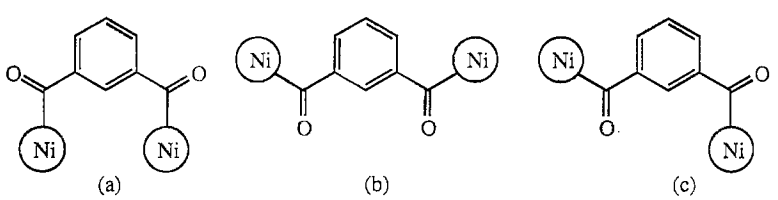
A number of related systems, such as the polyazamacrocyclic complexes $[Ni_2^{III}(L81)]$, $[Cu_2^{II}(L156)]^{4+}$, $[Cu_2^{II}(L157)]^{4+}$, $[M_2^{II}(L162)]^{4+}$ (M = Ni, Cu), $[Ni_2^{II}(L178)]^{4+}$, $[Ni_2^{II}(L179)]^{4+}$, $[Ni_2^{II}(L380)]^{4+}$, $[Ni_2^{II}(L381)]^{4+}$, $[Ni_2^{II}(L461)]^{4+}$ etc., containing two spatially separated binding sites, were described in Chapter 2. All these ditopic compounds were constructed by making use of template reactions.

Practical use is often made of the nucleophilic behaviour of β-diketone-derived monomacrocyclic complexes. Such compounds undergo many reactions reminiscent of the electrophilic substitution reactions of aromatic compounds. For example, by interaction of [Ni(L1790)]I with isophthaloyl dichloride, the binuclear complex $[Ni_2(L1791)]I_2 \cdot H_2O$ was obtained [134], whose structure has been confirmed by X-ray diffraction (Eq. 8.56) [135].



(8.56)

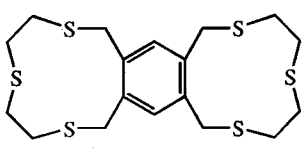
Three conformations are possible for this compound with respect to the mutual orientation of the two $[NiN_4]$ chromophores (Eq. 8.57). The iodide of $[Ni(L1647)]^{2+}$ crystallised as conformer (b) [135].



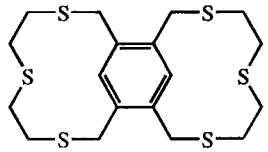
(8.57)

An interesting example of template building, to give the ditopic crown thioether L1792, has been well documented (Eq. 8.58) [136]. For the preparation of L1792 the template method developed for the synthesis of 1,4,7-trithiacyclononane (L1230) (Section 6.2) has been adapted. Thus reaction of tetrabromodurene $(1,2,4,5\text{-}(BrCH_2)_4C_6H_2)$ with $[Me_4N][Mo(CO)_3(SCH_2CH_2SCH_2CH_2S)]$ afforded the complex $[Mo_2(CO)_6(L1792)]$. The latter, when treated with $[Me_4N]$-

[($SCH_2CH_2SCH_2CH_2S$)], regenerates [Me_4N][$Mo(CO)_3$($SCH_2CH_2SCH_2CH_2S$)] and liberates L1792 in 20% overall yield. It is noteworthy that the employment of the Cs_2CO_3/DMF procedure results in exclusive formation of the *meta* analogue L′1792.



L1792



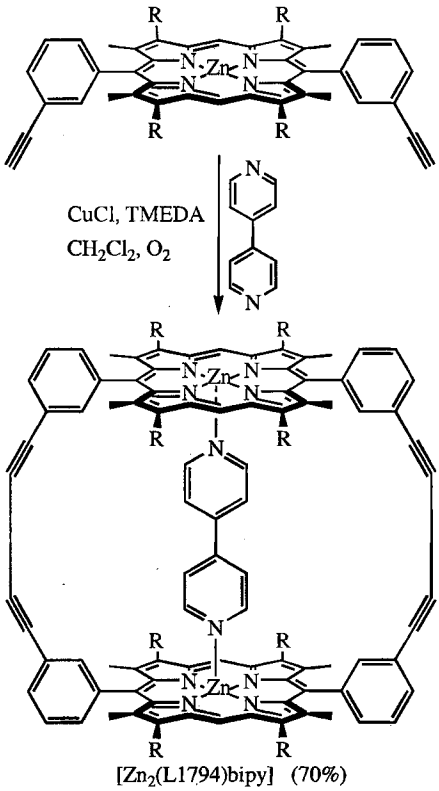
L′1792 (8.58)

Metal-free L1792 reacts with two equivalents of [$Cu(CH_3CN)_4$]ClO_4 and two equivalents of PPh_2Me with formation of the binuclear copper(I) complex [Cu_2(L1792)(PPh_2Me)$_2$](ClO_4)$_2$. If one equivalent of bidentate phosphine is involved in the reaction, then the complex [Cu_2(L1792)(μ-$PPh_2CH_2CH_2PPh_2$)]-(PF_6)$_2$ is generated. X-Ray diffraction study showed that the first complex has an *anti* arrangement, with metal centres on opposite sides of the benzene ring, whereas the bidentate phosphine induces a *syn* arrangement for the second, with metal ions on the same side of the benzene ring.

A very elegant approach has been developed for building up cyclic porphyrin oligomers, which uses organic templates in directed synthesis [137]. The appropriately selected pyridine-containing molecule (template) organizes, through N_{py}–M coordination and for their subsequent interaction several metal-porphyrin monomers (ligsons) bearing reactive functions. The terminal alkynes, now in close proximity, underwent Glaser coupling [138] to produce the final cyclic porphyrin oligomer by the formation of linear and relatively rigid symmetrical diyne links. After the template has executed its directing role it can often be removed to give the template-free final compound. Note that template complementarity is crucial for the success of the synthesis. It should also be noted that the nature of the final oligomer formed depends on the template employed. For example, oxidative coupling of the porphyrin ligsons [Zn(L1793)] through the terminal alkynes in the presence of 4,4′-bipyridyl (bipy) results in the successful formation of the cyclic porphyrin dimer isolated as the complex [Zn_2(L1794)bipy] (Scheme 8-9) [139].

The same reaction, carried out in the presence of tri(4-pyridyl)triazine (tptz), affords the complex [Zn_3(L1795)(tptz)] (Scheme 8-10) in 50% yield [139, 140].

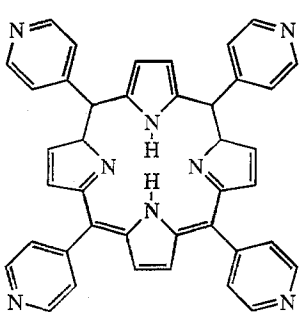
Removal of the template and the zinc, by treating the complex with dilute mineral acid, affords the free-base trimer which is then remetallated to generate binding sites. Some binding properties of the template-free cyclic porphyrin trimer L1795 have been reported [140, 141]. The structure of one of the complexes prepared by direct complexation reaction [Zn_3(L1795)Py_3] has been determined by X-ray diffraction [142]. The ruthenium(II) complex [Ru(L1793)(CO)(CH_3OH) has also been oligomerised in the presence of tptz as template to give a similar trimer, isolated as [Ru_3(L1795)(CO)$_3$(tptz)] [143]. The strong binding of the template does not permit its clean removal.



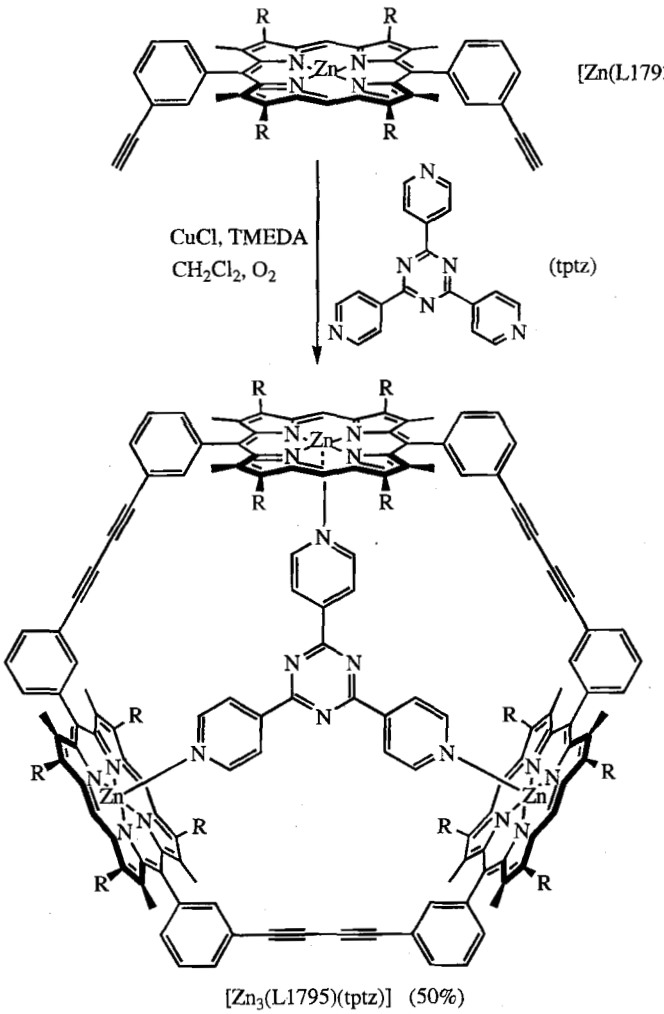
TMEDA = *N, N, N, N* - tetramethylenediamine; R = $CH_2CH_2CO_2CH_3$

Scheme 8-9. Templated construction of [Zn_2(L1794)bipy].

With the *meso*-tetra-4′-pyridyl-porphyrin H_2L1796 (Eq. 8.59) as template, the linear tetramer resulting from intermolecular coupling of [Zn(L1793)] can be converted into the corresponding cyclic porphyrin tetramer [Zn_4(L1797)(H_2L1796)] in 90% yield [144]. X-Ray structure analysis [145] established the structure shown



H_2L1796 (8.59)



Scheme 8-10. Templated construction of [Zn_3(L1795)(tptz)].

in Figure 8-11. The four porphyrin macrocycles are orthogonal to the central porphyrin-template. Four symmetric template bonds Zn–N of 22.0(2) nm are responsible for the conformation of the cyclic porphyrin tetramer. Zinc atoms deviate from the mean plane of the N_4 donor set by 2.9 nm towards the pyridyl groups of the porphyrin template.

Starting from zinc(II) 5,15-dioxo-10,20-bis(aryl)porphyrin [Zn(L1798)] the corresponding dimer [Zn_2(L1799)] and trimer [Zn_3(L1800)] are produced nearly quantitatively in the presence of bipy and tptz as templates. The yield of cyclic tetramer [Zn_4(L1801)] assembled in the presence of H_2L1796 exceeds 70% (Eq. 8.60) [146].

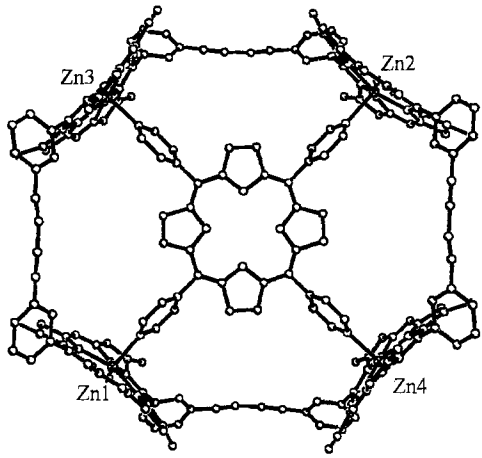
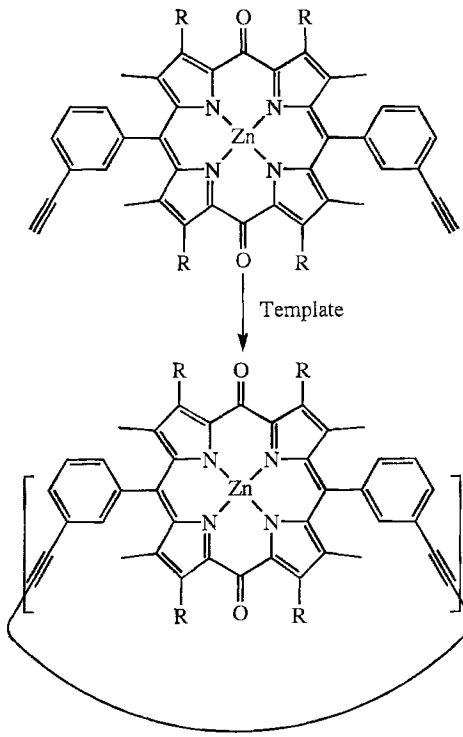


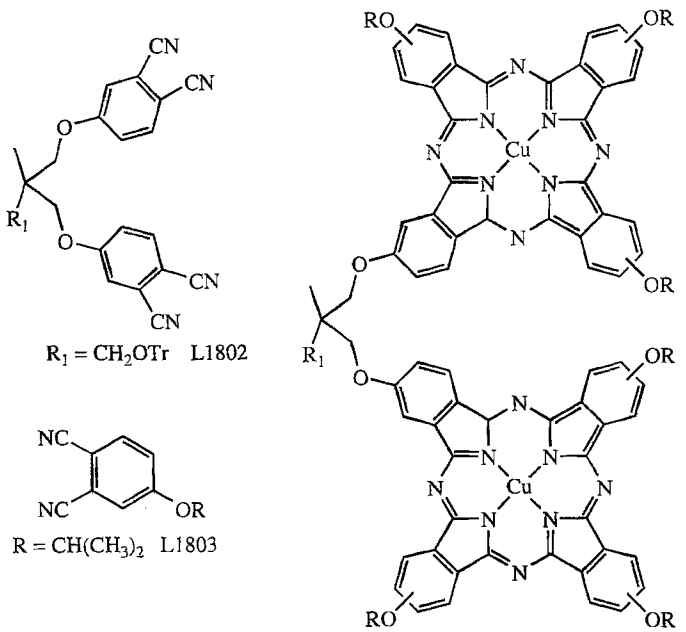
Figure 8-11. Fragment of the crystal structure of the tetrameric zinc porphyrin complex $[Zn_4(L1797)(H_2L1796)]$ with the disordered methyl ester side chains omitted for clarity.



