

TOPICS IN
STEREOCHEMISTRY

VOLUME 6

A WILEY-INTERSCIENCE SERIES

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TOPICS IN
STEREOCHEMISTRY

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VOLUME 6

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To the memory of
JIRI SICHER

INTRODUCTION TO THE SERIES

During the last decade several texts in the areas of stereochemistry and conformational analysis have been published, including *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965). While the writing of these books was stimulated by the high level of research activity in the area of stereochemistry, it has, in turn, spurred further activity. As a result, many of the details found in these texts are already inadequate or out of date, although the student of stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.

For both human and economic reasons, standard textbooks can be revised only at infrequent intervals. Yet the spate of periodical publications in the field of stereochemistry is such that it is an almost hopeless task for anyone to update himself by reading all the original literature. The present series is designed to bridge the resulting gap.

If that were its only purpose, this series would have been called "Advances (or "Recent Advances") in Stereochemistry." It must be remembered, however, that the above-mentioned texts were themselves not treatises and did not aim at an exhaustive treatment of the field. Thus the present series has a second purpose, namely to deal in greater detail with some of the topics summarized in the standard texts. It is for this reason that we have selected the title *Topics in Stereochemistry*.

The series is intended for the advanced student, the teacher, and the active researcher. A background of the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental import, aimed primarily at an audience of organic chemists but involved frequently with fundamental principles of physical chemistry and molecular physics, and dealing also with certain stereochemical aspects of inorganic chemistry and biochemistry.

It is our intention to bring out future volumes at approximately annual intervals. The Editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of Editorial Advisors who have been of great assistance by suggesting topics and authors for several articles and by helping us avoid duplication of topics appearing in other, related monograph series. We are

grateful to the Editorial Advisors for this assistance, but the Editors and Authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

N. L. Allinger

E. L. Eliel

January 1967

PREFACE

Volume 6 continues our annual series of volumes of *Topics in Stereochemistry* with five chapters on diverse subjects pertinent to the area.

The first chapter consists of reprintings of the two classical papers by D. H. R. Barton and O. Hassel, papers that undoubtedly were decisive in leading to the award of the Nobel Prize in Chemistry for 1969 to these two men. The paper by Hassel appeared in 1943, in Norwegian, in a journal that is not widely available; it has been translated for the present volume by Kenneth Hedberg. This paper, often quoted but seldom read, is concerned with experimental work, primarily electron diffraction studies, that led to a determination of the puckered nature of the cyclohexane ring, and the identification of the axial and equatorial substituents therein. The 1950 paper by Barton showed how, using the cyclohexane structure deduced by Hassel, one could correlate large numbers of chemical facts that previously had been impossible to interpret.

The second chapter, "Pyramidal Atomic Inversion," by J. B. Lambert, discusses the well-known inversion of ammonia, amines, and related compounds, including compounds of phosphorus and sulfur. Both experimental and theoretical approaches to the problem are discussed. With the advent of low-temperature nmr, it is possible to determine activation parameters for such inversions in a great variety of cases. With the development of the *ab initio* method utilizing Gaussian orbitals, it is also possible to carry out fairly exact (Hartree-Fock) calculations for the structures of small molecules, in both ground and transition states, and thus calculate inversion barriers. The two results are generally in very good agreement. In more complicated molecules, semiempirical methods have been applied, but there is room for improvement in the values calculated in this way.

"Resolving Agents and Resolutions in Organic Chemistry," by S. H. Wilen, constitutes the third chapter. This chapter is a summary of much of the very practical knowledge, available in the literature but not easy to find, as to how one might approach the task of resolving a racemic compound. To keep the size of this chapter commensurate with the available space, extensive lists of resolutions have not been included; however, a rather complete list of such resolutions, extracted laboriously from the original literature, is being

published by the University of Notre Dame Press simultaneously with this review under the title "Tables of Optical Resolutions," by S. H. Wilen.

E. G. Janzen has contributed a chapter on the "Stereochemistry of Nitroxides," which outlines how electron spin resonance studies of nitroxides have been used to furnish structural and stereochemical information on this class of radicals.

The concluding chapter of the book is "Conformational Analysis and Configurational Effects for Chelate Complexes," by D. A. Buckingham and A. M. Sargeson. The chapter is largely concerned with force field calculations and their use in interpreting and predicting most of the stereochemical features found with compounds of this general type. Applications of this kind of calculation to a variety of problems in organic chemistry are well known, but the extension of these ideas to metal chelates, described in this chapter, is relatively novel.

It is with sadness that we dedicate this volume to the memory of Jiri Sicher, a long-time friend and, until his untimely death on September 8, 1970, a member of the Advisory Board of *Topics in Stereochemistry* since its inception. Professor Sicher spent the last year of his life at the University of Lausanne, Switzerland, after a long and productive career at the Institute of Organic Chemistry of the Czechoslovak Academy of Sciences in Prague. We greatly miss his warm friendship and his sage scientific advice.

N. L. Allinger
E. L. Eliel

February 1971

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Conformational Analysis—The Fundamental Contributions of D. H. R. Barton and O. Hassel

The 1969 Nobel Prize in Chemistry was awarded to Derek H. R. Barton and Odd Hassel, for their work in the field of conformational analysis. Although both Barton and Hassel have published prodigiously over the years, that part of their work which earned them the Nobel Prize is concentrated in not much more than a dozen papers in each case. Of these twenty or twenty-five odd papers, two—one for each Nobel Laureate—may easily be recognized as the most significant ones: O. Hassel, *Tidsskr. Kjemi Bergvesen og Met.*, **3**, 32 (1943), and D. H. R. Barton, *Experientia*, **6**, 316 (1950). Both papers, significant as they are, have appeared in journals of relatively limited circulation, the former, moreover, in the Norwegian language which is not understood by most chemists. We have therefore, with the kind permission of Professors Barton and Hassel, and with the consent of the journals which carried the original articles, republished them in this volume. Most chemists reading these two very fundamental and pacesetting papers today will be struck by the fact that almost every detail in them has a very familiar ring. What this shows, of course, is that the papers have received the rare acclaim of really important pieces of work: their subject matter has become one of the essential working tools of the average chemist.

We are indebted to Professor Kenneth Hedberg, Oregon State University, for the English translation of Hassel's paper.

THE CONFORMATION OF THE STEROID NUCLEUS (1)

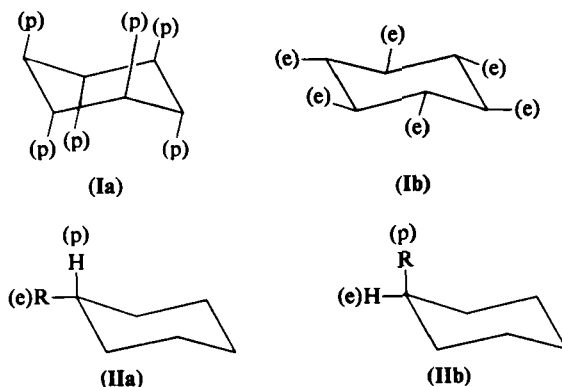
D. H. R. BARTON (2)
Cambridge, Massachusetts

[Reprinted from *Experientia*, **6**, 316 (1950). By permission of the author and publisher.]

In recent years it has become generally accepted that the chair conformation of cyclohexane is appreciably more stable than the boat. In the chair conformation it is possible (3,4) to distinguish two types of carbon-hydrogen

bonds; those which lie as in (Ia) perpendicular to a plane containing essentially the six carbon atoms and which are called (3) *polar* (p), and those which lie as in (Ib) approximately in this plane. The latter have been designated (3) *equatorial* (e).*

The notable researches of Hassel and his collaborators (5,6) on the electron diffraction of cyclohexane derivatives have thrown considerable light on these more subtle aspects of stereochemistry. Thus it has been shown (5) that monosubstituted cyclohexanes adopt the equatorial conformation (IIa) rather than the polar one (IIb). This is an observation of importance for it indicates that the equatorial conformations are thermodynamically more stable than the polar ones. It should perhaps be pointed out here that although one conformation of a molecule is more stable than other possible

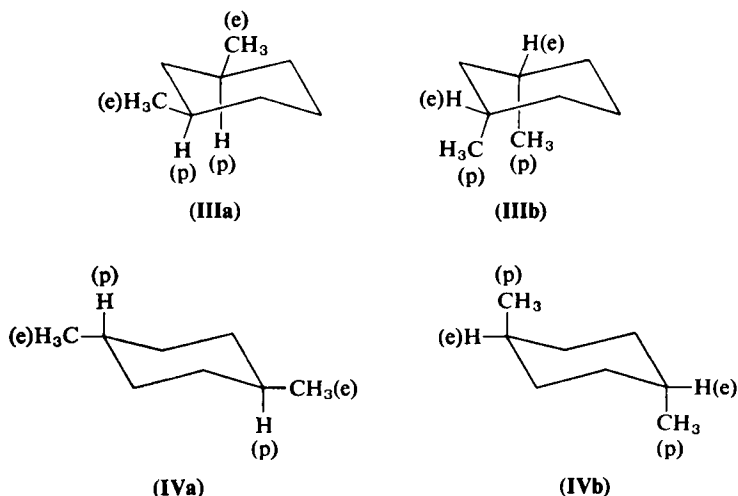


conformations, this does *not* mean that the molecule is *compelled* to react as if it were in this conformation or that it is rigidly fixed in any way. So long as the energy *barriers* between conformations are small, separate conformations cannot be distinguished by the classical methods of stereochemistry. On the other hand a small difference in free-energy content (about one kilocal at room temperature) between two possible conformations will ensure that the molecule appears by physical methods of examination and by thermodynamic considerations to be substantially in only *one* conformation.

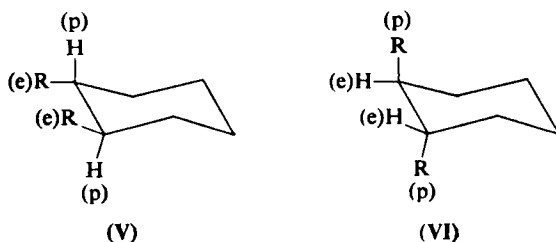
The equatorial conformations are also the more stable in both *cis*-1,3- and *trans*-1,4-disubstituted cyclohexanes (3). Thus *cis*-1,3-dimethylcyclohexane adopts the diequatorial conformation (IIIa) rather than the dipolar one (IIIb), whilst *trans*-1,4-dimethylcyclohexane exists as (IVa) rather than (IVb).

Thermodynamic calculations (3) show that *trans*-1,2-dimethylcyclohexane takes up the diequatorial conformation (V; R = CH₃) rather than

* Editor's comment: The word "axial" is currently used to mean the same thing as the word "polar" in this paper.

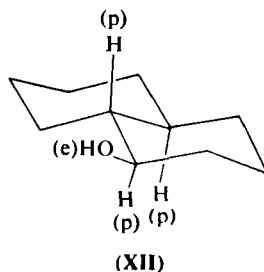
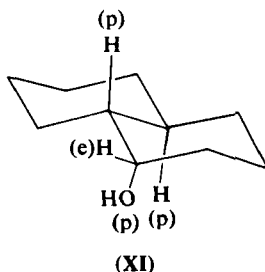
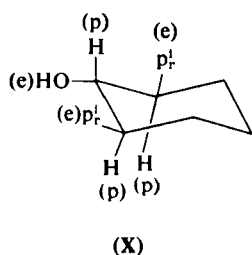
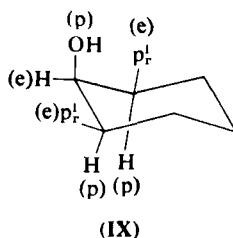
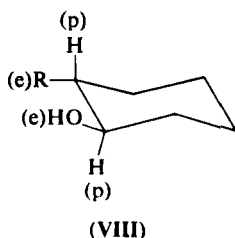
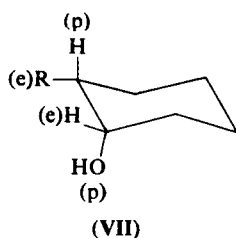


the dipolar one (VI; R = CH₃). For *cis*-1,2-disubstituted cyclohexanes there are two possible conformations. In both of these one of the substituents forms an equatorial bond, the other a polar one. Since these differences in thermodynamic stability between equatorial and polar conformations are presumably of steric origin (3), it would appear logical to make the larger substituent form the equatorial bond.

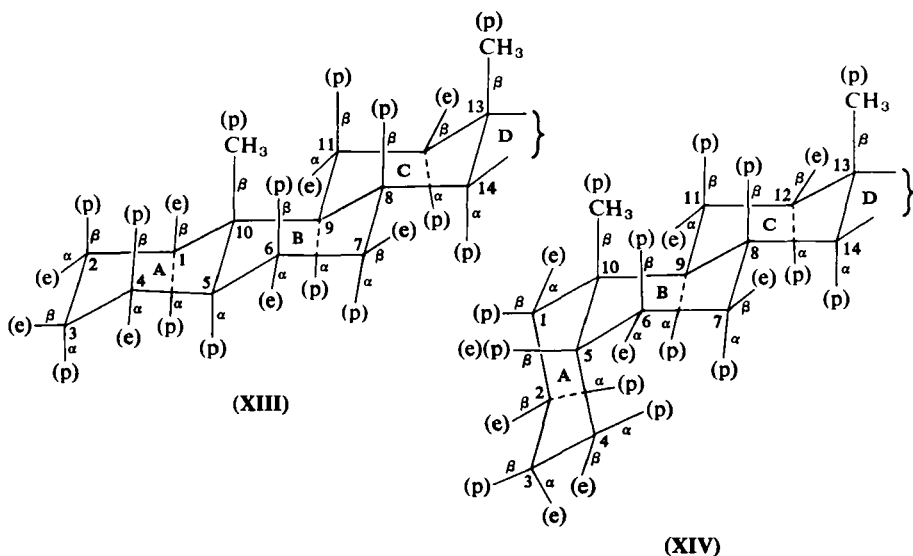


Considerations of the same type can be extended to 2-substituted cyclohexanols. Thus (7,8) the *cis* alcohols (VII; R = alkyl), on equilibration by heating with sodium, furnish almost entirely the *trans* isomers (VIII; R = alkyl). In the former one substituent is polar, one equatorial; in the latter both are equatorial. The same conclusion on relative stability is reached from a consideration of thermochemical data (9). Similarly (10) the 2,6-disubstituted cyclohexanol (IX), with two equatorial and one polar substituents, is isomerized to (X) on equilibration. The situation is the same (8) with the bicyclic *trans*- α -decalol. Here the isomer (XI) is isomerized to (XII) on equilibration.

A consideration of the conformations (11) (XIII) and (XIV), assumed by the steroid nucleus when the A/B ring fusion is respectively *trans* and *cis*,



provides a striking illustration of the usefulness of the concept of polar and equatorial bonds. The relationship between the α - and β -nomenclature introduced by Fieser (12) and the occurrence of polar and equatorial bonds is also summarized in (XIII) and (XIV).



Thermodynamic Considerations. In a number of cases equilibration of hydroxyl groups at secondary positions in the steroid nucleus has been carried out. At other positions the corresponding ketones have been reduced

by sodium and alcohol, a process which (in cyclohexane derivatives) is well established to give the thermodynamically more stable alcohols in approximately the same proportions as from equilibration experiments (7,8). It is possible therefore to see how well the concept of more stable equatorial conformations is obeyed. As set out in Table 1 the expected relationships are observed. Also included in this table is a reference to the equilibration of 5 α ,6 β -dibromocholestane with the 5 β ,6 α -isomer, for this is clearly relevant to the issue under discussion.

TABLE 1

Observation	Exptl. method	References
<i>Cholestane Series</i>		
2 α (e) more stable than 2 β (p)	Reduction of 2-one	L. Ruzicka, P. A. Plattner, and M. Furrer, <i>Helv. Chim. Acta</i> , 27 , 524 (1944).
3 β (e) more stable than 3 α (p)	Equilibration	pp. 98, 636 ^a
4 α (e) more stable than 4 β (p)	Reduction of 4-one ^b	R. Tschesche and A. Hagedorn, <i>Ber.</i> , 68 , 2247 (1935); L. Ruzicka, P. A. Plattner, and M. Furrer, <i>loc. cit.</i>
6 α (e) more stable than 6 β (p)	Reduction of 6-one	pp. 223, 653 ^a
7 β (e) more stable than 7 α (p)	Reduction of 7-one ^c	I. M. Heilbron, W. Shaw, and F. S. Spring, <i>Rec. Trav. Chim.</i> , 57 , 529 (1938).
5 β (e, p), 6 α' (e)-dibromide more stable than 5 α (p), 6 β (p)-dibromide	Equilibration	D. H. R. Barton and E. Miller, <i>J. Amer. Chem. Soc.</i> , 72 , 1066 (1950).
<i>Coprostone Series</i>		
3 α (e) more stable than 3 β (p)	Equilibration	pp. 99, 636 ^a
11 α (e) more stable than 11 β (p)	Equilibration	p. 408 ^a
12 β (e) more stable than 12 α (p)	Equilibration	pp. 461, 657 ^a

^a All references reported in this way are to L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, 1949.

^b The configurations are assigned (*vide infra*).

^c According to the standard tables of D. H. R. Barton and W. Klyne, *Chem. Ind.* (London), **1948**, 755, 7 β -hydroxycholestane should have $[\alpha]_D$ ca. +52°, whilst the 7 α -isomer should exhibit $[\alpha]_D$ ca. +8°. I. M. Heilbron, W. Shaw, and F. S. Spring, *loc. cit.*, observed $[\alpha]_D$ +51° and therefore the configuration of their alcohol must be 7 β -.

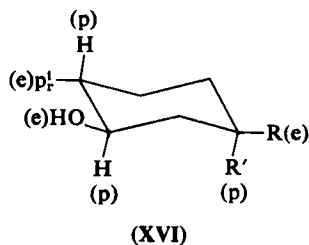
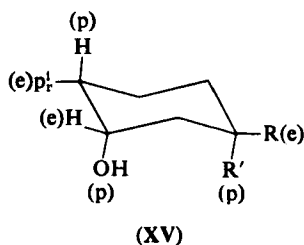
Elimination Evidence. Reactions whose mechanisms require concerted 1:2-elimination should proceed more readily when the four centers involved (the two carbon atoms and the two substituents) lie in one plane. For concerted ionic elimination reactions in cyclohexane derivatives the optimum

TABLE 2

Observation easy elimination of	References
<i>Cholestane Series</i>	
6 β -OH (p) and 5 α -H (p)	D. H. R. Barton and W. J. Rosenfelder, <i>J. Chem. Soc.</i> , 1949 , 2459.
6 β -H (p) and 5 α -Cl (p)	D. H. R. Barton and E. Miller, <i>J. Amer. Chem. Soc.</i> , 72 , 1066 (1950).
6 β -Br (p) and 5 α -Br (p) 7 α -OH (p) and 8 β -H (p)	D. H. R. Barton and E. Miller, <i>loc. cit.</i> pp. 241, 242, 631 ^a
<i>Coprostone Series</i>	
7 α -OH (p) and 8 β -H (p)	pp. 118, 631 ^a
11 β -OH (p) and 9 α -H (p)	pp. 408, 630 ^a
11 β -Br (p) and 9 α -H (p)	pp. 460, 631 ^a

^a All references reported in this way are to L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, 1949.

arrangement of the substituents for the minimization of the activation energy is that in which both are polar (13,14). There is much evidence in the literature which confirms this. Thus (7) *cis*-2-substituted cyclohexanols (VII) undergo acid-catalyzed dehydration [elimination of H (p) and OH (p)] more readily than the *trans* isomers (VIII). In the menthol series (17) neomenthol (XV; R = CH₃, R' = H) loses water easily relative to menthol (XVI; R = CH₃, R' = H) and neoisomenthol (XV; R = H, R' = CH₃) dehydrates easily relative to isomenthol (XVI; R = H, R' = CH₃) (18). There are a number of interesting examples of this sort of phenomenon in steroid compounds. A summary is given in Table 2.



Steric Hindrance Evidence. The applicability of steric hindrance evidence in the assignment of configuration has long been recognized, although such assignments are not always reliable (19). It seems possible to explain the

relative magnitudes of many of the phenomena of steric hindrance in cyclohexane derivatives on the basis that polar bonds are more hindered than the corresponding equatorial bonds. An inspection of models makes this reasonable for a polar bond is always close in space to two other polar bonds each attached to the next but one carbon atom, whereas there is no similar relationship for equatorial bonds.

In support (7) of this generalization it has been observed that *cis*-2-substituted cyclohexanols (VII) with polar hydroxyls are more difficult to esterify, and their esters more difficult to hydrolyse, than the corresponding *trans* alcohols and their esters. The same effects are observed with *trans*- α -decalol (20). The esters of the alcohol (XI) (polar hydroxyl) are more difficult to hydrolyze than those of the alcohol (XII) (equatorial hydroxyl). In the menthol series (17) menthol (XVI; $R = CH_3$, $R' = H$) is more easily esterified than the neomenthol (XV; $R = CH_2$, $R' = H$) and a similar relationship holds for isomenthol (XVI; $R = H$, $R' = CH_3$) and neoisomenthol (XV; $R = H$, $R' = CH_3$).

However, a reverse relationship holds (7) for chromic acid oxidation of 2-substituted cyclohexanols. Here the *cis* alcohols are oxidized more rapidly than the *trans*. This observation is adequately accommodated by the present theory if the rate-determining step is attack upon the carbon-hydrogen bond rather than upon the carbon-hydroxyl linkage.*

The situation in the steroid field is summarized in Table 3. In every case the expected order of hindrance holds good. Also included are data for oxidations of alcohols by Br^+ to give the corresponding ketones. If such oxidations are assumed to involve attack upon the carbon-hydrogen bond then the results are in agreement with the other observations summarized in the table.

Although the concept of polar and equatorial bonds is not, of course, applicable to cyclopentane, it is of interest to note that the 17α -bond in the steroid nucleus has, because of the ring fusion to a six-membered ring, the character of a polar bond with respect to that ring. Also the 17β -bond has in its relationship to ring C the aspect of an equatorial bond. These facts are in agreement with the greater thermodynamic stability of 17β -substituents and the greater degree of steric hindrance shown by 17α -substituents (21).

Use of the Concept. It will be clear that it is possible to assign configurations on the basis of the concept of polar and equatorial bonds. One such example has already been given in Table 1. An additional illustration is provided by *trans*- β -decalol (8,19). The more stable epimer m.p. 75° must have the hydroxyl in the equatorial conformation as in (XVII); this is in

* Editor's comment: This explanation has been superseded: cf. J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

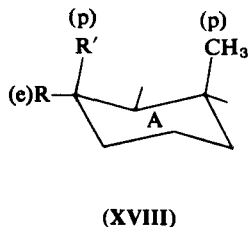
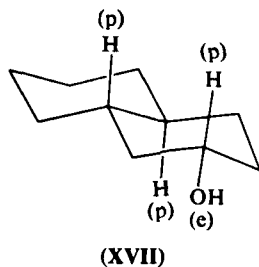
TABLE 3

Observation	References
<i>Cholestane Series</i>	
2 β -OH (p) more hindered than 2 α -OH (e)	A. Fürst and P. A. Plattner, <i>Helv. Chim. Acta</i> , 32 , 275 (1949).
3 α -OH (p) more hindered than 3 β -OH (e)	pp. 635, 636 ^a
6 β -OH (p) more hindered than 6 α -OH (e)	p. 223 ^a
6 α -H (e) more easily oxidized than 3 α -H (p)	L. F. Fieser and S. Rajagopalan, <i>J. Amer. Chem. Soc.</i> , 71 , 3938 (1949).
3 β -H (e) more easily oxidized than 3 α -H (p)	G. Vavon and B. Jacobowicz, <i>Bull. Soc. Chim. Fr.</i> , 53 [4], 581 (1933).
<i>Coprostone Series</i>	
3 β -OH (p) more hindered than 3 α -OH (e)	pp. 635, 636 ^a
6 β -OH (p) more hindered than 6 α -OH (e)	p. 652 ^a
11 β -OH (p) more hindered than 11 α -OH (e)	p. 408 ^a
12 α -OH (p) more hindered than 12 β -OH (e)	p. 658 ^a
7 α -OH (p) and 12 α -OH (p) more hindered than 3 α -OH (e)	p. 125 ^a
7 β -H (e) and 12 β -H (e) more easily oxidized than 3 β -H (p)	p. 126 ^a ; L. F. Fieser and S. Rajagopalan, <i>J. Amer. Chem. Soc.</i> , 71 , 3935 (1949).

^a All references reported in this way are to L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, 1949.

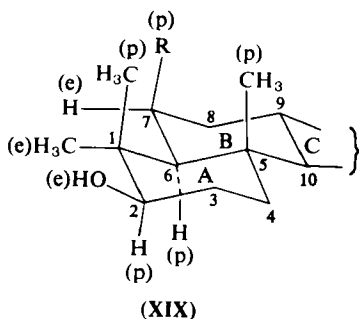
agreement with the fact that its esters are more rapidly hydrolyzed than those of the epimeric (polar hydroxyl) alcohol. Other examples are mentioned below.

Extension to Di- and Triterpenoids. It would seem reasonable to extend the concept of equatorial and polar bonds to the correlation of the stereochemistry of other ring systems built up from fused cyclohexane units. Thus ring A of the diterpenoid abietic acid may be represented (22) by (XVIII; R = CO₂H, R' = CH₃) with the carboxyl occupying an equatorial conforma-



tion. It is understandable then that the esters of this acid should be more easily hydrolyzed than those of (say) podocarpic acid where ring A is as shown in (XVIII; $R = CH_3$, $R' = CO_2H$), for in the latter the carboxyl occupies the more hindered polar conformation.

Now that it is recognized (22) that rings A and B of the α - and β -amyrin groups of triterpenoids and also (23) those of the lupeol group are trans fused, it is possible to make a tentative representation of their stereochemistry as shown in (XIX; $R = H$). Placing the hydroxyl in the equatorial conformation explains the more facile hydrolysis of β -amyrin acetate relative to epi- β -amyrin acetate (24) and of lupanol relative to epi-lupanol (25). It also accounts for the easy elimination of water accompanied by molecular rearrangement, which is induced in these compounds or their derivatives by treatment with phosphorus pentachloride (26). Such a reaction then becomes comparable to the very easy dehydration of isoborneol to give camphene, in that all the four atomic centers of importance in the reaction lie in one plane. The marked hindrance of the 7-hydroxyl group in sumaresinolic acid and its easy elimination under acid dehydrating conditions (27) are best explained if it has the polar conformation as in the part expression (XIX; $R = OH$).



In connection with the nomenclature of triterpenoids it would appear desirable to extend Fieser's α -, β -convention for steroids to cover triterpenoid stereochemistry also. A convenient reference point is the C_5 methyl group. Substituents on the same side of the main-ring plane as this methyl group should be regarded as having the β -configuration, those on the opposite side as having the α -configuration. Thus sumaresinolic acid would be designated $2\beta,7\beta$ -dihydroxyolean-12-ene-17-carboxylic acid.

REFERENCES

1. The word "conformation" is used to denote differing strainless arrangements in space of a set of bonded atoms. In accordance with the tenets of classical stereochemistry, these arrangements represent only one molecular species.
2. Harvard University Visiting Lecturer, 1949-50, Harvard University, Cambridge 38, Mass.

3. C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.*, **69**, 2488 (1947).
4. O. Hassel's nomenclature (5) is different, but the distinction remains the same.
5. O. Hassel and H. Viervoll, *Acta Chem. Scand.*, **1**, 149 (1947).
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THE CYCLOHEXANE PROBLEM

O. HASSEL

[Translated from *Tidsskrift For Kjemii Bergvesen og Metallurgi*, 3 [5], 32 (1943), by Kenneth Hedberg, Oregon State University, Corvallis, Oregon. By permission of the author and publisher.]

If one assumes that the valence angles of the carbon atom are equal to the "tetrahedral angle" ($109^{\circ}28'$), or in any case not substantially different from this angle, then the possibility that the carbon atoms in cyclohexane form a coplanar six-membered ring is excluded. Among the forms of the carbon skeleton compatible with an angle in the vicinity of 110° the "chair" form occupied a special position. In this form the cyclohexane molecule has ditrigonal skaleno-hedral symmetry (symbol D_{3d}) in which it has, besides a threefold symmetry axis, a center of symmetry (Fig. 1a). This form is "stiff" in the sense that a transformation into other forms is impossible without significant deformations of the valence angles. According to the knowledge we have at present about the forces between carbon atoms in compounds of this type, it seems very likely that the molecule must be provided with a not inconsiderable amount of energy in order to be converted into the other conceivable strain-free forms. On the other hand, it is hardly possible, *a priori*, to say anything definitive about the energy difference between the cyclohexane molecule in the symmetric chair form and in these other forms, even though it might seem improbable that this energy difference is considerable. One has been inclined to the opinion, therefore, that cyclohexane in thermodynamic equilibrium will contain perceptible amounts of molecules with lower symmetry than the chair form.

In order to clarify this point one has had to turn to physical-chemical methods of investigation and, in addition to studying the hydrocarbon itself, it was natural to take up the study of a series of its simpler derivatives. Since these investigations have in large part been carried out in our laboratory, we shall, in the following, give a short characterization of the results which are currently available in the literature and report a number of new results which have not yet been published. Before we do this, however, we shall discuss briefly the views held by A. Langseth (1) concerning the cyclohexane structure. Langseth's results rest upon Raman spectroscopic investigations and were completely unexpected. They were to the effect that the molecule itself had hexagonal bipyramidal symmetry (symbol D_{6h}) and that the carbon atoms therefore formed a coplanar regular hexagon, corresponding to a C—C—C angle of 120° . In Langseth's opinion the question of whether cyclohexane itself has symmetry D_{3d} or D_{6h} is in a way related to the question

of the most stable form for the ethane molecule. If we imagine the two methyl groups in ethane rotated in relation to each other about the C—C bond, the H atoms will, in a certain position (the so-called “cis”^{*} position), lie directly opposite each other and have the smallest possible mutual distance; by a rotation of 60° from this position the corresponding “trans”^{*} form of the ethane molecule is generated where the H atoms are as distant from each other as possible. It is easy to see that the relative position of hydrogen atoms in the symmetric cyclohexane model corresponds to the ethane trans form, while a coplanar molecule to some degree corresponds to the cis form. One then disregards the circumstance that the C—C—C angle is increased from 109.5° to 120° and assumes that the energy difference between the two forms is primarily dependent upon the relative position of the H atoms. It is our opinion that such a view is not justified.[†] Nor does it find support in those results which are available concerning the orientation of methylene groups in organic compounds with long chains, where an arrangement corresponding to the trans position appears to be most stable. Another argument that in our opinion ought not to be overlooked is the existence of two isomeric forms of decalin.

The newer methods for electron diffraction investigation of vapors worked out in our institute allow an objective determination of the intensity curve, and by Fourier analysis one is able to calculate from this curve those internuclear distances which are most decisive for the scattering of electrons. A careful investigation of the scattering from cyclohexane (2) shows very clearly that the ratio between the carbon-carbon distances is, to say the least, very close to that which valence angles of 109°28' would give. A coplanar carbon six-membered ring is therefore ruled out. The experimental scattering curve agrees on the whole so well with the curve one calculates theoretically for molecules of the classical “chair” form that the possibility that a significant fraction of the molecules have a less symmetric shape must be regarded as excluded. Recent Raman investigations by Saksema (3a) and by Kohlrausch and Wittek (3b) are in excellent agreement with this result. We have mentioned that A. Langseth has attempted to connect the question of the shape of the cyclohexane rings with the question of the mutual orientation of the two halves of the ethane molecule. On the basis of Raman-spectroscopic

^{*} Editor's comment: These are the forms now called “eclipsed” (= “cis”) and “staggered” (= “trans”).

[†] Translator's comment: Langseth and Bak (1) actually did not ignore the valence angle strain introduced by a coplanar conformation of the carbon ring. They state, in effect, that if the potential for rotation about the C—C bonds has a minimum corresponding to eclipsing of the H atoms, the classical boat form (C_{2v}) of the molecule will be more stable than the chair form. They point out that such a potential would additionally tend to flatten the ring but that this state could be reached only by overcoming the opposing CCC bond angle strain.

investigations of *sym*-tetrachloroethane ($\text{CHCl}_2\text{—CHCl}_2$) (4) he claims to have proved that the *cis* form is present in significant amounts, that is, that form where the two halves of the molecule lie symmetric to a plane perpendicular to the C—C bond, and the two pairs of chlorine atoms therefore have the smallest possible separation. This Cl—Cl distance, however, is so small that in our opinion it must result in considerable mutual repulsion, and therefore, in connection with systematic investigations of ethane derivatives, we have also studied tetrachloroethane. Through this we have been able to determine with certainty that the *cis* form, if indeed it represents a form with a minimum on the potential energy curve, must be present in very minor amounts.

In all cases where cyclohexane or its simple substitution products have been thoroughly investigated by physical methods, one has found structures containing the symmetrical valence-skeleton characteristic of the “chair” form. As shown in Fig. 1b, six of the C—H bonds are parallel with the threefold axis of the molecule (dashed in the figure), while the six other C—H bonds form an angle of $109^\circ 28'$ with this direction. A bond of each type extends from each C atom. It follows from this that *two* different monosubstituted cyclohexanes with the described carbon skeleton must actually be found. Those cases where two such stereoisomeric monosubstituted derivatives supposedly have been isolated, however, scarcely bear up under closer examination. One can easily convince oneself that an inversion of the carbon ring will convert each of the isomeric compounds into the other. This conversion evidently requires such a small activation energy that a separation of the two isomeric molecules is impossible under ordinary conditions. However, it seems reasonable that the difference in energy of the two forms is, in many cases, large enough that one form will predominate in the equilibrium mixture. This is undoubtedly the case for the chlorocyclohexanes in question, as is shown below.

If the configuration* of a substituted cyclohexane is to be completely described, one must specify not only the C atoms where the substitution has taken place, but also which of the two hydrogen atoms is substituted; namely, the “erect” one, if the C—H bond is parallel with the 3-fold axis, or the “reclining” one. In the first case we will designate the H atom and correspondingly the substituent with the letter ϵ ($\epsilon\sigma\tau\eta\kappa\omega\varsigma$) “standing” and in the second case with the letter κ ($\kappa\epsilon\iota\mu\epsilon\nu\omicron\varsigma$) “reclining”.† Some examples of halogen compounds whose configurations are determined with complete certainty are the following:

* Editor's comment: In the early 1940s, the term “configuration” included what we now call “conformation.”

† Editor's comment: These terms correspond to “axial” ($=\epsilon$) and “equatorial” ($=\kappa$) as now used.

Dichlorocyclohexane	m.p. 101°	1(κ),4(κ)
Dibromocyclohexane	m.p. 111°	1(κ),4(κ)
Diiodocyclohexane	m.p. 142°	1(κ),4(κ)
Tetrabromocyclohexane	m.p. 185°	1(κ),2(κ),4(ϵ),5(ϵ)
β -Benzenehexachloride		1(κ),2(κ),3(κ),4(κ),5(κ),6(κ)
β -Benzenehexabromide		1(κ),2(κ),3(κ),4(κ),5(κ),6(κ)

In many other cases the configuration is less certain, but an unambiguous decision will often be feasible with use of modern diffraction methods. In a few cases, such as α -benzenehexachloride, the decision has proved to be difficult. An X-ray crystallographic determination of the space group alone proved insufficient to answer the question, and one will be forced to carry out a complete crystal structure determination. An attempt at an electron diffraction determination carried out by O. J. Lind as his thesis problem for the *cand. real.* degree makes it seem most likely that the configuration is 1(ϵ),2(κ),3(κ),4(ϵ),5(κ),6(κ), but 1(ϵ),2(ϵ),3(κ),4(κ),5(κ),6(κ) and 1(ϵ),2(κ),3(κ),4(κ),5(κ),6(κ) also seem possible. When we are concerned with halogen derivatives, space considerations exclude a number of configurations since 1,3-dihalides with both halogen atoms in the ϵ -position would bring these two atoms so near each other (2.5 Å) that such a configuration must be regarded as improbable for the dichloride and completely excluded for the dibromide and diiodide.

Of particularly great interest, naturally, is the above-mentioned question regarding the configuration of the monosubstituted derivatives. The older methods of electron-diffraction structure determination were not precise enough to reveal whether, in the vapor phase, we were dealing with the κ or ϵ form of chlorocyclohexane. With the procedure now in use in our laboratory this is no longer the case. Together with *cand. real.* Henry Viervoll we have,

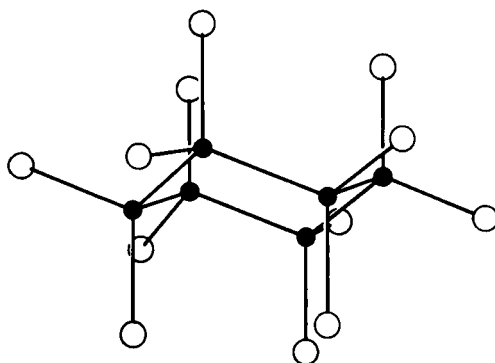


Fig. 1a

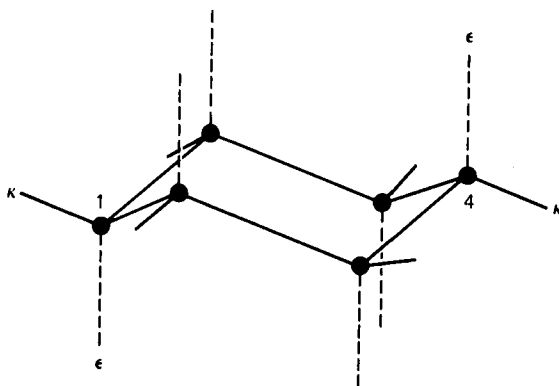


Fig. 1b

therefore, carried out an analysis of this compound. We employed a difference method which has proved to be valuable in cases where very good photometer curves are available both for a hydrocarbon and for its monohalogen derivative. After the molecular scattering curves for both materials are determined, the difference curve is plotted and subsequently subjected to Fourier analysis. The dominant internuclear distances which are characteristic for the halogen compound but which do not appear in the hydrocarbon itself—in the case under discussion the distances between the chlorine atom and the carbon atoms of the ring—ought to appear as obvious maxima in the radial distribution curve. It turns out that besides the C—Cl distances which are common to both the κ form and the ϵ form, the curve has maxima corresponding to distances characteristic for the κ form but not for those distances which only can appear in the ϵ form. We are thus able to draw the conclusion that the amount of κ molecules is in any event considerably larger than the amount of ϵ molecules. It is thus also to be expected that the difference in energy between the two molecules is large enough to lead to a considerable excess of the one type of molecule in an equilibrium mixture. That the κ form is lower in energy and therefore the more stable form is interesting and undoubtedly will prove to be of importance for understanding the relative stability of derivatives with several halogen atoms. It appears, indeed, that substitution in the κ position takes place more easily than in the ϵ position.

In addition to the examples named above we may recall the interpretation of the configurations we have given earlier* for dibromocyclohexane with m.p. 45° and diiodocyclohexane with m.p. 67.5° , according to which both must be regarded to be 1(κ),3(κ) compounds. Since the findings for these two materials are not so clearcut as the above results (p. 14), we have not

* Referring to an earlier paper by Hassel (editor's comment).

included them among our examples.* We have (also) found from an electron diffraction study by the "visual" method that the configuration of another dibromide which is liquid at room temperature, apparently corresponds to the 1(κ),4(ϵ) compound.

The "snapping-over" inversion of the cyclohexane ring which was mentioned in connection with chlorocyclohexane must be expected to take place in the hydrocarbon itself as well as in its derivatives. The three carbon atoms (for example 1, 3, and 5) which lie in a plane *ca.* 0.5 Å over the plane containing the three remaining carbon atoms when the molecule is oriented with the threefold axis vertical, after the process will lie 0.5 Å *lower* than these C atoms. For the hydrocarbon itself, the resulting form will be identical with the original, and one thus sees that the statistical weight of the "chair" form must be considered doubled. For derivatives, this will ordinarily not apply, in that bonds which before the inversion were κ -bonds are converted into ϵ -bonds and vice versa. Even if the configuration before and after the mentioned transformation may be completely different, and in general must be expected to correspond to a not inconsiderable difference in energy, one easily understands that the two forms cannot be regarded as completely independent structures. According to experience with chlorocyclohexane, however, one would expect that the energy difference is most often large enough that in the liquid or gas phase one form will be practically completely missing. We saw above that steric reasons will prevent a configuration with two halogen atoms in 1,3 positions both bound as ϵ atoms.

In some cases the configuration will be identical before and after the inversion, just as for the hydrocarbon itself. This applied, for example, to the above-mentioned 1,2,4,5-tetrabromide. This molecule has a 2-fold symmetry axis as its only symmetry element (symmetry C_2) and is therefore different from its mirror image. One might imagine that an inversion of the ring would in this case transform the *d*-form into the *l*-form and vice versa. This is not the case, however, as examination of a model shows. In other words, the optically active forms must be quite stable and must have a normal rate of racemization.