(8.60)

Attempts to involve other templates to provide the formation of cyclic oligomers with expanded cavities have also been reported [147, 148].

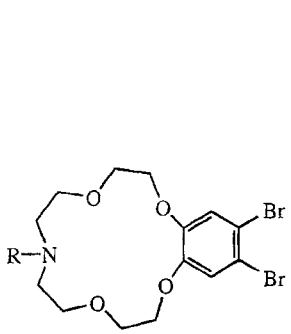
Various binuclear phthalocyanines covalently linked by five [149, 150], four [151], three [152], two [153], one [154] and zero [155] atom bridges have also been described. Several methods exist for obtaining these compounds from the respective starting blocks, including the template approach illustrated below. The reaction of L1802 with an excess of L1803 and copper(I) cyanide at 130°C in DMF, with subsequent repeated chromatographic separation of the byproducts, gave the dimer [Cu_2(L1804)] (Eq. 8.61) [150].



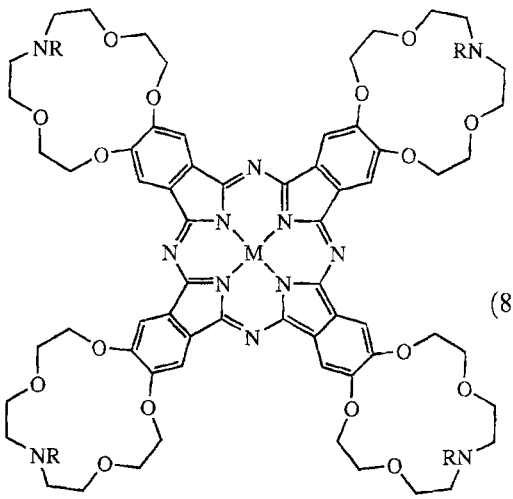
(8.61)

Synthesis of a number of polynucleating systems containing phthalocyanine frameworks assembled from several crown ether or other related blocks by benzene ring linkages has been described [156–163]. The reaction of $GeCl_4$ with H_2L640 (p. 185) [156, 157] or 4′,5′-diiminoisoindolino-15-crown-5 under anhydrous conditions results in the formation of $GeCl_2$(L640) [155]. The latter hydrolyses to give $Ge(OH)_2$(L640) which in turn gives Ge(SPh)(L640) on treating with thiophenolate [155].

Interaction of L1805 with CuCN in pyridine in a sealed glass tube at 205–210°C results in formation of the complex [Cu(L1807)], which is a tetra(azacrown) analogue of [Cu(L640)] (Eq. 8.62).



R = H L1805
R = $COCH_3$ L1806

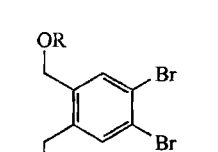


R = H, M = Cu [Cu(L1807)]
R = $COCH_3$, M = Ni [Ni(L1808)]
R = $COCH_3$, M = Pb [Pb(L1808)]

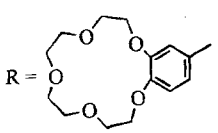
(8.62)

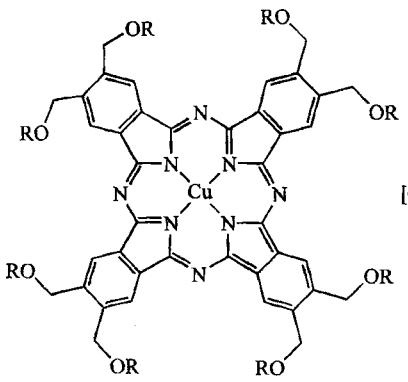
Template condensation of L1806 was carried out similarly by using $NiCl_2 \cdot 6H_2O$, PbO or $Lu(CH_3COO)_3 \cdot 3H_2O$, forming H_2L1808, which was isolated as the respective metal complexes. The metal–ligand ratio in the nickel and lead products is 1:1, whereas lutetium forms a sandwich-like complex of composition $HLu(L1808)_2$, in which coordination of two ligands to the central atom by all pyrrole nitrogen atoms is postulated [161]. On treating [M(L1808)] (M = Ni, Pb) or $HLu(L1808)_2$ with concentrated sulphuric acid, deacetylation takes place with the formation of $[M(L1807)] \cdot 2H_2SO_4$ and $HLu(L1807)_2 \cdot 4H_2SO_4$.

The polynucleating macrocycle H_2L1810, containing one central porphyrin and eight peripheral crown ether units, was synthesised by treating L1809 with CuCN in refluxing quinoline under argon. The ligand was isolated as its copper complex [Cu(L1810)] (Eq. 8.63) [159].



L1809

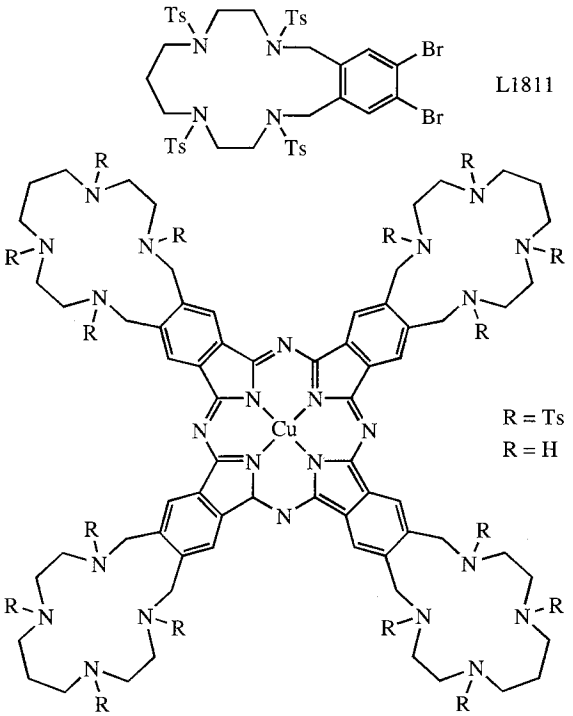




[Cu(L1810)]

(8.63)

The cyclotetramerisation reaction of L1811 in tetramethylurea in the presence of CuCN leads to the tetrakis(tetraazamacrocycle)phthalocyanin L1812 in the form of its monocopper complex (Eq. 8.64) [162, 163].



(8.64)

Detosylation of the peripheral aza groups of [Cu(L1812)] with concentrated H_2SO_4 and neutralisation with sodium hydroxide leads to [Cu(L1813)]. Treatment of a solution of the latter in anhydrous methanol with chloride or perchlorate salts of the transition metal ions Co^{II}, Ni^{II}, Zn^{II}, Cu^{II} gives $[CuM_4(L1813)]X_8$, where X = Cl or ClO_4 [163].

8.5 References

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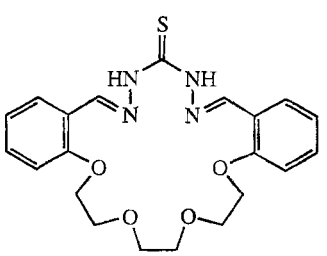
Chapter 9

Other macrocyclic compounds

9.1 Isothiocarbazide- and/or oxime-based macrocycles, calixarenes, metallamacrocycles

In addition to the classes and groups of macrocyclic compounds discussed in previous chapters there exist a number of other macrocycles and groups of macrocycles that are also produced by template synthesis. Some of these have the same donor atom sets as considered previously, but incorporated in different cyclic backbones. Information on these compounds may provide a useful basis for the development of further synthetic activity with which to further develop matrix reaction chemistry.

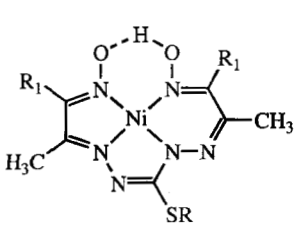
The macrocyclic compound L1814 (Eq. 9.1) contains a variety of functional groups and possesses sufficient flexibility for it to be considered as a promising analytical reagent for use with metal ions. It is obtained by reaction of the corresponding dialdehyde with thiocarbohydrazide in water-alcoholic solvent in the presence of catalytic amounts of Ga^{III} or Al^{III} templates (0.01–0.05 mol of appropriate salt per mol of starting ligsons) [1].



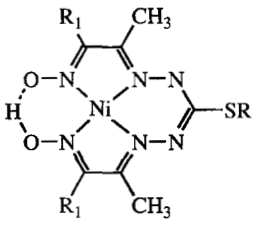
L1814 (9.1)

The products [Ni(L1815)] to [Ni(L1820)] are obtained by template condensation of sulphur-substituted isothiocarbohydrazides with diacetyl monoxime, 1,2-cyclohexanedione monoxime or isonitrosoacetone in the presence of nickel salts in boiling methanol followed by neutralisation with pyridine. Chromatographic separa-

tion of these products yields two series of metal-containing diamagnetic substances of the same composition, but of different colour: the more mobile representatives (A) are greenish-brown, and the less mobile (B) are bluish-green [2–5]. NMR and mass spectrometry showed that the corresponding pairs of substances were isomers. The symmetric structure is assigned to the product B, whereas isomer A is asymmetric, resulting from the absence of equivalent protons in identical hydrogen-containing groups (Eq. 9.2).

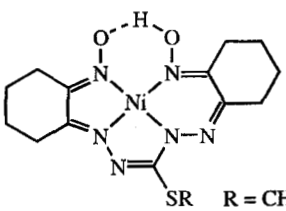


(A)

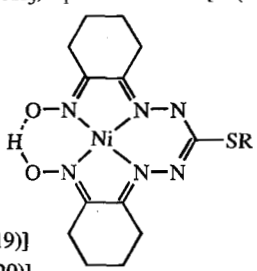


(B)

$R = R_1 = CH_3$ [Ni(L1815)] $R = C_6H_5CH_2$, $R_1 = CH_3$ [Ni(L1817)]
$R = C_2H_5$, $R_1 = CH_3$ [Ni(L1816)] $R = CH_3$, $R_1 = H$ [Ni(L1818)] (9.2)

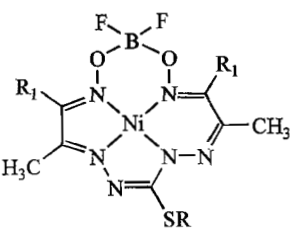


(A) $R = CH_3$ [Ni(L1819)]
$R = C_2H_5$ [Ni(L1820)]

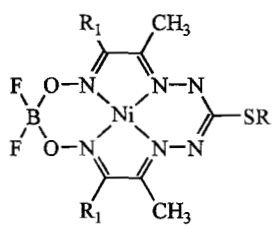


(B)

In the case of complexes [Ni(L1815)] to [Ni(L1817)], both isomers have been found to react with triethyloxonium tetrafluoroborate in boiling chloroform to produce the corresponding isomeric forms (A and B) of the macrocyclic products [Ni(L1821)]–[Ni(L1823)] (Eq. 9.3) [4, 6–8]. Both isomers are diamagnetic, so that



(A)



(B)

$R = CH_3$ [Ni(L1821)]
$R = C_2H_5$ [Ni(L1822)]
$R = C_6H_5CH_2$ [Ni(L1823)] (9.3)

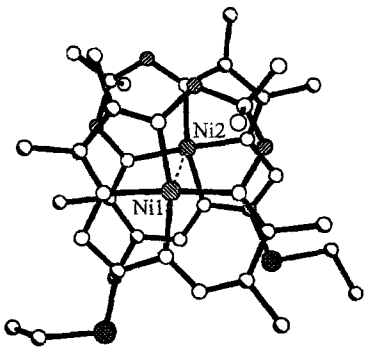


Figure 9-1. Portion of the crystal structure of [Ni(L1822)].

square-planar structures are assigned to these complexes. NMR, IR and mass spectra (fragmentation routes) showed isomer B to be a symmetric structure, and A to be asymmetric. However, in the case of both [Ni(L1821)]–[Ni(L1823)] and their precursors [Ni(L1815)]–[Ni(L1817)], the structure of isomer A cannot be determined unambiguously on the basis of these spectra.