If one considers 1,2- or 1,4-disubstituted cyclohexanes, one must expect that the $\kappa,\kappa(=\epsilon,\epsilon)$ form corresponds to the so-called trans compound and the κ,ϵ form to the cis compound. If the 1,3-compound is considered, the question is more in doubt. We must remember that steric reasons in this case, will normally exclude the ϵ,ϵ configuration. The experimental data are still

* The interpretation is (nevertheless) quite certain in this case, since the electron diffraction results are supported by dipole moment measurements. If we include consideration of dipole moment measurements, the first alternative for α -benzenehexachloride (p. 14) disappears and we are left with the choice between the two last interpretations.

too sparse for us to delve into this question more deeply. We will only mention that two independent X-ray crystallographic investigations of the so-called trans quinitol (1,4-cyclohexanediol) have given the result that the molecule must appear in a configuration characterized by a center of symmetry, something which is possible only if we have a $\kappa, \kappa(\epsilon, \epsilon)$ configuration. This result therefore supports the view we have just advanced concerning 1,4-disubstituted cyclohexanes. It seems peculiar that dipole moment measurements of 1,4-cyclohexandione in solution have led to the result that this substance has an electric moment. An electron diffraction investigation carried out with *cand. real.* Henry Viervoll gives the result that in the gas phase the molecule has a symmetric structure very near that which one would expect for a diketone with a carbon skeleton corresponding to the chair form. The explanation of the measured dipole moment in solution must apparently be sought in a partial enolization.*

Since a complete summary of the older work in the literature is too lengthy to give here, we content ourselves with calling attention to references in an earlier article in this journal (5).

* This hypothesis has been superseded: cf. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Wiley-Interscience, 1965, p. 474.

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Pyramidal Atomic Inversion

JOSEPH B. LAMBERT

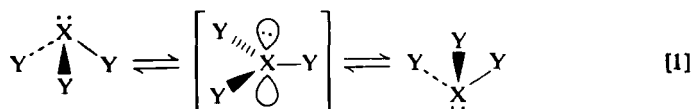
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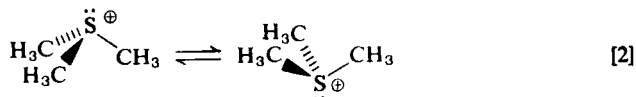
I. INTRODUCTION

An atom bonded to three substituents in a pyramidal geometry and possessing one unshared electron pair may spontaneously undergo an inversion of configuration. Such a process of "pyramidal atomic inversion" must involve passage through a transition state (eq. [1]), in which the lone

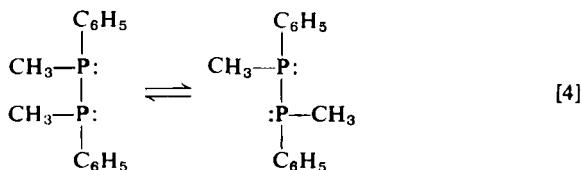
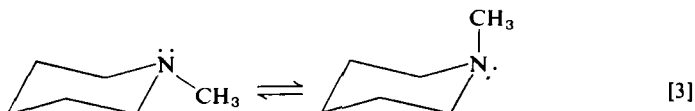


pair possesses pure p character and the bonds from the central atom X to the substituents Y are sp^2 . This review discusses the nature of this process and the history of its investigation from the discovery in the late 1920s through the work reported by late 1970. Atomic inversion is one of the most subtle of molecular processes, since only a reversal of configuration results, no bonds are broken, and no second chemical reactant is required. Specifically excluded from the present review are inversion mechanisms that involve dissociation, higher molecularity, electronically excited states, or solely rotational isomerism.

By way of example, atomic inversions may occur in the trimethylsulfonium ion (eq. [2]), *N*-methylpiperidine (eq. [3]), 1,2-dimethyl-1,2-diphenyldiphosphine (eq. [4], in the Fischer projection), and the cyclopropyl



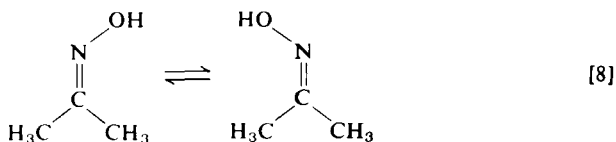
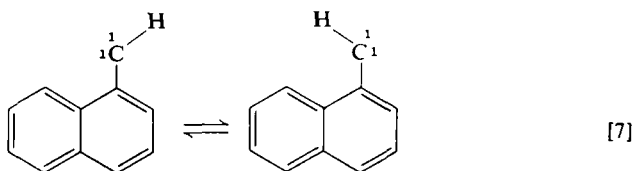
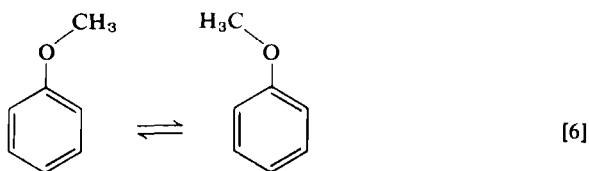
carbanion (eq. [5]). Related to pyramidal atomic inversion are interconver-



sions illustrated by methyl phenyl ether (eq. [6]), the triplet α -naphthyl-



carbene (eq. [7]), and acetone oxime (eq. [8]). These processes may occur



either by a "lateral shift" or by a simple bond rotation. In the lateral-shift mechanism, the central atom and its two substituent atoms remain in the same plane when passing through the sp -hybridized transition state. Such a mechanism is a two-dimensional analog of the pyramidal atomic inversion, which requires a central atom with three substituents and an sp^2 -hybridized transition state. "Linear atomic inversion" has been the subject of a recent review by Kessler and will not be treated here (1).

This review begins with a discussion of the alternatives to the pyramidal mechanism for inversion (Sect. II). Theoretical approaches for determining barrier heights are discussed in Sect. III and the experimental methods in Sect. IV. Factors that can influence the rate of inversion are the subject of Sect. V. Finally, in Sect. VI the literature of pyramidal inversion is reviewed. The subject as a whole has not been comprehensively reviewed (308), although numerous texts (2-5) and articles (1,6-11,309) have dealt with it in part.

II. ALTERNATIVE MECHANISMS OF INVERSION

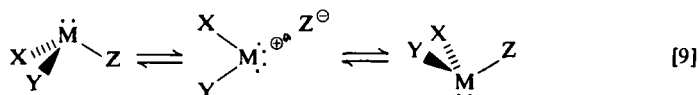
A. Tunneling

As early as 1924, Meisenheimer and co-workers (12) suggested that an inversion process was responsible for the inability of trivalent nitrogen to sustain optical activity. Only five years later, Barker (13) found the first direct experimental evidence for inversion in the doubling of the $10\text{-}\mu$ band of ammonia. Dennison suggested to Barker (13) that the spectral phenomenon arose because the molecule was inverting between two equivalent forms. "The potential energy function plotted in terms of h [the distance of the nitrogen from the plane of the hydrogens] decreases in either direction from the plane of the hydrogen atoms to a minimum corresponding to the equilibrium positions and then rises again." In this manner the barrier to nitrogen inversion was first described (13). Dennison and Hardy (14) obtained higher resolution data in 1932 and recognized that the spectral doubling could only be explained in terms of quantum-mechanical tunneling through the barrier, rather than by a classical traversal over the barrier. By successively improved mathematical descriptions of the potential function, authors have been able to fit the vibrational data with a high degree of accuracy (see Sect. IV) and to come to agreement that the barrier height is about 2020 cm^{-1} in the gas phase (15-18).

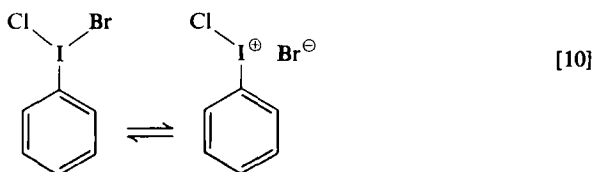
The first thoroughly documented case of atomic inversion, ammonia, therefore utilizes a mechanism different from that designated as the topic for this review. Nonetheless, these investigations thoroughly characterized and popularized the phenomenon. Quantum mechanical tunneling will be important only for cases with very light substituent atoms, such as the proton, and for relatively low barriers. The ammonia case is thus somewhat singular. Almost all other inversion examples discussed herein may be confidently assumed to occur by the classical kinetic process. Furthermore, we shall limit our discussion to barrier heights (for which the question of tunneling vs. classical traversal is irrelevant), rather than to rates (for which a choice of mechanisms is important).

B. Dissociation-Recombination

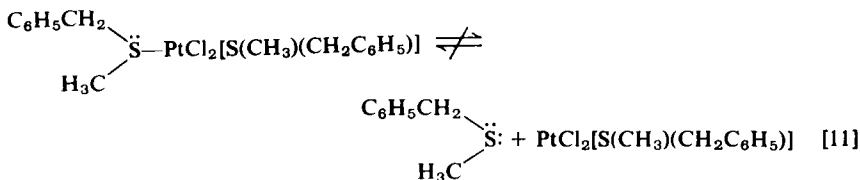
If one of the three substituents on the central atom is removed and subsequently reattached, the result can be inversion of configuration, even though a pyramidal mechanism was not operative (eq. [9]). For this reason



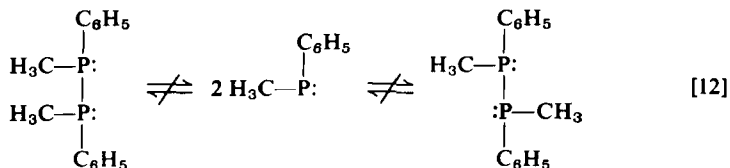
neutral, trivalent iodine will probably not exhibit pyramidal atomic inversion (eq. [10]). In most systems such a mechanism need not be considered since



the covalent bonds involved are of considerable strength. Nonetheless, in suspect cases independent evidence must be obtained to ensure that the pyramidal mechanism is operative. In a study of inversion about sulfur bonded to platinum, dissociation-recombination was a serious alternative (eq. [11]) (19,20). Because the ^{195}Pt - ^1H coupling was present throughout the



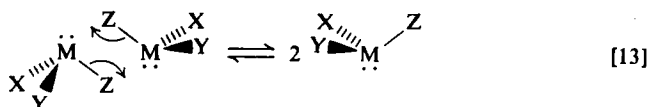
temperature range of nmr observation, it was possible to conclude that the sulfur-platinum bond remains intact during the inversion process. Similarly, homolytic dissociation of the phosphorus-phosphorus bond could be excluded as a mechanism for inversion of diphosphines (eq. [12]) because the methyl groups remain coupled to both phosphorus atoms over the entire



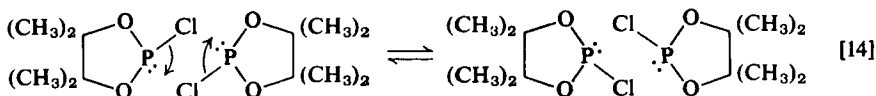
temperature range of the experiment (21,22). Only if there were very rapid recombination within the solvent cage might this method fail. Both thermal and photochemical homolytic scissions have been observed as mechanisms for sulfoxide inversions (23).

C. Bimolecular Exchange

A frequently encountered complication is ligand exchange through bimolecular encounters (eq. [13]), the net result of which can be a configurational

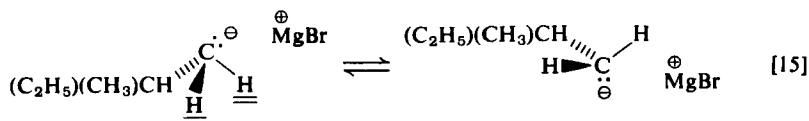


inversion. This mechanism may be detected by carrying out the experimental measurements over a large range of substrate concentrations (22). In this manner Fontal and Goldwhite (24) showed that an observed phosphorus inversion involved breaking of a phosphorus–chlorine bond



(eq. [14]). Cowley and Dierdorf (25) found that phosphorus–arsenic bonds also exchange in this fashion and, furthermore, that the ^{31}P nucleus fails to exhibit couplings at the upper end of the temperature range. Loss of coupling is required by bond breakage.

Inversion processes have been observed in a number of organometallics that contain partially ionic metal–carbon bonds. Although the process illustrated by eq. [15] formally requires an inversion in order that the indicated protons change from an AB to an A_2 pattern, a bimolecular metal

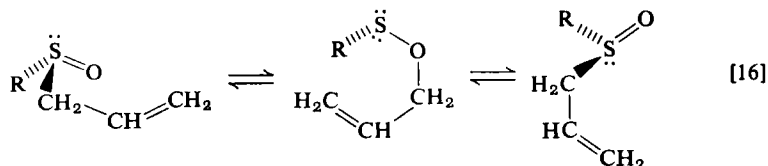


exchange will bring about the same spectral result. Concentration experiments have proved that some such reactions are of second or higher order in the organometallic (26,27). A simple pyramidal inversion is thus excluded in favor of a polymolecular process (eq. [13]).

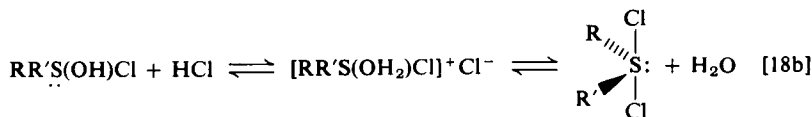
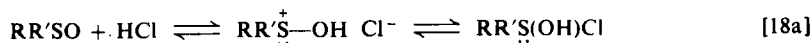
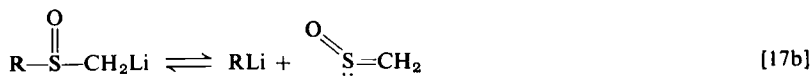
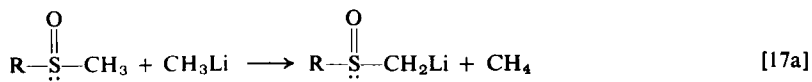
A second complication arises in these organometallic systems because of the existence of molecular aggregates. If the organometallic, for instance, exists only as a dimer over the range of concentrations studied, and if the ligand exchange occurs between the subunits of a single dimer, the process would appear to be of first order, and yet not be a pyramidal inversion. A systematic study of inversions in conjunction with the measurement of the degree of aggregation (28), as well as of the dependence on concentration, has not yet been made. As a result, the inversion mode in a clearly defined aggregate has not been elucidated. In treating Group-IV systems, conclusions should be based on both kinetic order and degree of aggregation. It is doubtful that aggregation need be considered in most Group V and VI inversions.

D. Other Chemical Reactions

Various intra- and intermolecular chemical reactions, specific for a particular series, have been documented as mechanisms for inversion. Sulfoxides, which are the most thoroughly studied class, have been reviewed by Mislow (23). Allyl sulfoxides may invert by a cyclic rearrangement mechanism (eq. [16]) (29,44). Such a process is unimolecular but much more



rapid than pyramidal inversion. Sulfoxide inversion has also been effected by various chemical reagents, such as methyllithium and protic acids (23). In these cases, the sulfoxide is transformed reversibly into an achiral intermediate. Equations [17] and [18] illustrate possible pathways for the reactions with methyllithium and hydrochloric acid, respectively (23). The methylene

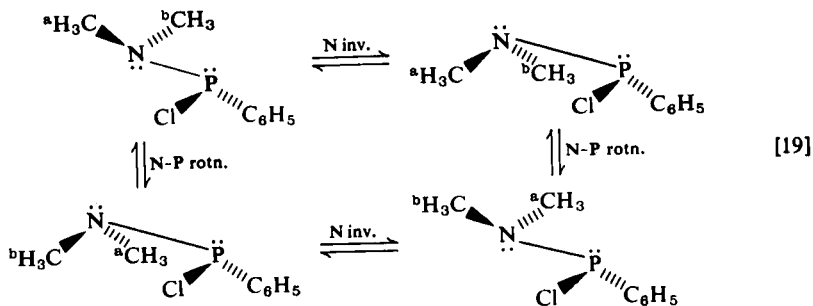


sulfine and the sulfodichloride return to racemized sulfoxide. Nucleophilic displacements also lead to inversion (302). Other chemical mechanisms can probably be uncovered for the stereomutation of specific functionalities by specific reagents.

E. Rotational Isomerism

Although a bond rotation cannot effect an atomic inversion, it frequently is an accompanying or even simultaneous process. More critically, a bond

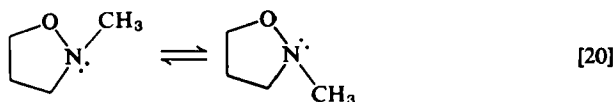
rotation may give rise to the same observables as pyramidal inversion. The nmr spectra of aminophosphines illustrate the problems inherent in trying to differentiate inversion from rotation. An interchange of the environments



of the a and b methyl groups in the anti isomer may be effected either by a rate-determining nitrogen inversion followed by a rapid N-P rotation, or by a slow rotation followed by a rapid inversion. (It is assumed here that phosphorus inversion is slow on the time scale of observation.) Thus a change in the resonances of the methyl groups from nonequivalent to equivalent gives no assurance that the measured barrier is due to inversion. The processes of rotation and inversion may even proceed to a common transition state. This ambiguity of interpretation has been encountered in the spectra not only of aminophosphines (30–32), but also of hydrazines (33–36,299), hydroxylamines (37–39), sulfenamides (40–43,45,163), sulfinamides (40), sulfonamides (41,45), diphosphines (21,22,46), diarsines (22,47), and nitrogen-carbon systems (48,49,298,299,335). Individual cases are discussed in Sect. VI.

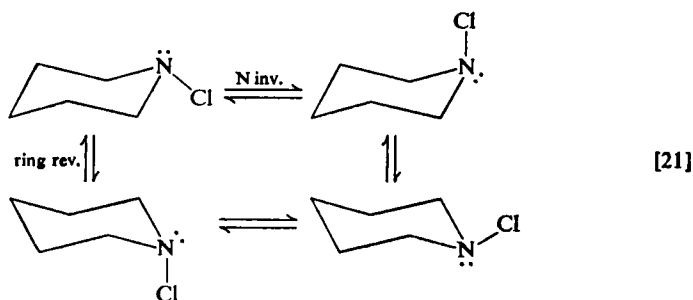
Four methods have been offered to determine whether the observed spectral phenomena are due to inversion or rotation (316). (1) A change from a nonhydroxylic solvent, e.g., methylene chloride, to a hydroxylic solvent, e.g., methanol, is thought to raise the barrier to inversion but have little effect on a rotational barrier (see Sect. V-B). Unfortunately, the data have been somewhat contradictory so the method is not yet reliable. (2) Bulky groups on the central atom decrease the inversion barrier (see Sect. V-C) but increase the rotation barrier. Some torsional barriers have been substantiated by observation of steric deceleration (32,39,42,43). (3) Conjugative groups will accelerate an inversion process (see Sect. V-D) but have only a small effect on rotation. Both inversion (46,49) and rotations (34,42,43) have been substantiated in this fashion. (4) Rotation about an X-Y bond may be eliminated by incorporation of both atoms into a rigid three-, four-, or five-membered ring or into a bicyclic framework. Thus, inversion about nitrogen bonded to oxygen was unambiguously characterized by the system of eq. [20]

(50,51). Several other examples of pyramidal inversion have been observed



by the use of cyclic molecules (see Sect. VI), thus furnishing analogies to aid in the analysis of the more ambiguous acyclic molecules.

Six-membered rings do not offer an unambiguous inversion path, since the process of ring reversal* is competitive (52). Thus the axial and equatorial isomers of *N*-chloropiperidine may interconvert by either mechanism (eq. [21]). Observation of only one set of nmr spectral changes cannot be interpreted unambiguously in terms of either mechanism without additional evidence, such as solvent, steric, or conjugative effects. Evidence for ring reversal (53–57) and nitrogen inversion (58,59) has been adduced for particu-



lar examples, but the great majority are either ambiguous or involve a process that has attributes of both atomic inversion and ring reversal (50–52,55,56, 60–69). In only three examples have both processes been observed independently within a single system (58,70,71). In both studies it was still difficult to determine which process was atomic inversion and which was ring reversal.

In summary, open-chain rotational isomerism and ring reversal are difficult to differentiate from pyramidal inversion by the usual nmr observables. Caution should therefore be exercised particularly when the inverting atom is in an acyclic system or a six-membered ring. Even in rings of other sizes, ambiguities will arise whenever the atom is exocyclic or, if endocyclic, whenever it possesses a nonaxially symmetric substituent.

* The term "ring reversal" is used in this review in preference to the more common "ring inversion" so as to provide an unambiguous distinction from "atomic inversion." The word "inversion" should properly refer only to a configurational but not a conformational process.

III. THEORETICAL APPROACHES

A. Ab initio Calculations

Reliable theoretical calculations of inversion barriers have particular significance not only as a means for determining unmeasurable barriers but also as a source of insight into the nature of the barrier. Advances in computational techniques now permit relatively accurate calculations for molecules containing as many as three heavy atoms (carbon, oxygen, phosphorus, etc.). For a given system, the accuracy of the final result is determined by the worker's choice of balance between the size of the basis set and his willingness to expend computer time. A barrier most simply may be obtained by difference from calculation of the energy of the ground state, preferably with the geometry optimized, and of the energy of the planar transition state. Alternatively, several energies along the reaction coordinate may be calculated, or the entire energy surface may be mapped (72). In calculating the barrier by subtraction of the ground-state and transition-state energies, it is assumed that relativistic and electron-correlation effects cancel. Especially successful calculations have come about by the inclusion of *d* orbitals as polarization functions.

Component analysis of the calculated energies has proved useful for characterizing barriers (73,74). The total energy of the molecule is divided into attractive (nucleus-electron) and repulsive (nucleus-nucleus, electron-electron, and kinetic-energy) terms (eq. [22]). Thus in ammonia, the nonplanar

$$E_{\text{tot}} = (E_{\text{ne}})_{\text{attr.}} + (E_{\text{nn}} + E_{\text{ee}} + T)_{\text{repul.}} \quad [22]$$

ground state is more stable with respect to the repulsive terms, but the planar transition state is more stable with respect to the attractive terms. In this system repulsive terms change more than the attractive terms, so the nonplanar form is stabilized relatively and the barrier is said to be "repulsive dominant." "Attractive dominant" barriers have been found for aziridine (74) and phosphine (75).

Table 1 lists the barriers determined recently by nonempirical SCF-LCAO-MO methods. Considerable work has also been reported for α -sulfenyl, sulfinyl, and sulfonyl carbanions (317-319). The extensive earlier work on ammonia has been listed in ref. 76. The most reliable value today is from calculations that include polarization functions in the basis set (76). Such functions have been omitted in the basis sets for the three-membered rings. Only for ammonia (5.8 kcal/mole (17)) and aziridine [> 12 kcal/mole (84)] are comparable experimental barriers available. The comparisons are

TABLE 1
Barriers to Atomic Inversion from *Ab initio* Calculations

Molecule	Barrier, kcal/mole	Ref.
NH ₃	5.08	76
	8.3	77
	1.7	78
	5.2	79
(CH ₃) ₂ NH	8.6	312
NH ₂ —CN	1.85	325
NH ₂ —F	20.3	325
NH ₂ —SiH ₃	0.7	324
	18.3	74
	15.5	80
	32.4	74
	35.14	80
PH ₃	37.2	75
	40.4	77
⊖CH ₃	5.46	82
	20.85	83
	52.3	81
⊖SiH ₃	39.6	77
⊕SH ₃	30.0	77

quite favorable. Even at the present stage of development, the theoretically determined barriers for some molecules may be as accurate as many determined empirically.

B. Semiempirical Calculations

The size of the molecule must still be greatly limited in *ab initio* calculations. Semiempirical methods have also undergone considerable development during the last few years, and some applications have been made to the determination of inversion barriers (Table 2). These studies likewise have

TABLE 2
Barriers to Atomic Inversion from Semiempirical Calculations

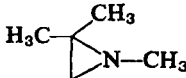
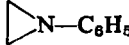
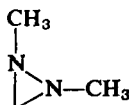
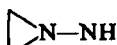
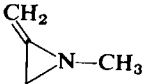
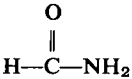
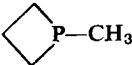
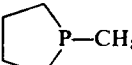
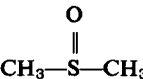
Molecule	Barrier, kcal/mole	Method	Ref.
NH_3	3.7	MINDO	88
	8.8	INDO	86
	13.5	CNDO/2	87
	3.2	CNDO/2	85
NH_2CH_3	5.8	MINDO	88
$\text{NH}_2\text{C}_2\text{H}_5$	5.7	MINDO	88
$\text{NH}(\text{CH}_3)_2$	6.7	MINDO	88
	6.8	CNDO/2	85
$\text{N}(\text{CH}_3)_3$	6.5	MINDO	88
NF_3	62.6	INDO	86
	13.8	MINDO	88
	21.3	CNDO/2	85
	18.0	CNDO/2	85
	49.5	CNDO/2	85
	14.6	CNDO/2	85
	33.9	CNDO/2	85
	34.5	CNDO/2	85
	27.2	CNDO/2	85
	33.4	CNDO/2	85
	22.3 ^a	MINDO	88
	9.7 ^b	MINDO	88
	29.0 ^a	CNDO/2	85

TABLE 2 (Continued)

Molecule	Barrier, kcal/mole	Method	Ref.
	10.5	MINDO	88
	1.5	MINDO	88
$\text{NH}_2\text{—NH}_2$	10.3	MINDO	88
$\text{NH}_2\text{—CN}$	4.5	Extended Hückel	311
$\ominus\text{CH}_3$	20.2	MINDO	88
	15.4	INDO	86
	17.8	CNDO/2	87
$\ominus\text{CH}(\text{CH}_3)_2$	23.2	MINDO	88
$\ominus\text{CH}_2\text{CH}_3$	13.4	CNDO/2	87
	36.6	MINDO	88
	14.1	CNDO/2	85
	40.1	CNDO/2	85
$\ominus\text{OH}_3$	0.1	INDO	86
$\text{P}(\text{CH}_3)_2\text{SiH}_3$	18.7	CNDO/2	85
$\text{P}(\text{CH}_3)_2\text{SCH}_3$	32.6	CNDO/2	85
$\text{P}(\text{SCH}_3)_2\text{CH}_3$	32.0	CNDO/2	85
$(\text{CH}_3)_2\text{P—P}(\text{CH}_3)_2$	23.6	CNDO/2	85
	45.7	CNDO/2	85
	41.7	CNDO/2	85
H_3S^+	29.3	CNDO/2	85
	37.5	CNDO/2	85
	4.8	MINDO	88

^a Ring nitrogen.^b NH_2 .

treated only relatively small molecules, but considerable expansion may be possible. The CNDO/2 and INDO results are generally too high (86,87,315). The MINDO calculations of Dewar and Shanshal (88) and the CNDO/2 calculations of Rauk et al. (85) are the most extensive and most successful. Substituent effects (see Sect. V) are soundly reproduced. Dewar and Shanshal also treat barriers of open-shell systems. The methyl radical is found to have a negative activation energy to inversion, in agreement with its ground-state planarity, whereas the cyclopropyl radical is predicted to have a barrier to inversion of 4.8 kcal/mole. This quantity is the only barrier to radical inversion to be mentioned in this review, since pertinent studies are sparse and the physical process involved may not be strictly comparable to that of closed-shell systems.

IV. EXPERIMENTAL METHODS

A. Infrared

The earliest experimental manifestation of an inversion process, aside from spontaneous amine racemization, was the observed doubling of infrared lines in the spectrum of ammonia (Sect. II-A) (13,14). Indeed, the vibrational modes that lead to atomic inversion have frequencies in the infrared, although for ammonia the inversion frequency itself is in the microwave region (89). Efforts were made immediately to determine the magnitude of the barrier (5-17,90,91) by fitting the spectral data with a wide variety of assumed potential functions. A general approach to the determination of inversion barriers from vibrational spectra was reported by Kincaid and Henriques (92) in 1940. They used a simple quadratic or parabolic potential (eq. [23]) that overestimates the inversion barrier (V_i), as Wall and Glickler (16) had

$$V_i = \frac{1}{2}k(|x| - |x_0|)^2 \quad [23]$$

discovered earlier in their analysis of ammonia. In eq. [23], the variable x is the distance of the atom X from the Y_3 plane in an XY_3 molecule, x_0 is the value of x at equilibrium, and k is $(4\pi^2\nu^2\mu)$, where ν is the frequency of the vibration leading to inversion, μ is the reduced mass

$$\left(\frac{3M_xM_y}{3M_y + M_x} \right)$$

of the molecule XY_3 , M_x is the mass of X, and M_y is the mass of Y. Even though the potential is peaked at the center instead of rounded, these authors

discovered numerous trends that have since been fully substantiated: the effects of alkyl substitution, angle strain, electronegative substituents, and row placement in the periodic table.

Because the barriers computed by Kincaid and Henriques were uniformly high, Costain and Sutherland (93) introduced the potential function given by eq. [24], in which Δl is the change in the X—Y bond length during

$$V_i = \frac{3}{2}K_1(\Delta l)^2 + \frac{3}{2}K_\theta(\Delta\alpha)^2 \quad [24]$$

the inversion process, $\Delta\alpha$ is the change in the YXY angle, and K_1 and K_θ are force constants obtained from the symmetric stretching and bending frequencies (ν_1 and ν_2), respectively. With this function, the authors were able to reproduce the experimental ammonia barrier very precisely and to make predictions about the barrier heights of phosphine and arsine. In 1954, Weston (94) utilized the Costain-Sutherland potential to calculate barriers for numerous systems, including NH_3 (5.93 kcal/mole), $\text{N}(\text{CH}_3)_3$ (8.19), PH_3 (27.4–31.8), PF_3 (45.1), AsH_3 (35.0), $\text{Sb}(\text{CH}_3)_3$ (26.7), and $^+\text{S}(\text{CH}_3)_3$ (16.5–24.1). He also defined the “racemization temperature” as the temperature at which the half-time of racemization is 2 hr. A molecule with a racemization temperature below ambient would not have sufficient configurational stability to permit resolution. Many of his predictions have been borne out. Several years later, Berry (95) utilized a somewhat different approach to calculate similar trends in the Group-V inversions.

The most extensive study of barriers derived from vibrational data is that of Koeppel et al. (96). Using the Costain-Sutherland potential, they calculated barriers for 46 molecules, in which the central atoms were C, Si, Ge, Sn, N, P, As, Sb, O, S, Se, Te, Cl, Br, and I. The substituent atoms included H, D, T, C, F, Cl, Br, I, and O. Unique information is provided on inversion about certain of these central atoms (Si, Ge, Sn, Sb, Se, Te, Cl, Br, and I).

Although vibrational spectra can potentially generate the barrier for almost any stable molecule with the XY_3 structure, the results are not entirely reliable for three reasons. (a) The structure of the molecule (which yields Δl and $\Delta\alpha$) must be known accurately. Uncertainty in α (the YXY angle) is particularly harmful to any such calculations. (b) The vibrational modes ν_1 and ν_2 must be observable and correctly assigned. Errors have resulted from incorrect assignments (91). (c) Most important, the calculation is no better than the assumed shape of the potential. The widely used Costain-Sutherland function undoubtedly suffers from systematic errors. Although more complex potentials have been developed (17), they probably will not find wide applicability. Only the barriers for ammonia (17) and methylamine (97) have been calculated from such potentials. The preceding limitations

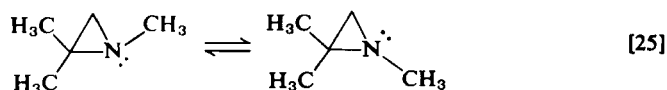
prevent vibrational data from serving as a prime source of inversion barriers, and data on only ammonia and methylamine will be included in the tables in Sect. VI. Nonetheless, the vibrational studies (92–94,96) have been instrumental in defining and clarifying the factors that control inversion rates (Sect. V).

B. Microwave

Microwave studies of ammonia date back to the earliest applications of this type of spectroscopy (98). Microwave data have lent themselves to far more accurate, though less general, calculations than have infrared data (17,89,99). The procedure is similar, however, in that a potential function must be chosen and the spectrum reproduced by calculation. The Swalen-Ibers potential, for example, contains quartic and Gaussian terms, as well as quadratic (17). Accurate calculations from microwave data can frequently produce the ground-state energies, several excited-state energies, and the inversion splitting in the lower levels. The microwave method is applicable only to relatively symmetrical molecules with low barriers. Actual barrier determinations have been made for ammonia (17), dimethylamine (100), formamide (101), cyanamide (102), and nitramide (102). Although inversion may involve tunneling in all of these cases, the interpretation of the barrier height remains unaffected. This method will probably continue as a reliable source of barriers in amine derivatives (323).

C. Nuclear Magnetic Resonance

Dynamic nuclear magnetic resonance (dnmr) methods have furnished the bulk of today's barrier data. This wide application results not only from instrumental and analytical simplicity, but also because the barriers that are susceptible to dnmr measurement are in the common range 5–25 kcal/mole. Below this range microwave spectroscopy is useful, and above it the methods of classical kinetics. Dnmr has been discussed in many of the standard textbooks (2–5,103,104) and in several review articles (1,6,8,10,105). Measurements are made with the sample at thermodynamic equilibrium. The inversion process must bring about an exchange between magnetically distinct sites at a rate comparable to the chemical shift that separates the resonance frequencies. Thus, for the case of 1,2,2-trimethylaziridine (eq. [25]), the geometrically different ring methyl groups will give distinct resonances if the rate of



nitrogen inversion is quite low ("slow exchange"). As the rate of inversion is raised by an increase in temperature, the two peaks will broaden. Peak coalescence is observed when the rate is comparable to the frequency difference at slow exchange. When the atom is inverting so rapidly that the time scale of observation can no longer differentiate the two methyl groups, they will produce only a single, sharp peak located at the average of the slow-exchange frequencies.

Analysis of these spectral changes can readily yield rate constants and activation parameters (106–109). A single rate may be calculated for the temperature at which the spectral broadening is the greatest (the "coalescence temperature," T_c). For site exchange between two uncoupled groupings with equal populations, as in eq. [25], the rate at T_c is given by eq. [26] (6), in which $\Delta\nu$ is the frequency separation of the two sites at slow exchange.

$$k_c = \pi\Delta\nu/\sqrt{2} \quad [26]$$

Formulas for rates at T_c have also been derived for more complicated spin systems (56). Although the method is potentially quite general, a single parameter analysis leaves much to be desired. The only available activation parameter is $\Delta G^\ddagger$ at the temperature of coalescence. Comparison between systems with appreciably different coalescence temperatures is thus not possible without arbitrary assumptions concerning $\Delta S^\ddagger$. If a high-speed computer is available, the more rigorous procedures described below are to be preferred. Comparisons by the T_c method within a homologous series, however, can sometimes be justified.

In the past, some workers have measured a single parameter in the spectrum (line width, peak-to-peak separation, peak-to-valley separation, etc.) and obtained rates and activation energies by the change of this parameter with respect to temperature (110). Such an approximate line-shape analysis can have serious systematic errors that make the derived rates unreliable (109). Much preferable is a comparison of the entire observed spectrum with one calculated from exact theoretical equations (106–109). Such a complete line-shape analysis utilizes all the data at hand and gives the most reliable activation parameters (E_a , $\log A$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$). The advantages of this method have been thoroughly discussed elsewhere (6,109). Line-shape equations are now available for virtually any three- or four-spin system (111), and for even larger multisite exchange cases (112).

If nonequivalent groupings fail to show site exchange at the upper limit of the temperature range of the spectrometer, one may calculate a lower limit to the rate from eq. [26]. If two groupings of nuclei are exchange-averaged at room temperature to a single peak and fail to exhibit nonequivalence at the lower limit of the instrumental temperature range, an upper limit to the rate

may *not* be calculated. Failure to observe low-temperature nonequivalence may result not only from a rate that is too rapid on the nmr time scale to perturb the spectrum, but also from near or exact coincidence of chemical shifts. If $\Delta\nu$ is accidentally close to zero, the spectrum will not be sensitive to the rate phenomenon. Thus, ring reversal in 1,4-dioxane was presumed to be very rapid, since its 60-MHz spectrum remains unchanged even at -150° . By utilizing a deuterated sample and a 100-MHz spectrometer, Anet and Sandstrom were able to observe the rate process because of the expanded and clarified chemical shift (113).

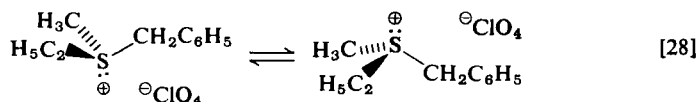
Saunders and Yamada (114) introduced an alternative method for measuring amine inversions. Dibenzylmethylamine $[(C_6H_5CH_2)_2CH_3N]$ in concentrated hydrochloric acid exhibits diastereotopic (115) methylene protons, because the protonated nitrogen atom retains configuration. As the acid concentration is lowered, the AB spectrum collapses to a singlet. Since inversion occurs only in the free amine, the inversion rate ($k_{inv.}$) may be calculated from the proton exchange rate (k_{ex}) by eq. [27]. A frequent drawback to the method is the lack of knowledge of the concentration of free base.

$$k_{ex} = k_{inv.} \frac{[\text{amine}]}{[\text{amine}] + [\text{amine salt}]} \quad [27]$$

In such instances k_{ex} , but not $k_{inv.}$, may be measured (71). Nonetheless, several applications have successfully explored systems inaccessible to the dnmr method (114,116–120,303,314). Direct comparisons between the dnmr and complexation methods are just now being made. One reasonably close comparison (117,121) seems to indicate that the rates from complexation measurements are slower (barriers higher) than those from dnmr methods. The reasons will be discussed in Sect. V-G. Inversion of amines complexed to cobalt (122–124) and platinum (125–127) has been studied by a similar technique. Again, the limiting factor appears to be reduction of higher-order exchange rates to first-order inversion rates.

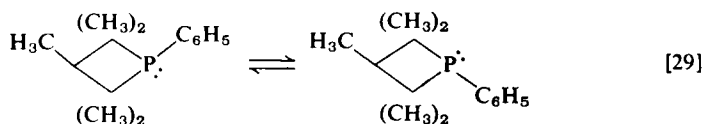
D. Racemization and Epimerization

Since configurational stability of a chiral (asymmetric) atom may permit optical activity, the first-order inversion process may be readily studied by following the decay of optical activity that accompanies racemization (eq. [28]). This procedure has been used with phosphines (128,129), sulfoxides



(130), sulfonium salts (131,132), thiosulfinates (133), and sulfonium ylids (134), as well as with various nitrogen compounds. There are two limitations to the method. First, in many cases optically active materials have not been obtainable. The inability to resolve selenoxides (135) and telluroxides (136) has prevented inversion studies of these functionalities. Second, polarimetric methods are most suitable for the barrier range 25–40 kcal/mole. Although dnmr picks up at the lower end of the range, higher barriers are generally beyond the capabilities of the technique. Thus, arsines (137–145) and selenonium salts (146) have defied racemization studies because of very high configurational stability.

If the molecule is capable of diastereoisomerism, atomic inversion may be observed by classical epimerization of the central atom (eq. [29]) (147,148).



For such molecules, the inversion may be followed by any number of physical techniques: nmr integration, polarimetry, uv or ir absorbance, etc. Limitations similar to those for racemization apply to epimerization studies. It is required that the compound be available as a nonequilibrium mixture of diastereoisomers, so that the decay to equilibrium may be studied by an appropriate device. Also, barriers may be above the range of kinetic observation, as was the case for a recently studied diastereomeric selenoxide (149).

Stereochemical transformations that proceed by true inversion require differentiation from those involving dissociation–recombination, bimolecular exchange, and other chemical mechanisms (23). Sulfoxides have been found to racemize not only by pyramidal inversion (130,150), but also by reversible homolytic fission (151) and by sigmatropic rearrangement (29). Since racemization requires stereomutation of the central atom, there is no difficulty in differentiating the observed process from rotational isomerization. For diastereomeric transformations, however, it is still necessary to prove that the two interconverting isomers are “invertomers” and not rotamers (152,153).

V. RATE-CONTROLLING FACTORS

A. Isotope Effects

Presently, there is no evidence that isotopic substitution on or of the central atom has a measurable effect on the inversion barrier. The resulting

structural differences are apparently too small to be reflected in the barrier. Multiple isotopic substitution has been used in infrared and microwave studies to define a single barrier independent of isotope for a number of amines: ammonia (16,17,89,154), methylamine (97,155), dimethylamine (100), and nitramide (156). Replacement of CH_3 by CD_3 has no effect on an nmr-determined barrier (157). In contrast, replacement of the N—H in 2,2,3,3-tetramethylaziridine by N—D raised the coalescence temperature by 14° and the Arrhenius activation energy by over 3 kcal/mole (158). Such an extraordinary result requires further examination. For molecules inverting by a tunneling mechanism, isotopic substitution on the central atom should have a considerable effect on the rate of inversion. The calculations by Koepl et al. (96) from vibrational data indicated negligible changes in the inversion rates of XY_3 (Y: H, D, T) for central atoms N, P, As, Sb, or O, although the methyl anion may be exceptional. More experimental attention must be directed toward this problem before the magnitude of an isotope effect can be confidently assessed.

B. Placement in the Periodic Table

From the earliest investigations of atomic inversion, it has been evident that first-row elements (amines, oxonium salts) undergo inversion much more rapidly than do elements from beyond the first row (phosphines, arsines, sulfonium salts, sulfoxides, etc.). The reason becomes clear from examination of the molecular geometries. The planar transition state ideally has intragroup (Y—X—Y) angles of 120° . The ground-state H—N—H angle in ammonia (107°) is much closer to this transition-state angle than that in phosphine (94°). Provided the bending force constants are similar, it is therefore to be expected that ammonia would invert more rapidly, since less distortion is required. That the Y—X—Y angle is a dominant factor in determining the magnitude of the barrier was explicitly recognized in the Costain-Sutherland equation (93). Equivalent to this geometric argument is one based on lone-pair hybridization. The ammonia lone pair ($\sim sp^3$) is much closer in energy to the transition-state lone pair (p) than is the lone pair in phosphine ($\sim s$) (78).

Such arguments do not answer the more fundamental question concerning the etiology of the structural differences. Murrell et al. have presented an interesting argument based on overlap considerations (159). Phosphine, with an almost unhybridized geometry, is considered the norm. One must then ask why ammonia is hybridized, even though the s - p promotion energy is not compensated by the formation of new bonds, as in methane. There must be an additional energy factor that favors sp^3 orbitals on nitrogen over p orbitals. For first-row elements, e.g., nitrogen, the $2s(\text{N})$ - $1s(\text{H})$ overlap is

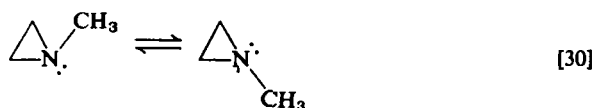
greater than the $2p(\text{N})-1s(\text{H})$ overlap. Thus, additional s character in the nitrogen orbital strengthens the N—H bond, and a hybridized form is favored. The elements beyond the first row, e.g., phosphorus, are less electronegative, so the P—H bond is more covalent and the bonding electrons move closer to hydrogen. As a result, the $3p(\text{P})-1s(\text{H})$ overlap gains on the $3s(\text{P})-1s(\text{H})$ overlap, and stronger bonds may be formed from the “unhybridized” phosphorus p orbitals. Murrell et al. (159) have calculated that an increase in s character from pure p to sp^3 increases overlap with the $1s(\text{H})$ orbital by 45% for nitrogen, but only 34% for phosphorus; 59% for oxygen, but only 27% for sulfur. Thus, overlap considerations determine the geometry, which in turn determines the magnitude of the inversion barrier.

Trends may also be found within a single row. Thus, the XYX angle increases from $^\ominus\text{CH}_3$ ($\sim 100^\circ$) through NH_3 (107°) to $^\oplus\text{OH}_3$ ($\sim 117^\circ$), and the barrier decreases accordingly. The INDO calculations (86) probably exaggerate the effect (Table 2), but the trend is plainly visible: $^\ominus\text{CH}_3$ (15.4 kcal/mole), NH_3 (8.8), $^\oplus\text{OH}_3$ (0.1).

C. Strain Effects

1. Angle Strain

If the inverting atom is incorporated into a small ring, the resultant angle strain will be greater in the transition state than in the ground state. Thus, the CNC angle in ground-state N -methylaziridine (eq. [30]), deviates



about 49° from the unstrained tetrahedral angle, but 60° from the normal 120° angle in the transition state. The added transition-state strain will raise the barrier with respect to the value in unstrained amines (97). This characteristic of aziridines was noted in early calculations (92) and substantiated by later computations (74,88). Almost 30 years after the original prediction, aziridines that are configurationally stable at and above room temperature were isolated (7,160,161). Higher barriers have also been found in the four-membered azetidine rings (162,163) and in azabicyclic systems (164–166,296). For a series of N -methylazacycloalkanes, the barrier decreases from about 19 kcal/mole for the aziridine (167) to 9 for the azetidine (162), 8 for the pyrrolidine (121), and 7 for the nearly unstrained azacycloheptane (121,296).

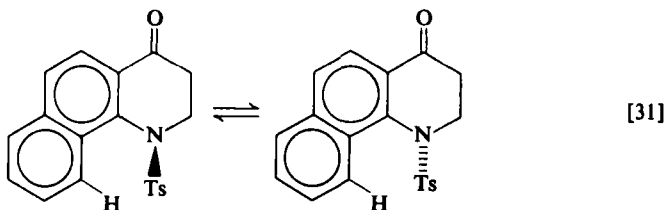
In six-membered rings, which have little strain in the ground state, the

transition state may still be strained because of difficulty in attaining an endocyclic 120° angle. Some evidence that nitrogen inversion in piperidines is slower than in open-chain amines has been presented (116), but the question is still open (114,117,119). Thus, inversion barriers in six-membered rings may not serve as worthwhile models for acyclic inversions. Such models may better be found in larger rings, such as azacycloheptane (homopiperidine), in which torsional ambiguities are absent (121).

2. Steric Strain

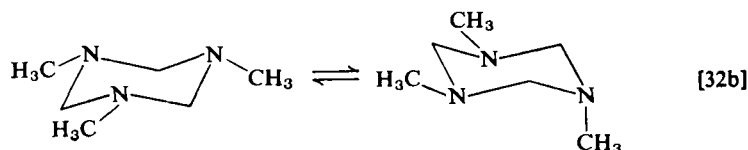
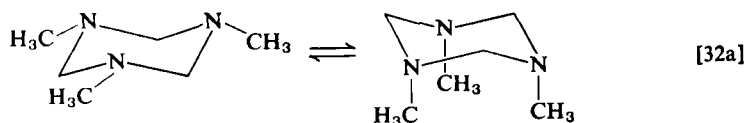
Nonbonded repulsions may be either aggravated or relieved in going from the ground state to the transition state of inversion. Steric effects may thus lead either to rate accelerations or decelerations. Replacement of a small alkyl group, such as methyl, on nitrogen by a large group, such as *t*-butyl, will lead to a lower barrier, since the transition state can better relieve ground-state strain in the latter case. A number of alkyl series have given experimental evidence for such an acceleration (163,167–170). Similarly, the phosphorus inversion barrier (147,171) in 1-*t*-butyl-2,2,3,4,4-pentamethylphosphetane (as in eq. [29]) is substantially lowered with respect to the normal phosphorus barrier (172) because the substituent on phosphorus interferes less in the transition state with the vicinal methyl groups in the 2 and 4 positions. A 1-methyl group apparently is not large enough to exhibit such an effect (147).

Greater crowding in the transition state can give rise to steric deceleration. Thus, in eq. [31], inversion about nitrogen is hindered by increased



interaction in the transition state between the tosyl group and the indicated proton. Speckamp et al. have presented several examples of steric deceleration (173,174), although competitive torsional processes should also be considered.

Another interesting phenomenon involving steric effects has been suggested by Gutowsky and Temussi (66) in their studies of 1,3,5-hexahydrotriazine. If ring reversal occurs without any nitrogen inversions, as is frequently the case (54,56), then three equatorial methyl groups would all become axial (eq. [32a]). These authors suggested that transition-state strain may be

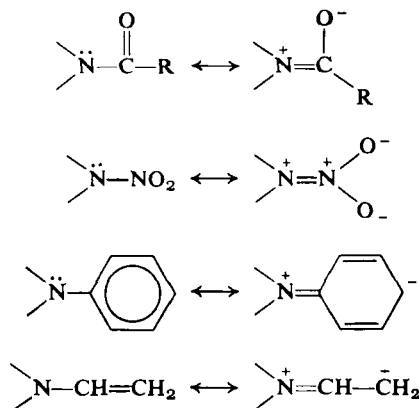


reduced if one or two nitrogen inversions occur simultaneously with ring reversal (eq. [32b]). If such is indeed the case, developing axial-axial interactions have altered the nature of the potential surface to include one or two atomic inversions at the transition state.

D. Conjugative Interactions

1. With *p* Orbitals

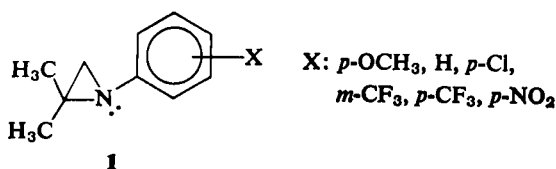
A π orbital on a substituent attached to the central atom is best able to be in conjugation with the lone pair at the transition state, since the electron pair occupies an essentially pure *p* orbital at this point along the reaction coordinate. Any substituent that can bring about $(p-p)_\pi$ conjugation will better stabilize the transition state and hence lower the barrier to inversion.



This effect was observed by dnmr experiments some time ago (168,175,176) and has been simulated in MINDO calculations (88). If conjugation is particularly effective, as when the π acceptor is $-\text{COR}$, $-\text{NO}$, or $-\text{NO}_2$

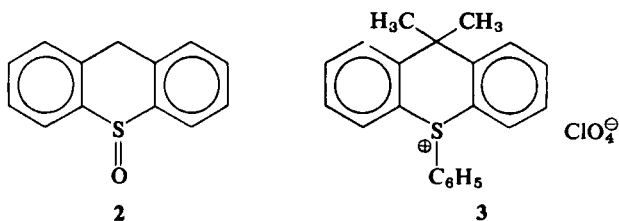
(49,101,102,156,177-179), the barrier drops below the range detectable by dnmr methods. Incorporation of the central atom into a small ring, however, can reduce the conjugative interaction and permit the observation of dnmr kinetics (180).

A systematic study of the $(p-p)_\pi$ interaction in nitrogen inversion has been carried out with the system **1** (181). The aziridine ring places the barrier

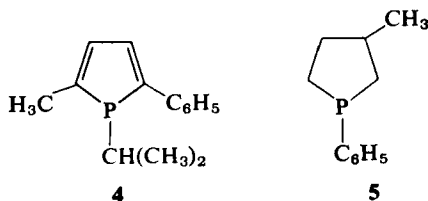


in a convenient range for dnmr experiments; the *gem*-dimethyl group renders the spectra particularly amenable to analysis; and the phenyl group serves as an alterable π -electron acceptor. A linear free-energy relationship was found to exist between the rate of inversion and σ^- substituent constants ($\rho = 2.8$ at -60°). The interaction between the lone pair and the aromatic ring therefore parallels the reactivity of the models used to develop the σ^- - ρ relationship. The effect of the unsubstituted phenyl group in aziridine is to reduce the barrier by about 7 kcal/mole with respect to the barrier of *N*-methylaziridine (167,181).

The studies above concern conjugation between the $2p$ lone pair and $2p$ orbitals on the substituents. If the central atom is from the second row of the periodic table or beyond, $(p-p)_\pi$ overlap is less effective. Thus, $3p$ lone pairs on phosphorus or sulfur are less sensitive to the presence of $2p$ -acceptor substituents. Studies of phenyl and allyl substituents on phosphorus (46,129,147,182) and sulfur (130,150,183) have demonstrated small rate accelerations. Systematic studies of phenyl-substituted sulfoxides (129,150) and phosphines (129) have revealed good Hammett linear free-energy relationships (σ_p) with reaction constants (ρ) of 0.58 and 1.0 respectively. Thus, both these second-row atoms are considerably less sensitive to π -acceptor substituents than nitrogen, and sulfur is somewhat less sensitive than phosphorus. These studies were performed by polarimetric methods. It is interest-



ing that trivalent sulfur with even two aromatic substituents (**2**) (150,184,185) does not invert on the nmr time scale, but the configurationally less stable system with three such substituents (**3**) (183) does. One extraordinary case of $(3p-2p)_\pi$ conjugation has been discovered in the phosphole **4**, for which the barrier is about 16 kcal/mole, compared to 38 kcal/mole in **5**. The transition state to inversion in **4** must have considerable aromatic character (186).



Elements from beyond the second row are increasingly insensitive to conjugation. Thus, even three aromatic substituents on arsenic (138–140,187) or antimony (188–191), in which $(4p-2p)_\pi$ and $(5p-2p)_\pi$ overlap is possible, respectively, are not sufficient to bring about racemization. Dnmr experiments are out of the question. Because antimony is particularly susceptible to chemical racemization (189,190), caution should be exercised in drawing conclusions from racemization experiments.

2. With *d* Orbitals

The transition state to inversion may also be stabilized by overlap of the *p*-hybridized lone pair with empty *d* orbitals of the appropriate symmetry on adjacent atoms. Unlike the $(p-p)_\pi$ case, there is little or no preferred steric orientation for $(p-d)_\pi$ overlap. Such an overlap was first suggested for *N*-chloroamines (37,192), but has since been refuted for these systems (7). Because of the more dominant effects to be discussed in Sect. V-E, F, the chlorine atom actually retards the rate of nitrogen inversion (52,160–162, 165,193,194). Such is probably the case for any central atom with a substituent that is more electronegative than carbon, regardless of whether it possesses empty *d* orbitals. Thus, *N*-bromoamines also invert very slowly (162,195). For substituents more electropositive than carbon, a rate acceleration may be caused either by *d*-orbital overlap or by the favorable inductive effect.

For most effective $(p-d)_\pi$ overlap, the conjugating elements should come from the same row in the periodic table. The first examples of *d*-orbital stabilization were observed in diphosphines (21,22) and sulfonamides (196,197). In the latter case, the electron-withdrawing nature of the sulfonyl group should be rate-retarding. The observed rate accelerations support the

d-orbital interpretation. Recent CNDO/2 calculations also indicate barrier lowering by *d*-orbital overlap (315), although the contrary result is obtained from *ab initio* calculations (312,318,319). Since 1965, inversion accelerated by (*p-d*)_n overlap has been suggested for diarsines (22,47), thiolsulfonates (133), thiophosphinites (198), silylphosphines (199), and possibly silylarsines (200). It has also been observed that sulfur inversion is accelerated by coordination with platinum (19,20,201) or iron (202), although it is not known if the effect is due to (*p-d*)_n overlap.

3. With Antibonding Orbitals

Back-bonding from filled metal orbitals to empty antibonding orbitals on ligands such as CO or CF₃ has been known for some time (203). Formally such an interaction between the lone pair and a substituent would be maximal at the transition state and hence lower the barrier to inversion. One possible example of such stabilization might be nitrogen with a CF₃ substituent. One antibonding molecular orbital of the CF₃ group is relatively low-lying and furthermore possesses the proper symmetry for overlap with the filled *p* lone-pair orbital. If such an interaction occurs, the trifluoromethyl group should be rate-accelerating rather than rate-retarding, as its electronegativity would have suggested (next section).

The evidence available from cyclic systems supports this hypothesis. Nitrogen with a fluoroalkyl substituent in azetidines (204,205), oxazetidines (206), diazetidines (207), and pyrazolidines (207) inverts more rapidly than in analogous systems with simple alkyl substituents (167). Some contradictory evidence has been derived from acyclic systems (48,208), although the ambiguity with torsional processes limits the interpretation of these data. It is quite possible that the influence of substituent antibonding orbitals on the inversion process may be found to be more general, if suitable molecules are examined.

E. Inductive Effects

Replacement of a carbon substituent by one that is more electronegative will raise the barrier to inversion about the central atom. The *s* character of the lone pair in the ground-state is increased by such a substitution, but in the transition state to be attained the lone pair remains *p*-hybridized. This effect was recognized in early theoretical studies (92), and proved its greatest utility as a means to generate stable nitrogen pyramids.

Fluorine has been found to convey configurational stability on nitrogen (300) even in open-chain systems (210,211). *N*-Chloro (160,161,165,193,194, 301) and *N*-bromo (162) compounds are also quite stable to inversion in

three-membered rings, although dnmr kinetics have now been obtained for four- (162), five- (52), six- (52), and seven-membered (212) rings and strained bicyclic systems (165). Similarly, oxygen and nitrogen stabilize the configuration of a nitrogen atom in three-membered rings (170,209,213–224), and to a lesser extent in other cyclic, bicyclic, and open-chain systems (34–37,39,50,62,70,157,206,225–233). As expected, the effect appears to be cumulative. Thus, a nitrogen atom with two oxygen substituents (233) inverts considerably more slowly than one with only a single oxygen substituent (50,51).

The only well-studied substituents from beyond the first row are bromine and chlorine. The rate-retarding effect of the increased electronegativity appears to dominate any ($p-d$) _{π} effects (Sect. V-D-2). The influence of other row-2, -3, and -4 elements is not known, although some sulfur and phosphorus compounds have been examined (197,234). The interpretation of these results is made difficult by the presence of competitive torsional processes.

F. Lone-Pair Repulsion

Heteroatom substituents with nonbonding electron pairs may provide a second mode of rate retardation of the inversion process. As the lone pair on the central atom passes from s (in phosphorus) or sp^3 (in nitrogen) hybridization in the ground-state to p in the transition-state, repulsion with lone pairs on adjacent atoms will increase (180). Such lone-pair–lone-pair interactions will thus serve to increase the barrier. Unfortunately, the effect in all cases studied up to now has been associated with lone pairs on substituents with higher electronegativities than carbon. The observed rate retardation of nitrogen substituted with fluorine, chlorine, bromine, oxygen, or nitrogen may result from lone-pair repulsions as well as from a purely inductive effect (Sect. V-E). The relative contributions have not been evaluated. One possible approach would be a comparison of the inversion rate of nitrogen substituted with a dimethylamino group with that of nitrogen with a trimethylammonium group. The latter group has a high electronegativity but lacks lone pairs. It is not appropriate to speak of the “heteroatom effect” in this context, since many “heteroatoms,” such as silicon and germanium, neither possess lone pairs nor are more electronegative than carbon.

G. Solvent Effects and Complexation

The barrier obtained from theoretical calculations refers to processes that occur in the vapor phase in the absence of intermolecular interactions. It has been learned, however, that introduction and change of solvent have

an important influence on the magnitude of the inversion barrier (176). As yet, no definitive study has been performed on a series of compounds in several different solvents to clarify these effects. The data reported are somewhat contradictory. In some cases very little effect has been found (70,197,212,235), whereas in others there are large changes (37) even among nonpolar solvents (18,128). Some workers have found special effects associated with solvents such as chloroform (235), methanol (50,59,176,236), and deuterium oxide (50,59), but others have not observed such effects (chloroform (236), methanol (70,197,212,306,337)).

The rate-retarding effect of methanol has been suggested by some authors to be a means of differentiating atomic inversion from bond rotation. The inversion requires breaking and reforming a hydrogen bond to the lone pair in a hydroxylic solvent, so the rate should be slower than in nonhydroxylic solvents. Bond rotation should exhibit no such effect. The test has proved successful in some cases (50,59,236), but unsuccessful in others (70,212). One of the systems from which the deduction was drawn (37) has been criticized (32) as possibly involving a purely torsional process. Another system, to which a torsional ring reversal was attributed because of the lack of a solvent effect (67) has been said to include an atomic inversion in the transition state (66). Clearly, further careful work must be done on well-defined systems. The weight of the evidence at present agrees with the interpretation of the methanol effect, although it remains to be seen whether it is general for all inversion processes.

The method described in Sect. IV-C for obtaining amine inversion barriers from proton-exchange rates (114,116-120) should be interpreted in light of the observed methanol-deuterium oxide effects, since these studies have been carried out in aqueous solution. Even the free amine under these circumstances must be hydrogen-bonded to water. The inversion process for which kinetics have been measured must therefore include breaking of this hydrogen bond. The measured barriers (117) will then be slightly higher than those for analogous systems obtained by dnmr methods in inert solvents (121,297).

More serious types of complexation than hydrogen bonding may also cause rate retardations. Harris and Spragg (71) found that amine inversion processes may be readily observed in sulfur dioxide solvent. The amine is present as an SO_2 complex, so inversion can occur only after dissociation to the free amine. The situation is analogous to that of the protonated amines discussed above (Sect. IV-C). Although exchange rates may be measured, the inversion rates can follow only if the dissociation constant is known. The apparent amine inversion barrier that includes complex dissociation is higher (71) than the barriers in free amines (121). It is not yet known whether the true barrier to inversion is also raised, as is in the protonation studies.

The effect of sulfur dioxide proved useful in slowing the rate of inversion in the only known trivalent oxygen example (237). Complexation with sulfur dioxide or other agents will continue to merit investigation.

VI. BARRIERS TO ATOMIC INVERSION

In the following sections, the barriers to atomic inversion reported through late 1970 are collected and discussed in an element-by-element fashion. The concepts developed in the previous sections will be applied in the discussion of these examples. In the tables, the following abbreviations will be used to indicate the method of barrier determination.

IR	infrared spectroscopy
MW	microwave spectroscopy
CLS	nmr spectroscopy, complete line shape
ALS	nmr spectroscopy, approximate line shape
CT	nmr spectroscopy, coalescence temperature
PC	nmr spectroscopy, protonation or complexation
CKR	classical kinetics, racemization
CKE	classical kinetics, epimerization

Some reported barriers will be omitted from the tables, because the numbers are clearly in error or unreliable. Most early dnmr measurements (ALS) fall into this category, as do many barriers calculated from vibrational data (see Sect. IV-A). Some doubtful dnmr barriers are included for reference only. Theoretically derived barriers have been listed in Tables 1 and 2 (Sect. III), and will not be included here.

A. First-Row Elements

1. Carbon

In general, carbanions are nonplanar (244), and calculations indicate smaller bond angles between substituents than in amines. Consequently, the lone-pair orbital has greater *s* character, and the barrier to inversion is higher than in analogous amines (96). Inversion studies of carbon are limited to organometallic systems, in which the "carbanion" is linked to a metal with a partially covalent bond (see Sect. II-C). Configurationally stable carbon atoms of this type have been known since Letsinger's preparation of the first optically active organolithium reagent in 1950 (245-251). Interpretation of the stereomutation of such carbon centers is clouded by both structural and mechanistic ambiguities. The organometallic is frequently present in solution

as aggregates of varying size. Thus, many organolithium reagents exist as tetramers (28), but some organoaluminum compounds are monomers (238). The degree of association can vary not only with the concentration but also with the solvent. A "unimolecular" inversion could thus involve one monomer unit when the predominant species is the monomer, but four monomer units when it is the tetramer. Since the metal is in part bound covalently to the carbon center, a dissociation must precede the actual inversion. Any interpretation must be able to separate the two processes, just as was required in complexation studies (previous section). Competitive torsional processes can also lead to interpretive difficulties (252-254).

The measured unimolecular inversion barriers in organometallics are subject to the limitations imposed by aggregation and bond covalency. Some inversion barriers are not even unimolecular. Under such conditions, a bimolecular electrophilic displacement may be occurring. The data reported for configurational inversions in organometallics are given in Table 3. These kinetic measurements have generally used the most reliable techniques available. Organolithium, magnesium, zinc, and aluminum compounds have yielded inversion kinetics, and many other species proved to be configurationally stable. All the compounds except **10** (240) and **15a-c** (304) involve primary centers. The molecularity was verified in a few cases (26,238,239), but the degree of aggregation was not considered. Solvent effects on $\Delta H^\ddagger$ and $\Delta S^\ddagger$ proved to be rather considerable (26,238).

At present it is almost impossible to derive from these data the barrier to unimolecular, pyramidal atomic inversion, even though these studies have contributed considerably to our understanding of the configurational stability of organometallics. Careful studies limited to a single solvent and to species that have a common molecularity and degree of association might yield important results. In the absence of vapor-phase experiments, reliable barriers to carbon inversion may come initially from accurate *ab initio* (72,82,83,255) and semiempirical (86-88) calculations.

2. Nitrogen

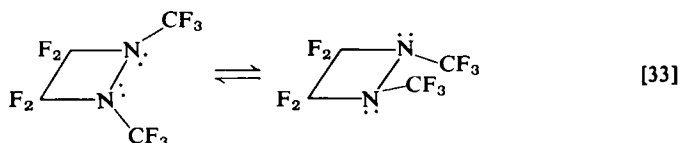
Nitrogen is the most thoroughly studied central atom in the field of atomic inversion. Its compounds very often are stable and readily procured, and the barriers are in a convenient range for measurement. Because of the great volume of study in this area, the review will be divided into seven parts.

a. Three-Membered Rings. Aziridines, diaziridines, and oxaziridines have played a central part in the development of the field of atomic inversion. Aziridines have been studied more widely than any other class (Table 4). The extremely high barriers in diaziridines (**71**, **72**) and oxaziridines (**73-75**) have permitted the preparation of stable nitrogen pyramids, and classical kinetic

methods have been used to measure these barriers (170,221,222). Some of the older data have been omitted from the table (168,176) and some studies were excluded because insufficient information was given (209,259,260). The most reliable barriers have been obtained by the CLS, CKE, and CKR methods (170,181,221,222,235). Unfortunately, the bulk of results have come from ALS and CT experiments. In many cases, the latter method can give reliable values of $\Delta G^\ddagger$ at the coalescence temperature, although these figures are not easily compared if the measurements are made at quite different temperatures.

Included among these results are illustrations of almost all the effects described in Sect. V: steric bulk (44, 45, 72), (*p-p*)_π conjugation (17–22, 29, 31, 32), antibonding-orbital conjugation (61–64, 69), possibly (*p-d*)_π conjugation (23–28, 30, 65–68), electronegative substituents (59, 60, 70–75), and solvent effects (58).

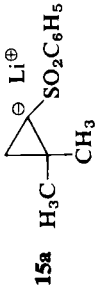
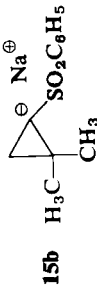
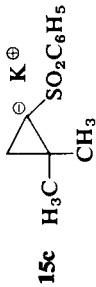
b. Four-Membered Rings. Angle strain is lessened somewhat with respect to three-membered rings, so barriers are uniformly lower. The simplest azetidines, **76** (212) and **78** (162) (Table 5) have barriers of about 9 kcal/mole, in comparison with 18–19 kcal/mole for the corresponding aziridines (167,235). The rate-retarding effects of chlorine, bromine, and nitrogen substituents may be observed [77 (212), 79, 80 (162), 87–92 (227)]. The normally retarding effect of oxygen in **82–85** and of nitrogen in **93** is somewhat mitigated by the perfluoro substituents, which can furnish low-lying antibonding orbitals. In molecules **87–92** the amide nitrogen inverts much more rapidly than the adjacent nitrogen, so the observed process is probably the inversion about the single nonamide nitrogen atom. The process that produces the spectral changes in **93** is not entirely clear, since a simultaneous or consecutive double inversion about both nitrogens is required (eq. [33]). Such double processes will be discussed again in the later sections on five-membered rings and bridged systems.



c. Five-Membered Rings. Studies in this series have been sparse (Table 6). Only two derivatives (**94**, **95**) of the parent pyrrolidine have been studied by the dnmr method. Both illustrate the lowering of the barrier as ring strain lessens. The rate retardation present in systems studied by the protonation method is illustrated by comparison of **94** with **96** and **97**. The effect of solvent has been studied in depth for **101**. In compounds **103** and **104**, probably only inversion about the nonamide nitrogen is observed,

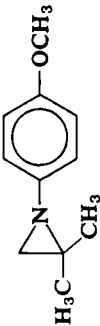
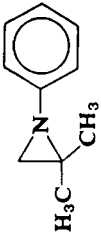
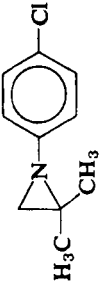
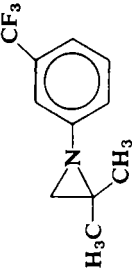
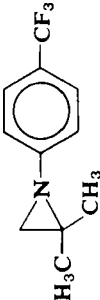
TABLE 3
Atomic Inversion About Trivalent Carbon

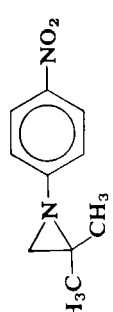
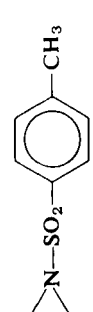
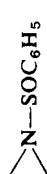
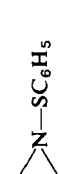
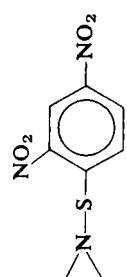
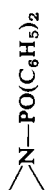
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Molecularity	Ref.
6 $\text{CH}_3\text{CH}_2\text{CHCH}_2\text{Li}$ CH_3	CLS	<i>n</i> -Pentane	—	—	4.5	—	-38	1.0	238
	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	—	—	8.0	—	-23	1.0	238
	CLS	Toluene	—	—	10.5	—	-20	—	238
7 $(\text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_2)_3\text{Al}$ CH_3	CLS	Toluene	—	—	28.0	—	22.5	1.0	238
8 $\text{CH}_3\text{CH}_2\text{CHCH}_2\text{MgBr}$ CH_3	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	—	—	12	—	-11	2.5	26,239
	CLS	THF	—	—	16.6	—	-2	—	26
	CLS	$\text{C}_6\text{H}_5\text{OCH}_3$	—	—	9.6	—	-14	—	26
9 $(\text{CH}_3\text{CH}_2\text{CHCH}_2)_2\text{Mg}$ CH_3	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	—	—	18.2	—	5	2.0	26
	CLS	Dioxane	—	—	4.9	—	-40	—	26
	CLS	THF	—	—	10.5	—	-25	—	26
10 $\text{CH}_3\text{CHCH}_2\text{C}_6\text{H}_5$ MgBr	—	$(\text{C}_2\text{H}_5)_2\text{O}$	—	—	—	17(25) ^a	—	—	240
11 $(\text{CH}_3)_3\text{CCH}_2\text{CH}_2\text{Li}$	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	15	13	—	—	—	1.0	241

12	$[(\text{CH}_3)_3\text{CCH}_2\text{CH}_2]_2\text{Mg}$	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	20	13	—	—	1.0	241–243
13	$[(\text{CH}_3)_3\text{CCH}_2\text{CH}_2]_2\text{Zn}$	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	26	16	—	—	—	241
14	$\text{CH}_3\text{CH} \begin{array}{c} \\ \text{CHCH}_2\text{MgCl} \\ \\ \text{CH}_3\text{C}_6\text{H}_5 \end{array}$	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	12	10	—	—	—	27
		CLS	THF	18	14	—	—	—	27
15	$(\text{CH}_3)_3\text{CCH}_2\text{CH}_2\text{MgCl}$	CLS	$(\text{C}_2\text{H}_5)_2\text{O}$	11	9.5	—	—	—	242,243
15a		CT	DMSO- <i>d</i> ₆ / THF- <i>d</i> ₈ (1:1)	—	—	—	18.0(55)	—	304
15b		CT	DMSO- <i>d</i> ₆ / THF- <i>d</i> ₈ (1:1)	—	—	—	17.4(45)	—	304
		CT	DMSO- <i>d</i> ₆ / THF- <i>d</i> ₈ (1:2)	—	—	—	18.5(65)	—	304
15c		CT	DMSO- <i>d</i> ₆ / THF- <i>d</i> ₈ (1:2)	—	—	—	16.6(30)	—	304

^a Calculated from the reported rate and the equation $\Delta G^\ddagger = RT(23.76 + \ln T/k)$; “room temperature” assumed to be 25°.

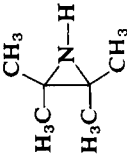
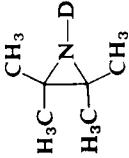
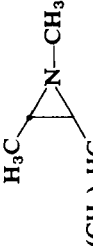
TABLE 4
Atomic Inversion about Nitrogen in Three-Membered Rings

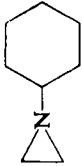
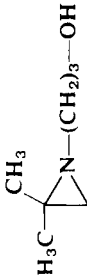
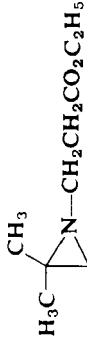
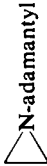
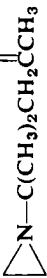
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
16 	MW MW	Vapor Vapor	— —	— —	$>12.0^a$ $>11.6^a$	— —	— —	256 84,257
17 	CLS	CF_2Cl_2	15.6	—	15.2	12.5(–26)	11.6	181
18 	CLS	CF_2Cl_2	—	—	13.6	11.2(–49)	10.4	181
19 	CT	CF_2Cl_2	—	—	—	11.0(–53)	—	181
20 	CT	CF_2Cl_2	—	—	—	10.7(–59)	—	181
21 	CT	CF_2Cl_2	—	—	—	10.0(–72)	—	181

22		CT	CHCl ₂	—	—	8.2(−107)	—	181
23		CT ^b	CDCl ₃	—	10.9	12.4(−30) ^c	3.6	197
24		CT ^b	CDCl ₃	—	—	12.4(−30) ^c	—	197
25		CT ^b	CDCl ₃	—	—	13.6(0) ^c	—	197
26		CT ^b	CDCl ₃	—	—	13.1(−11) ^c	—	197
27		CT ^b	CDCl ₃	—	—	12.7(−18) ^c	—	197
28		CT ^b	CH ₂ Cl ₂	—	—	8.2(−108) ^c	—	197
29		CT ^b	CS ₂	—	—	11.7(−40) ^c	—	180
30		CT ^b	CDCl ₃	—	—	12.8(−25) ^c	—	180
31		CT ^b	CH ₂ =CHCl	—	—	9.9(−86) ^c	—	180

(Continued)

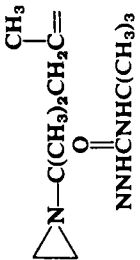
TABLE 4 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
32 	CT ^b	CH ₂ =CHCl	—	—	7.1(−138) ^c	—	180
33 	ALS	CCl ₄	11.0, 11.9	—	—	—	158
34 	ALS ^a	CCl ₄	14.3, 15.0	—	—	—	158
35 	CT	CDCl ₃	—	—	16.5(30) ^c	—	258
36 	CT	None	—	—	19.4(108) ^c	—	168,175
37 	CT	None	—	—	19.2(105) ^c	—	168
38 	CT	None	—	—	18.7(96) ^c	—	168

39		CT	None	—	—	—	18.8(95) ^c	—	168
40		CT	None	—	—	—	10.3(−65) ^c	—	168,175
41		CT	None	—	—	—	17.8(55) ^c	—	168
42		CT	None	—	—	—	17.6(55) ^c	—	168
43		CT	None	—	—	—	17.6(58) ^c	—	168
44		CT	None	—	—	—	17.0(52) ^c	—	7,169
45		CT	CCl ₄	—	—	—	17.0(41) ^c	—	7,169
46		CT	None	—	—	—	17.0(52) ^c	—	7
47		CT	None	—	—	—	16.8(44) ^c	—	7

(Continued)

TABLE 4 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
	CT	C ₆ H ₆	—	—	—	16.7(39) ^o	—	7
	CT	None	—	—	—	17.1(52) ^o	—	7
	CT	None	—	—	—	17.6(65) ^o	—	192
	CT	None	—	—	—	17.3(58) ^o	—	192
	CT	None	—	—	—	17.5(60) ^o	—	192
	CT	None	—	—	—	17.5(63) ^o	—	192
	CT	None	—	—	—	18.8(83) ^o	—	192
	CT	None	—	—	—	17.6(57) ^o	—	192

56		CT	None	—	—	18.3(75) ^c	—	192
57		ALS	None	19	11	—	—	167
58		CLS	None	24.1	17.0	17.9(—) ^f	17	235
		CLS	None	23.5	16.7	17.7(—) ^f	16	235
		CLS	C ₆ H ₆	23.4	16.3	18.2(—) ^f	14	235
		CLS	CDCl ₃	32.5	21.7	18.9(—) ^f	38	235
		CLS	Acetone- <i>d</i> ₆	24.2	16.6	18.3(—) ^f	15	235
59		CKE	CCl ₄	20	—	—	—	161
60		ALS	C ₆ H ₅ NO ₂	22.7	13	—	—	195
61		ALS	CCl ₄	9.1	9.6	—	—	205
62		ALS	CCl ₄	6.9	8.3	—	—	205
63		ALS	CCl ₄	6.8	7.9	—	—	205
64		ALS	CCl ₄	5.8	7.8	—	—	205

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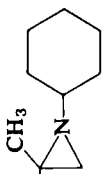
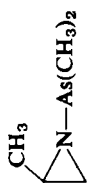
TABLE 4 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
CH₃	CT	CH ₂ Cl ₂ —CFC1 ₃	—	—	—	9.1(−87)	—	163
CH₃	CT	CDCl ₃	—	—	—	12.2(−25)	—	163
CH₃	CT	CH ₂ Cl ₂	—	—	—	11.9(−58), 12.4(−23)	—	163
CH₃	CT	CDCl ₃	—	—	—	13.2(−21), 13.4(−3)	—	163
F₂	ALS	None	5.5	8.7	—	—	—	204
	CKE	C ₆ H ₆	—	—	—	23.8(29.5) ^c	—	160
	CKE	C ₂ Cl ₄	—	—	—	32.4, 31.4(115)	—	221

72		CKR	C ₂ Cl ₄	28.4	—	27.7	—	6	170
73		CKE	C ₂ Cl ₄	—	—	—	27.3(70)	—	222
74		CKE	C ₂ Cl ₄	—	—	—	27.1, 26.3(70)	—	222
75		CKR	C ₂ Cl ₄	34.8	—	34.1	—	5	170
75a		ALS	C ₆ H ₅ NO ₂	7.0	6.1	—	—	—	307
75b		CT	CCl ₄	—	—	—	16.1(30) ^o	—	192
75c		CT	CCl ₄	—	—	—	17.8(26) ^o	—	192
75d		CT	None	—	—	—	10.6(—62)	—	321

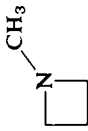
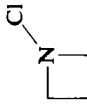
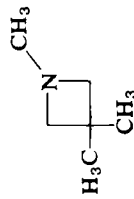
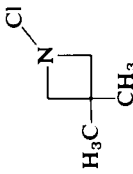
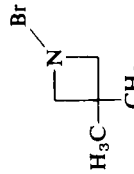
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TABLE 4 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
75e 	CT	CDCl_3	—	—	—	17.6(54), 17.5(75)	—	220
75f 	CT	CDCl_3	—	—	—	17.5(51), 17.4(73)	—	220
75g 	CT	CDCl_3	—	—	—	17.7(79)	—	220
75h 	CT	CH_2Cl_2	—	—	—	10.3(-73), 10.1(-76)	—	220
75i 	CT	None	—	—	—	33(120)	—	220

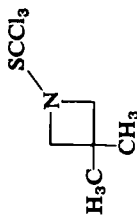
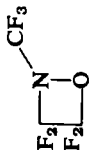
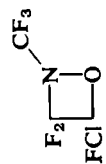
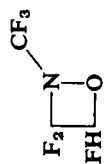
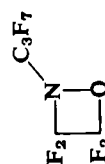
^a This quantity is V_t .^b In these cases, the rate-determining step may be the torsional process about the N—X bond.^c This quantity was calculated from the reported rate and the equation $\Delta G^\ddagger = RT(23.76 + \ln T/k)$.^d This anomalously high isotope effect was discussed in Sect. V-A.^e The barrier was calculated from the reported data.^f This quantity is averaged over a temperature range close to 60°.

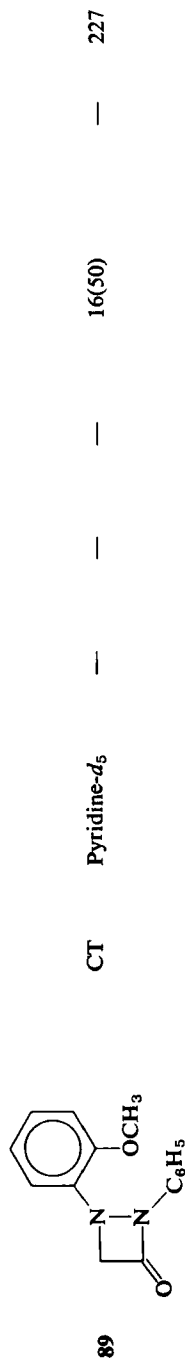
TABLE 5
Atomic Inversion about Nitrogen in Four-Membered Rings

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
76 	CLS	CHClF ₂	12.5	15.3	11.9	10.2(-69)	9.5	212
77 	CT	CHClF ₂	—	—	—	~13.4(-20)	—	212
78 	CT	CFC13	—	—	—	8.5(-98), 8.85(-93)	—	162
79 	CT	CFCl ₃	—	—	—	11.5(-54), 11.4(-46)	—	162
80 	CT	CH ₂ Cl ₂	—	—	—	11.9(-47), 11.6(-43)	—	162

(Continued)

TABLE 5 (Continued)

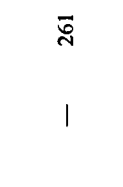
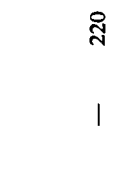
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
	CT ^a	CH ₂ Cl ₂	—	—	—	12.0(−45), 12.1(−30)	—	163
	CT	CFCI ₃	—	—	—	~10(−30)	—	206
	CT	CFCI ₃	—	—	—	~10(−30)	—	206
	CT	CFCI ₃	—	—	—	~10(−30)	—	206
	CT	CFCI ₃	—	—	—	~10(−30)	—	206



(Continued)

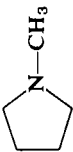
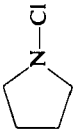
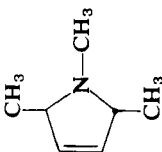
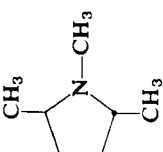
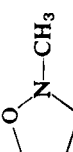
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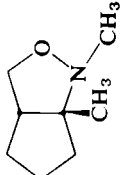
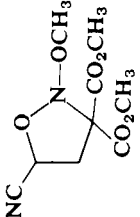
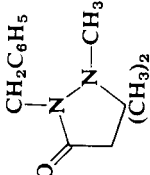
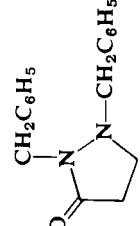
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
90	CT	Acetone	—	—	—	13.4(2)	—	227
91	CT	Acetone	—	—	—	13.7(7)	—	227
92	CT	Acetone	—	—	—	13.3(-1)	—	227
93	ALS	—	7.25	—	—	—	—	207

93a 	CT	CHClF ₂	—	—	6.2(–150)	—	261
93b 	CT	CFCl ₃	—	—	10.2(–65), 10.3(–74)	—	220
93c 	CT	CFCl ₃	—	—	9.9(–70), 9.8(–82)	—	220

^a The processes observed for these compounds may be torsional rather than inversional.