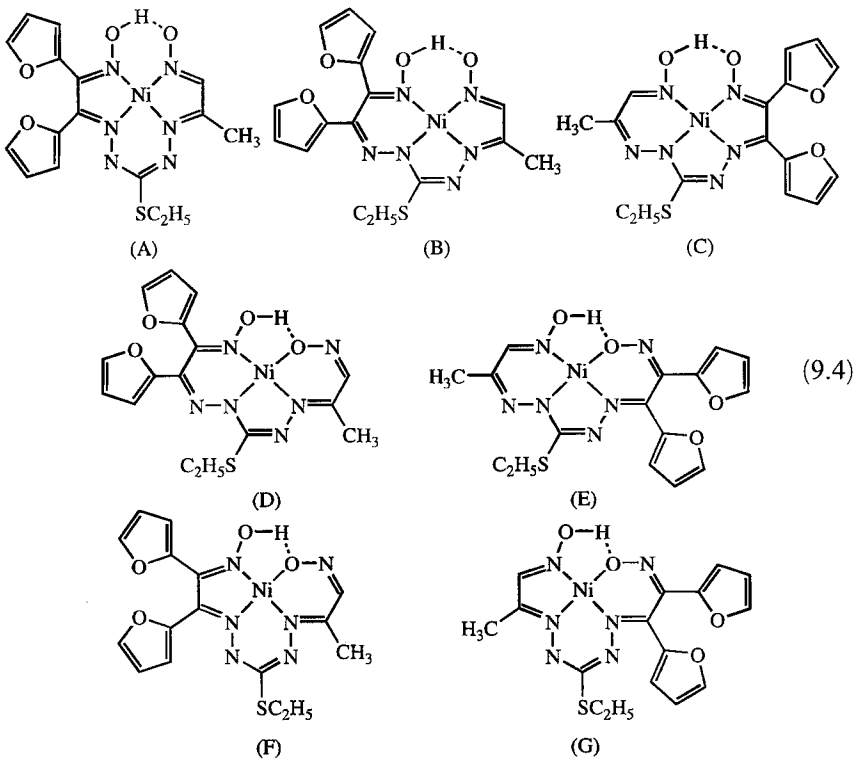
An X-ray diffraction study [9] showed a 5,5,6,6 arrangement of metallochelate rings, uncommon for macrocyclic complexes, in asymmetric [Ni(L1821)] and [Ni(L1822)] (Figure 9-1).

The hexaazamacrocycle is bonded to the central atom through four nitrogen atoms. The five-membered isothiocarbazide metallocycles are practically planar, the diimine rings have an envelope-like conformation, and the six-membered metallocycles are in the boat form. The angles between ring planes are not more than 7°, so the complexes as a whole are essentially planar. In the unit cell the complexes are packed as dimers with Ni···Ni distances of 34.01 nm which, however, do not form a continuous stacked structure. This can be explained by taking into account that the fluorine atoms are out of the plane (by 17 nm) of the macrocycle. The structure of [Ni(L1821)] is not significantly different from that of [Ni(L1822)] [9]. The complex [Ni(L1821)] (isomer A) and the quasimacrocyclic isomers A of compounds [Ni(L1815)]–[Ni(L1817)] are likely to have analogous structures.

Condensation of the ligsons 5-ethylisothiocarbohydrazide, isonitrosoacetone and α-furil monoxime has been carried out using nickel(II) as a template [10]. From this combination of starting materials it is possible to form seven variants of the final product [Ni(L1824)] (Eq. 9.4).

X-Ray diffraction revealed that variant C in which the organic ligand is coordinated so as to form metallocycles in the sequence 5,5,6,6, with the use of the same donor atoms as for the ligands in complexes [Ni(L1821)] and [Ni(L1822)], resulted from this synthesis [9]. The results [10] suggest that the quasimacrocyclic precursors [Ni(L1815)]–[Ni(L1820)] and [Ni(L1824)] (the A isomers) are, by their geometry, preorganised for the substitution of the hydrogen atom of their oxime groups by the reactive BF_2 grouping [10].

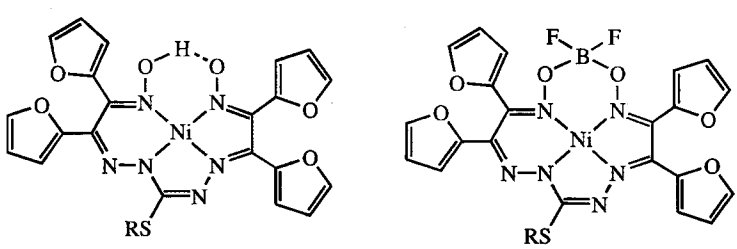
By template condensation of *S*-methyl and *S*-benzylisothiocarbohydrazides with α-furil monoxime on a nickel(II) template, the hexaazaquasimacrocyclic complexes [Ni(L1825)] to [Ni(L1827)] were obtained, which were converted into hexaazadi-



(9.4)

oxaboramacrocyclic products [Ni(L1828)] to [Ni(L1830)] by interaction with boron trifluoride etherate (Eq. 9.5) [11].

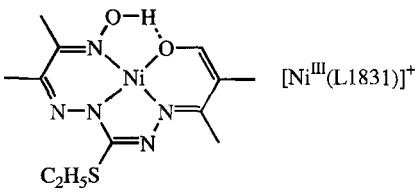
The formulae given for [Ni(L1825)]–[Ni(L1827)] and [Ni(L1828)]–[Ni(L1830)] are proposed on the basis of mass and ^{1}H NMR spectra and confirmed by an X-ray diffraction study of [Ni(L1826)] [12].



(9.5)

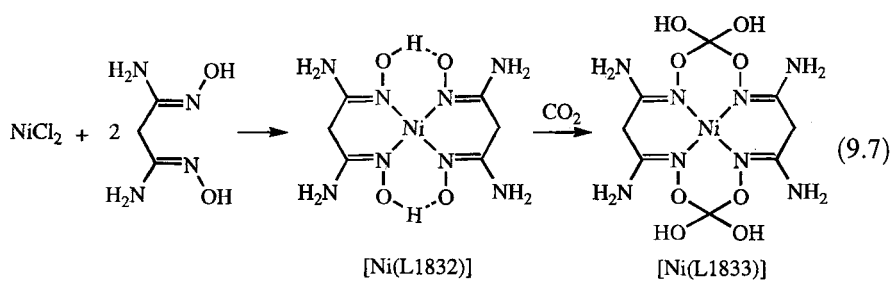
R = CH_3	[Ni(L1825)]	R = CH_3	[Ni(L1828)]
R = C_2H_5	[Ni(L1826)]	R = C_2H_5	[Ni(L1829)]
R = $C_6H_5CH_2$	[Ni(L1827)]	R = $C_6H_5CH_2$	[Ni(L1830)]

The reactions of isomers A and B of [Ni(L1815)] with halogens in toluene, chloroform and methylene chloride have been studied. Neither isomer reacts with molecular iodine, whereas bromine and chlorine oxidise the starting complexes to their nickel(III) analogues. Oxidation by bromine leads to the formation of nickel(III) complexes in which, according to ESR data, the nickel environment is conserved. Chlorine oxidation of isomer B again gives the nickel(III) product without change of donors of the organic ligand. However, chlorine reacts with the A isomer to form two oxidation products in solution: the first retains the N_4 donor set; the second has an N_3O set of donors involved in coordination, as shown in the formula (Eq. 9.6) for $[Ni^{III}(L1831)]^+$ (C) [13,14].



$[Ni^{III}(L1831)]^+$ (9.6)

An unusual template reaction is performed in the case of complexes of dioximes and their derivatives reacting with CO_2. Starting from malonamide oxime the tetraazamacrocyclic complex [Ni(L1833)] is obtained (Eq. 9.7) [15]. Structures of [Ni(L1833)] (Figure 9-2) and of its quasimacrocyclic precursor [Ni(L1832)] were established by X-ray crystallography [15].



(9.7)

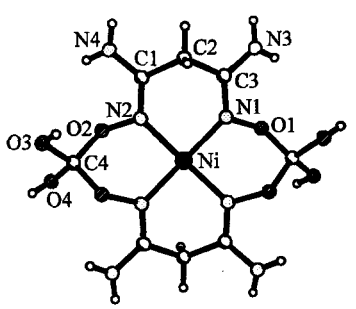
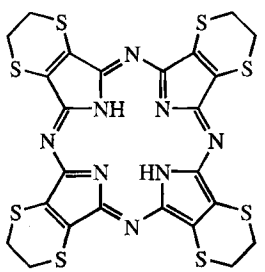


Figure 9-2. The structure of [Ni(L1833)].

This is presumably the only example of an orthocarbonic acid derivative formed by addition of CO_2 to the oxime groups. Unfortunately the electronic structure of [Ni(L1833)] has not yet been studied. According to X-ray diffraction results nickel has the formal oxidation state of zero.

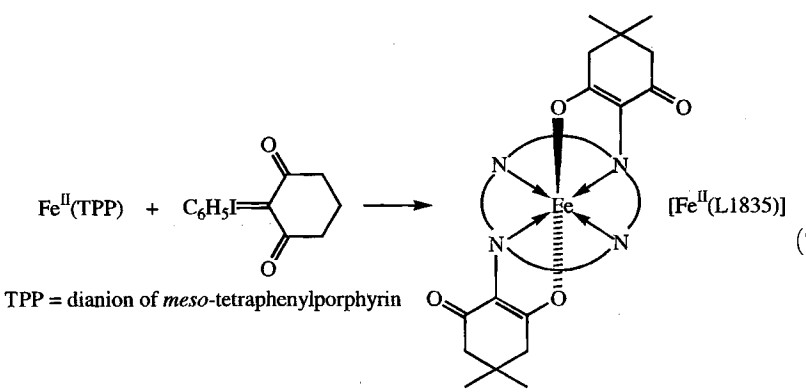
The tetraazaporphin derivative H_2L1834, which has pyrrole rings condensed with dithiaheterocycles, is assembled by heating a molten or boiling quinoline solution of a mixture of 3,6-dithiacyclohexane-1,2-dicarbonitrile and an appropriate metal chloride or acetate [16]. Bivalent copper, zinc, magnesium, cadmium, iron, cobalt, nickel, lead and tin, and trivalent aluminium, gallium, indium and chromium, and tetravalent germanium, tin and zirconium ions all acted as templates, to give the respective metal complexes of H_2L1834 (Eq. 9.8).



H_2L1834 (9.8)

To obtain metal-free H_2L1834, the starting ligson is refluxed with lithium amylate in amyl alcohol, then the complex formed is isolated and demetallated by sulphuric acid [16].

The complex [Fe(L1835)] is synthesised in 95% yield by reaction in toluene (Eq. 9.9).



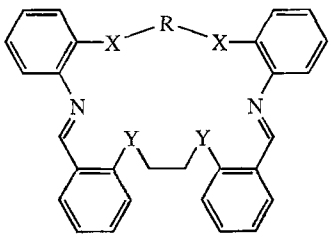
$Fe^{II}(TPP)$ + C_6H_5I → $[Fe^{II}(L1835)]$ (9.9)

TPP = dianion of *meso*-tetraphenylporphyrin

Whatever the mechanism of this process may be, the formation of two five-membered chelate rings suggests a template reaction. The appearance of these rings

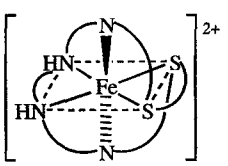
is attributed to the insertion of O–C–C fragments of the ligsons between two iron-nitrogen bonds in *trans* positions [17].

Template construction of the macrocyclic compound L1836 (Eq. 9.10) is carried out by condensation of 1,2-bis(2-aminophenylthio)ethane with 4,7-diaza-2,3;8,9-dibenzodecane-1,10-dione in methanol in the presence of one of a number of metal perchlorates [18]. When using iron(II), cobalt(II) or nickel(II), the final product is isolated as $M(L1836)(ClO_4)_2 \cdot CH_3OH$. If the reaction is carried out on a zinc(II) matrix, besides a complex of this composition, metal-free L1836 is also produced. Using chromium(III) perchlorate gives L1836 as the sole product. The latter can be also synthesised by demetallation of the iron(II) and zinc(II) complexes by treatment of their solutions with pyridine.



$R = (CH_2)_2$, X = S, Y = NH L1836
$R = (CH_2)_2$, X = NH, Y = NH L1837
$R = (CH_2)_3$, X = NH, Y = NH L1838
$R = (CH_2)_3$, X = O, Y = NH L1839 (9.10)

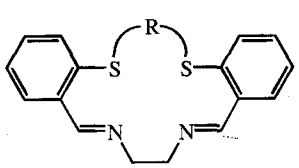
An X-ray diffraction study of $[M(L1836)](ClO_4)_2 \cdot CH_3OH$ showed [18] that the ligand used its coordination capacity fully and the complex cation has the structure which approaches the idealised configuration given here (Eq. 9.11). Thus the



(9.11)

macrocyclic ligand is flexible enough to be coordinated to the central atom in an octahedral manner.

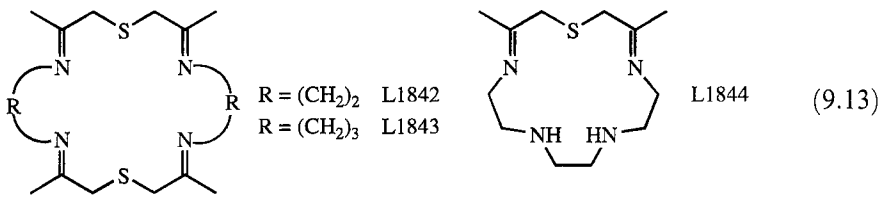
The systems L1837–L1839 [18] as well as L1840 and L1841 [19] are prepared in an analogous way. The latter two compounds are synthesised on an iron(II) matrix in acetonitrile and isolated as the corresponding complexes (Eq. 9.12). On coordi-



$R = (CH_2)_2$ L1840
$R = (CH_2)_2S(CH_2)_2$ L1841 (9.12)

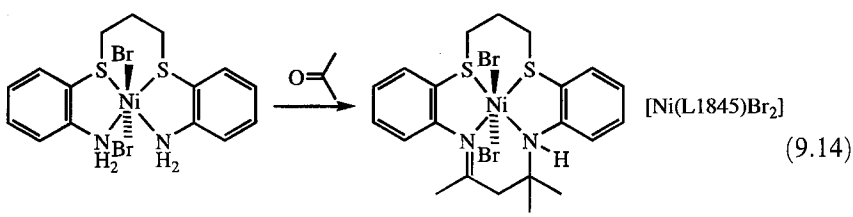
nation to a metal L1841 acts as a pentadentate ligand occupying four planar and one apical positions around the central atom [18].

The macrocyclic compounds L1842–L1844 (Eq. 9.13) are assembled by (2 + 2) or (1 + 1) reactions of 4-thiaheptane-2,6-dione with en, 1,3-diaminopropane or trien in absolute methanol in an inert atmosphere in the presence of nickel chloride or nitrate. The substances synthesised form complexes with the template cations employed [20]. Like similar compounds reported earlier [18, 19], L1842–L1844 have the necessary flexibility to use all their donor atoms in octahedral coordination compounds [20] completely, so can act as hexa- and pentadentate ligands respectively.



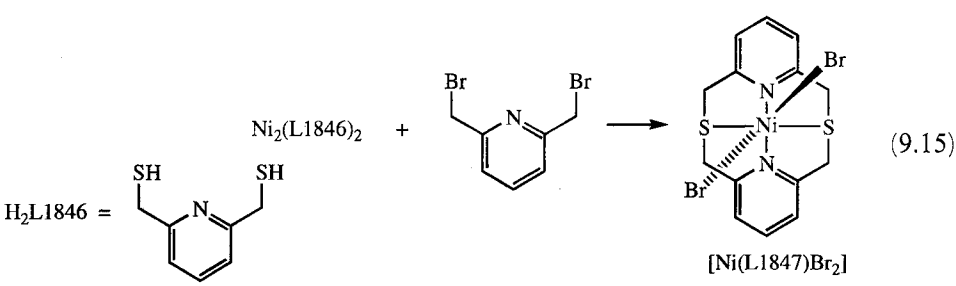
(9.13)

The assembly of the macrocyclic compound L1845, containing azomethine and secondary amino groups as well as thioether sulphur atoms, is performed by aldol condensation. This substance is isolated as its nickel(II) complex [21, 22]. Metal-free L1845 is generated by boiling a suspension of Ni(L1845)Br_2 in water (Eq. 9.14) [22].



(9.14)

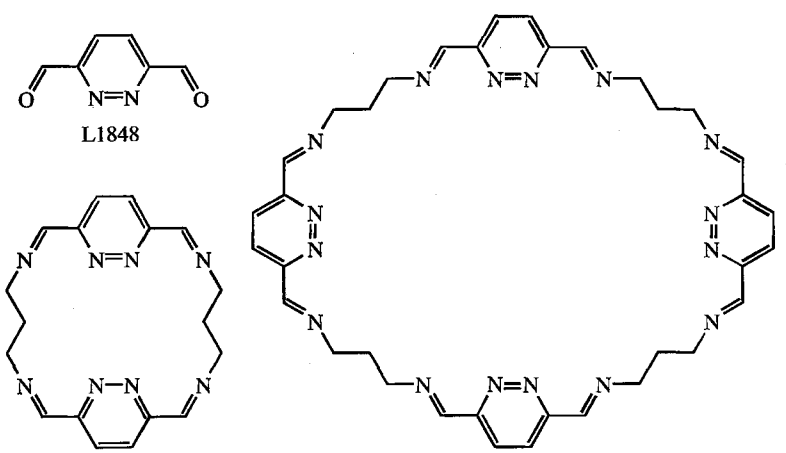
The nickel(II) complex with the pyridinophane L1847 is synthesised by a template reaction (Eq. 9.15). Although the structure of Ni_2(L1846)$_2$ has not yet been established, its dimeric nature has been indicated by mass spectrometry [23].



(9.15)

Analysis of molecular models of L1847 indicates that the cavity size of this 12-membered macrocycle is too small for this compound to be used as a ligand occupying the equatorial plane of an octahedral complex. The X-ray structure determination of $[Ni(L1847)Cl_2]$, obtained by a double exchange reaction, demonstrates [23] that the sulphur atoms of the distorted ligand occupy *trans*-axial positions, the pyridine nitrogens take *cis* positions in the plane, and the remaining two positions in this plane are occupied by chloride anions. Ligand L1847 must therefore be flexible for its synthesis on a nickel(II) matrix to proceed readily.

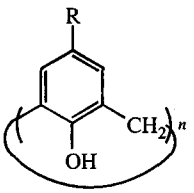
Macrocyclic compounds of 2 + 2 and 4 + 4 stoichiometries derived from 3,6-diformylpyridazine (L1848) and 1,3-diaminopropane as ligsons have recently been reported [24, 25]. It has been discovered that the reaction between the corresponding ligsons and lead(II) perchlorate in 1:1:1 molar ratio produces the complex $Pb_2(L1849)(ClO_4)_4$ in 60% yield (Eq. 9.16). If, however, the starting materials are mixed in 2:2:1 ratio, the complex $[Pb_2(L1850)](ClO_4)_4$ results in 66% yield. The ability of lead(II) to promote the formation of both 2 + 2 and 4 + 4 macrocyclic ligand products by simple changing the ratio of reagents employed is noteworthy.



(9.16)

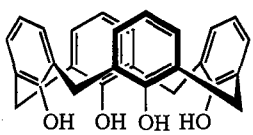
Transmetallation of $[Pb_2(L1850)](ClO_4)_4$ with four equivalents of manganese(II) perchlorate in the presence of an excess of NaSCN proceeds with ring contraction leading to $[Mn_2(L1849)(NCS)_4]$. The latter is also formed on transmetallation of $Pb_2(L1849)(ClO_4)_4$ under analogous conditions. The stoichiometry of condensation products *L1849* and *L1850* was confirmed by X-ray diffraction studies of $[Pb_2(L1850)](ClO_4)_4$ and $[Mn_2(L1849)(NCS)_4]$ [24, 25].

Macrocyclic systems represented by the general formula of Equation (9.17) are quite unusual and important due to their ability to form complexes and serve as models of enzyme functioning. These compounds are called calixarenes [26, 27]



(9.17)

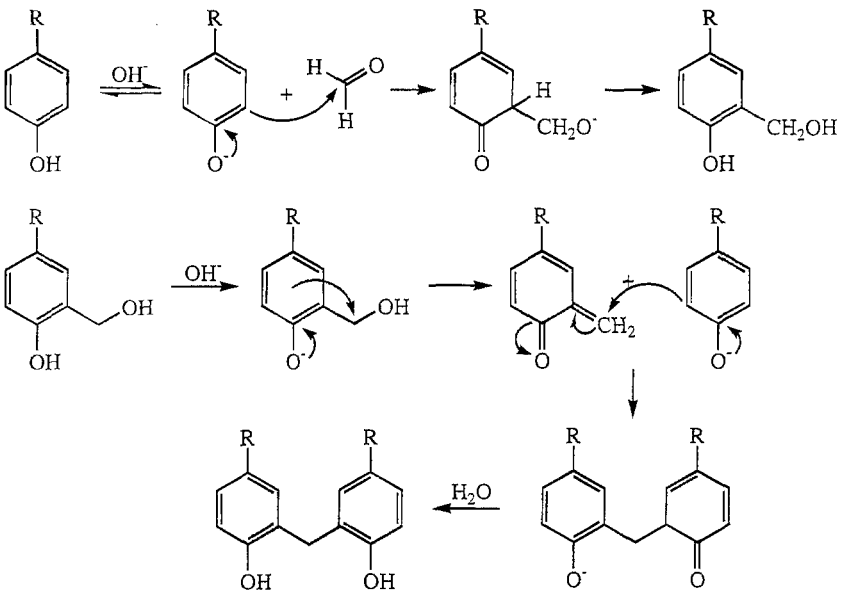
from the Greek word *calix* (vase), due to their vase-like geometry. The suffix 'arene' emphasises the inclusion of aryl units. An example is calix[4]arene (H_4L1851; Eq. 9.18), the number in brackets indicating the number of phenol units in the cyclic skeleton. Although the term "calixarene" describes the shape (outline) of cyclic tetra- and pentamers precisely, it becomes less appropriate for higher members of the series. For example, the octamer in the crystalline state is almost planar. However, the name has became common for the whole series of substances [26, p. 96].



H_4L1851 (9.18)

Calixarenes are the products of condensation of *p*-alkyl-phenols and formaldehyde, which is the main route for the synthesis of these compounds. These starting materials are those used for production of bakelite, and indeed calixarenes were first made during a study of the formation of this material [28, 29]. The product isolated was assumed to be exclusively calix[4]arene. Later, after numerous studies, it was found that a mixture of calixarenes is actually formed on reaction of the corresponding ligsons, and the precise course of the reaction depends on many factors [26, 27, 30–33]. The basic variables relevant to the one-flask process in the presence of bases are as follows:

- alkali concentration – catalytic amounts are required for cyclic octamers (and tetramers), whereas stoichiometric amounts of base are necessary to synthesise calix[6]arenes;
- temperature – the formation of cyclic octamers and hexamers dominates if the reaction is carried out at relatively low temperatures (boiling in xylene, for instance), whereas cyclic tetramers predominate at higher temperatures (for example, boiling in diphenyl ether);
- nature of the ligsons – the production of cyclic tetramers is successful only in the case of certain *p*-substituted phenols;
- cation effect – octamers and tetramers are the dominant reaction products if the smaller alkali metal cations are employed, whereas the cyclic hexamer is assembled more successfully when larger cations are involved.



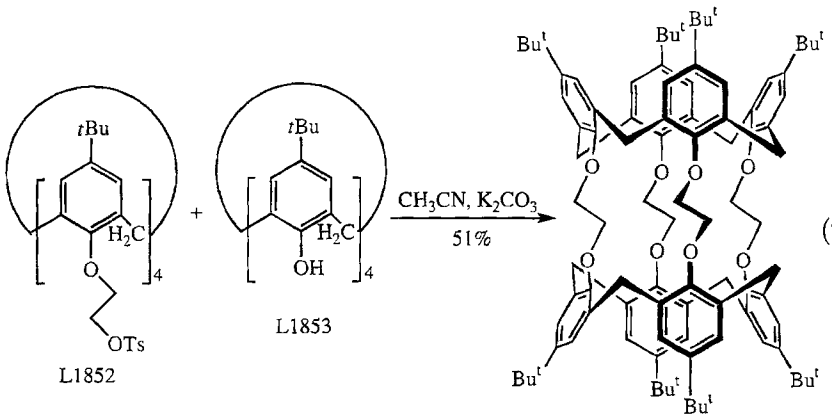
Scheme 9-1. Initial steps in the assembly of calixarenes.

Note that various multistep pathways are available for the assembly of these macrocyclic substances in alkaline, acidic or neutral media by one-flask syntheses.

The process of calixarene assembly must be based on reactions that give substances containing two (or more) units (the initial steps of these reactions are shown in Scheme 9-1). These intermediates, with a zigzag arrangement of aromatic rings, are shrunk into conformations suitable for the final design of closed-ring products due to participation of intramolecular hydrogen-bonds of OH groups. In spite of numerous systematic studies, the mechanism of calixarene formation remains to a certain extent unclear. Several series of results suggest that hydrogen-bonding plays a key role in the arrangement of reacting fragments. The fact that quite strong hydrogen-bonding has been observed in calixarenes by IR and ^{1}H NMR spectroscopy, and by X-ray diffraction studies, [34–36] provides evidence in favour of this conclusion.