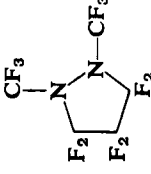
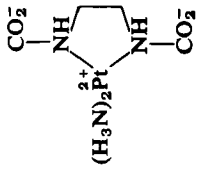
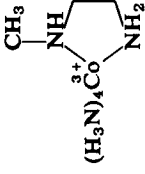
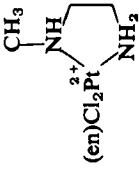
TABLE 6
Atomic Inversion about Nitrogen in Five-Membered Rings

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
94 	CT CLS	CHClF ₂ CHClF ₂	— 10.2	— 15.0	— 9.6	8.1(−100) 8.4(−98)	— 7.9	121 212
95 	CLS	CF ₂ Cl ₂	13.8	16.4	13.2	10.3(−68)	14.5	52
96 	PC	H ₂ O	11.3	12.7	—	—	—	117
97 	PC	H ₂ O	11.4	12.9	—	—	—	117
98 	CT CT	CDCl ₃ D ₂ O	— —	— —	— —	15.6(42) 16.9(62)	— —	50 50

67	99		CT	CH ₂ Cl ₂	—	—	14.8(5)	—	51
	100		CT	CH ₂ Cl ₂	—	—	10.3(–74)	—	51
101		CT	None	—	—	—	13.1(–32)	—	236
		CT	CS ₂	—	—	—	13.2(–32)	—	236
		CT	Toluene- <i>d</i> ₈	—	—	—	13.3(–24)	—	236
		CT	CDCl ₃	—	—	—	13.7(–21)	—	236
		CT	CH ₂ Cl ₂	—	—	—	13.6(–25)	—	236
		CT	Acetone- <i>d</i> ₆	—	—	—	13.3(–28)	—	236
		CT	CH ₃ OH/H ₂ O	—	—	—	14.2(–18)	—	236
102		CKE	CDBr ₃	29.2,	14.2,	—	—	—	233
				29.7	14.1	—	—	—	—
103		CT	Acetone- <i>d</i> ₆	—	—	—	10.7(–49)	—	226
104		CT	Acetone- <i>d</i> ₆	—	—	—	11.6(–32)	—	226

(Continued)

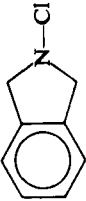
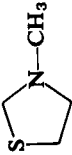
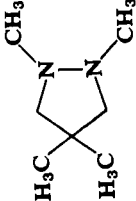
TABLE 6 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
 105	ALS	—	8.6	—	—	—	—	207
 106	CT	CDCl ₃	—	—	—	12.1(-29), 12.0(-55)	—	229
 107	PC ^a	H ₂ O	—	—	15.4	—	—	126
 108	PC ^a	H ₂ O	—	—	—	13.4(25) ^b	—	123
 109	PC ^{a,c}	H ₂ O	—	—	—	13.9(25) ^b	—	127

110		PC ^{a,c}	H ₂ O	—	—	12.0(25) ^b	—	122
110a		CT	CHCl ₂	—	—	7.4(—117)	—	330
110b		CT	CHCl ₂	—	—	8.5(—98)	—	330
110c		CT	CDCl ₃	—	—	13.0(—11)	—	330
		CT	D ₂ O	—	—	15.0(30)	—	330
110d		CT	CFCI ₃	—	—	8.5(—98)	—	330
110e		CT	CFHCl ₂	—	—	9.5(—79)	—	330
		CT	CFCI ₃	—	—	9.0(—87)	—	330
110f		CT	CFCI ₃	—	—	8.5(—98)	—	330

(Continued)

TABLE 6 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
 110g	CT	CFCl_3	—	—	—	8.8(-92)	—	330
 110h	CT	CH_2Cl_2	—	—	—	8.6(-100)	—	330
 110i	CT	CH_2Cl_2	—	—	—	11.1(-45)	—	322

^a Inversion in these molecules actually occurs in the singly deprotonated form.

^b This quantity was calculated from the reported rate and the equation $\Delta G^\ddagger = RT(23.76 + \ln T/k)$.

^c The symbol "en" stands for " $\text{H}_2\text{N}-\text{CH}_2\text{CH}_2-\text{NH}_2$."

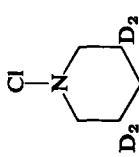
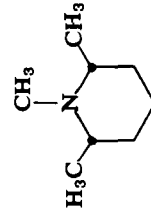
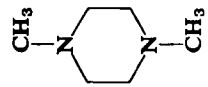
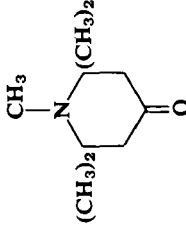
whereas in **105** and **106** some type of double inversion must occur. The inorganic platinum and cobalt complexes **107–110** have yielded unimolecular inversion rates for the deprotonated form through detailed kinetic analyses (122–127). Structural and electronic effects on such inversion barriers have not been studied. It is not known if the process to which the kinetics are attributed in **107–110** is strictly analogous to the nitrogen inversion of dnmr techniques. At the least, there are solvation differences due to the aqueous environment.

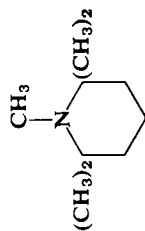
d. Six-Membered Rings. Investigations of the very common six-membered ring are difficult to interpret because atomic inversion and ring reversal are frequently indistinguishable. Table 7 lists the systems in which the observed process is most likely to be atomic inversion. Many related studies have been omitted because of the likelihood that ring reversal is being observed (53–57,60,61,63–68,163,178,262,297). Even of those included in Table 7, only a few can be assigned with complete confidence to an inversion process. The proton-exchange method (117) (**114**, **115**), however, is mechanistically reliable as a source of inversion barriers. The methanol effect in **118** and **121** substantiates the inversional nature of these barriers (50,59). Compounds **117**, **131**, and **133** are the only systems that exhibit two separate coalescence phenomena in the nmr spectrum (58,70). The torsional and inversional barriers are therefore distinguishable portions of the potential-energy surface for these molecules. Such a statement is not necessarily true for all systems. Even when the processes give distinct spectral changes, the problem remains to assign which coalescence is attributable to which process. For the molecules **131** and **133**, reasonable arguments have been presented for the assignment (70). Because of the ambiguities inherent in six-membered rings, experiments for studying atomic inversion are best performed elsewhere.

e. Seven-Membered Rings and Higher. Rings of seven members are ideal models for pure atomic inversion. The only competitive torsional process, pseudorotation, is generally too rapid to be observed by the dnmr method. Any observed coalescence may confidently be assigned to atomic inversion (121). The same argument may be used for five-membered rings. The unstrained bond angles about nitrogen in the seven-membered series also give these compounds as close a resemblance to open-chain systems as can be offered by simple cyclic compounds. Thus far, only the homopiperidines **137** and **138** (Table 8) have been studied. The barrier in the *N*-methyl compound is quite low (7 kcal/mole). The *N*-chloro compound has a barrier about 1.5–2 kcal/mole higher.

f. Bridged Compounds. Two classes of bridged compounds have yielded important results in the field of atomic inversion. Compounds such

TABLE 7
Atomic Inversion about Nitrogen in Six-Membered Rings

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
111 	CLS ^a	CH ₂ Cl ₂	17.0	15.5	16.4	13.7(-1)	10.6	52
112 	PC	H ₂ O	—	—	—	14.1, 14.6(33) ^b	—	116
113 	PC	H ₂ O	—	—	—	9.6, 10.9(44) ^b	—	120
114 	PC	H ₂ O	10.5	14.8	—	—	—	117



115

PC

H₂O

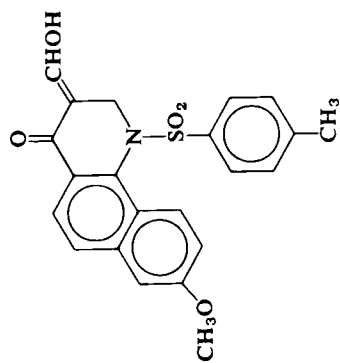
10.8

14.1

—

—

117



116

ALS^a

(C₃H₅)₂O

23

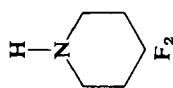
14.1

22

—

9.6

174



117

CLS

Acetone

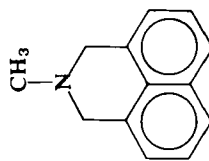
10.5

—

—

—

58



118

CT

CDCl₃

—

—

—

9.7(—72)

—

59

CD₃OD

—

—

—

10.2(—62)

—

59

D₂O/CD₃OD

—

—

—

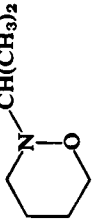
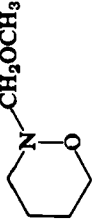
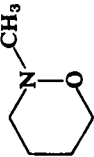
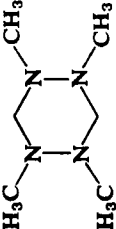
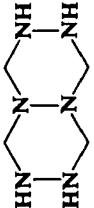
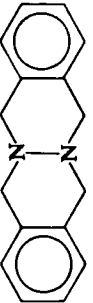
10.9(—50)

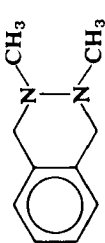
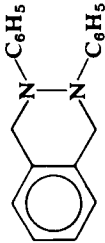
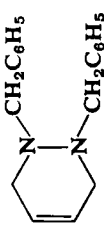
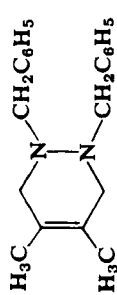
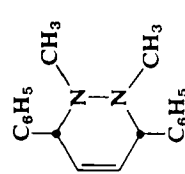
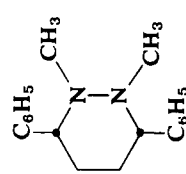
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59

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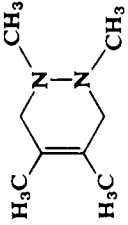
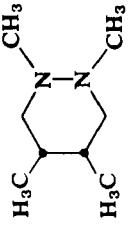
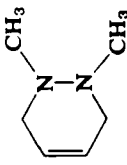
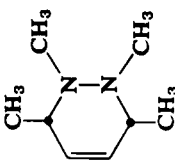
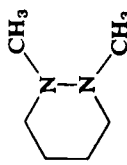
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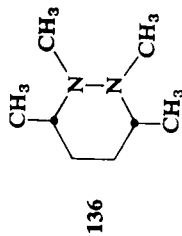
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
119 	CT ^a	CH ₂ Cl ₂	—	—	—	12.5(−46)	—	51
120 	CT ^a	CH ₂ Cl ₂	—	—	—	11.5(−51)	—	51
121 	CT CT CT CT	None Hexane CH ₂ Cl ₂ D ₂ O/CD ₃ OD	— — — —	— — — —	— — — —	13.7(5) 13.7(3) 13.7(5) 15.0(33)	— — — —	50 50 50 50
122 	CT ^a	Cyclopropane	—	—	—	11.8(−24), 11.6(−35)	—	69
123 	CT ^a	D ₂ O	—	—	—	16.6(58)	—	229
124 	CT ^a	CDCl ₃ / pyridine- <i>d</i> ₅	—	—	—	12.4(—)	—	228

125		CT ^a	Acetone/ pyridine- <i>d</i> ₅	—	—	12.0(−27)	—	228
126		CT ^a	Acetone/ pyridine- <i>d</i> ₅	—	—	12.2(−23)	—	228
127		CT ^a	Acetone/ pyridine- <i>d</i> ₅	—	—	11.5(−37)	—	228
128		CT ^a	Acetone/ pyridine- <i>d</i> ₅	—	—	12.0(−27)	—	228
129		CT ^a	CDCl ₃	—	—	13.8(1), 13.4(1)	—	62,70
		CT ^a	CF ₂ Cl ₂	—	—	13.3(−1)	—	70
130		CT ^a	CDCl ₃	—	—	11.2(−44)	—	62,70

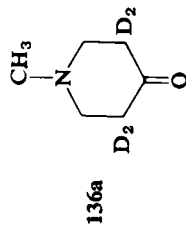
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TABLE 7 (Continued)

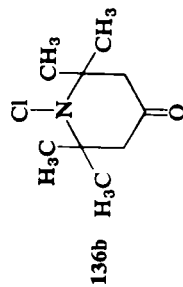
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
 131	CT	CDCl_3	—	—	—	12.4, 12.8(–12) 12.3(–14.5)	—	62,70
	CT	CF_2Cl_2	—	—	—	—	—	70
	CT	CD_3OD	—	—	—	12.4(–13)	—	70
 132	CT^a	CDCl_3	—	—	—	12.3(–44)	—	62,70
	CT^a	CF_2Cl_2	—	—	—	12.5(–46.5)	—	70
	CT^a	CD_3OD	—	—	—	12.3(–48)	—	70
 133	CT	CF_2Cl_2	—	—	—	12.0(–20)	—	70
	CT	CD_3OD	—	—	—	12.3(–15)	—	70
 134	CT^a	CF_2Cl_2	—	—	—	12.0(–35)	—	70
	CT^a	CD_3OD	—	—	—	12.3(–33)	—	70
 135	CT^a	CF_2Cl_2	—	—	—	11.6(–30)	—	70
	CT^a	CD_3OD	—	—	—	12.1(–20)	—	70



CT ^a	CF ₂ Cl ₂	—	—	—	11.5(−39)	—	70
CT ^a	CD ₃ OD	—	—	—	11.6(−36.5)	—	70



CT	CHFC1 ₂	—	—	—	8.6(−94)	—	296

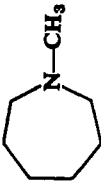
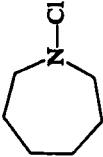
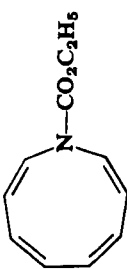
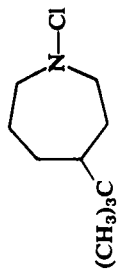


CT	CHFC1 ₂	—	—	—	8.1(−106), 8.2(−115)	—	220

^a The barriers quoted for these systems may very well be torsional, or a combination of torsional and inversional.

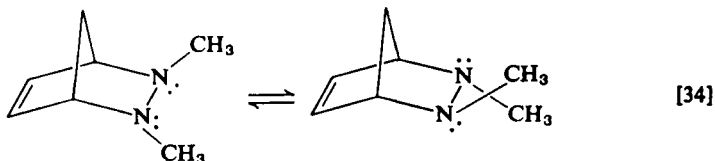
^b This quantity was calculated from the reported rate and the equation $\Delta G^\ddagger = RT(23.76 + \ln T/k)$.

TABLE 8
Atomic Inversion about Nitrogen in Seven-Membered Rings and Higher

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
 137	CT	CHClF ₂	—	—	—	6.8(−125)	—	212
	CT	CHClF ₂	—	—	—	6.4(−140)	—	296
 138	CLS	CH ₂ Cl ₂	11.2	15.0	10.6	9.3(−86)	8.2	212
	CLS	CH ₂ Cl ₂	11.2	15.3	10.6	9.2(−87)	9.4	212
	CT	CF ₂ Cl ₂	—	—	—	8.8(−93)	—	212
	CT ^a	CD ₃ OD	—	—	—	8.9(−91)	—	212
	CT	CH ₂ Cl ₂	—	—	—	8.4(−100)	—	296
 138a	CT ^a	CHCl ₃	—	—	—	13.7(−10)	—	295
	CT ^a	Acetone	—	—	—	13.0(−22)	—	295
	CT ^a	CH ₃ OH	—	—	—	13.3(−18)	—	295
	CT ^a	CH ₃ CN	—	—	—	12.6(−28)	—	295
 138b	CT	CH ₂ Cl ₂	—	—	—	8.9(−90)	—	220

^a This barrier may be entirely torsional; see ref. 334.

as **139** and **140** (Table 9) have a single nitrogen atom at a position subject to considerable angle strain (164–166). As a result, the barrier is similar in magnitude to that in azetidines or aziridines. More thorough studies have been made of molecules containing two nitrogen atoms that are singly bonded to each other (157,225,230,232). Although conformational processes have also been observed in some of these molecules, in most of them the process is a rapidly consecutive inversion about two nitrogen atoms (eq. [34]).



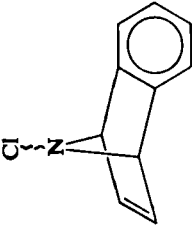
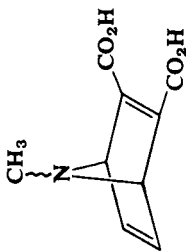
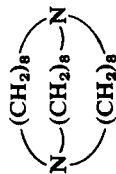
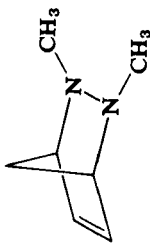
A simultaneous inversion about both atoms has been rejected. Apparently, inversion about only one atom produces a strained system with considerable encouragement to proceed with the second inversion.

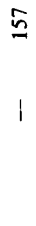
g. Open-Chain Systems. The dnmr method is not well suited for investigation of open-chain systems, since it cannot differentiate between atomic inversion and bond rotation. For this reason we have omitted from Table 10 many cases that are probably pure rotation or merged inversion-rotation (30–33,35,38–40,42,43,48,234,264,265). Some doubtful cases [**169** (37), **170** (34), and **171** (36)] were included because the original authors had good reason to believe that the observed barriers were inversional. The protonation method of Saunders has been extremely successful in obtaining barriers to inversion in acyclic amines (114,119). Microwave spectroscopy has made a considerable contribution to the measurement of the low barriers to inversion of primary and secondary amines (100), particularly those with nitrogen in conjugation with a substituent (101,102,156,177). As yet, there is no acyclic system in which rotation and inversion have been observed as distinct processes. If two coalescence phenomena can be observed, as in the cyclic cases **117**, **131**, **133**, reliable barriers to inversion might be assigned by the dnmr method.

3. Oxygen

The larger angles in oxonium ions, R_3O^+ , render the barrier to inversion smaller than that in similarly constituted amines. The calculated barrier for the hydronium ion is less than 1 kcal/mole (86). Consequently, the only system for which dnmr studies have been successful utilizes a strained three-membered ring (**172**) to enhance the barrier (Table 11) (237). The solvent used in this study, sulfur dioxide, would also tend to raise the barrier through complexation (71).

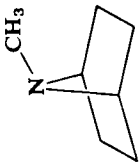
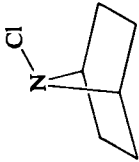
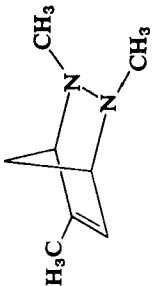
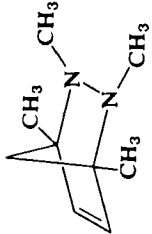
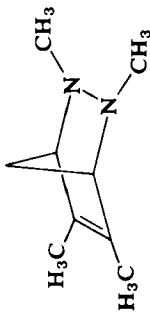
TABLE 9
Atomic Inversion about Nitrogen in Bridged Systems

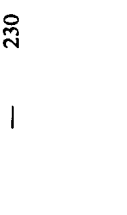
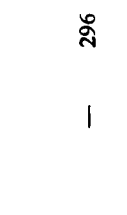
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
 139	CT	CCl_4	—	—	—	23.5(23)	—	165
 140	CT	$\text{DMSO}-d_6$	—	—	—	19(96)	—	164
 141	CT	CFCl_3	—	—	—	7.7(25)	—	263
 142	ALS ALS ALS	Pentane CDCl_3 D_2O	— — —	— — —	16.2 16.9 —	14.1(8) 14.5(15.5) 16.1(47)	7.6 8.3 —	157 157 157

	143	CT	CDCl ₃	—	—	14.5(22)	—	157
	144	ALS CLS CLS	CDCl ₃ CDCl ₃ None	— 16.0 14.6, 16.7	— 14.9 14.1, 15.7	13.2(–19) — —	6.0 — —	157 225 225
	145	ALS	Pentane	—	15.7	12.8(–26)	11.5	157
	146	ALS ALS	CDCl ₃ Pentane	— —	14.9 12.4	12.3(–27) 11.8(–37.5)	10 2.8	157 157
	147	CT	CDCl ₃	—	—	12(–30)	—	157

(Continued)

TABLE 9 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
148 	CT	CHFCI ₃	—	—	—	9.5(–80)	—	220
149 	CT	CDCl ₃	—	—	—	14(70)	—	220
150 	CT	CDCl ₃	—	—	—	14.8(15)	—	232
151 	CT	CDCl ₃	—	—	—	13.5(–90)	—	232
152 	CT	CDCl ₃	—	—	—	15.2(20)	—	232

	CT	CFCl ₃	—	—	10.2(–83)	—	230
	CT	CFCl ₃	—	—	11.4(–64)	—	230
	CT	CFCl ₃	—	—	11.8(–48)	—	230
	CT	CHFC1 ₂	—	—	8.4(–98)	—	296
	CT	CHFC1 ₂	—	—	10.6(–54)	—	296

(Continued)

TABLE 9 (Continued)

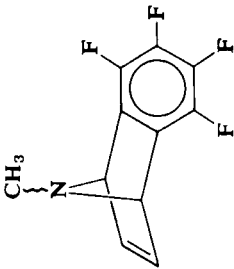
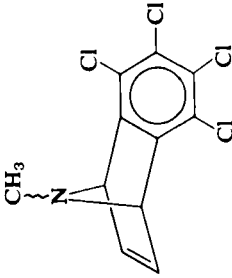
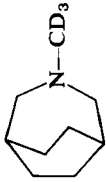
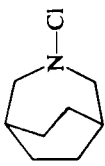
Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
 155c	CT	CDCl ₃	—	—	—	14(1)	—	166
 155d	CT	CDCl ₃	—	—	—	14(-2)	—	166
 155e	CT	CHCl ₂	—	—	—	8.8(-92)	—	220
 155f	CT	CHCl ₂	—	—	—	10.1(-65)	—	220

TABLE 10
Atomic Inversion about Nitrogen in Open-Chain Systems

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
156 NH_3	IR	Vapor	—	—	5.78 ^a	—	—	17
	IR	Vapor	—	—	5.94 ^a	—	—	15
157 NH_2CH_3	IR	Vapor	—	—	5.96 ^a	—	—	154
158 $\text{NH}(\text{CH}_3)_2$	IR	Vapor	—	—	4.83 ^a	—	—	97,155
	MW	Vapor	—	—	4.4 ^a	—	—	100
159 $\text{NH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{H}$	MW	Vapor	—	—	1.1 ^a	—	—	101
160 NH_2-CN	MW	Vapor	—	—	2.0 ^a	—	—	102
	IR	Vapor	—	—	1.3 ^a	—	—	313
161 NH_2-NO_2	MW	Vapor	—	—	2.7 ^a	—	—	102,156
162 $\text{NH}_2-\text{C}_6\text{H}_5$	MW	Vapor	—	—	$\sim 2.0^{\text{a,b}}$	—	—	102
163 $\text{NH}_2-\text{C}_6\text{H}_4-\text{F}$	MW	Vapor	—	—	$\sim 2.6^{\text{a,b}}$	—	—	102,177
164 $(\text{C}_6\text{H}_5\text{CH}_2)_2(\text{CH}_3)\text{N}$	PC	H_2O	10.3	12.9	—	—	—	114,119
165 $(\text{C}_6\text{H}_5\text{CH}_2)(\text{C}_2\text{H}_5)(\text{CH}_3)\text{N}$	PC	H_2O	10.8	12.0	—	—	—	119
166 $\text{C}_6\text{H}_5-\text{CH}(\text{CH}_3)\text{CH}(\text{C}_6\text{H}_5)\text{CH}_2(\text{CH}_3)\text{N}$	PC	H_2O	10.6	13.2	—	—	—	119
167 $\text{C}_6\text{H}_5-\text{CH}(\text{CH}_3)\text{CH}(\text{C}_6\text{H}_5)-\text{C}_6\text{H}_4-\text{CH}_2(\text{CH}_3)\text{N}$	PC	H_2O	10.2	13.5	—	—	—	119
168 $\text{C}_6\text{H}_5-\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)-\text{C}_6\text{H}_4-\text{CH}_2(\text{CH}_3)\text{N}$	PC	H_2O	10.6	12.6	—	—	—	119

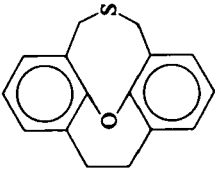
(Continued)

TABLE 10 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2 \\ \\ \text{N}-\text{OCH}_3 \\ \\ \text{CH}_3 \end{array}$	CLS ^c	<i>n</i> -Hexane	12.9	12.8	—	—	—	37
$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{N}-\text{NH}_2 \\ \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array}$	CLS ^c	CS ₂	12.4	12.7	—	—	—	37
	CLS ^c	CHCl ₃	11.7	11.8	—	—	—	37
	CLS ^c	CH ₂ Cl ₂	9.4	10.0	—	—	—	37
	CT ^c	CCl ₃ F/CH ₂ Cl ₂	—	—	—	8.5(−95)	—	34,299
$\begin{array}{c} \text{CH}_3 \\ \\ (\text{CH}_3)_2\text{N}-\text{N}-\text{CH}_2\text{C}_6\text{H}_5 \end{array}$	CT ^c	CF ₂ Cl ₂	—	—	—	6.8(−130)	—	36
$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{N}-\text{OH} \\ \\ (\text{C}_6\text{H}_5\text{CH}_2)_2\text{N} \end{array}$	CT ^c	CH ₂ =CHCl	—	—	—	6.5(−137), 6.0(−146)	—	298,299
	CT ^c	CDCl ₃	—	—	—	12.8(−16)	—	306
	CT ^c	CD ₃ OD	—	—	—	12.2(−30)	—	306
	CT ^c	CDCl ₃	—	—	—	12.9(−13)	—	306
$\begin{array}{c} \text{O} \\ \\ (\text{C}_6\text{H}_5\text{CH}_2)_2\text{N}-\text{O}-\text{CCH}_3 \end{array}$	CT ^c	CD ₃ OD	—	—	—	12.3(−25)	—	306
$\begin{array}{c} \text{O} \\ \\ (\text{C}_6\text{H}_5\text{CH}_2)_2\text{N}-\text{O}-\text{CCH}_3 \end{array}$	CT ^c	CDCl ₃	—	—	—	12.1(−34)	—	306
	CT ^c	CD ₃ OD	—	—	—	12.3(−27)	—	306
$\begin{array}{c} \text{O} \\ \\ (\text{C}_6\text{H}_5\text{CH}_2)_2\text{N}-\text{O}-\text{CCH}_3 \end{array}$	CT ^c	CDCl ₃	—	—	—	12.0(−29)	—	306
	CT ^c	CD ₃ OD	—	—	—	12.3(−23)	—	306

^a This quantity is V_t . ^b This number is estimated from the angular data given in the references. ^c The process involved may be torsional in these systems; see ref. 335.

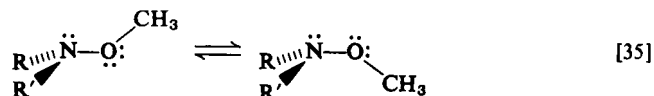
TABLE 11
Atomic Inversion about Oxygen

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
172 	CT ^a	SO ₂	—	—	—	10(−50)	—	237
173 	CT ^b	C ₆ H ₅ Cl	—	—	—	20(130)	—	266

^a Barrier to inversion about trivalent oxygen. process is also possible.

^b Barrier to inversion about divalent oxygen, although a competitive torsional

Divalent oxygen, R_2O , may invert either through a linear “ sp ” transition state or through a bent “ sp^2 ” transition state. The latter process is indistinguishable from bond rotation. Linear inversion has been found to be a relatively high-energy process, according to both indirect (39,267) and direct (173) (266) experimental results. Linear inversion in H_2O has a calculated barrier of about 34 kcal/mole (266), compared with the almost negligible barrier to pyramidal inversion in H_3O^+ . Therefore, a process such as that depicted in eq. [35] must occur by a torsional mechanism rather than by a



linear inversion mechanism (36–38,267). The success of the studies on **173** resulted from the constraints imposed by the ring structure. Linear inversion about oxygen is more strictly analogous to the inversion of oximes, imines, etc. (1), than of amines.

B. Elements beyond the First Row

1. Group IV

No examples of true pyramidal inversion about trivalent silicon, germanium, tin, or lead have been reported. The problems of higher-order reactions and of aggregation would be expected to impair such studies, as was the case with trivalent carbon. Ligand exchange and other chemical reactions have been found to cause stereomutation of tetravalent tin halides (268,269,305). It is not unreasonable to expect that investigators will turn to the inversion properties of these elements, but interpretations will be difficult.

2. Group V

a. Phosphorus. Because of the considerable configurational stability of phosphorus (172,272–289), classical kinetics have been the prime source for inversion barriers. The recent advent of general methods for the production of optically active trivalent phosphorus compounds has permitted more systematic studies to be carried out (287–289). Phosphorus inversion is accelerated by (p - p) $_{\pi}$ conjugation, as shown in the substituted phenyl series **178–180** (129) (Table 12). More dramatic is the reduction in barrier height conveyed by the presence of d orbitals on an adjacent substituent, as in the diphosphines **185–188** (21,22,46) and the silylphosphines **189** (199). The extreme rate acceleration in the phosphole **4** must be due to aromatic character in the transition state to inversion (186). Mechanisms other than pyramidal

inversion, such as ligand exchange (24,25), have been observed in the stereomutation of phosphorus. In some acyclic phosphine systems, rate processes have been observed by the dnmr method, but it is doubtful that any involves phosphorus inversion (30–32). A rapid phosphorus inversion, accelerated by $(p-d)_\pi$ bonding, has been implicated in the stereomutation of allylmethylphenylphosphine sulfide (198). Because of the multitude of structural variations yet to be explored and the unusual ability of phosphorus to conjugate with both p and d orbitals, this field should continue to be actively explored.

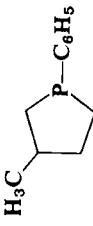
b. Arsenic. Like phosphorus, arsenic is in general configurationally stable (137–142,145,187,320). Systematic racemization studies have not yet been carried out, and early attempts along these lines were unsuccessful (141,142). Inversion has been observed in dimethyldiphenyldiarsine (22,47) (Table 13), because of the lowering of the transition-state energy by $(p-d)_\pi$ bonding. Rotational processes are also possible in this system (152,153), but the inversion step is probably rate-determining. Arsenic inversion accelerated by $(p-d)_\pi$ overlap may also have been observed in cyclic silylarsines (200) and in cyclic polyarsines (290,291). Alternative mechanisms of stereomutation (disproportionation, chemical, photochemical) have been reported (143,144, 292).

c. Antimony and Bismuth. Pyramidal inversion has not been observed about antimony or bismuth. Several optically active stibines have been reported (188–191). Early reports of racemization (188–191) were probably due entirely to chemical stereomutation. An attempt to observe inversion of diastereomeric distibines was unsuccessful for synthetic reasons (271).

3. Group VI

a. Sulfur. The configurational stability of sulfur is sufficient to support optical activity (185) and to prevent the use of dnmr methods in all but very special cases (19,20,183). Classical kinetic methods (Table 14) have therefore found wide application in stereomutation studies of sulfonium ions (131,132,293), sulfoxides (130,148,150), sulfonium ylids (134), and thiol-sulfinates (133). Typical sulfoxide barriers lie in the range 35–43 kcal/mole (130), and sulfonium ions in the range 25–29 kcal/mole (134). The lower barrier in the ylid **208** is presently unexplained. The rapid rates of inversion in **209–213** may be attributed to $(p-d)_\pi$ overlap between sulfur and the attached atom (19,20,133). A systematic variation of aromatic substituents on sulfur (130) has produced a comparison of the $(p-p)_\pi$ conjugative effect on sulfur inversion with that on phosphorus (129) and nitrogen (181) inversion. The mechanism of sulfur inversion in the platinum complexes **210–213** has been described in different terms by the original authors (19,20). Alternative

TABLE 12
Atomic Inversion about Trivalent Phosphorus

	Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
174	$(\text{CH}_3)(\text{CH}_3\text{CH}_2\text{CH}_2)(\text{C}_6\text{H}_5)\text{P}$	CKR	Decalin	28.6	11.1	—	32.1(130)	—	128, 129
		CKR	<i>n</i> -Decane	29.7	11.6	—	—	—	128
		CKR	Methyl-naphthalene	30.7	12.4	—	—	—	128
175	$(\text{CH}_3)(\text{cyclohexyl})(\text{CH}_3\text{CH}_2\text{CH}_2)\text{P}$	CKR	Decalin	—	—	—	35.6(130)	—	129
176	$(\text{CH}_3)(\text{CH}_2=\text{CHCH}_2)(\text{C}_6\text{H}_5)\text{P}$	CKR	Decalin	—	—	—	32.8(130)	—	129, 182
		CKR	Benzene	32.2	12.8	—	32.6(130)	—	129
177	$(\text{CH}_3)[(\text{CH}_3)_3\text{C}](\text{C}_6\text{H}_5)\text{P}$	CKR	Decalin	—	—	—	32.7(130)	—	129
178	$(\text{CH}_3)(p\text{-CH}_3\text{OC}_6\text{H}_4)(\text{C}_6\text{H}_5)\text{P}$	CKR	Decalin	—	—	—	30.8(130)	—	129
179	$(\text{CH}_3)(p\text{-CH}_3\text{C}_6\text{H}_4)(\text{C}_6\text{H}_5)\text{P}$	CKR	Decalin	—	—	—	30.3(130)	—	129
180	$(\text{CH}_3)(p\text{-CF}_3\text{C}_6\text{H}_4)(\text{C}_6\text{H}_5)\text{P}$	CKR	Decalin	—	—	—	29.1(130)	—	129
181	$(\text{CH}_3)(\beta\text{-naphthyl})(\text{C}_6\text{H}_5)\text{P}$	CKR	Benzene	—	—	—	29.7(130)	—	129
	$(\text{CH}_3)_2$								
182		CKE	None	—	—	29.8	—	-8	147, 171
	$(\text{CH}_3)_2$								
183		CKE	None	—	—	28.2	—	-8	147
	$(\text{CH}_3)_2$								
184		CKE	CHCl_3	—	—	—	26.4(70) ^a	—	270
5		CKE	C_6H_6	—	—	—	36(170)	—	186

4		CLS	CFC13	—	—	17.1	16(25)	3.1	186
		CLS	(<i>n</i> -C ₄ H ₉)PS	26	14	25	23.6(155)	3.2	21, 22 46, 271
185		CT	(C ₆ H ₅) ₂	—	—	—	23.6(155)	—	271
186		CT	None	—	—	—	24(155)	—	46
187		CLS	None	—	—	—	22.6(155)	—	46
188		CT	None	—	—	—	22.5(155)	—	46
189		CT	C ₆ D ₆	—	—	—	18.9(62)	—	199
189a		CT	C ₆ D ₆	—	—	—	19.1(70)	—	199
189b		CT	C ₆ D ₆	—	—	—	21.4(109)	—	199
189c		CT	C ₆ D ₆	—	—	—	19.3(72)	—	310

^a This quantity was calculated from the published data.

TABLE 13
Atomic Inversion about Trivalent Arsenic

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{As} - \text{As} \\ \diagdown \quad \diagup \\ \text{CH}_3 \quad \text{C}_6\text{H}_5 \end{array}$	CLS	None	27	14	26	23.6(173)	6.1	22, 47

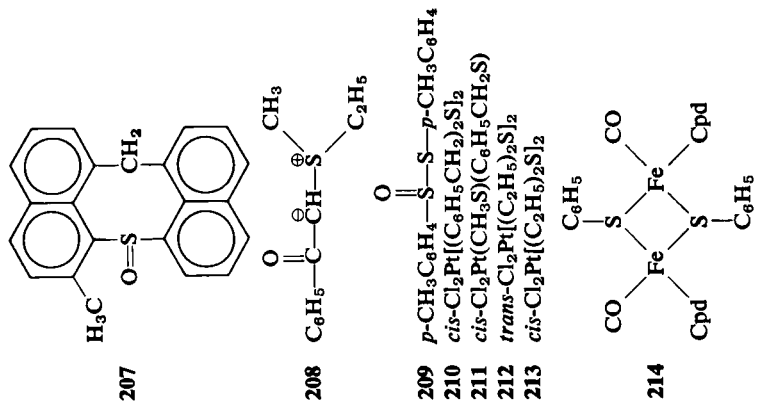
TABLE 14
Atomic Inversion about Trivalent Sulfur

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
191 $(\text{CH}_3)(\text{C}_2\text{H}_5)[\text{C}(\text{CH}_3)_3]\text{S}^+\text{ClO}_4^-$	CKR	$\text{C}_2\text{H}_5\text{OH}$	—	—	25	—	—	293
192 $(\text{CH}_3)(\text{C}_2\text{H}_5)(1\text{-adamanty})\text{S}^+\text{ClO}_4^-$	CKR	HOAc	—	—	26	—	8	132
193 $(\text{CH}_3)(\text{C}_2\text{H}_5)(\text{C}_6\text{H}_5\text{CH}_2)\text{S}^+\text{ClO}_4^-$	CKR	CH_3OH	—	—	—	$26.6(50)^a$	—	131
194 $(\text{CH}_3)(\text{C}_2\text{H}_5)(p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2)\text{S}^+\text{ClO}_4^-$	CKR	CH_3OH	—	—	—	$26.6(50)^a$	—	131
195 $(\text{CH}_3)(\text{C}_2\text{H}_5)(p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2)\text{S}^+\text{ClO}_4^-$	CKR	CH_3OH	—	—	—	$26.6(50)^a$	—	131
3	CT	Benzo- phenone	—	—	—	$25.4(200)$	—	183
196 $\text{CH}_3\text{—}\overset{\text{O}}{\parallel}\text{S—}p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	Benzene or xylene	—	—	43	—	3	150
	CKR	<i>p</i> -Xylene	38.4	11.7	37.4	—	-8.0	130
197 $\text{C}_6\text{H}_5\text{—}\overset{\text{O}}{\parallel}\text{S—}p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	Benzene or xylene	—	—	39	—	0	150
	CKR	<i>p</i> -Xylene	37.2	12.3	36.2	—	-5.1	130
198 $o\text{-CH}_3\text{C}_6\text{H}_4\text{—}\overset{\text{O}}{\parallel}\text{S—}p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	Benzene or xylene	—	—	37	—	-2	150
	CKR	<i>p</i> -Xylene	37.5	12.8	36.6	—	-2.8	130

(Continued)

TABLE 14 (Continued)

Compound	Method	Solvent	E_a , kcal/mole	$\log A$	$\Delta H^\ddagger$, kcal/mole	$\Delta G^\ddagger(T)$, kcal/mole	$\Delta S^\ddagger$, eu	Ref.
199 $2,4,6-(\text{CH}_3)_3\text{C}_6\text{H}_2-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	Benzene or xylene	—	—	34	—	-3	150
	CKR	<i>p</i> -Xylene	36.3	13.7	35.4	—	1.3	130
200 1-Adamantyl- $\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	43.0	14.3	42.0	—	3.8	130
201 $p\text{-CF}_3\text{C}_6\text{H}_4-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	—	—	—	38.0(210) ^a	—	130
202 $m\text{-CF}_3\text{C}_6\text{H}_4-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	—	—	—	38.6(210) ^a	—	130
203 $p\text{-ClC}_6\text{H}_4-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	—	—	—	38.9(210) ^a	—	130
204 $p\text{-CH}_3\text{OC}_6\text{H}_4-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	—	—	—	39.2(210) ^a	—	130
205 $o\text{-CH}_3\text{OC}_6\text{H}_4-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	—	—	—	39.3(210) ^a	—	130
206 $o\text{-ClC}_6\text{H}_4-\text{S}(=\text{O})-p\text{-CH}_3\text{C}_6\text{H}_4$	CKR	<i>p</i> -Xylene	—	—	—	39.9(210) ^a	—	130



207	—	—	—	—	25.2(75)	—	148
CKE	—	—	—	—	—	—	—
208	—	—	—	23.3	—	—	134
CKR	CCl ₄	—	—	—	—	—	—
209	—	—	—	23	—	—	133
CKR	C ₆ H ₆	—	—	—	—	—	—
ALS	CDCl ₃	18.0	13.8	17.4	16.6(34.5)	3	19
210	—	—	—	—	—	—	—
CKR	CH ₂ Cl ₂	19.2	14.8	18.6	16.5(36)	7	20
ALS	CH ₂ Cl ₂	—	—	—	—	—	—
211	—	—	—	—	—	—	—
CKR	CT	—	—	—	13.9(1)	—	20
212	—	—	—	—	—	—	—
CKR	CDCl ₃	—	—	—	16.8(60)	—	20
213	—	—	—	—	—	—	—
CKE ^b	THF	30.7	—	—	—	—	202
214	—	—	—	—	—	—	—
CKE ^b	CS ₂	31.8	—	—	—	—	202

^a This quantity was calculated from the reported rate and the equation $\Delta G^\ddagger = RT(23.76 + \ln T/k)$. ^b "Cpd" represents "cyclopentadienyl."

modes of sulfur stereomutation (dissociation, chemical) have been observed in several cases (23,29,151).

b. Selenium and Tellurium. Selenoxides (135,170), selenonium ions (146), and telluronium ions (146,294) have been found to be configurationally stable. Telluronium ions (146,294), like stibines (188,191), are sensitive to chemical racemization. No studies of unimolecular atomic inversion of selenium or tellurium have been reported, but there is no reason why systems cannot be devised that would yield successful observations.