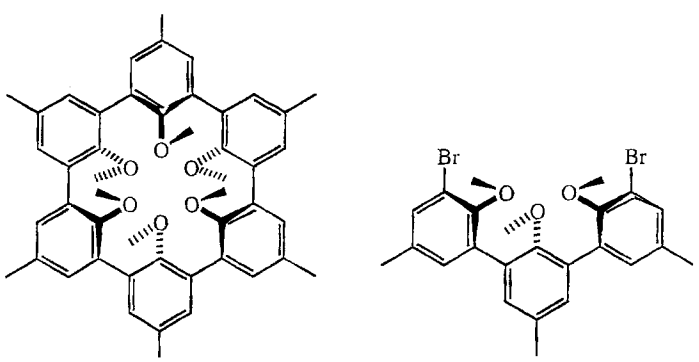
With a small quantity of alkali (for the ratio phenol:paraformaldehyde:base = 45:75:1) sodium, potassium and caesium hydroxides yield practically the same mixture of products in which the cyclic octamer dominates; lithium is much less effective. Magnesium and calcium hydroxides have no effect on the course of the reaction, and barium hydroxide favours the formation of linear oligomers. An increase in the amount of alkali metal hydroxide to give the proportion of reagents 2:4:1 results in a significant difference in the influence of base on the course of the process [32]. In particular, when using potassium, rubidium and caesium hydroxides the main product of the reaction is calix[6]arene. Rubidium(I), having a radius compatible with the product, is the most effective template.

The potassium cation as template provides the formation of calix[4]tubus L1854 from tetratosylate L1852 and *p-tert*-butylcalix[4]arene (L1853) in 51% yield (Eq. 9.19) [37]. Direct complexation reactions showed the high selectivity and strong binding ability of L1854 towards potassium ion in contrast to other alkali metal ions.



(9.19)

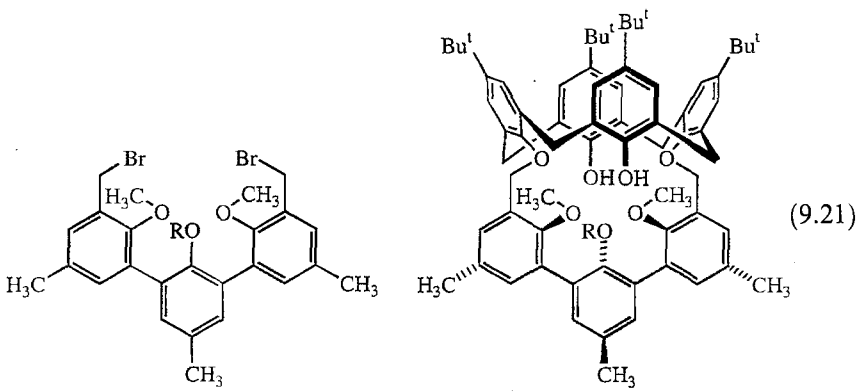
The compound L1855 (Eq. 9.20) is referred to as a spherand. The name originated from the word 'sphere' because, unlike crown ethers and cryptands, the shape of its macrocyclic cavity is suitable for occupation by spherical particles, such as separate atoms or simple ions, rather than by complex molecules or ions. The suffix 'and' emphasises the ligand abilities of such systems. L1855 is prepared by template condensation of L1856 on a lithium(I) matrix in THF at −80°C, followed by addition of $Fe(acac)_3$, boiling in benzene and washing of the solution formed with



(9.20)

an aqueous solution of $H[FeCl_4]$. The product is isolated as $[Li(L1855)][FeCl_4]$ [38]. This undergoes demetallation when heated in a sealed tube for a long time at 150°C in a CH_3OH/H_2O mixture (in proportion 1:4 by volume), to release the metal-free ligand.

Reaction of *p-tert*-butylcalix[4]arene L1853 with five equivalents of NaH in THF in the presence of a catalytic amount of 18-crown-6 and L1857 gives rise to the calixspheranddiol H_2L1858 in 80% yield (Eq. 9.21) [39]. When the larger potassium cation is involved as KH, or the reaction is carried out under high dilution conditions, only small amounts of H_2L1858 result.



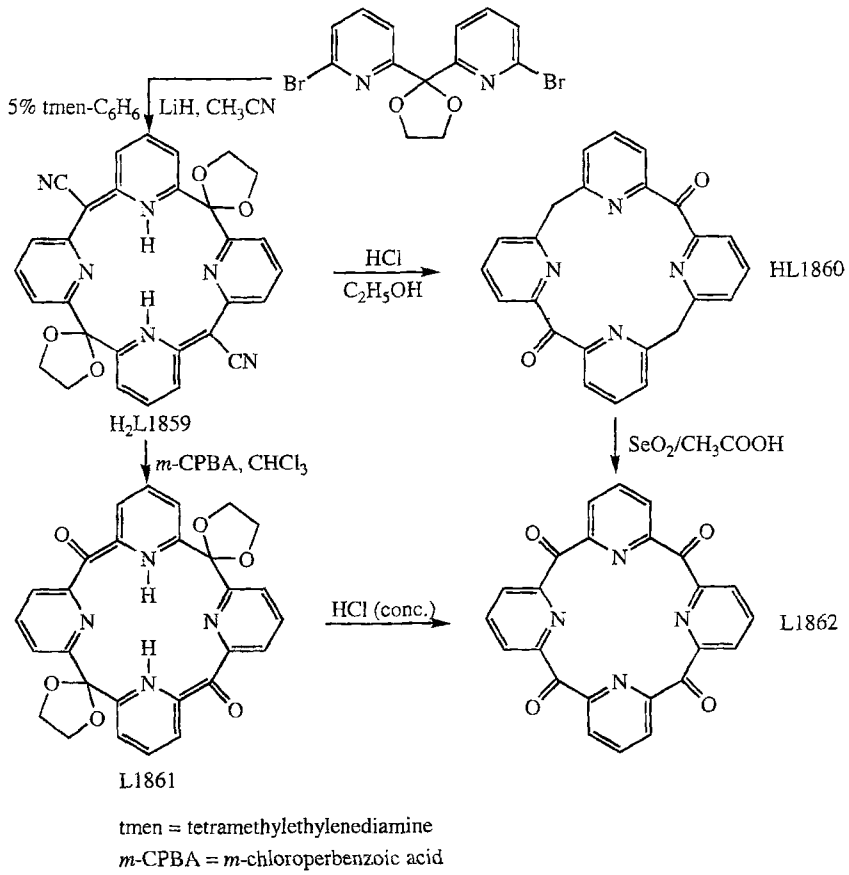
(9.21)

The macrocycle H_2L1859 is obtained by the reaction on a lithium(I) matrix shown in Scheme 9-2. It can be converted into compounds L1860–L1862 [40]. X-Ray crystallographic determination of the structure of the tetraketone L1862 has been carried out, to verify the structure shown in Scheme 9-2. This substance incorporates a new macrocyclic system that may be considered as a pyridine-containing xanthoporphyrinogenic model, while at the same time looking like a calixarene with substitution of pyridine units for phenols [40].

The template synthesis of (+)-L1865 was carried out starting from L1863 and triphenol (+)-L1864 via the stereospecific pathway shown in Scheme 9-3.

In this case the new ring formed has the same chirality as the initial parent ring. No *meso* isomer has been detected in the reaction mixture. The conformational requirements of the $-OCH_2CH_2O-$ and $-OCH_3$ groups predetermine to a large extent the assembly of (+)-L1865 as sole reaction product [41].

Although metallamacrocyclic compounds are, strictly, outside the scope of this book, one specific example is included here to demonstrate the ability of inorganic anions to control the overall topology of the reaction product. It concerns 'mercuracarborands'. This kind of metallamacrocycle originates from one of the three possible carborane isomers, *closo*-1,2-$C_2B_{10}H_{12}$, and mercury atoms connected by C–Hg–C moieties (Eqs. 9.22 and 9.23) [42, 43]. The *closo*-1,2-$C_2B_{10}H_{12}$ isomer (a three-dimensional icosahedron), as a result of the increased acidity of two adjacent CH units, can easily be deprotonated and then functionalised with electrophilic

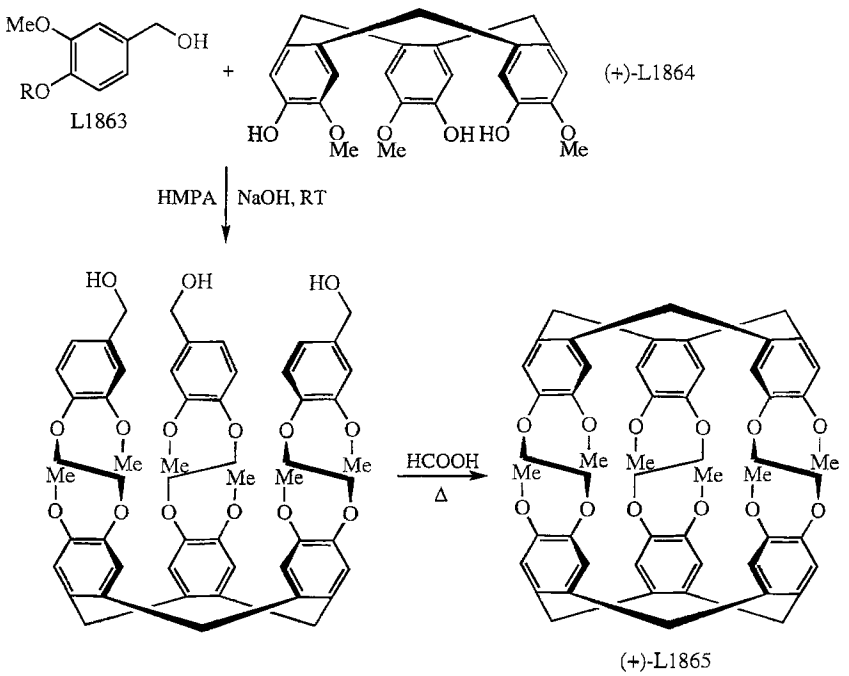


Scheme 9-2. Synthetic pathway to the modified pyridine-containing calixarene L1862.

reagents. Mercury(II) is one possible electrophile. In contrast, the BH vertices undergo an electrophilic substitution which resemble the behaviour of arenes. One such substituted derivative is 3-Ph-1,2-$C_2B_{10}H_{11}$.

closo-1,2-$C_2B_{10}H_{12}$ *closo*-3-Ph-1,2-$C_2B_{10}H_{11}$ (9.22)

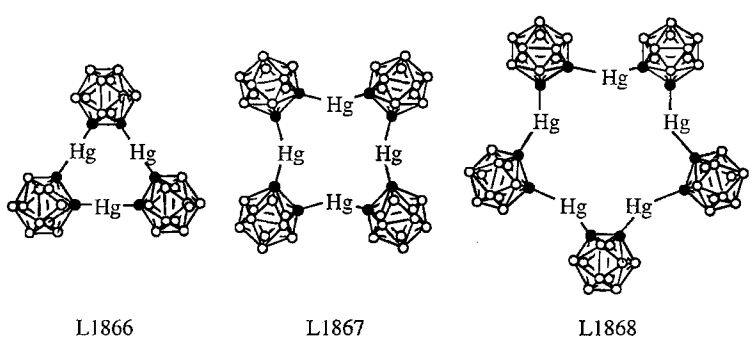
Note that in organomercury compounds, Hg^{II} forms two linear (or very near linear) non-polar σ bonds. In addition, the presence of two empty p orbitals conveys strong Lewis acidity to the plane perpendicular to the essentially covalent σ bonds, which can be involved in Lewis acid-base interaction. In mercuracarborands the



Scheme 9-3. Stereospecific assembly of the chiral D_3 isomer (+)-L1865.

Lewis-acidic properties of the Hg atoms involved are even more pronounced due to the presence of the electron-withdrawing carborane cages.

It has been discovered that lithiation of *closo*-1,2-$C_2B_{10}H_{12}$ by *n*-BuLi at its CH groups affords *closo*-1,2-Li_2-1,2-$C_2B_{10}H_{10}$. The latter reacts with $Hg(CH_3COO)_2$ in ether with the formation of L1866 in 65% yield [44].



(9.23)

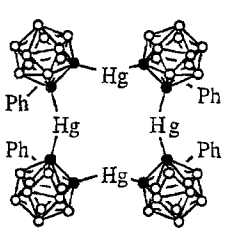
Addition of LiCl to the solution of L1866 produces the complex Li[L1866(Cl)], in which the chloride is bonded to three Lewis acid centres. As L1866 behaves as a charge-reversed analogue of [9]crown-3 it was called [9]mercuracarborand-3. The structure of $(L1866)_2 \cdot 8CH_3CN$ has been determined by X-ray diffraction and shows

two cocrystallised acetonitrile adducts L1866A·3CH_3CN and L1866B·3CH_3CN in the crystal. The average C–Hg–C angles are 177.1(8) and 175.5(8)° for L1866A and L1866B, respectively. The macrocyclic rings of both molecules are almost planar.