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Note Added in Proof

Barriers have recently been reported for phosphorus inversion in methyl-*n*-propylphenylphosphine (326) ($E_a = 33.3$ kcal/mole, $\log A = 13.8$ in DMSO, 32.5 and 13.4 in quinoline, 30.6 and 12.4 in diethylphenylamine, 29.8 and 11.4 in caproic acid, 27.9 and 10.7 in decalin, 32.6 and 10.9 in trimethyl borate, and 30.1 and 11.8 without solvent by the CKR method); sulfur inversion in the *S*-methyl sulfonium perchlorates (328) of 2-methyltetrahydrothiophene ($\Delta G^\ddagger$ (100°, acetic acid) = 15.0 kcal/mole by the CKR method), 3,3-dimethyltetrahydrothiophene (15.1), and 3,3-dimethylthiane (15.3); sulfur inversion in 2,5-di-*tert*-octylthiophene 1-oxide (329) ($\Delta G^\ddagger$ (26°, CCl_4) = 14.8 kcal/mole by the CT method), in which the transition state is stabilized by aromatic electron delocalization; nitrogen inversion in 1-dimethylaminomethyl-2, 2-dimethylaziridine (331) ($E_a = 15.7$ kcal/mole, $\log A = 13.4$ in toluene by the CLS method); nitrogen inversion in a series of 1,2-diazetidines (332); nitrogen inversion in *N*-chloro- and *N*-methylpyrrolidine (330) ($\Delta G^\ddagger$ (-64, CF_2Cl_2) = 10.4; $\Delta G^\ddagger$ (-107, CHCl_2F) = 7.9, respectively, by the CT method); nitrogen inversion in geneserine (333) ($\Delta G^\ddagger$ (-22, CDCl_3) = 12.8 kcal/mole by the CT method); nitrogen inversion in dibenzylmethylamine (336) ($\Delta G^\ddagger$ (-135, vinyl chloride) = 6.7 kcal/mole by the ALS method); nitrogen inversion in chlorodiethylamine (337) ($\Delta G^\ddagger$ (-71, CS_2) = 10.2 kcal/mole; $\Delta G^\ddagger$ (-61, CD_3OD) by the CT method), dibenzylchloroamine ($\Delta G^\ddagger$ (-71.5, CHCl_2F) = 9.9; $\Delta G^\ddagger$ (-74, CD_3OD) = 9.8), and chlorodi(iso-butyl)amine $\Delta G^\ddagger$ (-81, CHCl_2F) = 9.5; $\Delta G^\ddagger$ (-80, CD_3OD) = 9.5.

Kessler and Leibfritz (338–340) have recently introduced an entirely empirical method by which nitrogen inversion barriers can be calculated. They recognized that the ratio between the free energies of activation for any two substituents is generally constant from system to system. Thus the ratio $\Delta G^\ddagger (N\text{-Cl})/\Delta G^\ddagger (N\text{-CH}_3)$ is close to 1.28 for a wide variety of nitrogen systems (338). With $\Delta G^\ddagger (N\text{-CH}_3)$ always in the denominator, ratios may be calculated to be 1.75 for $N\text{-OR}$ (339), 1.45 for $N\text{-NR}_2$, 0.59 for $N\text{-C}_6\text{H}_5$, and 0.57 for $N\text{-SO}_2\text{C}_6\text{H}_5$ (340). With the effect of substituents placed on a quantitative basis by this method, the inversion barriers for unmeasured or unmeasurable systems can be obtained. A barrier of 19–20 kcal/mole has been predicted in this manner for $N\text{-chlorooxazolidine}$ (340). The calculated inversion barriers for $N\text{-chloro-}$ (10.1 kcal/mole) and $N\text{-methylpiperidine}$ (7.9) confirm that the barriers measured in these systems (52–54) (13.5 and 12 kcal/mole, respectively) refer to the ring reversal process as reported. In an entirely different vein, a recent study (327) has found that in the $n \rightarrow \pi^*$ excited state of cyclopentanone the oxygen atom is $32\text{--}35^\circ$ out of the plane of the ring. A double-well potential ($V_i = 2.0$ kcal/mole) describes the inversion process about the carbonyl carbon atom.

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Resolving Agents and Resolutions in Organic Chemistry*

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* References and data on a large number of resolutions principally from the literature of the past 20 years have been assembled in **S. H. Wilen, Tables of Resolving Agents and Optical Resolutions, University of Notre Dame Press, Notre Dame, Ind.,** being published simultaneously with this review.

I. INTRODUCTION

Resolutions are one of the key unit processes utilized by organic chemists, whether their interests are synthetic, mechanistic, or structural. This follows from the critical utility and value of chiral substances both as substrates for research and as end products of interest and of commercial value. The ability to *produce* chiral substances from achiral ones—the result of resolution—broadens experimental possibilities by making available optically active substances not found in nature's cupboard.

Many chemists agree that, unlike many other unit processes, the carrying out of resolutions is still very much an art, in which trial and error is the principal experimental approach.

This survey was undertaken, in part, because of this author's conviction that the remedying of this condition must begin with a thorough survey of resolutions and an assessment of whatever principles are known which govern resolutions. I hope to convince my fellow chemists that research in this area is needed, and is in fact worthwhile, so that ultimately resolutions, like many other unit processes, will be less of an art and more of a science.

II. OPTICAL ACTIVATION AND TYPES OF RESOLUTIONS

The period since the most recent reviews of resolutions (see the General References) has been characterized by the introduction of a wide variety of new resolving agents and by much experimentation with nonclassical resolution procedures, particularly involving the use of chromatographic techniques. At the time of writing of this review, chromatographic techniques do not yet constitute practical methods for preparative resolutions except for isolated cases—often for the production of only partially optically pure compounds on a small scale. However, active work in the development of chromatographic resolution procedures may change this situation before long.

For the moment, the much wider array of resolving agents now available has enriched the scope and potential success of classical resolution, i.e., procedures involving enantiomer separation *via* conversion into diastereomeric covalent compounds or salts which constitute the principal subject of this review.

The important practical methods for the production of optically active compounds are:

1. Spontaneous resolution by crystallization.

2. Resolution *via* diastereomer formation.
3. Enzymatic optical activation.*
4. Kinetic resolution.
5. Chromatographic resolution.
6. Asymmetric synthesis.
7. Stereospecific synthesis from chiral precursors.

The first three of these resolution processes are the classical ones all of which were discovered by Pasteur over 100 years ago (1).

Spontaneous or induced crystallization of optically active compounds from solvents remains an important technique. A review appeared in 1963 (2). At one time, the number of such resolutions known was quite small and they were considered extraordinary. This is no longer the case. A micro-diagnostic method utilizing the unique properties of liquid crystals permits prediction of spontaneous resolutions *via* crystallization (3). Crystallization of a preponderance of one enantiomer by inoculation has been accomplished in a fair number of instances, particularly for amino acids. The entrainment technique (see p. 157), is evidently generally applicable (4). In the spontaneous crystallization of one enantiomer, adventitious seeding may be responsible for its occurrence (5).

A noteworthy application of resolution by mechanical separation of single crystals is the isolation of chiral heptahelicene described by Martin and co-workers (6). The extraordinarily high optical rotation of these substances makes this process relatively simple even for chemists who are not trained crystallographers (7). The same procedure has been applied by Wynberg and Groen to the resolution of thieno heterohelicenes (8). Spontaneous resolution by crystallization of a cumulene (9) and of a chiral organoboron compound containing an asymmetric boron atom (10) is also of interest.

Resolution *via* diastereomer formation, the most widely applied of the classical resolution procedures, has been reviewed most recently by Eliel, by Theilacker, and by Velluz (General References). This is the main subject of the present review (Sect. III, V, and VII).

A most significant long-term trend is the increasing use of enzymatic optical activation† for the preparation of macro amounts of optically active

* *Optical activation* is the most general term describing methods for securing one enantiomer of a compound in excess of the other. *Optical resolution*, or commonly *resolution*, refers to optical activations which originate with racemic compounds and, in a strict sense, which do not involve the incorporation of new atoms or groups (including all or part of the resolving agent) in the *desired* chiral compound.

† Biochemical asymmetric synthesis and asymmetric destruction. The latter is properly a resolution.

substances of interest to biochemists and to organic chemists. This development has reduced appreciably the need to experiment with classical resolution procedures and in any event has made accessible compounds, such as deuterium-labeled compounds, whose low activity virtually precludes practical resolution by other methods, of amino acids, of glycols, and of steroids. Extensive reviews of some of these methods have appeared (deuterium compounds, refs. 11,12; amino acids, ref. 13); biological optical activations are not treated in this review.

Kinetic resolutions of preparative interest are discussed in Sect. IV.

Research in the application of chromatographic techniques to resolutions is now (1970) so extensive that separate reviews of the field are in order. Several such reviews have appeared (14-19).

In summary, two general techniques are available for resolution *via* chromatography. The first, formation of diastereomers by acid-base reaction, condensation, or complex formation, is followed by chromatographic separation of the diastereomeric mixtures. This procedure is simply an extension of the methods discussed in Sects. III and V of this review in which a difference in affinities for surfaces (adsorption) or a difference in solubilities (partition) replaces another kind of difference in solubilities (heterogeneous equilibrium) to permit separation of diastereomers.

The second, and more difficult, chromatographic resolution process requires stereoselective sorption of enantiomers on, or in, chiral chromatographic columns. Both of these processes may be utilized with all the common modes of chromatographic separation, viz., column adsorption chromatography, gas chromatography, thin-layer chromatography, liquid and ion-exchange chromatography, and countercurrent distribution.

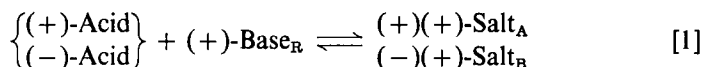
Asymmetric syntheses constitute another large group of reactions much utilized in the optical activation of many classes of organic compounds. This group of reactions is the subject of several recent reviews (20-23) and consequently is not reviewed here.

The seventh type of optical activation, stereospecific syntheses from chiral precursors, is closely woven into the fabric of organic synthesis. Discussion of such syntheses is realistically out of place in this review.

III. RESOLUTION VIA DIASTEREOMER FORMATION

Conversion of mixtures of enantiomers into diastereomers by reaction with chiral reagents constitutes the principal conventional—or classical—and practical resolution method.

Equilibria typified by equation [1] describe resolutions *via* diastereo-



mer salt formation. Covalent diastereomeric compounds formed under non-equilibrium conditions are alternative products of conventional resolutions and, with the wide range of resolving agents now available, these are increasingly involved in resolutions. The availability of mild cleavage procedures, e.g., the use of lithium aluminum hydride in the recovery of chiral alcohols from one of the separated diastereomeric esters, often determine the practicability of such resolutions.

Principal desirable features of conventional resolutions of type [1] are: (a) ready availability and stability of the resolving agent, here the $(+)\text{-Base}_R$ (other desirable properties for resolving agents are given below); (b) complete and preferably rapid reaction under mild conditions which are nondestructive to either substrate or resolving agent; (c) easy isolation of the product mixture with minimal loss; (d) easy and complete separation of the diastereomeric product mixture in high yield; (e) facile and complete reversal of the equilibrium to the desired optically active compound under conditions minimizing racemization; (f) isolation of both enantiomers, each optically pure; and (g) recovery in high yield and reuse of the resolving agent should be facile.

Rarely do resolutions meet even a majority of these seven desirable features. Feature (d), in which differential solubility of diastereomers is the property utilized virtually exclusively,* is the one feature most difficult to achieve. In fact, diastereomers, whether salts or covalent compounds, may not crystallize at all. Even when crystalline, they occasionally completely resist separation.†

An additional set of difficulties encountered in resolutions relates to possible racemization during diastereomer cleavage and, not infrequently, hydrolytic or disproportionative decomposition in workup.

Any optically active substance may, in principle, be utilized in the separation of racemic substances into their enantiomers and hence serve as a resolving agent. The principal limitation restricting the use of chiral substances universally as resolving agents is the need for appreciable interaction

* Formation of covalent diastereomeric mixtures, in particular as in the resolution of alcohols through their esters with optically active acids, makes readily apparent the fact that resolutions are often a consequence both of a solubility difference between the diastereomeric components of the mixture *and* of a reaction rate difference (see Sect. IV). Analysis of crude diastereomeric ester mixtures by nmr spectroscopy (p. 118) clearly shows that the two possible esters formed are present in unequal concentrations; in effect, a partial kinetic resolution has taken place when reaction is incomplete (24).

† An occasional finding is that a double salt of a racemic substrate with a resolving agent is less soluble than that of one of the enantiomers of the substrate with the resolving agent. In the case of colchinel methyl ether, this situation completely prevented resolution from succeeding with a variety of resolving agents (25).

between the resolving substance and the one being resolved (the substrate)—interaction which must be diastereomeric and readily reversible. Interaction may involve salt or compound formation, formation of a π complex, of an inclusion compound, or the interaction may be transient—though no less real—as in the case of chromatographic resolutions.

Other desirable features of resolving agents are: ease of preparation or low price and stability of supply, if commercially available; availability in a state of high optical purity; stability under conditions of use and of storage; low cost or ease of reuse with minimal loss in optical purity.

The optical purity of a resolving agent* directly determines the maximum optical purity attainable for the substrate in a resolution. This is a direct consequence of the operation of the Marckwald principle (p. 113) since, in effect, with an optically impure resolving agent, both enantiomers of the latter are performing counterproductive resolutions simultaneously (26).

As long as resolving agents were naturally occurring, this point was academic. However, now that synthetic resolving agents and semisynthetic ones, i.e., natural products modified synthetically and hence possibly partially racemized, are commonly used, it becomes a matter of much greater concern just how enantiomerically pure a resolving agent is. A practical related problem is the absence, in some cases, of reliable optical rotation data for the optically pure resolving agents.

Until fairly recently one had to be satisfied with the limited number of naturally occurring resolving agents, principally acids and bases, which above all met the condition of ready availability.

The literature of the last 10 to 15 years attests to the widespread use of a greater variety of resolving agents than before. Many fully synthetic or natural product-derived resolving agents have been prepared and tried out in resolutions, often without establishing whether they are generally useful. For example, use of α -methylbenzylamine, a fully synthetic resolving agent, is now very common. This compound and many analogs are readily resolved with tartaric acid (27); both enantiomers of α -methylbenzylamine are commercially available.

* *Enantiomeric purity* of a chiral substance is defined rigorously in eq. [2]:

$$\% \text{ enantiomeric purity} = \frac{M_+ - M_-}{M_+ + M_-} \times 100 \quad [2]$$

where M_+ is the mole fraction of the dextrorotatory enantiomer (here the predominant one), and M_- the mole fraction of the levorotatory one. The *optical purity* of the same substance, an experimentally measured quantity, is defined in eq. [3] and is equivalent to enantiomeric purity:

$$\% \text{ optical purity} = \frac{[\alpha]_{\text{mixture}}}{[\alpha]_{\text{one enantiomer}}} \times 100 \quad [3]$$

The two terms are generally used interchangeably (see p. 117).

Use of synthetic resolving agents implies the possibility of designing such reagents in order to meet more of the desirable features of resolutions outlined above. A further key advantage in the use of synthetic resolving agents was identified by Marckwald in 1896 (28) as the possibility of obtaining both enantiomers of a given compound in a resolution if both enantiomers of the resolving agent were available. If $(\pm)$ -A could be resolved with $(+)$ -B, the less soluble diastereomer being $(+)$ -A $(+)$ -B, then $(+)$ -A would be recovered in the resolution. Similar resolution of $(\pm)$ -A with $(-)$ -B would then perforce yield $(-)$ -A $(-)$ -B as the less soluble product from which $(-)$ -A could be recovered. To illustrate, in eq. [1] (p. 111) $(-)$ -Base_S could have been used as well. This procedure is often applied to the mother liquor of the first of these two complementary resolutions both for economy and because partial enrichment of the mother liquor in the desired second enantiomer facilitates the procedure.

The *Marckwald principle* could seldom be applied until fairly recently, since virtually all resolving agents were naturally occurring and hence, particularly for alkaloids, available in only one enantiomeric form.* The few synthetic resolving agents known were too difficult or expensive (e.g., the above-mentioned α -methylbenzylamine) to resolve to make them readily available for application of this procedure.

It is significant that, whereas a given mixture of enantiomers may be resolved *equally well* with *either* enantiomer of a resolving agent (Marckwald principle), *reciprocity* does not operate in resolutions, i.e., if a given resolving agent $(-)$ -A serves to resolve a particular mixture of enantiomers $(\pm)$ -B, it is not required that one of these enantiomers (optically enriched or pure), e.g., $(+)$ -B, necessarily serves as resolving agent for $(\pm)$ -A (30a).

The explanation for the difference between these two situations lies in the fact that in the first case (Marckwald principle), the relationships between the product sets are enantiomeric and hence equally possible. In the second case (reciprocity), the relationships of the product sets are not enantiomeric but rather are diastereomeric to the products in the first case, and hence not equally probable. This is shown in Figure 1.

* An interesting observation by Woodward et al. (29) corresponds to the possibility of applying a quasi-Marckwald procedure to resolutions with a pair of *alkaloidal* resolving agents. Quinine and quinidine are enantiomeric in the vicinity of the basic nitrogen atom responsible for salt formation (see N_a in **22** and **23**; p. 134). Cinchonine and cinchonidine are a similar pair of "quasi-enantiomeric" alkaloids. In accord with the Marckwald principle, it would be reasonable to expect that the quinine salt of a given enantiomer of an acid might have opposite solubility to the quinidine salt of the opposite enantiomer of this acid.

While some examples of the applicability of this suggestion could be adumbrated (e.g., ref. 29), this approach is clearly of limited use since such pairs of readily accessible alkaloids, other than the four compounds cited, are rare.

(a) Resolving Agent	"Marckwald" Products
$\begin{array}{c} (+)B \\ (-)B \end{array} \times \frac{(+)A.(+)B \text{ \& } (-)A.(+)B}{(-)A.(-)B \text{ \& } (+)A.(-)B}$	mirror images
(b) Resolving Agent	"Reciprocity" Products
$\begin{array}{c} (-)A \\ (+)B \end{array} \times \frac{(-)A.(+)B \text{ \& } (-)A.(-)B}{(-)A.(+)B \text{ \& } (+)A.(+)B}$	not mirror images

Fig. 1. Comparison of products of "Marckwald" and of reciprocal resolutions.

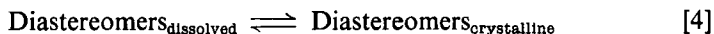
The design of reciprocal or quasi-reciprocal resolutions on the assumption that reciprocity does hold *in theory* is erroneous. In one reported case, resolutions designed in this way failed (31).

While not required, such reciprocal resolutions are nonetheless not forbidden and are in fact fairly common. An example is the resolution of glutamic acid with $(-)$ -2-amino-1-butanol and the reciprocal resolution of the butanolamine with $(+)$ -glutamic acid (32). The advantage of a reciprocal resolution is well illustrated by the resolution of *N*-acetyltryptophan with α -methylbenzylamine and its reciprocal. From 60.5 g of $(-)$ - α -methylbenzylamine, 12.5 kg of *N*-acetyl-L-tryptophan and 8.6 kg of $(-)$ -amine were obtained in seventeen consecutive reciprocal resolutions (33).*

A. Principles

Attempts at rationalizing resolutions are beset by too many as yet unpredictable and hence uncontrollable variables. It would seem that the choice of resolving agent should be the controlling variable. The conditions of resolution, particularly the solvent, are in fact critical to the success of the operation.

Recall that two equilibria obtain in classical resolutions, one a homogeneous one, viz., eq. [1] above, and [4], a heterogeneous one that operates when, as is typically the case, separation of diastereomers is carried out by crystallization.



The choice of solvent, particularly with respect to this second equilibrium, is an unpredictable variable.

* Part of this improvement was due to the operation of the Pope and Peachey procedure (see p. 131).

An interesting point, made by Stewart and Allen in 1932, is that, for resolution *via* diastereomeric salts, formation of *crystalline salt* is ordinarily necessary for resolution in practice. Equilibrium [4] may not be bypassed; partitioning of diastereomeric salts between two immiscible liquids does not usually achieve resolution (34). Covalent diastereomers are often separable by partition chromatography, however.

In spite of the general feeling that empiricism is the main principle governing resolutions—the amazing thing about classical resolutions is that they have been so successful while being so empirical—some useful guiding comments may be made to assist in the selection of conditions for success. It seems that experimenters have been guided more by availability of, or by customary use of, particular resolving agents than by otherwise obvious considerations such as those of acid and base strengths which ought to be of some concern in salt-forming resolutions, i.e., the most common type.

The use of weak bases to resolve acids of moderate strength, and the converse, is far from exceptional* and, predictably, this can lead to difficulties, i.e., salt formation may not occur at all or, if incomplete, the salts may not precipitate. It is recognized that the quantitation of this argument is difficult since most acidity/basicity data are framed within an aqueous medium system while resolutions seldom are carried out in water. The basic argument, which has been pointed out earlier by Theilacker (35) and has, in fact, been known for over 60 years (36), is valid nonetheless. Recent successes in resolutions with resolving agents such as ephedrine, amphetamine, α -methylbenzylamine, and dehydroabietylamine are probably due in part to their having greater strength as bases than do the principal alkaloid bases.

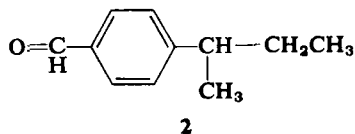
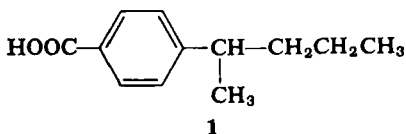
Woodward and co-workers (29), have proposed that resolutions which depend on separation of diastereomeric salts by crystallization are more likely to succeed when the acidic and basic functional groups responsible for salt formation are proximal in space “to those factors which render each asymmetric.”† Diastereomer salt differences are more likely to be maximized in such cases. It was pointed out that, e.g., the use of acid succinates in alcohol resolutions, where the carboxyl group is more than one or two carbons removed from the asymmetric carbon or other site of chirality of the alcohol, would make such resolutions difficult.

Cram has described a resolution which seems to bear out the principle above (37). The key step in the optical activation of 2-phenylpentane, involved the resolution of 4-(2'-pentyl)-benzoic acid (**1**). The acid **1** was chosen

* The classical alkaloid resolving agents brucine, strychnine, quinine, and analogs are relatively weak bases ($pK_b \sim 6$).

† This observation is apparently a very old one and has been regarded by some as a well-known fact (171). However, the statement of it by Woodward et al. may well be the first in print.

because locating the carboxyl handle closer to the asymmetric carbon in the molecule proved synthetically prohibitive. Although the resolution was successful, 24 recrystallizations were required to achieve separation of the



diastereomeric salt. The problematic resolution of *p*-sec-butylbenzaldehyde (2) with α -methylbenzylamine bisulfite (38a) may suffer from the same defect.

Availability of additional polar or polarizable groups, in close juxtaposition to the key functional group in a resolving agent, which permit two, and preferably more, point contacts in the diastereomer formed on reaction with the substrate is likely to be as important as closeness of the chiral center to the functional group of the resolving agent. Interaction, i.e., solvation, by hydrogen bonding, charge transfer, π -complex formation, and the like, are evidently responsible for differentiation of corresponding nuclei in enantiomers by nmr spectroscopy in chiral solvents (see, e.g., (39)). Differentiation fails when such interactions are not strong, e.g., when chiral hydrocarbons are used as solvents.

Dalgliesh has postulated that, in paper chromatographic resolutions, enantiomer molecules must be able to contact the optically active adsorbent at least at three points in each molecule if they are to be resolved (40). It is suggested that precisely the same kinds of interactions are likely to enhance differentiation of diastereomers, whether salts or covalent compounds, particularly in crystal lattices where multiplication of interactions lead to macroscopic effects directly useful in separation.

Resolving agents containing aromatic rings, e.g., α -methylbenzylamine, hydroxyl groups, e.g., tartaric acid, or other polar groups and combinations thereof, e.g., *O,O'*-dibenzoyltartaric acid, are likely to fulfill the requirements for multiple interaction with many substrates and so be generally useful as resolving agents. Rigid multifunctional molecules like brucine evidently meet the same requirements. On the other hand, it is suggested that chiral compounds which are completely devoid of groups permitting two or three point contacts are unlikely to be broadly useful resolving agents. Compare, for example, the resolving power of two inexpensive and easily resolvable compounds, 2-aminobutane and 1-amino-2-butanol: the latter is much more useful.

It may be that the pursuance of a rational approach to resolutions is untimely. Although chromatographic resolutions are not yet generally useful on a preparative scale, it is possible, perhaps likely, that they soon will

be.* Being conservative in my estimate of the time scale of this development, I feel that research on nonchromatographic resolutions is still worthwhile.

B. Experimental Techniques in Resolution

Resolutions are often beset by practical problems and by experimental difficulties. The following techniques may assist in reducing the tedium of resolutions, increase the chance of success, and make the assessment of the *optical enrichment*† attained more accurate.

Since more than one resolving agent must usually be employed in resolution trials, and availability and cost of materials dictate economy, it is desirable to work on a small scale (0.001 mole) and to use a systematic procedure for preliminary tests to establish which resolving agent and solvent combination yields the best results. Such a procedure has been developed by Fredga and used by him and his students routinely to good advantage (41).

For the resolution of natural products prepared in racemic form through total synthesis, it has been suggested that it is advantageous to explore salt-forming properties of the naturally occurring, hence optically active, material with various resolving agents before initiating the resolution of the synthetic material (29).

Many laboratories now have reliable photoelectric polarimeters‡ which are simple to operate and have greatly reduced the tedium necessarily accompanying the measurement of optical rotatory power during all resolutions. Moreover, most photoelectric polarimeters allow measurement of rotation at wavelengths shorter than the traditional sodium D line (589 nm). This is desirable since rotations of chiral compounds at the D line are often quite weak and occasionally fortuitously zero. Rapid measurement at lower wavelengths is therefore an asset in resolutions. Spectropolarimeters, if available, may also be used for this purpose. Photoelectric polarimeters may also

* For an example of such a resolution, see p. 145.

† This is the gradual increase in optical purity of the substrate being resolved which occurs in a resolution. If M'_+ is the mole fraction attained for the dextrorotatory enantiomer (p. 112):

$$\text{enantiomeric enrichment} = \frac{M'_+ - 50}{50} \times 100 \quad [5]$$

The term is quantitatively equivalent to enantiomeric purity, i.e., an enantiomeric enrichment of 80% achieved in a resolution corresponds to the attainment of 80% enantiomeric purity.

Optical enrichment, measured polarimetrically, is assumed to correspond to *enantiomeric enrichment*, just as optical purity generally is equivalent to enantiomeric purity. This parallelism is not universal for either enrichment or purity (42).

‡ Such instruments are manufactured by, e.g., Bellingham and Stanley, Bendix, Hilger and Watts, Jeolco, Jouhan, Perkin-Elmer, Stanley, and Zeiss.

permit the measurement of optical rotation in deeply colored solutions. This may be difficult to do visually in manual polarimeters.

It is a far from uncommon finding that recrystallization of a diastereomer mixture leads to limiting optical enrichment.* Indeed, in classical resolutions, this has usually been deemed to be the criterion of complete resolution. Cases are known in which changes in rotation during recrystallization of diastereomer mixtures cease when the compound of interest is far from being sterically pure. Instructive examples are given in ref. 43.

Professor A. Fredga has kindly pointed out to this author in a personal communication that if attainment of optical purity is desired in a resolution, then application of the Marckwald principle (p. 113) may lead to erroneous results if changes in rotation cease for both enantiomers of the desired product prior to attainment of optical purity. On the other hand, if the two enantiomers of the desired product are obtained with *different* resolving agents, or by independent methods, and the same numerical value for the optical rotation is obtained, this constitutes a very good criterion for complete resolution, i.e., optical purity. For that reason, Professor Fredga has avoided, as far as possible, the use of both enantiomers of a base for resolving one acid. Should application of independent methods for determining optical purity (see below) become commonplace, this limitation would, of course, be removed.

Completeness of resolution, i.e., attainment of optical purity, can be assessed by monitoring the progress of the resolution and by direct determination of the optical purity of the product at its conclusion. Monitoring has been carried out by thin-layer chromatography (to follow the disappearance of one diastereomer) (e.g., 44), or similarly for volatile diastereomers by gas chromatography (45). Nuclear magnetic resonance spectroscopy is a very powerful resolution monitoring tool. The progress of a resolution is marked by the disappearance of some peaks due to diastereotopic atoms, typically protons, in the diastereomeric mixture undergoing enrichment (46).†

Quantitation of these procedures permits the determination of the optical purity of the product of a resolution. In the case of substances for which literature rotation data are available, optical purity is often determined polarimetrically. If the literature data are reliable, and precision no greater than $\pm 2\%$ is sufficient (47), this is satisfactory. Otherwise, a direct determination of optical purity, e.g., by gas chromatography, should be carried

* Neither melting points nor rotations of diastereomers are as reliable as the recovery—on a small scale, if necessary—of the desired enantiomer and the measurement of its rotation (see, e.g., 43c).

† This technique has so far been limited to covalent diastereomers; however, this point warrants investigation.

out. Methods for the determination of optical purity have been reviewed by Raban and Mislow (48; see also 24, 39).*

Crystallization techniques employed in resolutions run the gamut from repeated recrystallization of the originally formed diastereomer mixture *via* a triangular scheme (49,50),† or *via* the double withdrawal technique (51), to isolation of a fully resolved diastereomer, sometimes in only one recrystallization (e.g., 52).‡

Low-temperature crystallization (49c) of difficultly crystallized, oily or unstable diastereomers is occasionally utilized in resolutions. The original partial resolution of *trans*-cyclooctene *via* the diastereomeric *trans*-dichloro-(*trans*-cyclooctene)-(1-phenyl-2-aminopropane)-platinum(II) complexes was carried out by fractional crystallization at about -20° . Both the less and the more soluble diastereomers are oils at room temperature (53).

An apparatus and procedure for low-temperature crystallization and conversion of salts into free amines has been described (34).

In a variant of the recrystallization procedure, due to Kantor and Hauser (55), the diastereomeric salts are formed in an insufficient amount of solvent to dissolve the solid products at reflux. Prolonged refluxing of this heterogeneous mixture apparently is accompanied by continuous recrystallization and concomitant optical enrichment. After isolation of the diastereomer salt mixture, the number of recrystallizations required to attain optical purity is appreciably reduced and the yield potentially increased. While this method would seem to be generally applicable, it has been little used (56).§

Leaching of diastereomer mixtures with cold solvent can lead to optical enrichment (58a).

Solubility differences between a racemate and the individual enantiomers of a substance may often be appreciable when the former is a racemic compound rather than a mixture. Consequently, following partial resolution, e.g., *via* diastereomers, the resolving agent-free mixture may be separable into racemate and enantiomer by selective solubilization, especially in the presence of a hydrogen bonding agent. Leigh has described several cases of efficient optical enrichment by this procedure (58b).

Increasingly, covalent diastereomeric mixtures formed in resolutions are separated chromatographically rather than by recrystallization. This is particularly expedient if the mixture is originally an oil. Not uncommonly, the

* In critical studies, the resolving agent should be checked for optical purity particularly if it has been recovered from a previous resolution. See the discussion on p. 112.

† The triangular method is more efficient than a linear sequence of recrystallizations.

‡ A perseverance record of some sort may well belong to the "resolute" workers who performed 159 recrystallizations of the salt of cinchonidine and 2-chlorobutanoic acid in the resolution of the latter (54).

§ An improvement in the original resolution of 2-butanol using the Kantor-Hauser procedure has been described (57).

eluted diastereomer fractions yield crystalline products which are readily further purified, and optically enriched, by recrystallization. This was the case in the resolution of bisnor-onocerandiol through the (–)-menthoxyacetate esters (59).

Ion exchangers have been increasingly applied to the cleavage of diastereomeric salts after resolution to effect recovery of the desired enantiomer in lieu of acid–base reactions (60). Some advantages of this procedure have been discussed by Tocanne and Asselineau (60d).

Optical enrichment of enantiomers by crystallization after isolation from the diastereomer product of resolution is a fairly common variant of the spontaneous or induced resolution by crystallization method. For example, in the resolution of 3-phenylbutanoic acid with (+)- α -methylbenzylamine (61) the optical purity of the isolated acid is appreciably enriched (from 57 to 76%) by seeding a petroleum ether solution of partially enriched acid with ($\pm$)-crystals, and removing racemate which subsequently crystallizes.

Both seeding* with one of the enantiomers and recrystallization without seeding are alternatives to the above. For example, (+)-2-(5-carbethoxypentyl)-4-thiazolidone, the more soluble isomer isolated in the resolution with brucine, was enriched from $[\alpha]_D^{25} + 31^\circ$ to 57° by one recrystallization from water (63).

Occasionally, a nondiastereomeric derivative of the optically enriched enantiomer is employed for further enrichment by recrystallization. An example is found in the resolution of *threo*-2,5-dimethyl-4-phenyl-3-hexanol with brucine on the acid phthalate of the alcohol. Purification of the enriched but optically impure alcohol, an oil at room temperature, was carried out by recrystallization of the crystalline *p*-nitrobenzoate derivative (5).

Optical fractionation, i.e., optical enrichment which usually occurs during recrystallization, must occasionally be avoided—as in cases where the product of an asymmetric synthesis is to be assessed for extent of optical activation, or in mechanistic studies where the extent of retention–inversion–racemization is significant. In such cases, purification of the product before determination of optical purity may have to be avoided altogether owing to potential optical fractionation. The assertion that distillation is a nonenriching purification process (43b) may not be subscribed to generally in view of the results of Nerdel and Diepers (64) (see p. 130).

IV. KINETIC RESOLUTIONS

Two of the types of kinetic asymmetric transformations (65) by which resolutions (in the limited sense defined on p. 109) may be carried out are

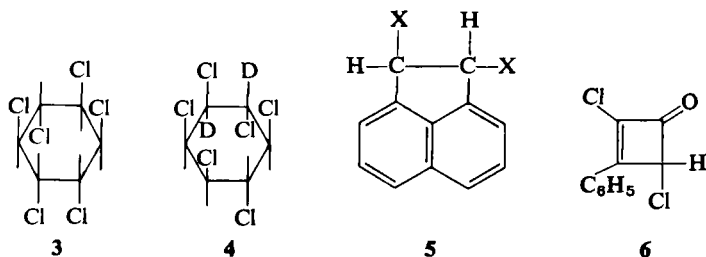
* For the case of diastereomeric salts, the importance of seeding with an optically pure specimen has been pointed out by Read and Reid (62).

asymmetric construction and asymmetric destruction. Both processes are closely related to asymmetric synthesis (p. 110) in the sense that, for all three, diastereomeric transition states rather than diastereomeric ground states of products govern the optical enrichment obtained.*

Reactions of racemic mixtures with chiral agents lead to the accumulation of an excess of one of the enantiomers of the starting compound provided the reaction is interrupted prior to its completion. This is a consequence of the involvement of diastereomeric transition states in such reactions, which in turn govern the relative rates of reaction of the enantiomeric substrate. Salt-forming reactions are excluded here because they are generally quite rapid; their transition states are not likely to differ appreciably in energy for diastereomer salt-forming reactions.

Optical enrichment is a consequence of the difference in rate of reaction of enantiomers with chiral reagents, but high optical purity is rarely attained. Nonetheless, kinetic resolution is a useful method, particularly the asymmetric destruction approach, for types of molecules whose functional groups make diastereomer salt or covalent compound formation or its reversal difficult.

The largest group of compounds resolved by asymmetric destruction is that of halogen compounds devoid of convenient handles for conventional resolution. A classic case is the resolution of α -benzene hexachloride (**3**), with brucine (67). Insufficient brucine was utilized so that dehydrochlorination



would be incomplete. The unreacted **3** was recovered optically enriched in the (–)-enantiomer. In this and some other, but not all, cases, the object of the asymmetric destruction was determination of configuration. *dl*-2,3-Dibromobutane was differentiated from *meso*-2,3-dibromobutane by resolution with brucine (68a). The configurations of δ -1,2,3,4,5,6-hexachloro-1,2-dideuteriocyclohexane (**4**) (69) and of the haloacenaphthene derivatives (**5**) (X = Br, Cl) (70), were established in the same way.

* Kinetic resolution and asymmetric synthesis are sometimes arbitrarily excluded from the definition of "chemical resolution" (66).

Halogen compounds potentially resolvable through conventional resolution, in view of the presence of reactive functional groups such as hydroxy or carbonyl, are occasionally resolved by asymmetric destruction for convenience, especially if partial resolution is adequate for the purpose required, e.g., for mechanistic studies. Examples: *threo*-3-chloro-2-butanol (68b) and *threo*-3-iodo-2-butanol (71); and halobutenones such as **6** (72) were both resolved with brucine. The method is not uniformly successful; the asymmetric destruction of *trans*-2,6-dibromo-cyclohexanone with brucine did not lead to optical enrichment (73).

Carboxylic anhydrides, particularly of the paracyclophane type (74,75), and of metallocene carboxylic acids (76) have been resolved by asymmetric destruction (typically hydrolysis) with brucine or with α -methylbenzylamine.

Methyl-1-naphthylphenylmethoxysilane was reduced to methyl-1-naphthylphenylsilane with a (+)-quinidine-lithium aluminum hydride complex by a combination of asymmetric synthesis and destruction: unreacted starting material and product were both optically enriched (77).

Amines (by partial sulfonylation with (+)-camphor-10-sulfonyl chloride) (78), a Grignard reagent (2-phenylbutylmagnesium chloride, by partial reaction with chiral ketones such as (–)-fenchone) (79) and alkylidene-phosphoranes (by incomplete reaction with chiral acyl halides) (80) undergo partial kinetic resolution. An ozonide has been partially resolved through asymmetric destruction with brucine (81).

Asymmetric destruction remains an important method for the optical activation of allenes. For example, 1,3-dimethylallene is enriched to *ca.* 12% optical purity by partial hydroboration with (+)-*sym*-tetra-3-pinanyldiborane (82).

It should be recognized that some of the examples cited have been of compounds possessing more than one chiral center and that reaction with the chiral agent most likely involved the destruction of just one of these centers. The products, if chiral, have undoubtedly been optically active themselves (although this was not established as a rule). One is dealing here with the converse of asymmetric synthesis where a chiral center is usually formed in the vicinity of a second chiral center already present in the molecule or externally introduced but involved in the transition state. Analysis of the asymmetric dehydration of achiral alcohols such as *trans*- or *cis*-4-methylcyclohexanol with (+)-camphorsulfonic acid in terms of asymmetric selectivity and kinetic resolution together being responsible for the optical enrichment of the product chiral alkenes clearly shows, as expected, that most of the enrichment is due to asymmetric selectivity (83).