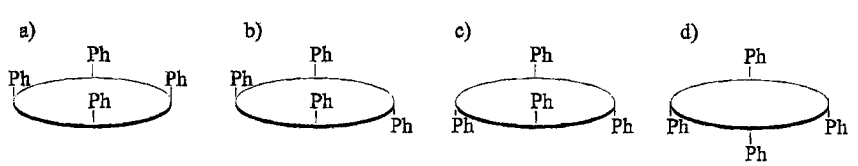
Originally it was supposed that the same complex Li[L1866(Cl)] could be obtained in one step starting from *closo*-1,2-Li_2-1,2-$C_2B_{10}H_{10}$ and $HgCl_2$. However, the reaction afforded the complex Li[L1867(Cl)] in 75% yield, where L1867 is a tetrameric metallamacrocycle [45]. The cyclic tetrameric structure of L1867, with a chloride anion located in the centre of the ring and bonded to all four mercury atoms at 29.44(2) nm, has been confirmed by X-ray diffraction. Complex L1867 adopts a rather strained conformation compared to the stereochemically preferred macrocycle L1866. For example, the C–Hg–C angle of 162.0(3)° deviates noticeably from linearity. This highly efficient synthesis of Li[L1867(Cl)], in which the chloride ion forms a three-centre two-electron bond with L1867, led to the conclusion that this chloride ion acts as a template in construction of L1867. Note that in L1866 or in a linear polymer the more favoured linear coordination of Hg(II) to carbon atoms is realised. The template can easily be removed by treating Li[L1867(Cl)] with $AgCH_3COO$ in ethanol.

The iodide anion, another suitable template, taken as HgI_2, also provides high-yield formation of L1867, isolated as complexes with iodide ion of 1:1 and 1:2 stoichiometries in Li[L1867(I)] and Li_2[L1867(I_2)] [46]. Iodide-free L1867 resulted in 80% yield from reaction of Li_2[L1867(I_2)] with two equivalents of $AgCH_3COO$ in ethanol, and was characterised by X-ray single crystal analysis [47]. The thiocyanate anion has been claimed to promote the construction of the [15]-mercuracarborand-5 (L1868) [43].

Further evidence of the template effect exercised by halide ions has been gained by carrying out halide-templated reactions of the phenyl-substituted lithiated carborane 3-Ph-1,2-Li_2-1,2-$C_2B_{10}H_9$ with mercury(II) [48, 49]. A strong dependence of the product distribution on the halide ion employed has been discovered. We recall here that for unsubstituted carborane ligsons both I^- and Cl^- (which markedly differ in size) promote the formation of tetrameric species L1867. The final tetramer L1869, assembled from a 3-phenyl-substituted ligson, can generally exist as four stereoisomers (Eq. 9.24).



L1869 (9.24)



In practice, three of the isomeric chloride ion complexes, characterised structurally, resulted from templated syntheses on the smaller chloride anion. The fourth isomer (a), with all phenyl substituents residing on the same side of the metallamacrocycle, does not form due to steric constraints. When the larger iodide ion was employed to template the formation of the tetrameric metallamacrocycle, the only stereoisomer formed was (c), with the alternating up down arrangement of phenyl groups. The steric interactions between I^- and the phenyl substituents are believed to be minimised in the transition state, leading to the formation of this stereoisomer to an extent which is not possible in the transition states for the formation of other three stereoisomers [47, 48].

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Chapter 10

Uses of template processes and products

10.1 Applications

The most important practical aspect of the material considered in this monograph is the concept of template synthesis as a modern synthetic strategy, resulting in the development of new principles and approaches. Through its use it is possible to synthesise a variety of complicated compounds, sometimes approaching or competing with natural systems in multiatomicity, composition, and uniqueness of structure and properties. This opens the way to new functional materials, and provides environments for elucidating new aspects of coordination chemistry of transition metal ions. For example, the use of dibenzotetraaza[14]annulenes as macrocyclic ligands has enabled the formation, structure and reactivity of transition metal–chalcogenido and metal–imido multiple bonds to be studied [1–6]. These aspects of template processes are examined in Chapter 11.

This chapter discusses the uses of template reactions and of their products. There are several examples of the industrial production of macrocyclic systems by template methods. The undoubted leaders among these are copper(II) phthalocyanine [Cu(L613)] and its derivatives, whose annual production is thousands of tons. Major applications are dyes and pigments for cars, with textile dyeing being less important [7–11]. Some phthalocyanine complexes can be used directly as pigments for automobile paint finishes, but for textile dyeing the template synthesis of the required dyestuff is carried out within the fabric, by interaction of copper (or nickel) salts impregnated in the textile cellulose with 1,3-diiminoisoindoleimine [11].

A number of highly conjugated polyazamacrocyclic nickel complexes [12] and their precursors [13], including [Ni(L1821)] to [Ni(L1823)], have been used as dyes for polymeric materials such as poly(vinyl chloride), and the complexes [Ni(L83)] to [Ni(L89)] were proposed for dyeing polyamides and polyethers [14]. Coordination compounds [Ni(L83)] to [Ni(L89)] have been used for producing special inks for polymeric materials (including cables) to be used in extreme conditions, such as high temperatures or aggresive environments [14].

The property of a number of macrocyclic ligands, primarily polyazamacrocycles with unsaturated cyclic backbones, to give coloured compounds with metal ions,

have been used for analytical purposes. For instance, formation of the coloured iron(II) clathrochelates [Fe(L916)] to [Fe(L926)] on template coupling of alicyclic α-dioximes by boron-containing agents has been used for detecting iron in 10^{-6}% concentrations in the presence of 10- to 20-fold excess of copper(II) and nickel(II) and of 100-fold excess of cobalt(II) and chromium(III) [15–17].

Porphyrin analytical reagents may be used in spectrophotometric detection of copper and zinc in sewage, and in biological and chemical products of high purity [18–21]. Copper may be detected spectrophotometrically in samples of nickel alloys [22] in the form of $[Cu(L183)]^{2+}$ in the presence of a large excess of cobalt(II) as well as of nickel(II). Selective detection of copper(II) can also be achieved by using TAAB for its extraction into an aqueous phase from organic media [23]. The macrocyclic compound L15 is used for masking copper(II) [24].

One of the most interesting practical properties of crown ethers is their almost unique and selective ability to form quite stable complexes with ions of alkali and alkaline earth metals, which makes them valuable in analytical chemistry [25, 26]. The strongest complexing agents have from 5 to 10 oxygen atoms in the macroring. Cryptands are even more effective for these purposes. For both classes of macrocyclic reagents, matching metal ion diameter to the size of the ligand cavity plays an important role in the complexing selectivity. High stability constants and selectivity are useful for concentrating and extracting metals from solution and for separating cations with similar properties [27–35]. The macrocycle that proves to be the best extractant for the cation is also the best template for its production. Thus, in the case of crown ethers, lithium salts are well extracted by 14-crown-4 and potassium by L1245. Sensing devices based on synthetic crown ether ionophores incorporated into lipid membranes and organic films have also been developed [36].

Strontium is separated from the other alkaline earth elements by using dicyclohexyl-18-crown-6 [35, 37]. Extraction or immobilization of the corresponding ligands on suitable carriers are effective ways for separating ions [27, 38–41]. For the separate detection of radionuclides $^{89,90}Sr$ and ^{137}Cs in soils and wastes, methods of extractive concentration by crown ethers (dibenzo-21-crown-7 and dicyclohexyl-18-crown-6) or their adducts with heteropolyacids have been suggested [42, 43]. In some cases, because isotopes of the same element give complexes with macrocyclic ligands differing significantly in stability, the latter are suitable for separating these isotopes. Phthalocyanines are also used for the concentration of radioisotopes [44, 45]. The method relies on the high chemical, thermal and radiation stability of metal–phthalocyanine complexes.

An electroactive thiophene-based sensor containing two dissimilar metal-binding sites has been elaborated [46]. It is able to detect metal ions coordinated by a crown ether ring and neutral organic species coordinated to the oxidised transition metal centre, for example Ni^{III} residing at an N_2O_2 binding site. Incorporation of the redox-active tetrathiafulvalene unit into the crown-ether backbone is another efficient way to metal-cation sensors [47, 48]. Using the template ability of Co^{II} the threading of a 2,9-diphenyl-1,10-phenanthroline moiety bearing two terminal electroactive pyrrole groups through the related macrocycle has been performed providing the formation of rotaxane. Electropolymerisation afforded a material (a thin film deposited onto a carbon felt electrode) that displays the properties of organic

conducting polymers and allows reversible metal exchange reactions in the material [49].

Macrocyclic complexes of transition metals are widely used as both oxidising and reducing agents as well as catalysts in many redox processes [17, 50–56]. In particular, macrobicyclic complexes such as $[Co(L824)]^{3+}$ and related compounds appear to be effective electron carriers in the photocatalytic decomposition of water [57–63].

Metal porphyrins act as catalysts for chain transmission in radical polymerisation [55] and for electrochemical oxidation of sulphur dioxide [64], as well as for oxidation of a wide range of organic substrates [65]. Cobalt and nickel complexes with L15 are effective in the electrocatalytic reduction of carbon dioxide [66]. Porphyrin complexes of cobalt and tetraazamacrocyclic complexes of nickel catalyse reduction of the proton [67–71].

Photochemical oxidation of methanol to formaldehyde is catalysed by iron [72] and cobalt [73] macrocyclic complexes, including those with L15 and L824. Polyazamacrocyclic compounds of cobalt also catalyse electrochemical reduction of oxygen to hydrogen peroxide [74, 75]. Complexes of silver with L15 and with L183 are used as antifogging agents in photographic materials [76]. Data on non-silver photographic systems based on transition metal complexes of chelating and macrocyclic ligands, and the formation of non-silver photographic images using template procedure, have been reviewed [77].

The complexes [Ni(L263)], [Ni(L272)] and [Ni(L274)] to [Ni(L281)], synthesised by template methods (as well as their respective free macrocycles isolated by demetallation) are possible electrophotographic materials for photoregistration in duplicators and electronic componets. Such compositions are notable for their high sensitivity and temperature stability (up to 360°C) [78, 79].

Porphyrins, phthalocyanines, crown ethers and their complexes, modified by long-chain peripheral substituents, exhibit attractive properties as liquid crystals [80–88]. The complex [Cu(L263)] forms part of a thermoreactive composition used for the manufacture of polymer coatings, glues and hermetic compositions, and for shaping various articles [89].

A number of unsaturated polyazamacrocyclic complexes and their derivatives exhibit unusual properties, such as high metal-like conductivities or, conversely, semiconductor behaviour [90–96]. Metallophthalocyanines and subphthalocyanines are promising non-linear optical materials for application in optoelectronic devices [97, 98]; Porphyrins have been used in organic light-emitting diodes [99].

Sarcophagine and sepulchrate metal complexes have found application as redox reagents [100, 101]. A suggested economical method to obtain hydrogen peroxide by reduction of molecular oxygen involves the use of macrobicyclic complexes of cobalt, rhodium, or platinum as redox intermediaries [102], in which the robust ligand systems ensure efficient and reversible electron transfer. The change of the metal environment geometry is restricted on change of oxidation state, which makes them useful for photoelectrochemical energy storage devices [103, 104]. These systems are also valuable precursors for a new class of powerful highly charged detergents [105, 106].

Slow electrocrystallisation of $[NBu_4^+][Ni(dmit)_2^-]$ (dmit = 2-thioxo-1,3-dithiol-

4,5-dithiolate) with $LiBF_4$ and 12-crown-4 in acetonitrile-acetone (1:1) solution at a constant current (1 μA) afforded the insulating salt Li_2[12-crown-4]$_3$[Ni(dmit)$_2$]$_7$·$2Me_2CO$. At room temperature this has a conductivity of 30 S cm^{-1}, exceeding by about two orders of magnitude the σ_{RT} value for [Li^+][Ni(dmit)$_2$]$_2$·$2CH_3CN$ [107]. In addition, the material displayed a semiconductor-semiconductor phase transition on the application of pressure or on lowering the temperature. Crystallisation of KTCNQ (TCNQ = 7,7,8,8-tetracyanoquinodimethane) in the presence of 15-crown-5 in acetonitrile results in a dark purple material with the stoichiometry (15-crown-5)$_2$KTCNQ. An X-ray diffraction study showed the formation of isolated $TCNQ^{\cdot-}$ dimers surrounded by (15-crown-5)$_2K^+$ units [108], which exhibit thermally activated triplet exciton behaviour. The latter is dependent on the counter ion and the solid-state structure.

Another property of macrocyclic compounds, namely lipophilicity, is used for the transfer of metal salts with hydrophilic anions into organic solvents by the reaction

$$MX(\text{solid}) + L_{solv} = [ML]X_{solv}$$

The dissolved substance is often an ion pair with an extremely weakly solvated anion; such anions are often described as 'naked'. A typical example of such a system is a solution of $KMnO_4$ in benzene containing L1245 [109–111]. Such a solution has oxidising properties and is widely used under the name 'purple benzene' in organic synthesis for the oxidation of saturated and unsaturated hydrocarbons, alcohols and aldehydes [50]. Similarly, $K_2Cr_2O_7$ dissolved in hexamethylphosphoramide (HMPA) containing 18-crown-6 has been used as a strong oxidising agent for organic compounds [112]. On the other hand, by using L1245 as a complexing agent, it is possible to transfer such strong reductants as KH and KBH_4 into organic solvents [113].

The cryptands, like the crowns, are effective in dissolving a range of inorganic salts in both polar and non-polar solvents [114]. For instance, in the presence of L1485, the solubility of $BaSO_4$ in water is increased by approximately 10^4 [115]. Another attractive property of crown ethers and cryptands is that they are able to transfer alkali metals into non-polar solvents [116]. On ligand-M interaction (M is an alkali metal), a disproportionation of the latter resulting in cation $[ML]^+$ and anion M^- formation takes place. These compounds are used as catalysts in anion polymerisation [117].

On treating sodium alloys of lead, tin, bismuth and other metals with solutions of cryptands of the type L1485, homopolyatomic anions such as Pb_9^{4-}, Sn_9^{4-}, Sn_5^{4-}, Sb_7^{4-} and Bi_7^{4-} are formed. The solutions of these ions are brightly coloured and have many important properties [50, 118].

Macrocyclic ligands are constituents of many membranes, used for separation, purification and concentration of ionic compounds (both non-organic and organic) [119–122], and of several ion-selective electrodes [119, 122–127]. For instance, H_2L263 and L1245 are highly effective as siderophores, i.e. as iron(III) carriers [128, 129], whereas calixarenes and their analogues (up to calix[7]arene) transport alkali metal cations through liquid membranes in alkaline media, but do not transport alkaline earth cations. The effectiveness of transport abilities increases from the

calix[4]arene to the calix[7]arene; the latter is specific for the caesium ion [130]. Liquid-membrane electrodes based on macrocyclic lactones and lactone-lactams manifest selectivity towards alkali and alkaline earth cations [131]. Lithium ion-selective electrodes are based on the 14-crown-4-derivative, including those for detection of this element in blood [132, 133]. Polymeric ligands containing tetra-azamacrocyclic units have been used as highly selective extractants for copper(II). The ligands H_2L263 [134, 135] and H_2L223 [136] were used as the complexing agents in these polymers. Macrocycles of the general formula $RCH_2O(CH_2)_3-$, where RH = L1245, L1247 or L1248, immobilised on silica gel, have been suggested for selective separation and concentration of metal ions [137].

Crown ethers appear to be effective in a great variety of organic syntheses. Chapter 3 of Reference 119 gives many examples of transformations involving crown ethers. Thus, exploiting the above-mentioned ability of these ligands to facilitate transfer of alkali metals salts into organic solvents, together with the fact that the anions are then 'naked', it becomes possible to carry out transformations of organic bromides and chlorides by reaction with KF into the corresponding fluorides, as for example in acetonitrile or benzene using L1245 as complexing agent [138].

Acetate, in the form of the potassium salt solubilised by L1245 in acetonitrile or benzene, reacts smoothly and quantitatively, even at room temperature, with a wide variety of organic substrates forming the respective acetates. For example, benzyl bromide was turned into benzyl acetate in 100% yield [139].

Naked cyanide has been demonstrated to be a synthetically useful reagent in a wide variety of substitution, elimination and addition processes [119]. The reaction of naked nitrite with primary alkyl halides yields nitro compounds as major products, with nitrite esters as the principal byproducts [140]. The use of crown ethers also permits the transformation of organic alkyl halides into the corresponding dialkyl peroxides [141] through the generation of 'naked' peroxide from KO_2 or NaO_2.

Ligand L1256 solubilises $NaBH_4$ in toluene, permitting its use as an effective reducing agent, such as the conversion of ketones into alcohols [142]. Dissolution of $LiAlH_4$ or $NaBH_4$ by cryptands such as [2, 2, 2] in organic solvents can be similarly utilised [143]. The practical significance of macrocyclic compounds in biology is extremely various and wide. Thus, macrocyclic polyamines form complexes with adenosinepolyphosphates [144, 145], manifest an inhibiting effect on reactions proceeding in microsomes [146], have superoxide dismutase activity [147], and influence the synthesis of proteins [148] and the permeability of cell membranes [149]. Copper(II) complexes, with such polythiamacrocyclic ligands as L1364, L1365 or L1366, are the structural and functional models of active centres of blue copper proteins [150, 151]. Dibenzotetraaza[14]annulene transition metal complexes also mimic the behaviour of the active sites of certain naturally occuring enzymes. For example, [Ni(L263)] is an effective catalyst of the reductive dehalogenation of alkyl halides by $NaBH_4$ or $NaBH(OCH_3)_3$ to alkanes, and resembles in this respect the active centre of methyl coenzyme M reductase (factor F_{430}) [152]. The cobalt(II) and rhodium(II) complexes of H_2L263 react with norbornene in the presence of dioxygen with the formation of Co^{III} and Rh^{III} species in which the C=C bond of an

alkene is inserted across the cobalt and one of the macrocycle γ-carbon atoms [153, 154], and can be regarded as biomimetic models of vitamin B_{12} coenzyme. The complex [Mn(L272)NCS] and other related derivatives catalyse the oxidation of *p*-nitroso-*N*,*N*-dimethylaniline to *p*-nitro-*N*,*N*-dimethylaniline by iodosylbenzene in a manner similar to cytochrome P-450 enzymes [155]. Other biomimetic models include iron(II) cyclidene compounds resembling the function of heme proteins. Their binding reactions of dioxygen and carbon monoxide have been studied [156–158]. The niobium(III) complex of calix[4]arene has been found to reduce and cleave N–N multiple bonds under certain conditions [159]. Porphyrins have been used as model systems with which to study energy transfer and concentration [160], and the *in vivo* photoactivation of drug precursors [161]. Photoinduced electron-transfer systems based on zinc(II) porphyrin–C_{60} fullerenes are also available [162]. There are many other examples of template processes and their macrocyclic products in use for modelling and mimicking natural processes in biological systems, and for revealing mechanisms of their activity [50, 92, 163–165].

An interesting variant [166] is the use of coordination compounds of cobalt as additives to stimulate biosynthesis of vitamin B_{12} by the blue-green alga *Spirulina platensis*. The best of the complexes proposed, namely $H_2[Co_2(HL878)_4O_2(H_2O)_2]F_2$ and $[CoCl(HL878)_2NH_3]$, increased the yield of the target product considerably, and have been used commercially. In this case the starting cobalt complex must play a template role in the biosynthesis of the vitamin B_{12}.

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Chapter 11

Conclusions

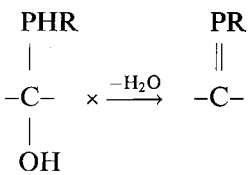
This book demonstrates the great advances made in the theory and practice of template processes. In the years since the publication of an earlier text on matrix reactions [1], a variety of new products have been added to the classes of known macrocyclic compounds. These are the sepulchrates and sarcophagines, catenanes, rotaxanes and knots, macrocyclic polylactones, polylactams and related compounds, calixarenes, spherands, *S*-substituted isothiosemicarbazide (and isothiocarbazide)-based polyazamacrocyclic systems, as well as other groups of products possessing closed macrorings. The construction of these substances has became possible or much easier because of the template method used as either the sole, or one of several, pathways for the controlled synthesis of the required compounds. Often, high dilution methods are the only alternative route. Recent work has produced polynucleating macrocyclic ligands and has opened new routes for the synthesis of mononuclear and binuclear ligand products, and also of systems containing more metal-binding sites. In addition, the template strategy has made it possible to synthesise polymacrocyclic compounds containing space-separated macrocyclic units. Compounds that contain metal-binding sites of a different nature have a wide range of functional properties. One notable feature of template synthesis is its use for assembling catenanes, rotaxanes and knots.

Synthesis of macrocycles needs ligsons (starting blocks), the coupling of which proceeds through the interaction of specific functional groups. Macrocyclisation occurs through the formation of new bonds of three types: carbon–heteroatom, heteroatom–heteroatom and carbon–carbon.

The organic reaction most widely exploited to effect ring closure is the addition of primary amines or hydrazines to a carbonyl function, resulting in C=N bond formation (Eq. 11.1).

$$\begin{array}{l} -\mathrm{C}- \\ \quad \| \\ \quad \mathrm{O} \end{array} + \mathrm{RNH_2} \longrightarrow \begin{array}{l} \quad\quad \mathrm{NHR} \\ -\mathrm{C}- \\ \quad | \\ \quad \mathrm{OH} \end{array} \xrightarrow{-\mathrm{H_2O}} \begin{array}{l} \quad\quad \mathrm{NR} \\ -\mathrm{C}- \end{array} \qquad (11.1)$$

The electronic state of both interacting species and the imine bond formed can be changed by coordination to a metal ion. This results in increased reactivity, or stabilisation, of the corresponding building blocks or ligand product. Some specific examples of hemiaminal macrocyclic intermediate stabilisation have been described. Typically these intermediates easily lose water to give more stable C=N bonds. In addition the coordinated C=N bond can be reduced smoothly to an amine function. This process is attended by a change in the stereochemistry of the nitrogen atom from trigonal planar (sp^2) to tetrahedral (sp^3). The increased conformational flexibility of the resulting macrocyclic amine and diminished coordinating ability, compared to an imine nitrogen donor, makes the demetallation step (template removal) much easier. Also of note is the ability of phosphines to add to carbonyl-containing compounds. In this case, however, the ring coupling reaction proceeds exclusively with formation of hemiphosphinal intermediates. The formation of C=P bonds by elimination (Eq. 11.2) is extremely difficult or even impossible, in contrast compared to imine bond generation.



(11.2)

Another basic organic reaction broadly used as a ring-coupling tool in template syntheses is nucleophilic displacement at a saturated carbon atom, involving attack by a nucleophile on polarised molecules, such as halide or tosylate derivatives. Their leaving group ability is essential for the success of the reaction. Potential donor groups involving oxygen, sulphur, nitrogen and phosphorus serve as typical nucleophiles. Despite the high reactivity of these groups, the course of the reaction can, to a certain extent, be controlled by coordination of a nucleophilic ligson to the metal ion. A wide selection of displacement reactions bridging *cis*-disposed coordinated nucleophiles are included in this book. The bridging in these chelate-producing template reactions occurs through the formation of new covalent C–O, C–S, C–N or C–P bonds.

Free radical anti-Markovnikov addition of coordinated phosphine to non-coordinated alkene, a still relatively rarely explored reaction providing the effective formation of a C–P bond, remains a promising strategy for macrocycle formation.

Nucleophilic displacement at centres other than carbon (for example, boron, silicon etc.) is an effective tool for producing new chelate rings *via* heteroatom–heteroatom bond formation. This procedure has been widely used for coupling oxime groups in the synthesis of clathrochelates and related monomacrocyclic oxime-based species.

Aldol condensation reactions and/or Curtis reactions are most often used to give C–C bonds. The role of the metal ion is reduced to bringing the functional groups into close proximity, to favour their interaction. Another common procedure is the Glaser reaction, which enables the coupling of terminal alkynes and inserting the

resulting linear –C≡C–C≡C– fragments into a macrocyclic framework. Its use in the synthesis of rotaxanes, catenanes and space-separated porphyrins is covered. A few cases of acetonitrile addition to a 1,3-diimine group, leading to a new chelate ring by C–C bond formation, have also been documented.

These basic procedures are supplemented by a number of much less explored ring-forming reactions as, for example, the formation of lactones (including enterobactin) and thiolactones. This involves the interaction of coordinated oxygens (sulphurs) of stannoxanes with diacyl dihalides, accompanied by elimination of the organotin fragment acting as a template from the ring, resulting in the corresponding macrocyclic products. An analogous reaction takes place when the nitrogen-carbon bond is formed in polylactam synthesis, where an organosilicon centre acts as the template. Examples of the assembly of natural products and related model systems involve carbon–carbon bond formation and, rarely, carbon-heteroatom bond formation in the culminating steps. The last variant may occur in the course of earlier steps in macrocyclisation, as in the syntheses of [Zn(L588)] and of [Cu(L631)].

The production of new macrocyclic systems has become possible due mainly to the development of new template centres for specific ligand products, such as the covalent-template approach to the synthesis of macrocyclic polylactones, polylactams and related compounds. Also of note is the the assembly of the catechoylamide systems H_6L1019 and H_6L1022 on an iron(III). In these situations the specific arrangement of functional groups required for macrocyclisation is a result of complex formation.