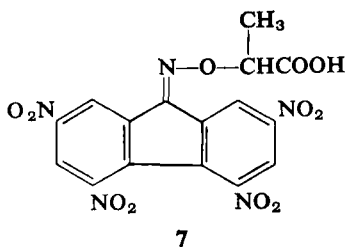
True asymmetric destruction would involve resolution of, e.g., compounds possessing but one asymmetric center. Propylene bromide and 2-bromobutane have been resolved by asymmetric destruction with brucine

(68a); the pentaatomic bromochlorofluoromethane has also been resolved in this manner (84a).*

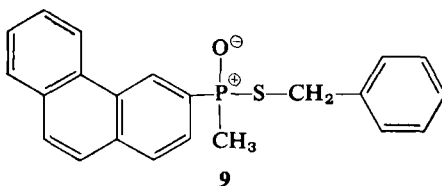
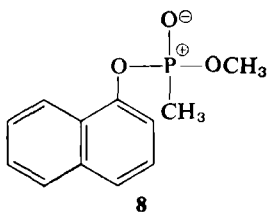
V. RESOLUTION VIA MOLECULAR COMPLEXES, METAL COMPLEXES, AND INCLUSION COMPOUNDS

A. Resolution via Molecular Complexes

The rational selection and synthesis of a chiral Lewis acid capable of forming crystalline molecular or π complexes (85,86) with racemic Lewis bases has led to the resolution of a variety of organic substances. α -(2,4,5,7-Tetranitrofluorenylideneaminoxy)-propionic acid (7), or TAPA, whose synthesis and resolution have recently been described in detail (87), was originally used in the resolution of 1-naphthyl *sec*-butyl ether and of methyl α -(1-anthracene)propionate (88) *via* separation of the crystalline diastereomeric complexes.†



It has since been utilized in the resolution of phosphorus ester derivatives 8 and 9 (89).



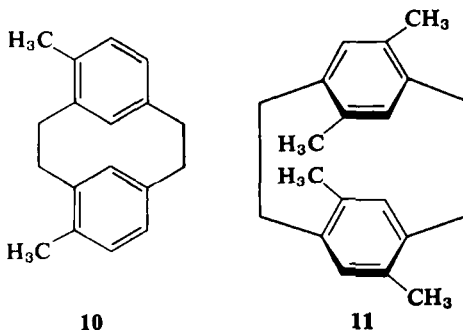
The most dramatic use of the TAPA reagent is in the resolution of

* Hassel (84b) has suggested that chiral haloforms may be resolved through addition compound formation with suitable optically active amines. This may, in fact, be the mechanism of the cited resolution of bromochlorofluoromethane.

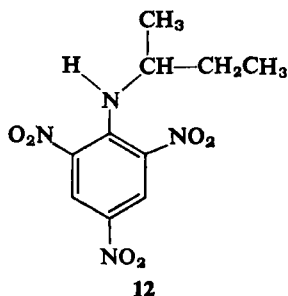
† Oximes may be resolvable through formation of aminoxy derivatives like 7.

aromatic hydrocarbons devoid of functional groups which exhibit dissymmetry caused by molecular overcrowding or by restricted rotation. The best known of these resolutions is that of hexahelicene (88a,90).*

The resolutions of 1-fluoro-12-methylbenzo[*c*]phenanthrene (91), the 1- and 2-methylcholanthrenes (92), and pentahelicene (93), with TAPA, have been described. Two cyclophanes, 4,14-dimethyl[2.2]metacyclophane (**10**) (94), and the tetramethyl[2.2]paracyclophane (**11**) (95), have also been resolved by means of TAPA.



The chiral π -acid *N*-*sec*-butylpicramide (**12**) is another potential complex-forming resolving agent (88a), itself resolved *via* the π -complex with (+)-2-naphthylcamphylamine (96). It does not seem to have been utilized in other resolutions.

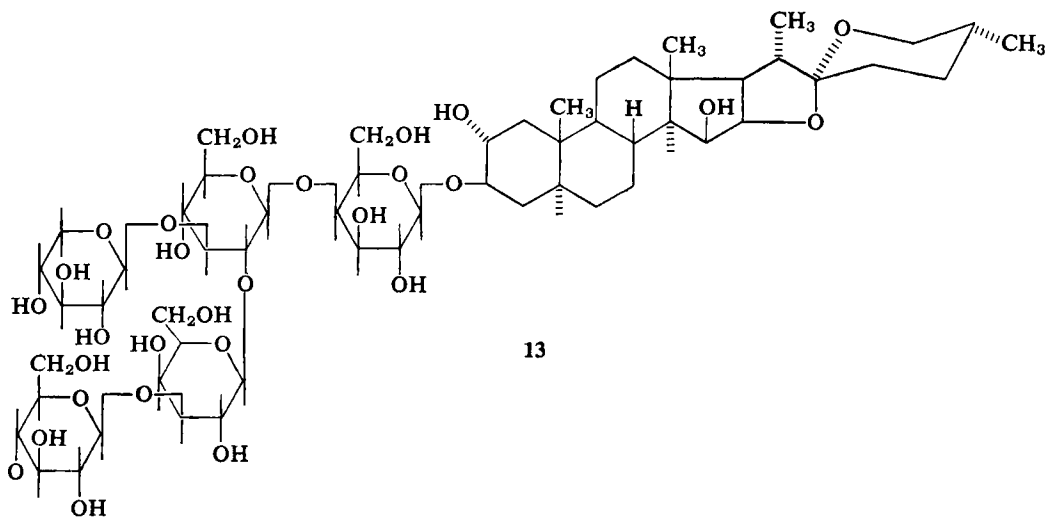


Less well-defined complexes, some undoubtedly also of Lewis acid-base type, have found some use in resolutions. A noteworthy example is the facile resolution of α -methylbenzylamine with (+)-2,3,4,6-tetra-*O*-acetyl-D-glucose

* In this resolution, the diastereomeric π -complexes are evidently in equilibrium with their component parts. The more stable complex remains in solution and the less stable one dissociates and deposits its chiral hydrocarbon component. Compare the resolution of heptahelicene by spontaneous crystallization (p. 109).

(97). Only one recrystallization of the adduct* is required since the glucose derivative combines exclusively with the (+)-form of the amine (60d).

Several alcohols, e.g., 1,2,3,4-tetrahydro-2-naphthol and terpineol, have been resolved through complex formation with digitonin (**13**) (98), a proce-



cedure developed evidently as a byproduct of the use of this substance in the isolation of sterols *via* formation of 95% ethanol-insoluble digitonides (1:1 molecular complexes) (99). A more recent use of digitonin is in the resolution of methyl β -hydroxy- $\Delta^{4,9,11,16}$ -etiocholatrienate (100).

The nucleoside inosine (hypoxanthine riboside) has been used in the resolution of the amino acid tryptophan through formation of a molecular compound (101).

B. Resolution via Metal Complexes

Over 30 years ago, Bailar suggested that chiral organic compounds which act as ligands in transition element complexes might be resolved *via* preferential—diastereomeric—coordination (102). Optically active chelates of copper(II), nickel(II), or cobalt(III) have since been utilized in the partial resolution of, e.g., carboxylic acids (103), and diamines, amino acids, and dicarboxylic acids (104).† These resolutions and others of a similar type have been reviewed (105).

* Whether the (1:1) adduct is a “complex” or is instead a lattice host clathrate, as suggested by Mislow (30b), may be a moot point. Further study seems to be required to settle this point.

† Some of these resolutions are kinetic resolutions.

Much more practical descendants of this type of resolution are the unprecedented resolutions of alkenes through their diastereomeric complexes with platinum(II). Simple chiral 1-alkenes such as 3,4-dimethyl-1-pentene (106), as well as cycloalkenes rendered chiral by restricted rotation in a sufficiently small ring, e.g., *trans*-cyclooctene (**15**), have been resolved by this extraordinary method.

The complex is constructed in two steps beginning with potassium tetrachloroplatinate(II), K_2PtCl_4 , and ethylene. Replacement of one chlorine ligand by ethylene is followed by replacement of a second chlorine ligand by a chiral amine, e.g., 1-phenyl-2-aminopropane (amphetamine) or α -methylbenzylamine. The resultant complex, e.g., (**14**) (*trans* configuration; *cis* complexes are also formed), is subject to alkene exchange (Fig. 2); ethylene is

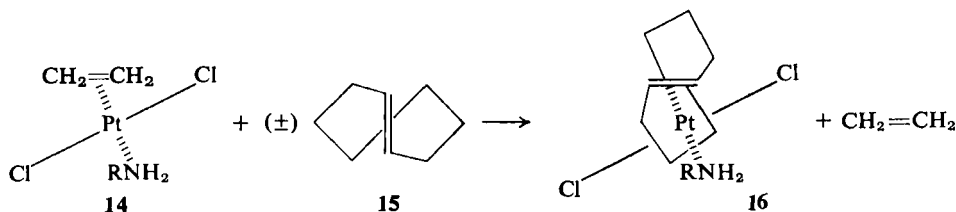


Fig. 2

displaced and bubbles out of solution. If the displacing alkene is racemic, the new complex, $[(\pm \text{alkene}) PtCl_2 (\text{amine})]$, e.g., **16**, is a mixture of diastereomeric complexes that may be separated by taking advantage of solubility differences.

trans-Cyclooctene (53b,107), the optically labile *trans*-cyclononene (108), other cycloalkenes (e.g., 109,110), the dienes *cis-trans*-1,5-cyclooctadiene (111) and *endo*-dicyclopentadiene (112), and an allene, 1,2-cyclononadiene (107) have been resolved by this procedure.

The generality of the method is attested to by the resolution of a phosphine (methylphenyl-*tert*-butylphosphine) (113), an arsine (methylethylphenylarsine) (114), and of a sulfoxide (ethyl *p*-tolyl sulfoxide) (115) *via* platinum complexes; it has been reviewed (116).

Other classes of organic compounds, e.g., alkynes and carbonyl compounds, are, in principle, resolvable by this route.

C. Resolution via Inclusion Compounds

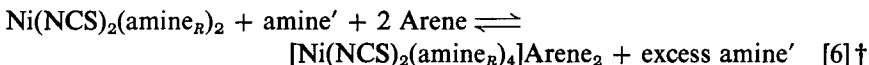
An uncommon resolution procedure takes advantage of the fact that certain substances crystallize in an array which leaves holes or canals within

the crystalline mass of sufficient size that other molecules may fit in forming "lattice inclusion compounds." A review is available (117).

In practice, guest molecules of the proper size and configuration may be trapped in the lattice when crystallization of host molecules takes place from a solution containing both. Resolution takes place because of a favored chiral interaction between guest and host molecules. Since this interaction does not necessarily involve functional groups, or even complex formation, but rather is dependent on a chiral fit, the term topological interaction—diastereomeric, to be sure—is most appropriate (118) for the effect responsible for resolution. Stability and solubility differences are possible between diastereomeric inclusion compounds and permit separation.

Desoxycholic acid forms complexes, called "choleic acids" (119), with monoterpenes, camphor, and dipentene which permit full or partial resolution (120).

A useful procedure for α -arylalkylamine resolution takes advantage of the clathration* of arenes (e.g., *tert*-butylbenzene) by *optically inactive*, i.e., achiral $[\text{Ni}(\text{NCS})_2(\text{amine})_4]$ complexes (121).



Since the (optically inactive) complex preferentially incorporates *racemic* amine' into itself during clathration, the method is unsuited to complete resolution departing from racemic amine. However, for amine optically enriched by a previous partial resolution, e.g., amine isolated from the mother liquor of a (+)-tartaric acid resolution, enrichment is appreciable in the unreacted (excess) amine. Examples: (+)- α -methylbenzylamine, enriched from 75% to 97.3% in optical purity; (+)- α -isoamylbenzylamine, enriched from 71.2% to 94.0% in optical purity.

Tri-o-thymotide (Fig. 3) a dissymmetric cyclic trilactone of unique C_3 symmetry, crystallizes from solutions of the racemate in one enantiomorphic form (total asymmetric transformation). It forms inclusion compounds with, e.g., 2-bromobutane, which deposit crystals in which the complex is composed of chiral host molecules containing a predominance of one of the enantiomers of the alkyl bromide as guest molecules. When the crystalline inclusion compound is dissolved in chloroform, the optical activity of the solution gradually changes as the host molecules racemize. The final, constant, activity of the solution attests to the partial resolution of the guest 2-bromobutane (122).

* A clathrate is an inclusion compound in which guest molecules are surrounded on all sides by the host lattice as if they were in a chamber (117).

† In eq. [6], amine_R stands for racemic amine, while amine' designates partially resolved amine. The amount of amine' taken should be sufficient to provide a minimum of 2 moles of racemic amine.

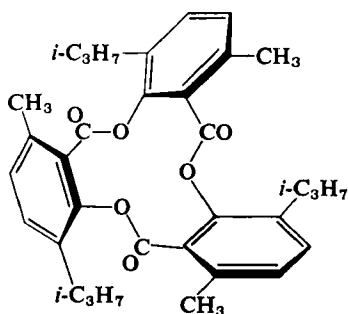
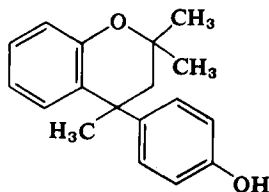


Fig. 3

An attempt has been made to apply clathration with tri-*o*-thymotide to the resolution of bromochlorofluoromethane, a chiral methane (123). The attempt "gave evidence of success"; however, the active haloform could not be isolated in sufficient quantity to confirm the resolution (see p. 123).

Chiral crystalline inclusion compounds can be prepared with some symmetrical host molecules by seeding or hand picking of enantiomorphic crystals. Urea has been utilized in this manner to partially resolve 2-chlorooctane, ethers such as heptyl 2-octyl ether, esters such as diheptyl malate and nonyl β -chlorobutyrate (124), and epoxystearates (125a). It is noteworthy that some chiral hydrocarbons, e.g., 3-methyl-octane, have been partially resolved by urea inclusion compound formation (125b).

Dianin's compound (17), a resolvable molecule which forms crystalline inclusion compounds with an extraordinary variety of organic substances (126) is potentially useful in resolutions.



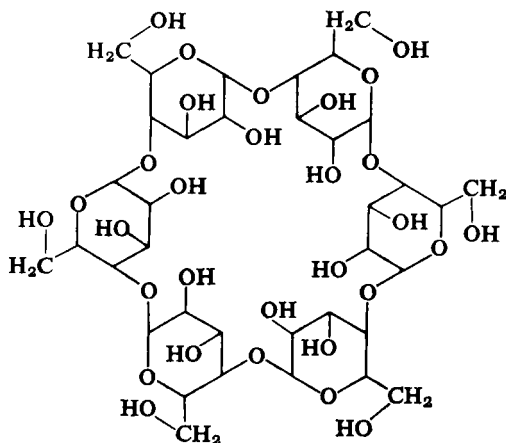
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Resolution is possible through formation of "molecular inclusion compounds" in which the holes filled by guest molecules are within individual host molecules rather than formed when host molecules crystallize. Obviously, very few substances have the requisite molecular structure or size to permit formation of this type of inclusion compound. Cyclodextrins (cycloamyloses),* are such substances; they have been used for the resolution

* Cyclodextrins are cyclic oligomeric carbohydrates consisting of six (α -cyclodextrin) or seven (β -cyclodextrin) glucose residues linked through the 1,4-hydroxyl groups.

of menthol, esters such as ethyl mandelate and ethyl phenylchloroacetate, and acids such as dibromocinnamic and dibromosuccinic acids (127a). Optical purities of the order of 3–12% have been attained in such resolutions.

More recently, preferential inclusion of *S*-(+)-isopropyl methylphosphonofluoridate (Sarin) in α -cyclodextrin (**18**) has been demonstrated (127b);

**18**

and alkyl alkylphosphinates have been resolved with relatively high optical purities by inclusion in β -cyclodextrin (127c).

Rationally constructed chiral macrocyclic molecules may provide intramolecular holes or channels of proper size to enclose guest molecules. Such “threading” is reminiscent of spontaneous catenation, if the insertions of a guest molecule within the macrocyclic host were to be followed by cyclization of the former. With a chiral host molecule, asymmetric topological induction might lead to preponderant formation of one of the diastereomeric catenanes.

VI. MISCELLANEOUS RESOLUTION METHODS

Although it is still true that “fractional crystallization is the most potent technique for resolving substantial quantities of optically pure stereoisomers” (128), the utility of a variety of other techniques for separating diastereomers and enantiomers directly has been demonstrated.

Chromatographic resolution of diastereomers as well as of enantiomers, already mentioned (p. 110), is a powerful technique under active development.

Solvent extraction, a partition phenomenon, has been shown to partially resolve racemic mixtures of compounds possessing at least two sites of hydrogen bonding provided that the organic phase of the extracting medium

possesses at least two hydrogen bonding sites as well (129). Camphoric acid and racemic diols, such as isohydrobenzoin and 2,3-bromobutane-1,4-diol, were partially resolved in tartaric acid ester-water media. Diisopropyl and diisoamyl tartrates were particularly effective as organic phases.

This partial resolution seems to be related to an earlier report of partial resolutions of racemic mixtures by recrystallization from similar optically active media (130). Here too, two sites of hydrogen bonding in both the solvent and the solute were required for resolution. Resolution *via* recrystallization from optically active solvents usually fails, however (131a). A recent successful case is that of a heptaheterohelicene which was resolved by crystallization from optically active α -pinene (8b).

Two alternative processes may be differentiated in resolutions by crystallization from an optically active solvent, a *thermodynamic* process requiring preferential solvation of one enantiomer, and a *kinetic* process in which preferential seeding is responsible for optical activation (2). Authentication of thermodynamic control is difficult (see 8b); a theoretical study of such resolutions has been made by Amaya (131b).

Countercurrent distribution has been applied on a preparative scale to the partial resolution of 1,2-(α -oxotetramethylene)ferrocene (132). Use of cyclohexane-(+)-diethyl tartrate solvent afforded enrichment to 12% optical purity in 460 steps. The method seems to be generally applicable.

Dialysis through an optically active membrane has led to the optical enrichment of ($\pm$)-tartaric acid (133).

Separation of diastereomers has been accomplished for alcohols and carboxylic acids through distillation of esters in which one or the other moiety is optically active. Highly optically enriched 2-butanol was thus obtained from the head fractions of *sec*-butyl lactate distillation (134).

Resolution of an enantiomer pair by fractional distillation of "diastereoazeotropes" (($\pm$)-2-octanol in ($\pm$)-limonene) was unsuccessful (135). In another report, optical enrichment was obtained on fractional distillation of samples of 2-(4-nitrophenyl)-butane or of 2-(4-aminophenyl)butane of low optical purity distilled in a spinning band column of high efficiency (64). The optical fractionation was ascribed to an azeotrope of minimum boiling point in the racemic mixture.

Some of the considerations bearing upon interaction between enantiomers and existence of azeotropes in liquid racemates have been discussed by Kwart and Hoster (136). These investigators have also found that an enantiomer of α -ethylbenzylphenyl sulfide and its racemate may be efficiently separated by sublimation of a partially resolved sample under reduced pressure. The sublimate was optically enriched and the residual solid was enriched in racemate.

Several variants of resolution methods involving crystallization deserve

comment. In the procedure of Pope and Peachey (137), the substrate being resolved is treated with one-half of the usual amount of resolving agent, i.e., whereas normally the molar ratio is 1:1, in this procedure it is 2:1. An achiral base or acid, depending upon the chemical character of the resolving agent, is added to provide a ratio of 2:2 and the mixture is resolved conventionally. In ideal cases, the separation depends not upon diastereomer solubility differences but upon much larger differences between one diastereomeric salt and a salt of the substrate and of the inactive co-base or co-acid.

Pope and Peachey called their method the "equilibrium method"* to emphasize the fact that four salts are in heterogeneous equilibrium when their system is used. Careful choice of the inactive base or acid is required to ensure that its salts remain in solution. This may permit but one salt, one of the two possible with the resolving agent, to precipitate. Although claimed to be an improvement in Pasteur's classic procedure (138), it has been little used.†

Whether related to this variant or not, it has been the experience of various investigators, on occasion, that the use of less than the stoichiometric equivalent of resolving agent, without added inactive species, is beneficial to a resolution (140,144). Thus, Shields was unsuccessful in attempted resolution of 1-phenylethanol, as the hydrogen phthalate ester and with brucine according to Kenyon (141), using equimolar amounts of ester and brucine, but succeeded when only half the usual amount of brucine was used (142).

The Marckwald procedure (p. 113) for the isolation of the enantiomer with the more soluble diastereomer, and which required both enantiomers of the resolving agent to be available, has been circumvented in a number of cases by a modification devised by Ingersoll utilizing the racemic form of the resolving agent (143). Read and Reid have pointed out also for this purpose that advantage may be taken of differences in solubility between normal salts (di-salts) and acid salts‡ where either substrate or resolving agent is dibasic (62). The same authors have described the utility of the Pope and Peachey procedure for the isolation of the more soluble enantiomer in a resolution.

As an alternative to salt formation between base and acid irrespective of which is resolving agent or substrate in the resolution, a salt of the base may often be treated with a salt of the acid with good results. This may be advantageous where, e.g., the base is unstable or difficult to work with, or where the

* Wittig et al. have used the designation "method of half-quantities" to describe the Pope and Peachey method (139). The case described by them was in fact not an example of this method since no inactive co-acid was employed along with the acidic resolving agent.

† Pope and Peachey conditions are often unwittingly utilized, with beneficial results (e.g., 33,54,174).

‡ These two species should not freely be used alternatively, e.g., in the resolution of dicarboxylic acids, the acid salts usually crystallize better (140).

salt of the acid is more readily available, as when the latter is the resolving agent. An example of the latter situation is the use of ammonium 3-bromo-camphor-9-sulfonate in lieu of the acid in the resolution of an amine hydrochloride.

Newman and Lednicer have described a resolution *via* complex formation with (–)-TAPA (see p. 124) in which not the complex but the substrate crystallizes in optically enriched form (90). This is evidently the result of equilibria between undissociated diastereomeric complexes and their dissociated components in which the former differ widely in stability. Armstrong had earlier described similar resolutions *via* conventional salt formation (145).

The purification, i.e., optical enrichment, of enantiomers by zone refining has been demonstrated (146).

VII. RESOLVING AGENTS

A. Resolving Agents for Acids

Naturally occurring alkaloids have been the most common resolving agents for the resolution of acids *via* salt formation for more than 100 years. They are now slowly being displaced by fully synthetic or natural product-derived bases. The reasons for this gradual change are the problems associated with the use of many of the alkaloids: cost, availability, toxicity and, not least in importance, the lack of availability of the enantiomeric alkaloid.

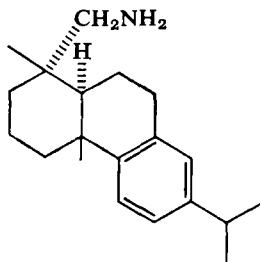
Synthetic basic resolving agents are often primary amines, while alkaloidal resolving agents are virtually exclusively tertiary amines and consequently weaker bases as a rule. Greater base strength can occasionally prove to be advantageous in facilitating salt formation. Other things being equal, one would certainly choose a strong base for salt formation if it were available.

On the basis of a rapid check of about 230 resolutions of acidic—typically carboxylic—acids in the literature (since 1960), brucine and quinine remain the two leading resolving agents for acids, together accounting for over one-third of all such resolutions. Cinchonidine and α -methylbenzylamine are next in line, followed by dehydroabietylamine, strychnine, ephedrine, and cinchonine.* Though the order is of no special significance, knowledge of which resolving agents work most often is undoubtedly useful.

Resolution *via* formation of diastereomeric amides is rare; recovery of the acid is a key problem. An example of a difficult resolution, which resisted crystalline salt formation with the “common, available” bases as well as

* This certainly underestimates the general utility of synthetic bases (particularly α -methylbenzylamine) by not including resolutions involving metal complexes and by not taking into account configuration and optical purity studies by the nmr method.

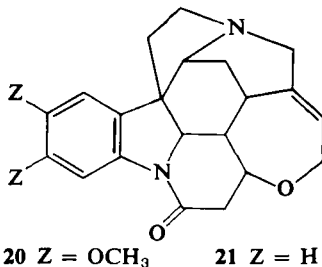
chromatographic separation of the diastereomeric menthyl esters, is that of a spirobifluorenedicarboxylic acid. *bis*-Amide formation with dehydroabietylamine (**19**) yielded a noncrystalline mixture which was chromatographed on

**19**

silica gel to separate the diastereomeric amides. The amides resisted both acid- and base-catalyzed hydrolysis. They were cleaved to the enantiomeric optically active acids *via* rearrangement of their *N*-nitroso derivatives (147).*

There follows a listing of resolving agents, the most common being listed first, with some information regarding their general utility.

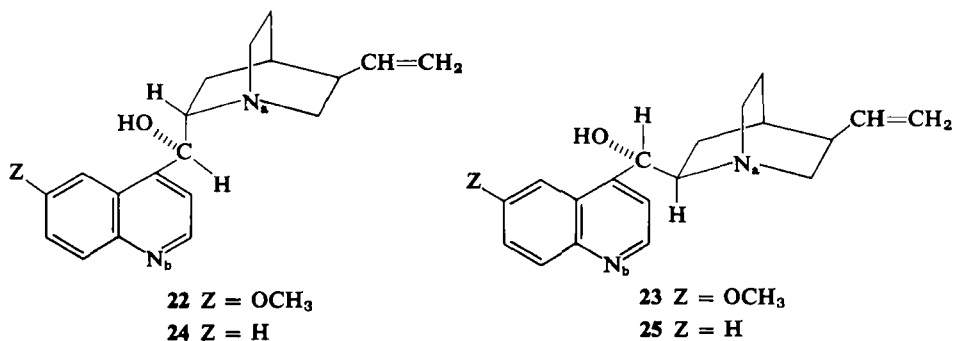
Brucine is the preeminent basic resolving agent; it is readily available (see, however, p. 163) usually in anhydrous form, but sufficiently expensive to make recovery worthwhile. Recovery of this and other alkaloids is usually not difficult, requiring only addition of a base, e.g., concentrated aqueous ammonia, to the filtrate remaining from the isolation of the resolved acid (149, 150). Both brucine (**20**) and its analog, *strychnine* (**21**) are very toxic and must be used with caution. The latter differs from its congener in that it is considerably less soluble in hydroxylic solvents.



Quinine (**22**), *quinidine* (**23**), *cinchonidine* (**24**), and *cinchonine* (**25**) are a quartet of alkaloids the first two of which are diastereomeric and differ from the second pair of diastereomeric bases by the presence in each of a methoxy group on the quinoline ring which confers increased solubility in hydroxylic solvents.

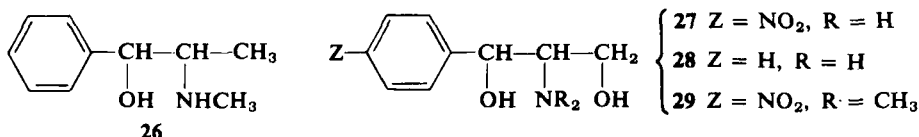
* By reaction with nitrogen tetroxide and sodium acetate in carbon tetrachloride at 0° (148). The recovered acid was chromatographed on silica gel.

Fredga recommends quinine and cinchonidine, particularly the latter, as being clearly superior to quinidine and cinchonine in the crystallization tendency and resolving power of their salts (171). Quinine is thermally unstable and its recovery in resolutions may have to be forgone (151).



A fairly typical resolution with an alkaloid is given in ref. 152.

The nonheterocyclic alkaloid *ephedrine* (**26**) and the related synthetic *threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (**27**) are much used in salt-forming resolutions. Examples for use of **26** are found in refs. 52 and 174.

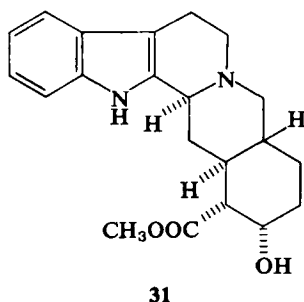
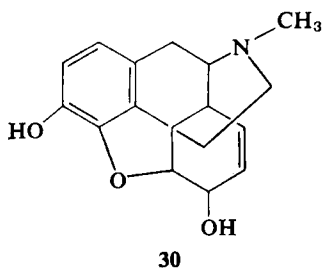


The base **27**, an intermediate in the synthesis of the antibiotic chloramphenicol, is available in both enantiomeric forms through resolution with (+)-camphorsulfonic acid (153). Its use as a resolving agent was introduced by Velluz and his co-workers initially for the resolution of amino acid derivatives, e.g., *N*-acetyltryptophan (154), but it is now finding more general use as a resolving agent for acids (155). *threo*-2-Amino-1-phenyl-1,3-propanediol (**28**) (156) and *threo*-2-(*N,N*-dimethylamino)-1-(*p*-nitrophenyl)-1,3-propanediol (**29**), the latter prepared by methylation of either (+)- or (–)- **27** (157), have also been employed as resolving agents.

Little utilized alkaloidal resolving agents are *morphine* (**30**)* and *yohimbine* (**31**). Mandelic acid,† particularly (158), and atrolactic acid (159) are resolved with morphine. Further examples are: for **30**, ref. 160; for **31**, ref. 161.

* On repeated recrystallization, morphine salts have a tendency to turn brown and give turbid solutions (171).

† An alternative and simple resolution procedure for mandelic acid utilizes ephedrine as the resolving agent (see, e.g., C. A. McKenzie, *Experimental Organic Chemistry*, 3rd ed., Prentice-Hall, New York, 1967, p. 257).



α -Methylbenzylamine (α -phenylethylamine) has the distinction of being the most frequently used of all the synthetic basic resolving agents. It is now easily resolved with the inexpensive (+)-tartaric acid, and both enantiomers are obtainable in a state of high optical purity in the resolution (162). An improved version of this resolution has been published (27,163). Natural products such as *trans*-humulinic acid (which resisted resolution with several alkaloids or with (–)-menthol *via* esterification) (164) and simpler acids such as α -trifluoromethylphenylacetic acid (165), a reagent useful in the determination of the optical purity of alcohols (166), are resolved with α -methylbenzylamine. For additional examples, see ref. 27.

Ring-substituted α -methylbenzylamines may have utility as resolving agents in special cases. For example, Cope and co-workers have employed (+)- α -methyl-*p*-nitrobenzylamine in a partial resolution of 1,2-nonadiene *via* a platinum complex (107) (see p. 126).

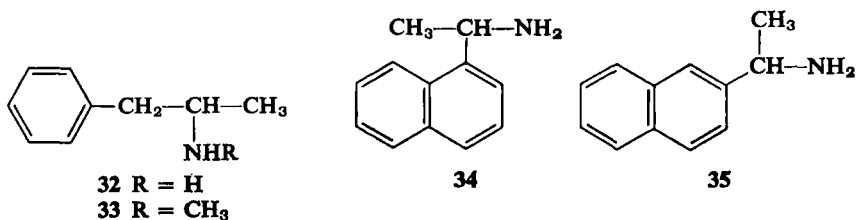
Amphetamine, " β -phenylisopropylamine" (32), was investigated by Matell (167) as a possible replacement for its homolog, α -methylbenzylamine, when the expensive (–)-malic acid was required for the resolution of the latter base (168). Use of amphetamine (both enantiomers are available) in resolutions is common.* Examples are given in ref. 169.

Deoxyephedrine (desoxyephedrine, metamphetamine) (33) has been used occasionally as a resolving agent.* For an example, see ref. 170.

α -(1-Naphthyl)-ethylamine (34) and α -(2-naphthyl)-ethylamine (35) are often used in resolutions. While 34 is commercially available, Fredga has pointed out that its salts have a greater tendency to separate as oils (171). On the other hand, salts of 35 tend to crystallize readily, and the use of this base is therefore recommended in preference to 34 (172). Examples are: for 34, see ref. 174; for 35, ref. 173.

2-Amino-1-butanol, which is also resolvable with (+)-tartaric acid (32,175), and both of whose enantiomers are commercially available, is

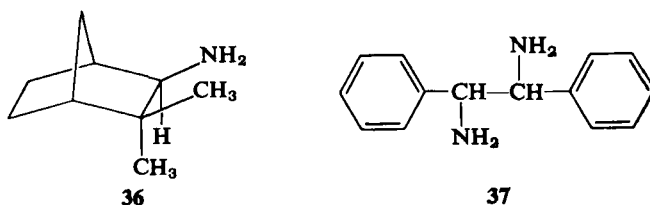
* Bases which are central nervous system active may be difficult to obtain from some suppliers.



increasingly being used as a resolving agent. For examples of resolutions employing this base, see refs. 32 and 176.

Dehydroabietylamine (**19**), a terpene-derived primary amine, was introduced as a resolving agent for acids independently by Sjöberg and Sjöberg (177) and by Gottstein and Cheney (178). The substance is nontoxic, low in cost, and it forms highly crystalline salts with many carboxylic acids. It is a much used resolving agent (for examples, see refs. 174 and 178).^{*} A topologically interesting chiral adamantane carboxylic acid has recently been resolved with **19** (179), as has chlorofluoroacetic acid (180).

α -*Fenchylamine* (**36**) forms salts of "exceptional crystallizing power." Its use as a resolving agent has been recommended and illustrated by Ingersoll and his co-workers (181).

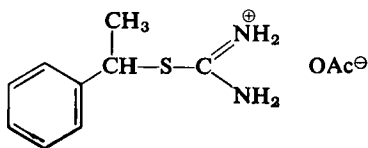


Stilbenediamine (**37**) has been used in a resolution *via* diastereomeric platinum complexes (114).

Quaternary alkaloid salts such as *quinine*- and *quinidine*-methohydroxides (**22**- and **23**- N_a -methohydroxides; see p. 134) have occasionally been employed for the resolution of weak acids for which no salts could be formed with the alkaloids (182). For examples, see refs. 182-184.

α -*Methylbenzylisothiuronium acetate* (**38**) has been synthesized and resolved specifically for use as a resolving agent for weak acids (185). (+)-*Arginine*, a guanidine derivative, has been employed in similar situations (182a) (186).

^{*} Isolation of dehydroabietylamine from the commercial mixture (Hercules Powder Co., Amine D) is no longer necessary since the free base is commercially available. Use of dehydroabietylammmonium acetate (an intermediate in the isolation procedure) (178) as a resolving agent is occasionally preferred (e.g., 174).

**38**

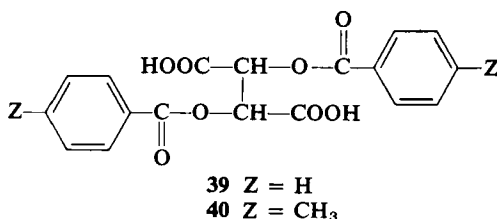
Acids are occasionally resolved through diastereomeric ester formation with chiral alcohols, such as (–)-menthol, e.g., (187). This practice is of considerably less importance than the converse, i.e., resolution of alcohols with acids *via* formation of esters (see p. 144).

B. Resolving Agents for Bases

It is interesting, though perhaps not too surprising, that, out of a large number of chiral acids which are resolving agents for bases, tartaric acid and its derivatives are employed in nearly one-half of such resolutions.*

Unsubstituted 1° alkylamines are, as a rule, resolved with (+)-tartaric acid in methanol solvent (188). α -Methylbenzylamine and its homologs (162,163,189), more highly substituted 1° amines (190), some 2° and 3° amines (e.g., 191), diamines (192), and a variety of basic heterocyclic compounds (e.g., 193) are also resolved by this very useful acid.

The *O,O'*-diacyltartaric acids extend the range of utility of the parent compound. *O,O'*-Dibenzoyltartaric acid (39) has, e.g., been found to partially

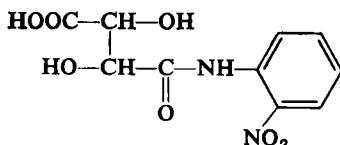


resolve amine oxides (194). *O,O'*-Di-*p*-toluoyltartaric acid (40) has successfully resolved a number of alkaloids (195) as well as simpler amines (196).

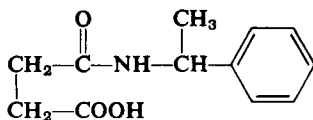
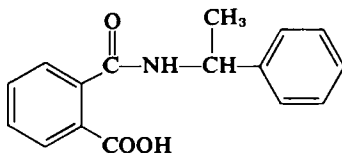
DeWitt and Ingersoll have called attention to the fact that the number and structural variety of classical acidic resolving agents known is quite small. Some of these agents are available in only one enantiomeric form, and this is a serious limitation because application of the Marckwald principle (p. 113) is thus precluded (197). This fact spawned a number of projects whose goals were to increase the number of useful resolving acids.

* This statement is based on a rapid check of about 125 resolutions of bases in the literature (since 1960).

Substituted tartranilic acids, e.g., *o*-nitrotartranilic acid (**41**), and analogs of **41** more highly substituted in the benzene ring, have been specially synthesized for, and applied to, the resolution of difficult-to-resolve bases (198,199).

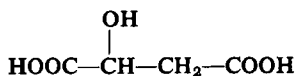
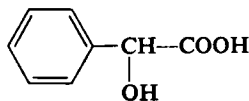
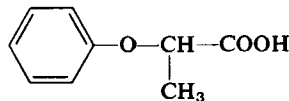
**41**

N-(α -Methylbenzyl)-succinamic acid (**42**) and *N*-(α -methylbenzyl)-phthalamic acid (**43**) have also been prepared for use as resolving agents. Both enantiomers of α -methylbenzylamine, of 2-amino-1-butanol, and of *threo*-2-

**42****43**

amino-(*p*-nitrophenyl)-1,3-propanediol (**27**) have been easily obtained in a state of high optical purity with **42** (200).

Malic acid (**44**) and *mandelic acid* (**45**) complement tartaric acid as resolving agents for bases. For examples see refs. 201 (for **44**) and 202 (for **45**).

**44****45****46**

Substituted mandelic acids have occasionally served as resolving agents (203,204), as has α -phenoxypropionic acid (**46**). For examples of resolutions with the latter acid, see ref. 205.

Next to tartaric acid and its derivatives, the strongly acidic sulfonic acids are the most useful resolving agents for amines and other basic compounds. The formulas of these camphor-derived resolving agents and their structural relationships to camphor are shown in Figure 4.*

Camphor-10-sulfonic acid (**47**) (Reychler's acid)[†] is the most widely used

* Many standard texts give incorrect structural formulas for some of these substances. For a leading reference, see ref. 206.

[†] Also known as ω - or β -camphorsulfonic acid.

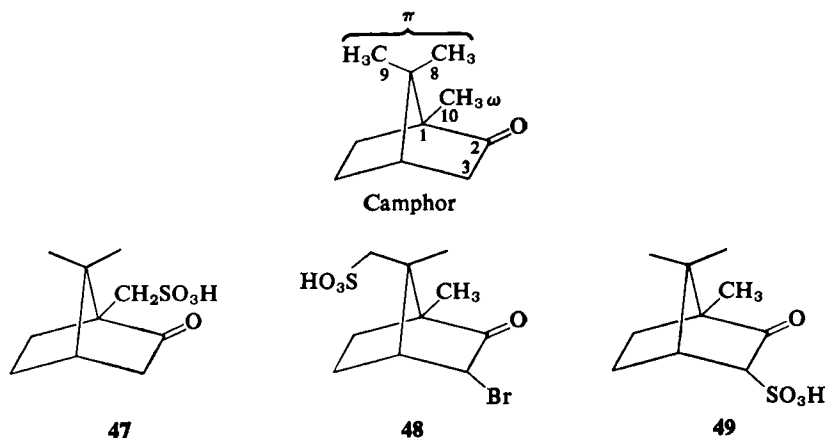


Fig. 4

of these sulfonic acids and the least expensive. Formation of diastereomeric salts is the usual form that resolutions with **47** take; amide formation with the **47**-sulfonyl chloride is rare [though resolution of alcohols through ester formation (see Sect. VII-C) is more common]. For example, amines (e.g., 207), tropinone oxime (208), tetraalkylammonium salts (e.g., 209) and synthetic alkaloids such as pseudoyohimbine (210) have been resolved with **47**.

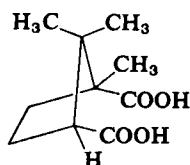
3-Bromocamphor-9-sulfonic acid (**48**) (α -bromocamphor- π -sulfonic acid),* also finds much use in the resolution of bases. Heterocyclic bases such as macronecine (211) have been resolved with **48** in the form of the **48**-ammonium salt. A 1° amine intermediate in the prostaglandin total synthesis has been resolved with **48**; resolution was apparently complete after only one recrystallization of the diastereomeric salt (212).

The methyl ester of (+)-3-camphorsulfonic acid (**49**) (α -camphorsulfonic acid) has found use as a salt-forming resolving agent for a base (see p. 155). A nucleophilic displacement on carbon rather than a proton transfer is responsible for diastereomer salt formation in this case.

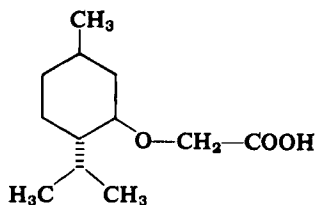
Cholestenesulfonic acid has been employed for the resolution of a few amino acids on a small scale (213). Corey and Shulman have introduced *1-phenylethanesulfonic acid* as a resolving agent for weak bases (p. 160).

Two carboxylic acids derived from the terpenes also have been occasionally used for resolutions. (+)-Camphoric acid (**50**) has, for example, been used for the resolution of α -(1-naphthyl)-ethylamine (214) and for that of the ($\pm$)-pinacol derived from *o*-aminoacetophenone (215).

* This compound is most often called 3-bromocamphor-8-sulfonic acid in the literature although the *anti* orientation of the sulfo and carbonyl groups is well established (206).