The copper(I) ion is characterised by tetrahedral coordination in complexes, and this plays a key role in the assembly of rotaxanes, catenanes and knots.

In some cases template centres not commonly used to synthesise the corresponding compounds can be involved as matrices. In particular, in addition to alkali and alkaline earth metal ions, certain fluorine-containing silver, mercury, nickel, copper and zinc salts are suited to the synthesis of crown ethers, whereas an organometallic iron(II) compound serves as an effective template in the synthesis of 12-crown-4.

A correlation exists between some 50 elements in the Periodic Table and their suitability for building up macrocyclic systems with specific sets of donor atoms (Table 11-1). Consequently, it should be possible to forecast the optimal template for the directed synthesis of a given product. Template centres used for the construction of both homoleptic and mixed donor atoms macrocycles are given in this table. Each box shows the chemical element, which can be sucessfully employed for carrying out templated syntheses, or which may be unable to act as a template. Where geometric shapes are shown, it means that the corresponding metal ions are able to manifest the template effect in cyclisation reactions. The types of donor atoms (solid black circles) incorporated in the final ligand product are most frequently nitrogen (amine or azomethine), oxygen (ether, alcohol or phenol) and sulphur (thioether or thiophenol) and much less frequently phosphorus and arsenic (grey circles). For metal ions, each geometrical figure indicates the type of donor atoms present in the ligand product (in most cases a macrocycle) assembled *via* templated synthesis. Thus, metal ions successfully explored for building up polyaza-, polyoxa-, polythia- and polyphospha-macrocycles are enclosed in hollow hexagons,

Table 11-1. Metal ion templates in the synthesis of homoleptic and mixed donor atoms macrocycles.

Ia	IIa	IIIb	IVb	Vb	VIb	VIIb	VIII			Ib	IIb	IIIa	IVa	Va	VIa	VIIa	O
H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac															

Lanthanide series	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Actinide series	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

pentagons, triangles and squares, respectively. Metal ions promoting the synthesis of oxaaza-, thiaaza-, phosphaaza-, thiaphospha-, thiaoxa- and thiaarsenic-macrocycles are in hollow diamonds, circles, octagons, trapeziums, solid squares and solid triangles, respectively.

Generally, the kind of macrocycle that can be assembled using metal ion templates depends on the ability of the corresponding metal ion to react with specific donor atoms. Thus the metal ions of the elements of Groups Ia and IIa, which generally react with donor ether oxygen atoms by an ion–dipole interaction (exceptions are magnesium and in some cases lithium and calcium), are the most appropriate templates for the synthesis of crown ethers.

The overwhelming majority of metal ions have been employed for template synthesis of polyazamacrocycles. Note that the first-row transition metal ions, which are the most frequently used for building up nitrogen-containing macrocycles, easily react with nitrogen atoms. Amines and 3d metal ions with up to five d electrons form donor–acceptor bonds involving the unshared pair of electrons of the nitrogen atom and the unoccupied orbitals of the metal ion, whereas 3d metal ions with a larger number of electrons (but less than 10) in the d electron shell are additionaly able to participate in π-backbonding to azomethine groups.

The elements in the central part of Periodic Table appear to be more universal templates. Specifically iron(II) and nickel(II) manifest the template effect in the synthesis of polyoxa-, polythia-, polyaza- and polyphospha-macrocycles.

Considering the denticity of ligand products typically assembled, the most often encountered are tetradentate macrocycles, followed by hexadentate species. Potentially tridentate macrocyclic products are described for nickel(II), copper(II), boron(III) and molybdenum(0); silver(I) and mercury(II) promote assembling pentadentate and hexadentate macrocycles; thallium(I), strontium(II), lanthanum(III) and the lanthanides(III) from Ce to Gd (Pm was not studied because of its radioactivity) hexadentate products; and the metal ions from Tb to Lu promote the formation of tetra- and hexa-dentate macrocyclic ligand products. Variable denticity of synthesised systems is common to most first-row transition elements as well as to alkaline metal ions which serve mainly to form crown ethers and related compounds.

Certain tendencies can also be observed for metal cations used in templated synthesis of macrocycles containing two kinds of donor atoms. For example, elements of Groups Ia, IIa and the first-row, as well as some second-row and third-row, metal ions (Ag, Cd, Pb, and U) promote the formation of oxaazamacrocycles. Silver(I) and cadmium(II) are suitable for the construction of thiaaza-macrocycles; nickel(II), silver(I) and cadmium(II) form azaphosphamacrocycles; and nickel(II), platinum(II) and molybdenum(0) form thiaphosphamacrocycles. The only templates used so far for preparation of thiaoxa- and thiaarsa-macrocycles are tin(IV) and palladium(II), respectively. Nickel(II), silver(I) and cadmium(II) appear to be the most universal matrices for the synthesis of macrocyclic compounds containing the most common mixed N/O, N/S, and N/P donor atoms.

A certain regularity is also observed in the denticity of the ligand products prepared. Thus, mostly hexadentate products are formed on templates of ions of metals of spherical symmetry, located at the margins and bottom of Table 11-1.

Tetra- and penta-dentate ligands are constructed mainly by using cations of the first-row transition elements, which manifest template functions in accordance with the stereochemical preferences of the appropriate metal ions.

The generalised data given in Table 11-1 make it possible to forecast the possibilities of using, as templates, ions of those metals which to date constitute the blank spots in that Periodic Table. In particular, it should be expected that ruthenium and iridium would be able to operate as templates for the synthesis of various macrocyclic compounds with N, P, or S heteroatoms, whereas such metals as cobalt, rhodium, iridium, ruthenium, osmium, chromium, and gadolinium and the following lanthanides will prove suitable for building up mixed-donor systems. By analogy with the lanthanides, elements of the actinide series can undoubtedly act as templates to obtain N- and N/O-containing macrocyclic compounds. Even if such possibilities cannot be realised in practice, because of the radioactivity of these elements, such ligands obtained on the lanthanides could, after their demetallation, be very suitable as complex-forming agents. This presents practical possibilities of a technological, analytical, and ecological nature as these elements are becoming, to an ever increasing extent, an inevitable component of present-day civilization.

The recent template synthesis of polyarsamacrocyclic systems suggests the possibility of extending the range of donor atoms appearing in the backbone of macrocyclic compounds to Se, Te and Sb.

The overwhelming majority of macrocyclic systems obtained to date result from exploitation of the template effect of metal ions organizing the ligsons for their subsequent interaction via donor–acceptor (coordinate bonding) or ion-dipole forces. Just as metal ions template particular reactions of ligsons, properly selected multidonor organic molecules can arrange specific metal-containing building blocks spatially, thus facilitating their subsequent interaction. A kind of exchange between the functional ability of the metal ion and the ligson takes place. The synthesis of space-separated oligomeric metalloporphyrins in the presence of appropriate pyridyl-containing molecules is a typical example.

Weak metalloid-donor atom (oxygen, nitrogen or sulphur) covalent bonds are responsible for the spatial organization of the corresponding ligsons for their favourable interaction around the matrix.

In recent years a more extensive exploration of other non-covalent interactions has led to the development of new templates. In principle, almost all design principles operative in the field of supramolecular chemistry [2–4] can be used to generate the template effect. They range from metal-ligand coordinate interactions – the strongest of the non-covalent interactions – to weak coulombic interactions.

Hydrogen-bonding, for example, being a directional and remarkably strong intermolecular force, is responsible for the creation of new kinds of catenanes, rotaxanes [5] and macrocycles constructed through H^+ template reactions.

By making use of aromatic π–π^* interactions a wide variety of rotaxanes and catenanes, derived from bipyridine- and hydroquinone-based ligsons, have became available. In this case each of the two interacting ligsons acts as template for each other and remain incorporated in the final rotaxane or catenane molecule [6].

Although the experimental material on template synthesis of macrocyclic compounds amassed so far is considerable, the method still has much potential for further development. It is not easy to predict the on-going development of the template

method. However, certain trends are clear. For example, there is no doubt that a wider range of template centres, including organic units and complex ions will be investigated in the design of new macrocyclic systems. Until now the use of such species has been rather restricted, but the few known examples clearly demonstrate the potential of such matrices.

Polynucleating macrocyclic systems able to bind up to nine metal ions have been obtained. However, the techniques developed for their synthesis could be extended to facilitate the production of yet more complex ligands able to coordinate even more cations. In addition, the strategy used for successive increases in the number of known polynucleating ligands probably has the potential for assembling new and highly polynuclear mixed-metal macrocyclic complexes.

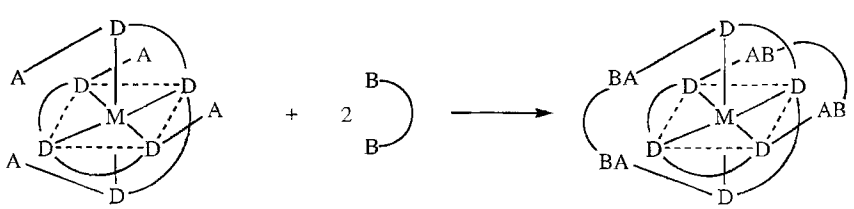
The study of rotaxanes and catenanes is extremely promising. Elaboration of their production methods will enable the fundamental properties of these interesting substances to be studied, including the establishment of the specific factors responsible for weaving molecular threads. The current interest in rotaxanes reflects their potential for various kinds of molecular switches (Section 4.2).

Turning to catenanes, there is an opinion that polymers consisting of interlocked rings have unique mechanical and rheological properties. In particular, the high elasticity of polysiloxanes is expected to be associated with the presence of catenane molecules embedded in regular polymeric networks. The results obtained so far suggest that reactions on transition metal matrices will enable the assembling of catenane polymers in the future, as well as of molecular braids. Further, the use of chiral templates and molecular nets will allow the creation of 'molecular macrame' components [7, 8].

A strategy of using polynuclear double helices as precursors to more complex interlocked and knotted systems should allow the carrying out of template synthesis of trefoil, pentafoil, heptafoil ... knots containing a set of two, four, six ... metals, respectively.

The template synthesis of heteromulticatenanes is promising in view of their application to electron transfer processes. The idea [7] of using octahedral patterns besides the currently favoured tetrahedral templates for constructing catenanes is realisable in principle. It is necessary for the two tridentate ligands, placed in the two mutually perpendicular planes of the octahedral complex, to contain terminal chains of sufficient length and appropriate functionalities for closing by a suitable ring-closure agent, as illustrated in Scheme 11-1.

The chelating properties of catenands are remarkable and are revealed, in particular, through their ability to stabilise unusual oxidation states and to form



Scheme 11-1. The possible route to catenanes using an octahedral metal ion template.

unexpectedly stable complexes with some metals. These properties will no doubt have analytical or electrochemical importance. A large number of macrocyclic compounds have excellent biomimetic properties, which makes possible their use as biological system models and as direct substitutes for the latter. The production of certain biological materials (enterobactin, vitamin B_{12} etc.) has already been realised by matrix reactions. In this connection one of the most important problems of template synthesis is the design of new and more efficient systems, including biological ones. In the distant future template synthesis inside biological objects might become possible, by incorporation of the corresponding matrices, and if necessary, ligsons into the organism, to design substances that are not being produced or are in short supply due to some misfunction.

The stringent demands for high thermodynamic stability and kinetic inertness for inorganic complexes of actual or potential value in medical diagnosis (such as ^{67}Ga, ^{111}In or especially ^{99m}Tc, together with gadolinium-containing contrast agents for magnetic resonance imaging) or radiotherapy (e.g. ^{67}Cu, ^{90}Y or $^{186\text{ or }188}$Re), are generally met by the use of multidentate ligands. These are usually macrocycles, often with pendant arms or substituents to optimise their properties. At the time of writing, the great majority of such macrocycles are prepared by standard methods of synthetic organic chemistry, without recourse to templating, whereas template-controlled ligand syntheses for this application almost exclusively produce complexes of acyclic ligands. Both groups are outside the remit of this book, but in the future the advantages of macrocyclic ligands, possibly also catenands, will possibly be combined with the attractions of template synthesis in the production of new and valuable pharmaceuticals.

The mechanisms of template processes have been studied. In particular, the factors involved in crown ether formation, including the matrix, solvent, temperature, anions etc. have been studied in detail. The kinetic or thermodynamic aspects of matrix reactions have been revealed, and the interplay of both aspects in specific cases or at separate stages in template macrocyclisation has been studied. Much information on the relationships between template nature (in particular geometry and electronic structure), the basic parameters of ligsons and the final ligand product has been collected. Light has also been shed on such matters as the fit of the template and the synthesised macrocycle size. Routes for the smooth solution of synthetic problems, the realisation of alternative routes, and the accommodation of ligand synthons to reaction products or reaction conditions have been revealed. It is reasonable to expect that the use of template reactions will be accompanied by extensive studies and a deeper understanding of the conditions required for their successful realisation. In turn, this must favour the further development of template syntheses.

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