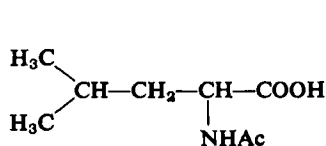
50



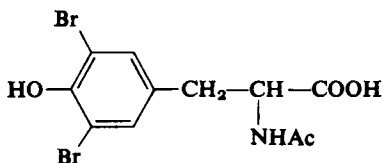
51

(-)-*Menthoxyacetic acid* (**51**) is seldom used in diastereomeric salt-forming resolutions of bases. For an example, see ref. 216. Its principal use is in alcohol resolutions through ester formation (p. 146).

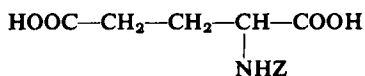
N-Acetyl-*L*-leucine (**52**) and *N*-acetyl-*L*-3,5-dibromotyrosine (**53**) are two members of a group of acidic resolving agents developed in 1951 by DeWitt and Ingersoll for the resolution of amines (197,217) and amino acids (218),



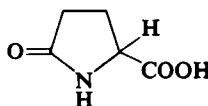
52



53



54 Z = H
55 Z = Ts



56

and which continue to be used. The alkaloid ($\pm$)-*N*-norromneine has recently been resolved with **52** and with **40** (219).

Glutamic acid (**54**) has found use as a resolving agent for amino alcohols (220-222), and its *N*-tosyl derivative, (**55**) has been used to resolve a heterocyclic amine (223). 2-Pyrrolidone-5-carboxylic acid (**56**) (pyroglutamic acid) is also a useful resolving agent for amines (224,225).

6,6'-Dinitro-2,2'-diphenic acid has occasionally been employed in the resolution of heterocyclic bases (226) (see also p. 154). It suffers from not being readily accessible.

D-Arabonic acid, its salts, and the γ -lactone, all available as intermediates in the commercial synthesis of vitamin B₂ have been employed as efficient resolving agents for ephedrine (227). It may be generally useful.

Levopimaric acid and *abietic acid* are potential resolving agents for bases. The latter was heretofore available only as a mixture of three isomers (from

ease of formation of these phthalates, particularly for secondary alcohols, and the record of success of such resolutions make this a choice method. Monosuccinate esters also are used in alcohol resolutions but to a much lesser extent. Alcohol resolutions were reviewed by Ingersoll in 1944; this review is still a most useful one (233).

The classical alkaloids are used almost exclusively in resolutions of alkyl hydrogen phthalates. Use of primary amine resolving agents is uncommon in these resolutions even though there is no evidence that ester-amide interchange is a complicating problem. The successful resolutions of bornyl and isobornyl hydrogen phthalates with (–)-menthylamine (234), of *trans*-2-methylcyclohexyl hydrogen phthalate with (–)- α -methylbenzylamine (235), and of 2-cyclohexenyl hydrogen phthalate with dehydroabietylamine (236) have been reported. The resolutions of the isomeric *cis*- and *trans*-2-methylcyclohexyl hydrogen phthalates have recently been repeated with (+)- and (–)- α -(2-naphthyl)-ethylamine as resolving agents (173). Higher optical rotations than those previously recorded (235) were obtained.

There are not very many examples of the use of substituted phthalate esters in this type of resolution. The 3-nitrophthalates have been used in isolated cases (237). The use of pyridine-2,3-dicarboxylic esters in the resolution of 2-butanol with brucine is suggested by the work of Kenyon and Thaker (238); such a resolution seems simpler than the conventional one with the hydrogen phthalate ester (239).

Mills and his co-workers have listed some of the defects inherent in the hydrogen phthalate ester procedure for the resolution of alcohols. Much effort was given by this group to the development of new resolution procedures for alcohols but with little success. Resolutions carried out with new covalent derivatives—*N*-menthylphthalamate esters (240a), *N*-menthyl-*p*-sulfamylbenzoate esters (240b)—and through salt formation of hydrogen phthalate esters with modified menthylamine-derived optically active bases (240c) gave negative or marginal results.

Few resolutions of 3° alcohols had been carried out at the time of the Ingersoll review, and such resolutions were fraught with problems (233). Since the description by Doering and Zeiss of a resolution of 2,4-dimethylhexan-4-ol *via* its hydrogen phthalate with brucine (241), many similar resolutions have been effected with little difficulty (242,243). Alkyl diaryl carbinols (244) and even trityl alcohols (245)* can be resolved through the hydrogen phthalate esters. Resolution of 3° alcohols, in particular, has been aided by alternative methods for the recovery of the chiral alcohol from the phthalate ester to the standard saponification procedure: reduction with lithium aluminum

* The synthesis of phenyl- α -naphthyl-*p*-tolylcarbinyl hydrogen phthalate, which is described in this paper, is reported to have failed in repetition (see ref. 258).

hydride, reaction with ethylmagnesium bromide, or direct action with alkoxide on the alkaloid salt (244).

Although most optically active hydrogen phthalate esters can be cleaved to alcohols by alkali with little or no racemization, some such esters, e.g., those of 1-(*p*-anisyl)-ethanol and, in particular, those of allylic alcohols, racemize during alkaline hydrolysis (246).^{*} Recovery of the alcohol by reaction of the hydrogen phthalate with lithium aluminum hydride overcomes the problem (e.g., 248).

Stoichiometries other than the typical 1:1 hydrogen phthalate ester to alkaloid ratio (249) have successfully been used in alcohol resolutions, e.g., 1:0.5 in the resolution of 2-butanol (250; see also ref. 251 for a modified 2-octanol resolution). The Pope and Peachey procedure (p. 131) has been applied to the resolution of alcohols (56,234,252).

The phthalate procedure is unsatisfactory for the resolution of alcohols such as 2,2,2-trifluorophenylethanol (**57**), since esters of these acidic alcohols hydrolyze readily (253).[†] Ethers of glycolic acids may be utilized to good advantage in such cases (254) (see Fig. 6). Diarylcarbinols (255a) and triarylcarbinols (255b) have also been resolved by this route.

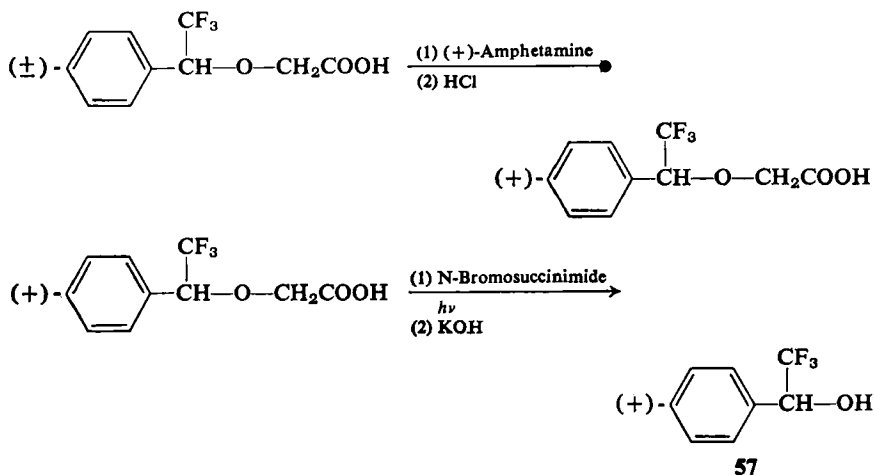


Fig. 6

The required glycolic acids may be prepared, as esters, either by reaction of the alcohol salt with ethyl bromoacetate or by conversion of the alcohol into the alkyl chloride and reaction of this with ethyl glycolate. An alternative

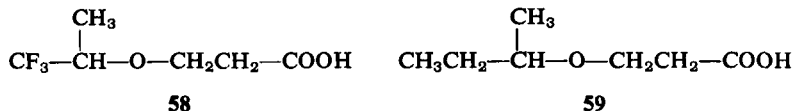
^{*} Disproportionation of alkyl hydrogen phthalate salts is also known to occur (247).

[†] Attempted resolution of the hydrogen phthalate of **57** yielded brucine phthalate in quantitative yield (253b).

cleavage procedure for the recovery of alcohol is the conversion of the resolved glycolic ester into an amide followed by Hofmann rearrangement of the amide (255b).

Resolution of triarylcarbinols *via* thioglycolic acid derivatives (256) appears to be less satisfactory than the glycolic acid route.

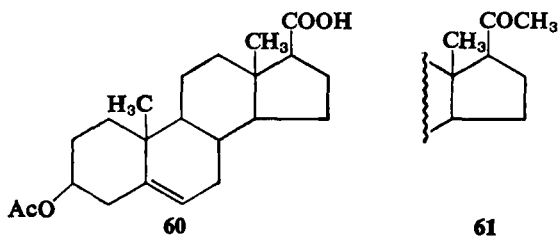
1,1,1-Trifluoro-2-propanol has been resolved with quinine through its hydracrylic acid derivative (58) (257). Trityl alcohols may also be resolved



by this route (258). However, use of hydracrylic acid derivatives appears to be limited to acidic alcohols. Alkaline cleavage of the resolved acid to the desired alcohol *via* reverse Michael reaction is a key limiting step; e.g., β -*sec*-butoxypropionic acid (59) does not cleave to 2-butanol under the conditions in which 58 does (257).

Resolution of alcohols *via* formation and separation of diastereomeric esters with optically active acids is carried out more now than a generation ago. An advantage of resolution of alcohols through esters rather than through salts is that the progress of the resolution can be followed conveniently and efficiently by nmr spectroscopy (46) (see also p. 118).

Esterification with 3 β -acetoxy- Δ^5 -etienic acid (60) is a highly effective

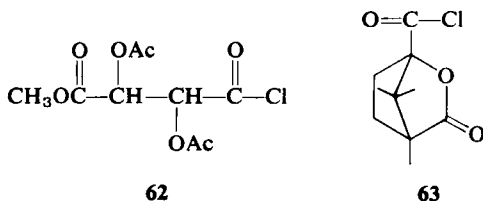


resolution procedure for alcohols. Esterification takes place *via* the acid chloride of 60 and is followed by separation of the crystalline diastereomeric esters. Resolution of 1 α -hydroxydicyclopentadiene (259), of *trans*-3-*tert*-butylcyclohexanol* (260), of *cis,cis*-1-decalol (261), and of two trifluoromethylcarbinols (262) has been effected with 60.

Common use of acid 60 as a resolving agent would seem to be limited by its cost. It may be prepared from the less expensive and more readily available pregnenolone acetate 61 by hypobromite oxidation (263). Chiral

* Conventional resolution of this alcohol *via* its acid phthalate ester is reported to have failed (260).

alcohols are recovered from the diastereomeric esters by lithium aluminum hydride reduction.

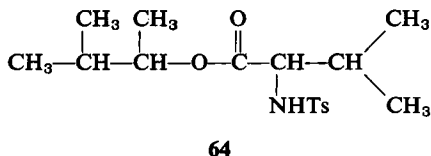


Esters formed with (+)-*O,O'*-diacetyltartaric acid monomethyl ester chloride (2,3-diacetoxy-3-carbomethoxypropanoyl chloride) (**62**) and racemic steroidal alcohols are crystalline. Fractional crystallization of these esters separates the diastereomer mixtures, yielding both enantiomers of the sterols after saponification (264). Resolution through formation of diastereomeric 10-camphorsulfonate esters (265) and of 3-bromocamphor-9-sulfonate esters (266) has been reported.

Gerlach has resolved *trans,trans*-spiro[4.4]nonan-1,6-diol by diastereomeric ester formation with ω -camphanic acid chloride (**63**). The ester mixture was separated by chromatography (267).

A straightforward resolution of 3,3-dimethyl-2-butanol, by gas chromatography of its *R*-(+)-lactate ester on a preparative scale, has been reported. The technique is suggested as being fairly general. It has the advantage of providing both enantiomers in a state of high optical purity (268).

Many 1° and 2° chiral alcohols form nicely crystalline tosylates of esters with L-amino acids in good yields. These diastereomeric derivatives, e.g., **64**,



formed by reaction of alcohol, amino acid (e.g., valine, alanine), and *p*-toluenesulfonic acid with water removal, are obtained sterically pure after two recrystallizations. Alkaline hydrolysis yields alcohols which are typically 100% optically pure (31,269a).^{*} Both enantiomers of 2-methyl-1-pentanol were obtained by resolution alternatively with L- and with D-valine (31). The high cost of unnatural amino acids is a limitation of this attractive procedure.

Formation of carbamates (from reaction of, e.g., menthyl chloroformate and alcohols) (269b) and of urethanes (from reaction of chiral isocyanates

^{*} Optical purity was determined by gas chromatography.

with alcohols)* is suggested as possible alternatives for the resolution of alcohols through covalent rather than ionic diastereomers.

Separation of esters of *menthoxyacetic acid* (233) continues to be used as a resolution procedure. Examples are: *trans*- and *cis*-2-*o*-tolylcyclohexanols (46,271); zearalenone 4-methyl ether (272). Although some of these esters do not crystallize, separation of mixtures of diastereomeric menthoxyacetates by column chromatography, e.g., on alumina, overcomes this disadvantage (46,271). This reagent remains a principal one for the resolution of phenols (233), although resolution of this class of compounds through formation of other esters (e.g., 60) may be possible.

Glycoside formation is an alternative resolution procedure for phenols.† Ethyl *p*-hydroxyphenyl sulfoxide has been resolved *via* glucoside formation; the latter is cleaved enzymatically, with emulsin (275).

Steroidal alcohols may be resolved by a method which may, in fact, be generally applicable. The alcohol is first converted into a hemisulfate ester salt 66 by reaction with, e.g., triethylamine-sulfur trioxide. Exchange of the triethylammonium ion for a chiral ammonium ion, *viz.*, that from optically active 2-amino-1-butanol, yields diastereomeric salts 67 which are separable

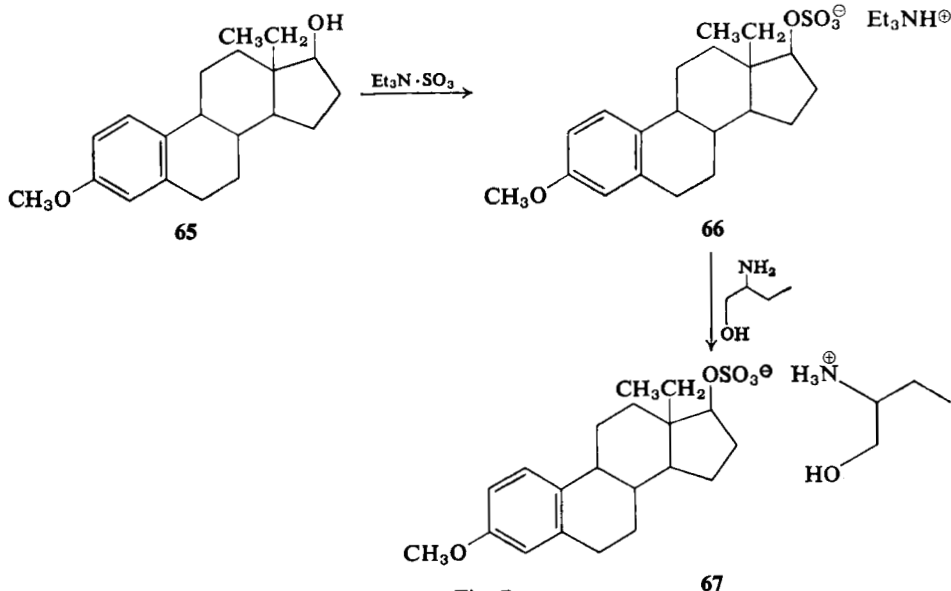


Fig. 7

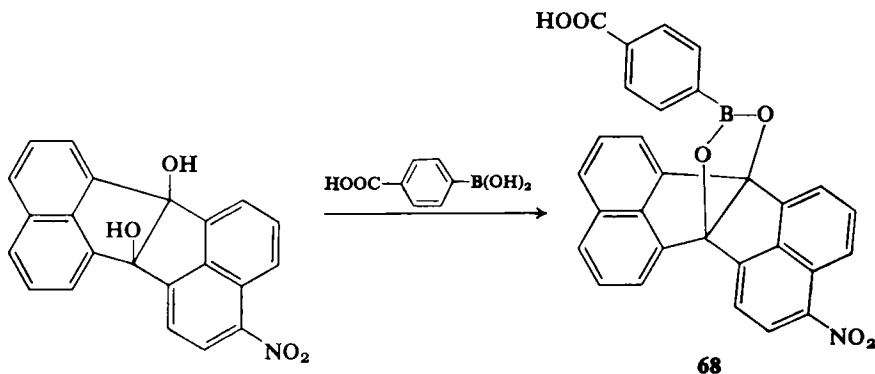
* α -Phenylethyl isocyanate (270) and dehydroabietane 1-isocyanate (273) along with the earlier applied menthyl isocyanates (233) are possible resolving agents for such a procedure.

† Alcohols have also been resolved in this way; e.g., (274).

by fractional crystallization. Heating of **67** in dioxane regenerates the now optically active alcohol (176). The resolution of **65** is an example; see Figure 7. This modern approach to the use of acid sulfates of alcohols in resolutions appears to overcome some of the objections to this otherwise difficult-to-apply route (see ref. 233).

Optical activation of simple glycols such as propylene glycol (276) and ($\pm$)-2,3-butanediol (277) has usually been carried out enzymatically. *trans*-1,2-Cyclohexanediol has been resolved as a monomenthoxyacetate ester (278).

In another procedure, the glycol is first converted into a cyclic boronate ester carboxylic acid, e.g., **68**, by reaction with *p*-boronobenzoic acid. The ester is conventionally resolvable with alkaloids or other basic resolving agents (279). Boronate esters evidently may be used in the resolution of other *cis*-glycols or of acyclic ones.



The resolution of propylene glycol by fractional distillation of its diastereomeric ketals with (–)-menthone or (+)-camphor in an efficient distilling column (over 100 theoretical plates) has been described (280).

The cited chemical procedures for glycol resolutions are superior to resolutions *via* dihydrogen sulfate esters (see ref. 233 for a summary of pertinent literature).

D. Resolution of Carbonyl Compounds

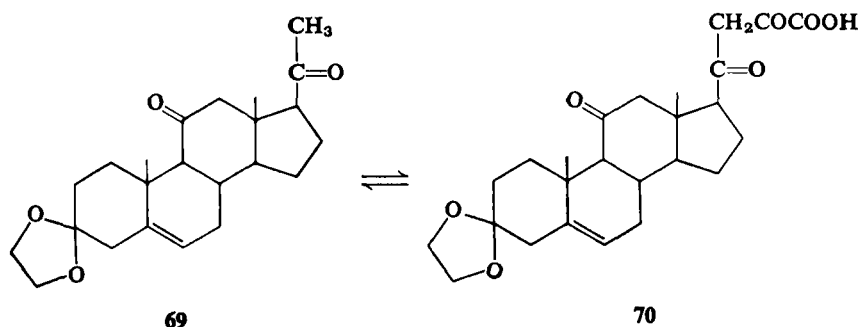
There are two general approaches that may be taken for the optical activation of aldehydes and ketones. The functionality may be modified to permit resolution by a method or reagent described in Sect. VII-A,B,C; or a special carbonyl-specific resolving agent may be employed.

Included in the first approach is the reduction of the carbonyl group to a hydroxyl group, resolution of the resulting alcohol, and oxidation of the

chiral alcohol to the desired optically active carbonyl compound under non-racemizing conditions. The first step may, of course, be omitted by beginning with the appropriate alcohol and this, in fact, is desirable since reduction could introduce an additional asymmetric center which, in turn, would require separation of a diastereomeric pair before resolution.

Macbeth and Mills have described resolutions of the *cis*- and *trans*-3-methylcyclohexanols *via* the hydrogen phthalate esters (281).^{*} The chiral alcohols, (–)-*cis*- and (–)-*trans*-3-methylcyclohexanols, were each oxidized to give (+)-3-methylcyclohexanone. This approach was stated to be superior, i.e., less tedious and wasteful, than the direct resolution of the ketone—presumably by the “best” method available at the time—with (–)-menthyldrazide (p. 151). Similarly, following failure to resolve 3-*tert*-butylcyclohexanone with tartramidic acid hydrazide (p. 152), optical activation of the ketone was achieved by resolution of the corresponding alcohol (p. 144) followed by oxidation (260).

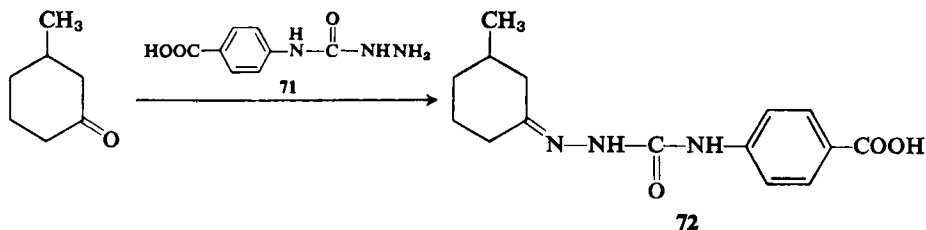
A second example of this general approach involves the optical activation of the ketoprogesterone derivative **69**. This methyl ketone was converted into



the oxalyl derivative **70** which was resolved with strychnine. Base-catalyzed reversal of the condensation led to optically active **69** (282). This procedure, while interesting, is certainly of limited applicability. Base-catalyzed racemization would also be expected to limit the optical purity of the enolizable ketones to which this procedure might be applied.

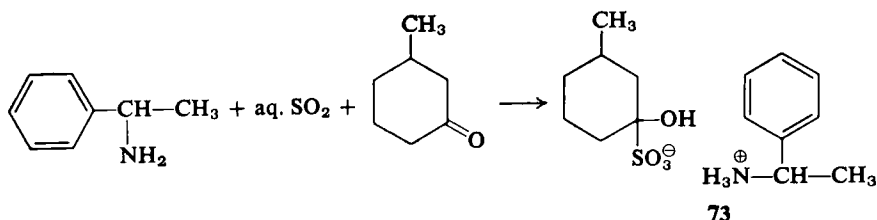
4-(4-Carboxyphenyl)-semicarbazide (**71**) is a reagent which was developed specifically for resolution purposes. Ketones, and presumably aldehydes as well, are first converted into the 4-carboxyphenylsemicarbazones, which may then be resolved with basic resolving agents (283). 3-Methylcyclohexanone has been resolved in this way through its 4-carboxyphenylsemicarbazone (**72**);

^{*} Optical enrichment of partially resolved *trans*-3-methyl-cyclohexanol was achieved by crystallization of its phenylurethane derivative.



brucine was the resolving agent.* Related methods to the use of derivatives such as **72** are resolutions through 4-sulfophenylhydrazine derivatives and through thioglycolic acids derived from thioketals (or thioacetals) (284).

Amine bisulfite addition compounds of aldehydes and ketones, e.g., **73**,† developed by Adams and Garber (38a), are simple to form and to decompose, yet resolution by this route has been limited to but a few cases, including



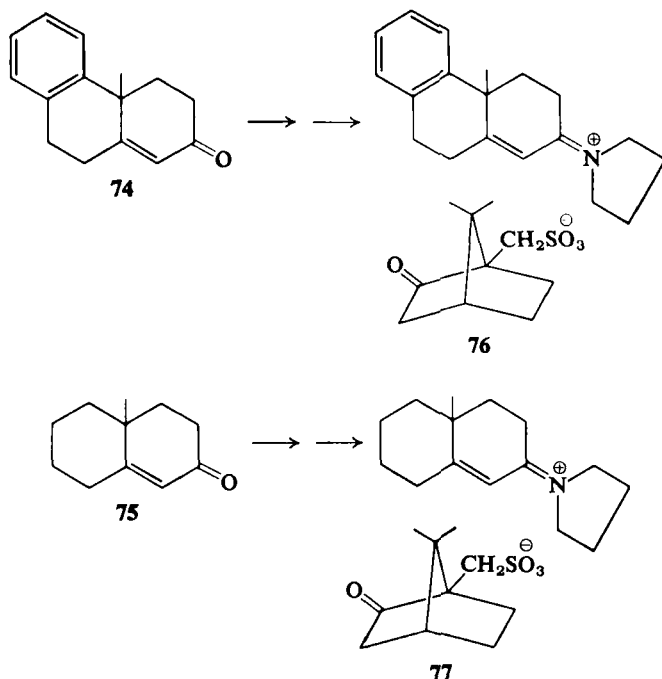
β -methylhydrocinnamaldehyde, 3-methylcyclohexanone (38a) and 3-*tert*-butylcyclohexanone (38b).

A special variant of this first approach, which is broadly applicable to enolizable ketones, avoids the need for special resolving agents, facilitates the formation of the derivative and the regeneration of the ketone, and maintains mild conditions. Undesirable reactions including racemization are thus avoided.

The first type of resolution employing this procedure requires conversion of the ketone into an enamine. Reaction of the weakly basic enamine with an optically active strong acid converts the former into a mixture of crystalline diastereomeric iminium salts which may be separated by systematic recrystallization. Hydrolysis of the separated salts under exceptionally mild conditions affords both of the enantiomeric ketones. Ketones such as **74** and **75** were, respectively, completely and partially resolved in this manner *via* the corresponding salts **76** and **77** (285).

* Hydrolysis of **72** was effected after resolution by heating it for 10 min with 9 *N* aqueous sulfuric acid. Only the (–)-enantiomer was obtained.

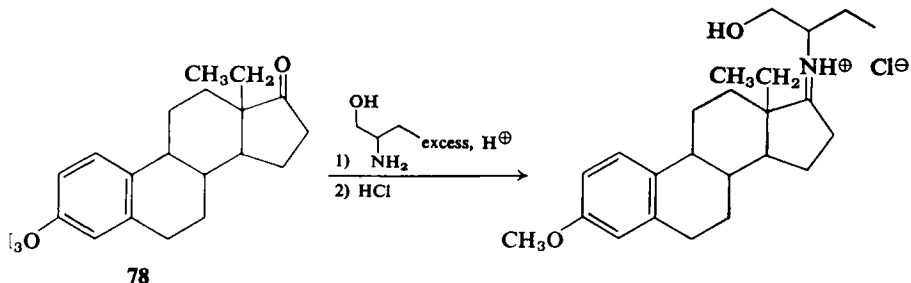
† Note that an additional asymmetric center is present in the derivative **73**. It did not impede the utility of this resolution procedure, however.



Ketones which form enamines only slowly or not at all are convertible into iminium salts by the procedure of Leonard and Paukstelis (286). While this method "is not a panacea" (285), the ease of conversion of carbonyl compound into the requisite enamine derivative and the use of ordinary, i.e., not specially synthesized, resolving agents are principal attributes which make the procedure a most powerful one.

A related type of resolution of carbonyl compounds developed by a group at the American Cyanamid Company utilizes chiral 1° amines to form diastereomeric imines (Schiff's bases) which may directly be separated by fractional crystallization. Either the imines or their hydrochloride salts may be employed (176). This procedure, when applicable, is one step shorter than the resolution through iminium salt formation since the nitrogen-containing derivatizing agent incorporates the resolving agent. Moreover, the procedure is evidently not limited to enolizable carbonyl compounds. The basic resolving agent utilized was 2-amino-1-butanol; other chiral 1° amines, e.g., α -methylbenzylamine and dehydroabietylamine, are usable here. Steroidal ketones such as **78** have been resolved by this method.

Schiff's bases with chiral amines also figure prominently in asymmetric syntheses. For example, reaction between ($\pm$)-spiro[4.4]nonan-1-one and ($-$)- α -methylbenzylamine yields a Schiff's base which, in turn, yields the

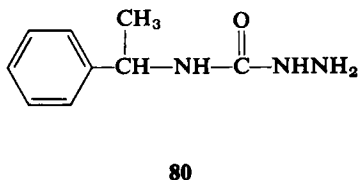
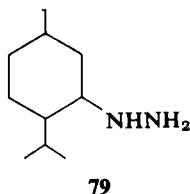


corresponding (+)-spiro amine upon catalytic hydrogenation (287). A similar asymmetric synthesis of a [2.2]metacyclophane-4-methylamine from the corresponding aldehyde has been described (288).

Direct resolution of carbonyl compounds through their Schiff's bases should certainly be considered, particularly when the latter are crystalline. Potential racemization upon hydrolysis of the diastereomeric imines may limit their use, however; see, e.g., (292).

A large number of resolving agents specific to carbonyl compounds have been synthesized and applied over the years in the second of the general approaches to carbonyl resolutions. None is known which is of general utility, yet many remain useful in specific application.

Hydrazines and semicarbazides were among the earliest types of resolving agents applied to the resolution of carbonyl compounds. *Menthylhydrazine* (**79**) and 4-(α -methylbenzyl)semicarbazide (**80**) are examples of such reagents.

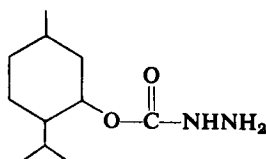
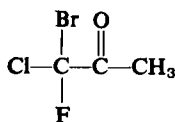


The racemic sugar arabinose was resolved with **79** (289). The resolution of benzoin was achieved with **80** (290). Related "early developed" resolving agents are listed in refs. 285 and 291.

(-)-*Menthyl N-aminocarbamate* (**81**) [($-$)-menthyldrazide]* forms menthydrazones with carbonyl compounds which may be separable, if diastereomeric (291). Racemic camphor was readily resolved (291)[†] with **81** to yield both enantiomers of the ketone; the same resolving agent has been

* The early development of this carbamate resolving agent by Woodward and co-workers may have suggested the later use of chiral isocyanates as resolving agents for amines and alcohols (see pp., 141 and 145).

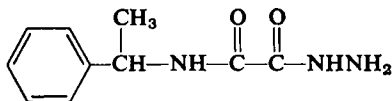
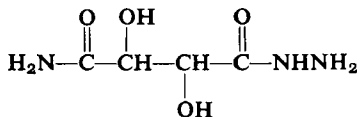
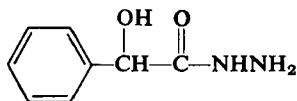
[†] In contrast, a recent attempt to resolve ($\pm$)-camphor-8-¹⁴C with **81** was considered unsuccessful. Only partial resolution was obtained (297).

**81****82**

used in the resolution of α -ionone (292) and of 3-methylcyclohexanone (293). 1,1,1-Bromochlorofluoroacetone (**82**) a precursor to chiral bromochlorofluoromethane, has recently been resolved by means of **81** (123).

(-)-Menthylhydrazide has been much used in the resolution of metallocene aldehydes and ketones. The first report of these resolutions is that by Thomson, who resolved a dissymmetric ferrocenone with **81** (294). Schlögl and his co-workers have developed a mild cleavage procedure for the recovery of optically active metallocene ketones from the diastereomeric menthydrazones; hydrolysis is effected by treatment with methanolic phosphoric acid in the presence of formaldehyde (295). As a recent example, the resolution of a ruthenocenone has been reported (296).

5-(α -Methylbenzyl)semioxamazide (**83**) has been employed in the resolution of 3-methylcyclohexanone (298). An attempted resolution of a ketonic paracyclophane with **83** failed when its semioxamazone could not be prepared (299).

**83****84****85**

Tartamidic acid hydrazone (tartramazide) (**84**) forms diastereomeric tartramazones with 2,6-dimethyloctanal which may thus be partially resolved (300). 2-Phenylcyclopentanone has been resolved with **84** (301).

β -Phenylindanone has been resolved with *mandelic acid hydrazone* **85** (302). The hydrazone was cleaved with pyruvic acid, presumably by exchange. This may be milder than, and hence superior to, the typical cleavage of hydrazones and kindred derivatives in which danger of racemization is ever-present, particularly if the carbonyl compound is enolizable.

Corey and co-workers have investigated the utility of ketal and thio-ketals in resolutions. The gas chromatographic separation of the diastereomeric dioxolanes formed from racemic camphor and (–)-2,3-butenediol was one of the first successful resolutions accomplished by this separation technique (303). An octahydroisoquinolone has also been resolved *via* its (–)-2,3-butanediol dioxolane derivatives (304).

(+)-2,3-Butanedithiol, prepared from the chiral diol, has been applied to the resolution of flavan-4-one (305). Raney nickel cleavage of the dithio-ketal derivatives yields chiral flavans; hydrolysis with mercuric chloride and mercuric oxide affords the chiral flavan-4-ones. Resolution with 2,3-butanedithiol is of limited applicability because some thioketals are liquids and are also not gas chromatographically separable.

Fractional distillation of ketals, e.g., of racemic menthone and of camphor with optically active propylene glycol in an efficient distilling column, is reported to be a useful resolution procedure for ketones (as well as for glycols; see p. 147) (280).

E. Resolution of Organometallic and Organometalloidal Compounds

A tremendous burst of research activity, beginning in the mid-1950s, on the stereochemistry of organometallic compounds has yielded a voluminous literature on chiral compounds of groups IIIa, Va, VIa and transition elements. Many elements are now known for which chirality is “centered” in an asymmetric atom other than carbon.*

Fortunately, much of this literature has been reviewed in recent years and, although most of these surveys do not deal specifically with resolutions, they do cite some and they do provide direct access to papers in which optical activation and resolution is described.

A key reference dealing with a wide variety of chiral organometalloidal compounds, even including chiral ammonium and sulfonium salts, is that of Sokolov and Reutov (306). Chiral organosilicon compounds and their optical activation are discussed in a book by Sommer (307), and along with chiral germanium, tin, and lead compounds, in a review by Belloli (308). The stereochemistry of metallocenes has been reviewed by Schlögl (309).

Stereochemistry and optical activity in organophosphorus and organo-arsenic compounds have been reviewed by Kamai and Usacheva (310). Organophosphorus compound stereochemistry, including resolutions, has been discussed in reviews by Hudson and Green (311), Horner (312), McEwen

* “Inorganic” coordination compounds with organic ligands which meet the non-carbon atom chirality criterion are well known; they properly fall outside the scope of this review.

(313), Cammarata (314), Mikolajczyk (315), and by Gallagher and Jenkins (316).

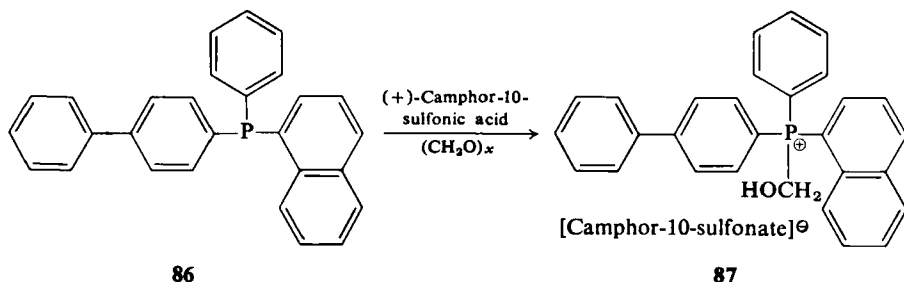
Selected resolutions principally from the recent literature are briefly described in this section. Most resolutions of organometallic compounds are quite conventional, whether the chirality center resides at a carbon atom or a noncarbon one. Two examples illustrate this point well.

1-Ferrocenyl-2-propanol, which contains an asymmetric carbon atom, has been resolved through its half-phthalate ester with strychnine (317). 2-Methylazaferrocene, a heterometallocene in which chirality is centered at the iron atom, has been resolved with (–)-6,6'-dinitrodiphenic acid (318).

Conventional resolutions of organometallic compounds are by no means limited to metallocene derivatives equipped with functional group handles, whether built-in or present as appendages. Since the first resolution of an organophosphorus acid was reported in 1958 (319), a large number of phosphoryl and thiophosphoryl compounds has been resolved. A variety of phosphonic (e.g., 320,321), phosphorothionic (322), phosphinothioic (323) and related organophosphorus acids, as well as carboxyphenyl arsines (324), and of arylcarbonylmetallic compounds (325,326), to cite but a few examples, are resolvable with alkaloidal or synthetic basic or acid resolving agents.

Molecules whose "chiral center" atoms are from groups Va and VIa in the periodic table, may, if in a suitably low oxidation state or appropriately substituted, have available an unshared electron pair which may permit resolution through ligancy in a diastereomeric metal complex. Two examples of organometalloidal compounds resolved by means of such complexes have been cited on p. 126; one was a phosphine (113); the other was an arsine (114). Many other resolutions utilizing this procedure should be possible.

Molecules embodying similar stereoelectronic features may be resolvable through onium salt formation and separation of diastereomeric salts, provided that the formation of the onium salt is reversible. An example of this process has been given by Wittig and co-workers in their resolution of the triarylphosphine (86) (139).



Hydroxymethylphosphonium camphor-10-sulfonate diastereomeric salts **87** are formed by reaction of **86** with the resolving agent and paraformaldehyde. (–)-**86** was obtained when the precipitated salt was cleaved by chromatography on alumina. The salt remaining in the mother liquor was cleaved to (+)-**86** with triethylamine.

Resolution of organometallic onium salt is often carried out with salts, e.g., of *O,O'*-dibenzoyltartaric acid, as resolving agent, e.g., (114) (see also p. 162). Resolution through quaternary salt formation may occasionally take an unusual turn when structural features permit. Racemic *N,N*-diethylamino-2-methylimidazol-1-yl phenylphosphinamidothioate (**88**) has been resolved through diastereomeric salt formation with methyl (+)- α -camphorsulfonate (**89**) (327).

The imidazolium group serves both as a resolving handle and as a facile leaving group in a stereospecific nucleophilic displacement following the resolution. This is shown in Figure 8.

After recrystallization, cleavage of the salt **90** was carried out in two steps: anion exchange to the iodide, (–)-**91** (with recovery of the resolving agent as sodium (+)- α -camphorsulfonate) followed by reaction of **91** with 2-methylimidazol-1-yl sodium which afforded (+)-**88**.

The last step in the sequence just given was shown to be a stereospecific displacement on phosphorus by the 2-methylimidazol-1-yl anion rather than a simple dequaternization occurring at the *N*⁺-methyl group by treatment of (+)-**88** with methyl iodide. The product was (+)-**91**.

Separation of diastereomeric menthyl esters of organosilicon compounds

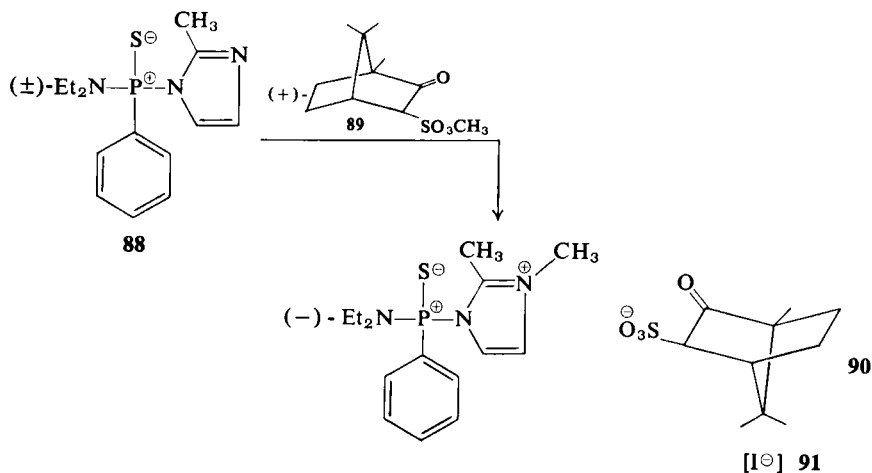
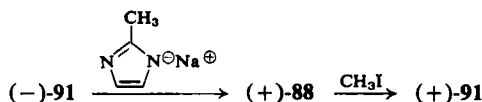
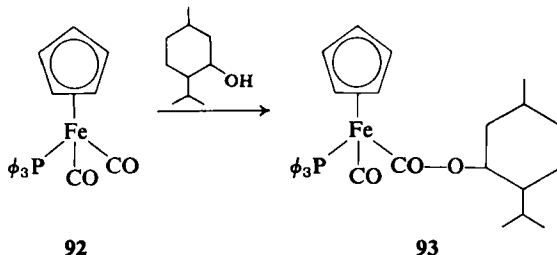


Fig. 8

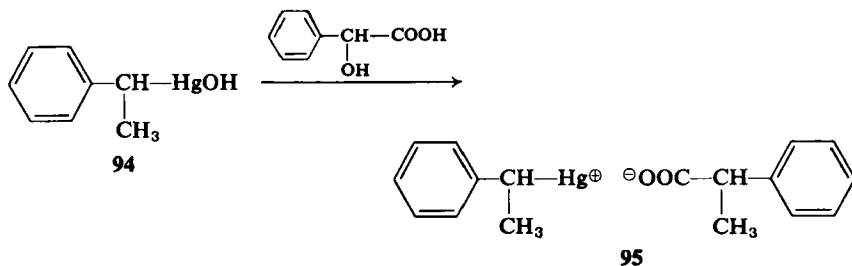


(silanols) (328), of organophosphorus acids [(obtained from phosphonic acids (329) or phosphinic acids (330–332)], and of organometal carbonyl compounds such as **92** (333), is one of the most widely used resolution



techniques for organometallic and organometalloidal compounds. The separated **93** diastereomeric esters (typically by recrystallization) are generally converted into other compounds, e.g., by stereospecific reduction or Grignard reaction.

Aliphatic organomercury(II) compounds, which are useful in elucidating mechanisms of electrophilic substitution reactions, are resolvable by diastereomeric salt formation between the alkylmercuric hydroxide and mandelic acid. *sec*-Butyl- (334), *sec*-1-methylpentyl- (335), and α -methylbenzylmercuric hydroxide (**94**) (336) have been partially resolved in this manner. Decompo-



sition of salts such as **95** is effected by an anionic-exchange reaction with, e.g., sodium bromide. The corresponding alkylmercuric bromide is thus produced in a stereospecific reaction.

F. Resolution of Amino Acids

This topic has been treated in an extensive review by Greenstein and Winitz (337). Some examples, principally from the recent literature,

will illustrate methods used in the resolution of this important class of compounds.*

Optical activation by biological methods is one of the three common methods employed to obtain optically active amino acids (13,338). Occasionally, this method fails and chemical resolution, i.e., *via* diastereomer formation, must be resorted to.

Research on crystallization techniques, i.e., spontaneous resolution by crystallization, is more active in the field of amino acids than for any other group of substances. Seeding techniques and entrainment (339) (see below) are much used, and often high yields of both enantiomers are obtainable. The series of papers by Watanabe and Noyori on the resolution of racemic glutamic acid is an instructive example (340).

Crystallization of amino acid derivatives also successfully leads to resolution. Seeding of racemic alanine benzenesulfonate in supersaturated aqueous acetone gave D or L enantiomer (depending on the chirality of the seeds) in high yield and high optical purity (341). † Lysine may be resolved by seeding of its 3,5-dinitrobenzoic acid addition compound (342). Repeated alternate seeding of a solution can yield D and L product with D and L seeds, respectively, in a virtually continuous process called entrainment in which the racemic solute is replenished as required. Glutamine, asparagine, glutamic acid, and aspartic acid have been resolved in this manner as well (343).

Diastereomer crystallization and ion-exchange chromatography have been applied to the resolution, e.g., of histidine (344) and of proline (345), respectively, by stereoselective, i.e., diastereomeric, interaction in metal complexes (compare p. 125).

Resolution through formation of diastereomers can be carried out on free as well as substituted amino acids. Owing to the opposing bifunctionality of amino acids, either acidic or basic resolving agents may be employed; some examples follow.

Histidine has been resolved with tartaric acid (346); glutamic acid with histidine (347); alanine with the alkaloid cytosine (348); and the diastereomeric β -hydroxyaspartic acids with lysine (for the *threo* isomer) and ornithine (for the *erythro* isomer) (349).

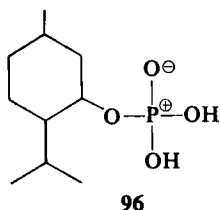
Lysine has recently been resolved with 2-phenoxypropionic acid (46) (350); with (–)-2-pyrrolidone-5-carboxylic acid (56) (224)‡ and with menthyl

* Direct entry to the literature is made possible by scanning Sect. 34 of individual issues of *Chemical Abstracts*.

† DL-Alanine is unsuitable because it forms a racemic compound. The benzenesulfonate appears to form a racemic compound also, but its solubility characteristics do not preclude the resolution.

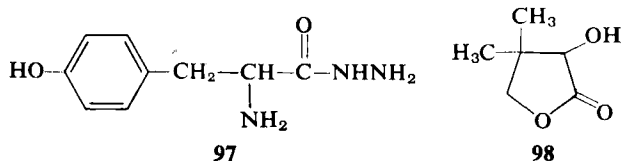
‡ This resolution was actually achieved by formation of a salt with α -aminocaprolactam.

dihydrogen phosphate (**96**) (351). The latter is prepared from pyrophosphoric acid and (–)-menthol.



N-Substituted derivatives in which the amino functional group is blocked are resolved with bases: e.g., *N*-benzoyl- β -hydroxyvaline with α -methylbenzylamine (352); *O*-benzyl-*N*-formylserine and *O*-benzyl-*N*-carbobenzoxyserine also with α -methylbenzylamine (353); *N*-acetyltryptophan with lysine (354) or with **27** (154); and *N*-tosylserine with *threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol (**27**) (355).

N-Benzyloxycarbonylamino acids, e.g., of proline, alanine, isoleucine (356a), pipecolic acid (356b), and *S*-benzylcysteine (357) are readily resolved with *tyrosine hydrazide* (**97**). Even half-molar amounts of this resolving agent give excellent yields (356).



In contrast, carboxyl derivatives of amino acids are resolved with acids; e.g., *tert*-butyl phenylalaninate with *N*-benzoyloxyphenylalanine (358); and *O*-methylserinamide with tartaric acid (359), and methionineamide with **56** (360).

Covalent diastereomeric derivatives also have served in the resolution of amino acids: e.g., menthyl esters of neutral amino acids such as norvaline (361); and for leucine, among other amino acids, by formation of pantoyl-leucine* by reaction with (+)-*pantolactone* (**98**) (155a,362).

A perfluoroalkylamino acid has been resolved *via* its *N*-trifluoroacetyl derivative (**99**). Cyclization of **99** with dicyclohexylcarbodiimide gave an oxazolone (**100**) with an activated carboxylate functionality. The latter was resolved with dimethyl L-(+)-glutamate (**101**) (see Fig. 9). Recrystallization of the dipeptide mixture yielded the pure LL compound (363).

Asymmetric syntheses figure prominently in the optical activation of α -amino acids. As recent examples, the synthesis of optically active aspartic

* Presumably the *N*-acyl derivative.

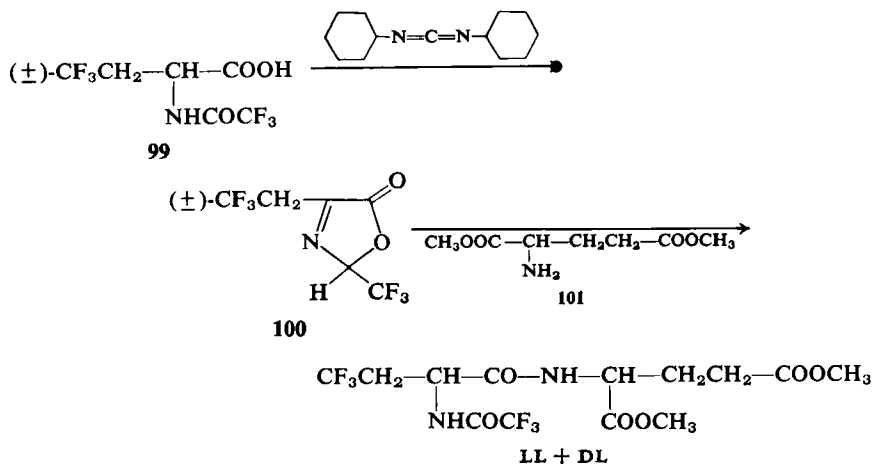


Fig. 9

acid through hydrogenation of a cyclic imine derived from a chiral alcohol (222), and the asymmetric synthesis of a variety of amino acids from α -keto acids using regenerable chiral indolines (364), may be cited.

An interesting point regarding amino acids is that, when they are resolved with other optically active amino acids or their derivatives, the separable *covalent* diastereomers formed are dipeptides or dipeptide derivatives. The panoply of peptide separation and analytical techniques can thus be brought to bear on their separation.

G. Resolution of Miscellaneous Classes of Organic Compounds

Resolution of alkenes and polycyclic arenes is now possible through the application of two powerful techniques: resolution *via* metal complexes (see p. 125) and *via* molecular complexes with chiral Lewis acids (see p. 123), respectively.

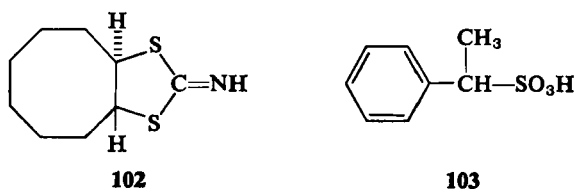
A derivative of cyclotrimeratrylene, an aromatic ether which exhibits conformational enantiomerism, has been partially resolved into stable enantiomers by chromatography on cellulose acetate (365). A dissymmetric aromatic vicinal disulfide has been similarly resolved (366).

Optical activation of simple alkylaromatic compounds otherwise requires incorporation of an acidic or basic handle, generally on the ring, and resolution and removal of the handle. Preparation of optically active 2,3-diphenylbutane (367) involved resolution of 4,4'-diamino-2,3-diphenylbutane with tartaric acid; deamination yielded the desired optically active hydrocarbon (see also p. 115).

Only two procedures for the resolution of alkyl halides are known. One of them involves the use of inclusion compounds and is of theoretical interest only (see p. 128). The other procedure, asymmetric destruction, is quite general in its applicability and is limited principally in that it produces halides of low optical purity (see p. 121). Most optically active halides are obtained by stereospecific synthesis from chiral precursors; for a review, see (368).

Aromatic ethers such as *sec*-butyl-1-naphthyl ether are resolvable *via* complex formation with TAPA (see p. 123).

An iminodithiocarbonate (**102**) has been resolved with the strongly acidic resolving agent (–)-1-phenylethanesulfonic acid (**103**) (369).



A resolution procedure specific to 2-sulfhydryl amines has been developed; it is illustrated in Figure 10. Taguchi and co-workers have resolved *trans*-2-aminocyclohexanethiol (**104**) *via* the thiazolidine (**105**) formed with D-glucose. Two diastereomeric forms of **105** were isolated by recrystallization. Cleavage of **105**, m.p. 161–163°, by exchange with cyclohexanone gave (+)-**106**; of **105**, m.p. 152–153°, gave (–)-**106**. Each **106** enantiomer was in turn hydrolyzed to the corresponding (–)-**104** and (+)-**104**, respectively, with hydrochloric acid (370). This procedure has been applied to the resolution of 1-amino-2-propanethiol (371); in this case, benzaldehyde was used to cleave the corresponding thiazolidine. Only two thiazolidines (**107**) were formed, although four are possible, and the two are enantiomeric. Stereospecific

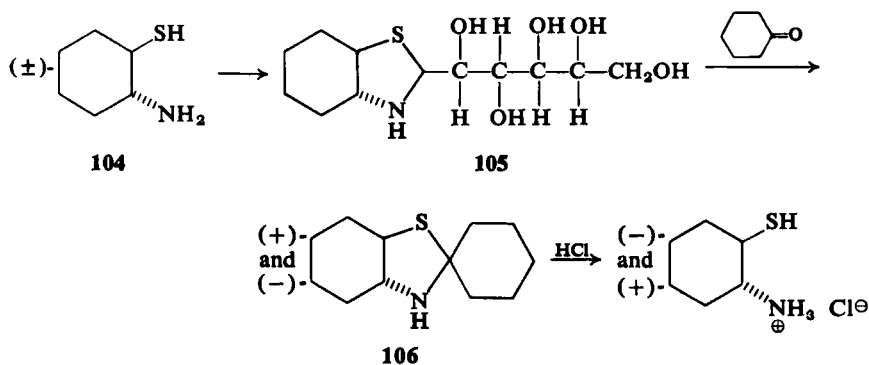
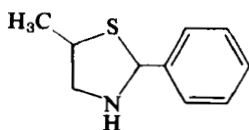
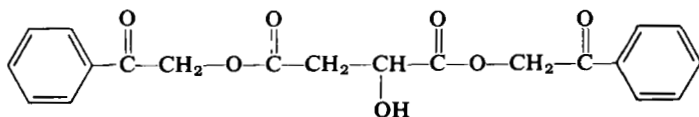


Fig. 10

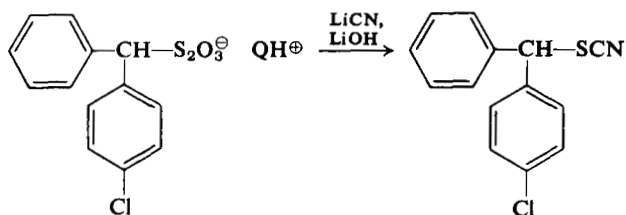
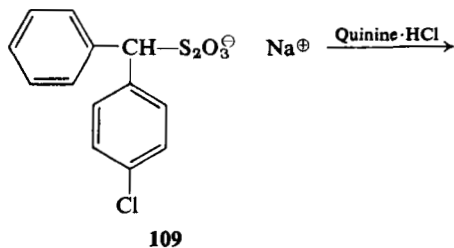
**107**

cleavage of the glucose derivative with benzaldehyde has been implicated to explain the result.

Dissimilarly substituted sulfoxides are chiral and resolvable. Optical activation of sulfoxides has been effected by conventional resolution of sulfoxides containing acidic or basic functional groups, by chemical or biological asymmetric synthesis, or by stereospecific synthesis from chiral precursors. Two cases of direct resolution have been reported. One is the resolution of ethyl *p*-tolyl sulfoxide through the intervention of a diastereomeric platinum complex (see p. 126). The second case involves the adsorption chromatographic resolution of racemic-1,2-bis(phenylsulfinyl)ethane on activated lactose (372). Both enantiomers were obtained.

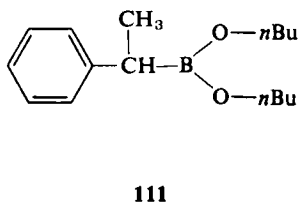
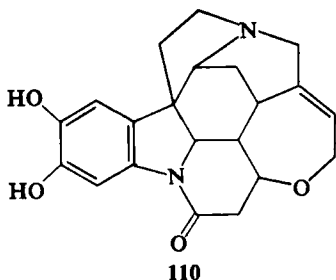
**108**

Sulfur acids, such as sulfonic acids, may be resolved through ester formation, e.g., with (–)-menthol (373). Esters of hydroxylic substances can serve a similar purpose. For example, methyl chlorosulfinate has been resolved with (+)-diphenacyl malate (**108**) (374).

**Fig. 11**

The resolution of a thiosulfate salt (**109**) with quinine hydrochloride, QH, is a route to optically active thiocyanates, for which no good direct resolution is available (375) (Fig. 11).

A chiral catechol, *bisdemethylbrucine* (**110**) has been employed to resolve



the boronic acid derivative (**111**). Chelate formation of **110** with boron was felt to be responsible for the success of the resolution (376).

Organic and organometallic salts are occasionally resolved directly by reaction with salts of basic or acidic resolving agents, as required; some examples follow.

Silver camphor-10-sulfonate has been used as resolving agent for two different biphenyl quaternary ammonium compounds (377,378); silver bromocamphor-9-sulfonate has served in the resolution of spiro-arsonium and phosphonium salts (379) and of quaternary arsonium salts (380). Other quaternary arsonium and phosphonium salts have been resolved with silver dibenzoyl hydrogen tartrate (114,381).

Strychnine methiodide and related quaternary salts of alkaloids have occasionally been used to resolve acids *via* their salts, e.g., the resolution of silver-*p*-nitrophenyl methyl phosphorothionate (382). Amidinium salts have been resolved with sodium mandelate (383).

Synthetic optically active polymers are relatively new, but their study now constitutes a major area of research. A recent review is that by Topchieva (384). An interesting development is the chromatographic resolution of polymers containing asymmetric carbon atoms in the main chain or in side chains utilizing synthetic optically active polymers as chromatographic adsorbents (see ref. 15 for leading references).

VIII. SOURCES OF RESOLVING AGENTS

Contemporary organic chemists are fortunate that a substantial number of resolving agents are available commercially. A few distributors of organic compounds and specialty houses carry a larger assortment of these reagents than others do and these are identified in Table 1.

TABLE 1
Commercial Suppliers of Resolving Agents^a

Supplier	Code
Aldrich Chemical Company	A
Fluka AG	F
Frinton Laboratories	FR
K and K Laboratories	KK
Koch-Light Laboratories	KL
Norse Laboratories ^b	N
Pfaltz and Bauer Inc.	PB
Sigma Chemical Company	S

^a Addresses of these suppliers are given in L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley-Interscience, New York, Vol. 1, p. 1297, 1967, and Vol. 2, p. 469, 1969.

^b Norse Laboratories, Inc., Santa Barbara, California 93103, also offers a custom resolution service.

Prices of resolving agents depend, particularly for natural products and their derivatives, on availability, and this may vary considerably from time to time. For example, brucine and strychnine are extracted from *nux vomica* produced in Brazil, India, and Vietnam. Heavy demand for the exceptionally bitter brucine, which is used in the denaturation of alcohol, may raise the price particularly if supply problems develop and strychnine demand (for vermin control) slackens.

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Stereochemistry of Nitroxides

EDWARD G. JANZEN

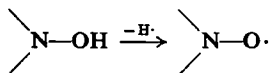
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1. THE NITROXIDE FUNCTION

A. Introduction

Molecules which are derived by hydrogen atom abstraction from hydroxylamines have come to be known as nitroxide radicals.



These radicals are unusually stable species. In the last four years, investigations involving nitroxide radicals have outnumbered studies of other stable free radicals. Not only have numerous derivatives of the nitroxide radical been detected in various reacting systems, but also the synthesis of many types of nitroxides has been accomplished.

The objective of this paper is to draw attention to the stereochemical information available from esr spectra of alkyl and alicyclic nitroxides. Both the structure of the nitroxide function and the conformation of the alkyl

or alicyclic group can be deduced from the esr spectra of suitably substituted nitroxides. The paper, "Conformation and Structure as Studied by Electron Spin Resonance Spectroscopy," by D. H. Geske (1) should be used as an introduction to this topic by those not familiar with esr spectroscopy. Although this chapter apparently covers the literature on this subject completely up to the end of 1966, no conformational questions concerned with nitroxides are discussed. In the period 1966–1970, a number of studies of this type have appeared and are discussed here.

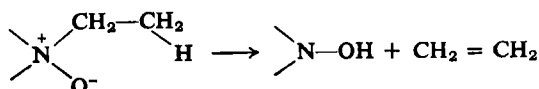
B. Preparation of Nitroxides

A very good chapter on the chemistry of nitroxides appears in the book by Forrester, Hay, and Thomson on stable free radicals (2). The following brief summary is abstracted from that chapter in order to familiarize the reader with the chemistry of nitroxide radicals. For more details the book should be consulted. Some statements also stem from experience in the author's laboratories.

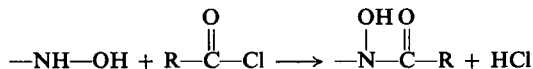
Nitroxides are commonly prepared by the following procedures.

1. Oxidation of hydroxylamine derivatives. This route probably gives the best yields of nitroxide radicals. Lead dioxide, silver ion, lead tetraacetate, peroxides, or air (oxygen) in mildly basic solution are commonly used oxidizing agents. Ultraviolet irradiation also has been used effectively in recent studies of alicyclic nitroxides.

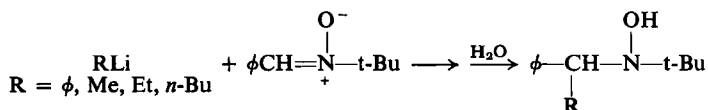
The problem then becomes the synthesis of hydroxylamine derivatives for this purpose. The following methods have been used: (a) pyrolysis of the *N*-ethyl *N*-oxide of a secondary amine:



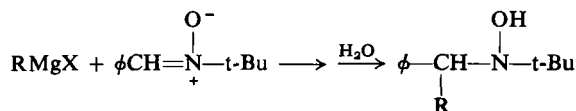
(b) acylation of primary hydroxylamine derivatives:



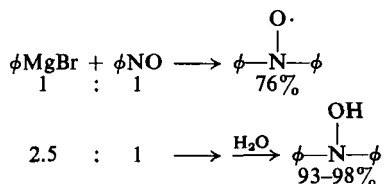
(c) addition of an organolithium to a nitron:



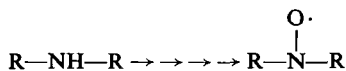
(d) addition of a Grignard reagent to a nitron:



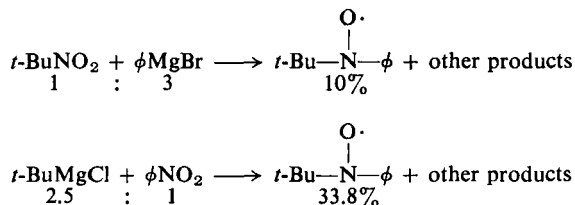
(e) addition of aryl Grignard reagents to nitrosobenzene:



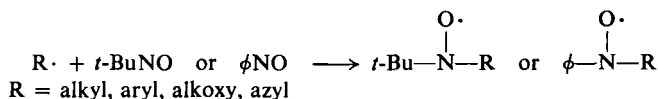
2. Oxidation of secondary amines. The not too ready availability of *N,N*-disubstituted hydroxylamine derivatives would make the direct oxygenation of a secondary amine to the corresponding nitroxide an attractive reaction. However, the oxygenating conditions required to make the nitroxide also often rapidly destroy the radical, particularly if the α -positions are unsubstituted. *p*-Nitro- and *m*-chloroperbenzoic acids have been used extensively for the oxidation, although hydrogen peroxide in basic aqueous solution, or in the presence of phosphotungstic acid also is effective. Photolysis of peroxides in the presence of secondary amines also produces nitroxides.



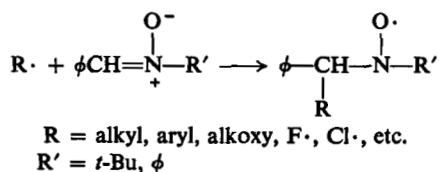
3. The addition of aryl or *t*-alkyl Grignard compounds to *t*-nitroalkanes, or the addition of *t*-alkyl Grignard compounds to aromatic nitro compounds (not a general method).



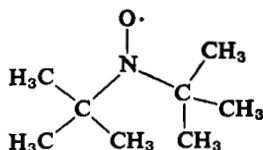
4. Radical addition to nitroso compounds.



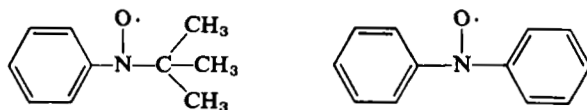
5. Radical addition to nitrones.



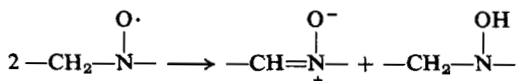
Although other methods of nitroxide synthesis are known, it should be pointed out that the yield of the radical depends largely on its stability. The stability of the radical in turn depends on the number and kind of groups attached to the nitroxide function. If both groups in a dialkyl nitroxide are tertiary, maximum stability is attained, e.g., di-*t*-butyl nitroxide.



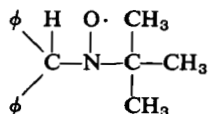
Aryl groups also stabilize the radical, although dimerization in the para position may occur at low temperatures or in the solid phase, e.g., *t*-butyl phenyl or diphenyl nitroxide.



If the α -positions are unsubstituted, disproportionation to the corresponding nitron and hydroxylamine occurs more or less rapidly.

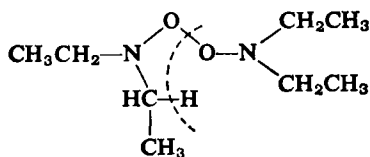


However, this reaction appears to be drastically slowed down by the presence of bulky groups near the nitroxide function. Thus, benzhydryl *t*-butyl nitroxide has recently been isolated (albeit in impure form) in our laboratories:



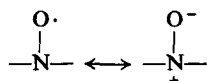
These observations are consistent with a recent proposal that a cyclic inter-

mediate precedes the transition state in the disproportionation of diethylnitroxide to diethylhydroxylamine and methyl *N*-ethyl nitrone (3):



C. Properties of the Nitroxide Function

The nitroxide function is a dipolar group with a dipole moment of 2.4 D (di-*t*-butyl and diphenyl nitroxide). The electron is delocalized over both

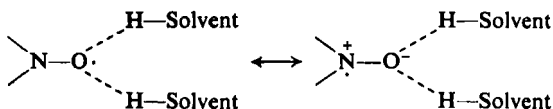


atoms with the spin density on nitrogen approximately 44% by molecular orbital calculations (30% by other estimations). The N—O bond length is 1.28 Å in di-*t*-butyl nitroxide and 1.23 Å in dianisyl nitroxide. Nitroxides display absorption at 230–325 nm, assigned to a $\pi \rightarrow \pi^*$ transition (di-*t*-butyl nitroxide, 240 nm, $\epsilon \simeq 3000$, solvent independent; diphenyl nitroxide, 320–325 nm) and at 410–570 nm assigned to an $n \rightarrow \pi^*$ transition (di-*t*-butyl nitroxide, 410–450 nm $\epsilon = 5 - 10$, solvent dependent; diphenyl nitroxide, 490–570 nm). A characteristic infrared frequency lies in the range 1310–1370 cm^{-1} (di-*t*-butyl nitroxide, 1345 cm^{-1} ; diphenyl nitroxide, 1342 cm^{-1}). References and more details are available in Forrester et al. (2).

The most common spectroscopic tool for the study of nitroxides is electron spin resonance. The esr spectrum of the nitroxide function consists of three lines, or groups of lines, due to the nitrogen hyperfine splitting (since $I_N = 1$, the number of lines = $2nI + 1 = 3$, where n = number of magnetically equivalent nuclei and I = nuclear spin). The lines are 13–15 gauss apart (this spacing is defined as the nitrogen hyperfine splitting constant, N -hfsc, with the symbol a_N or A_N) which is a good separation on the esr scale for the observation of further coupling to other nuclei. The lines are relatively sharp, not easily saturated, and sensitive to the viscosity of (and hence mobility in) the medium containing the radicals. The latter property is made use of in the technique of spin labeling (2,4a), where a stable nitroxide is attached to, or placed in, an environment where information concerning the freedom of motion at the site of the radical is desired.

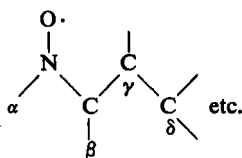
For nitroxides fully substituted with alkyl groups in the α positions, no further strong splitting is seen (although C-13 and N-15 satellite peaks and

hfs from protons on more distant carbon atoms can be detected under suitable conditions). Polar and protic solvents cause an increase in the N-hfsc, probably because of an enhanced contribution of the dipolar resonance form in high dielectric or hydrogen-bonding solvents:

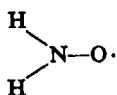


Inductive electron-withdrawing effects produced by substitution on nitrogen cause the opposite effect on the N-hfsc, probably because of deemphasis of the contribution of the dipolar resonance form. This effect can be correlated with Hammett's sigma constants (5).

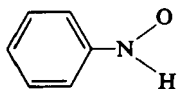
Nuclei with spin attached directly to nitrogen or one, two, or even three (carbon) atoms removed from the nitroxide function show further hyperfine splitting. From the esr point of view, the following position nomenclature has evolved:



Hydrogens attached directly to nitrogen (α -position) give large hyperfine splittings. Thus



$A_N = 11.9$, $A_H = 11.9$ gauss (unstable) $A_N = 9.13$, $A_{NH}^H = 12.12$ gauss (fairly stable)



Hyperfine splitting from hydrogens in the β position have a strong well-understood angular dependence. Splitting from more remote hydrogens also varies as a function of angle, but this angular dependence is not as well understood.

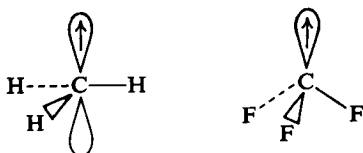
This chapter will concern itself with a description of systems where stereochemical information can be derived from the hyperfine splitting of nuclei in β - and γ -positions.

D. Structure of the Nitroxide Function

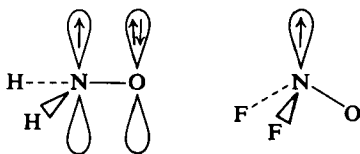
The structure of the nitroxide function based on esr and X-ray data is believed to be essentially planar with the unpaired electron (to the extent of at

least 80–90% (4)) in a N—O π^* orbital. Some observations, however, point to deviations from pure sp^2 hybridization in the case of fluoro and alkoxy nitroxides.

It is quite generally agreed that the methyl radical is planar. The esr arguments are based on the magnitude of the C-13 ($I = \frac{1}{2}$) splitting (6). Since the major contribution to hyperfine splitting comes from the spin density in s -orbitals, the greater the s -character of the hybrid orbital containing the unpaired electron, the larger the hyperfine splitting expected. The C-13 hyperfine coupling for an unpaired electron entirely localized in a $2s$ -orbital is calculated to be 1130 gauss (7). The relatively low value of 38.5 gauss for the C-13 coupling in methyl radical is consistent with the planar structure visualized wherein the unpaired electron is essentially in a pure p -orbital. The C-13 splitting for trifluoromethyl radical (6), however, is 271.6 gauss. (The C-13 splittings for $\text{CF}_2\text{H}\cdot$ and $\text{CFH}_2\cdot$ fall between the values for $\text{CH}_3\cdot$ and $\text{CF}_3\cdot$). This result is interpreted in terms of a nonplanar structure for the trifluoromethyl radical. A crude calculation ($\frac{1}{4} \times 1130 = 283$) suggests approximately sp^3 hybridization for this radical.



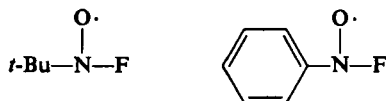
The same kind of reasoning makes the planar structure for a nitroxide reasonable. The calculated N-hfsc for an unpaired electron in a nitrogen $2s$ -orbital is 552 gauss (7). The N-hfsc of 13–15 gauss found for aliphatic nitroxides is a relatively small fraction of this, a condition which strongly suggests a planar nitroxide structure with the unpaired electron occupying a π -orbital on the nitrogen and oxygen atom. Difluoronitroxide, however, has a large N-hfsc (8): $A_N = 94.3$, $A_F = 142.2$ gauss. By analogy to the C-13 data for methyl and trifluoromethyl radical, this finding is interpreted in terms of a nonplanar structure for $\text{F}_2\text{NO}\cdot$ with the unpaired electron in an sp^5 orbital ($\frac{1}{6} \times 552$). Unfortunately, this radical is very unstable and has been detected only at low temperatures in a matrix.



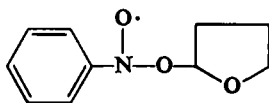
It would be of interest to know the N-hfsc for other analogs of this radical, e.g.,



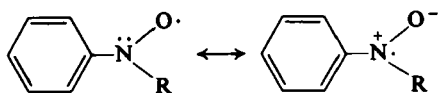
We have been unable to make the following to date:



In connection with a different study, data have been obtained which can best be interpreted in terms of a (meta and para) substituent effect on the planarity of the nitroxide function in phenyl tetrahydrofuranoxo nitroxides (9):



The photolysis of a series of meta- and para-substituted nitrobenzenes in tetrahydrofuran produced the corresponding series of phenyl tetrahydrofuranoxo nitroxides at room temperature. The N-hfsc's correlate roughly with Hammett's sigma constants (Fig. 1). Better correlations have been obtained from other phenyl nitroxides, nitrobenzene anion radicals, and diphenylhydrazyls (5). The success of such correlations is attributed to a normal substituent effect on the relative contributions of the two main resonance forms for the nitroxide function. This substituent effect "indirectly"



influences the spin density on the nitrogen atom and hence the N-hfsc. However, it can be seen that the use of σ^- is necessary for the phenyl tetrahydrofuranoxo radicals, and that a better analysis of the data is obtained by the separation of the substituents into two groups: (a) those which are capable of electron withdrawal by resonance *p*-nitro, *p*-cyano, *p*-acyl, *p*-carboethoxy, etc., and (b) all the other substituents. Two lines with approximately the same slope correlate the data best. Since the N-hfsc intercept for the *p*-nitro group is lower than for the other group, i.e., the N-hfsc's are smaller for this group of radicals than predicted from sigma values even if σ^- is used, it is tempting to

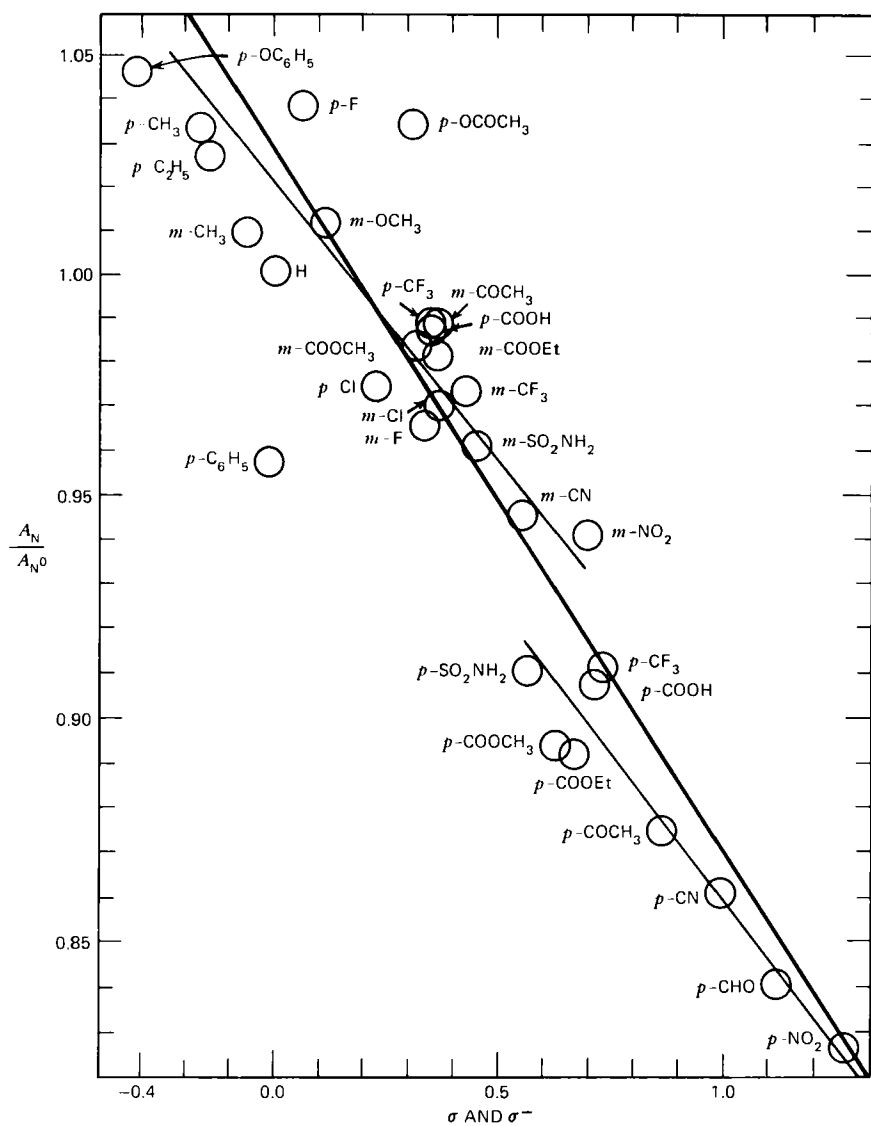
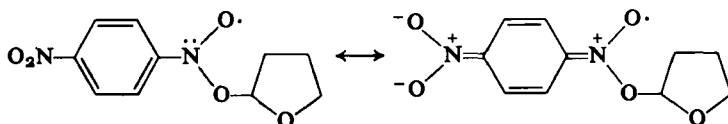
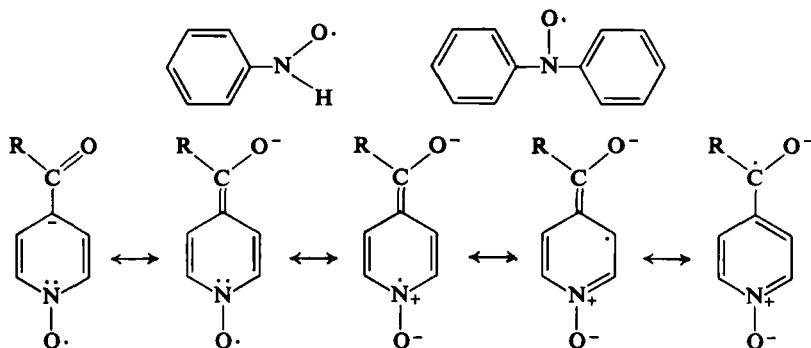


Fig. 1. Plot of the ratio of the nitrogen hyperfine coupling constant for the substituted phenyl tetrahydrofuranoxo nitroxide over the unsubstituted nitroxide as a function of Hammett's σ and σ^- constants.

suggest that the nitroxide function is more planar in the *p*-nitro group of radicals because of enhanced resonance:

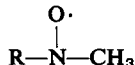


This interpretation suggests that substituent effects can affect the planarity of the nitroxide function by conjugation. It thus appears that the fluoro and alkoxy nitroxides are more nonplanar than hydrogen- or alkyl-substituted nitroxides. On the other hand, aryl and aromatic nitroxides are most likely to be completely planar functions. A comparison of the following nitroxides using Hückel molecular orbital theory to calculate spin densities supports this statement (10):



II. STEREOCHEMISTRY OF THE ALKYL GROUP IN ALKYL NITROXIDES

A. Methyl Nitroxides



The nitrogen and β -hydrogen hfsc's ($A_{\text{CH}_3}^{\text{H}}$) for methyl-substituted nitroxides are listed in Table 1. The stability of these radicals ranges from very short-lived and detectable only in a flow system ($\text{CH}_3\text{N}(\text{O}\cdot)\text{H}$) to relatively long-lived with lifetimes of many hours in solution ($\text{CH}_3\text{N}(\text{O}\cdot)-t\text{-Bu}$ and $\text{CH}_3\text{N}(\text{O}\cdot)-\text{C}_6\text{H}_5$). In all cases, the hyperfine pattern due to methyl-hydrogen

TABLE 1
Methyl Substituted Nitroxides^a

	A_N	$A_{OH_3}^H$	Solvent	Ref.
$\begin{array}{c} O\cdot \\ \\ CH_3-N-H \end{array}$	13.8	13.8	CH ₃ OH	^b , 11
$\begin{array}{c} O\cdot \\ \\ CH_3-N-CH_3 \end{array}$	16.1 15.2	13.4 12.3	CH ₃ OH CCl ₄	^c 11
$\begin{array}{c} O\cdot \\ \\ CH_3-N-CH_2OH \end{array}$	15.3	13.3	CH ₃ OH	^c
$\begin{array}{c} O\cdot \\ \\ CH_3-N-C(CH_3)_3 \end{array}$	16.4	12.7	CH ₃ OH	^c
$\begin{array}{c} O\cdot \\ \\ CH_3-N-C(CH_3)_2CH_2C(CH_3)_3 \end{array}$	15.1	12.1	CH ₂ Cl ₂	12
$\begin{array}{c} O\cdot \\ \\ CH_3-N-C(C_6H_5)_3 \end{array}$	15.3	9.96	Dioxane	13
$\begin{array}{c} O\cdot \\ \\ CH_3-N-C_6H_5 \end{array}$	11.0	10.4	CH ₃ OH	^c

^a The hyperfine coupling is given in gauss (here and in subsequent tables).

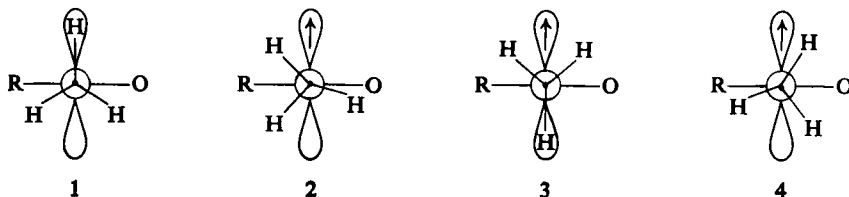
^b C. J. W. Gutch and W. A. Waters, *J. Chem. Soc.*, **1965**, 751.

^c G. Chapelet-Letourneux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, **1965**, 3283.

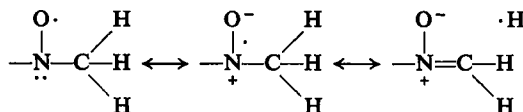
splitting consists of a 1:3:3:1 quartet due to equivalent coupling from three β -hydrogens. The magnitude of the methyl β -hydrogen coupling is relatively constant for a variety of radicals of differing structure (12.1–13.8 gauss), the only sizable deviation occurring for trityl methyl and phenyl methyl nitroxides. The smaller value in the latter case is undoubtedly due to the delocalization of the unpaired electron into the phenyl ring, leaving a lower spin density on the nitrogen atom for the methyl group to interact with.

Because the coupling observed from the methyl hydrogens is always due to three equivalent hydrogens, the three protons must exist in equivalent magnetic environments on the esr time scale (at least at room temperature). The methyl is either rotating freely or rocking about the 3-fold symmetry axis so that all protons are in equivalent average environments. From the following

projections (1-4) it can be seen that an oscillation of $\pm 30^\circ$ about any equilibrium position places the hydrogens in all possible dihedral angles with respect to the nitrogen p -orbital.*



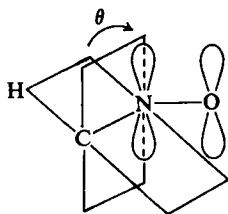
The mechanism of the methyl proton hyperfine coupling is most readily (but not necessarily most accurately) ascribed to hyperconjugation:



The magnitude of this coupling depends both on the spin density on nitrogen and on the dihedral angle between the p -orbital on nitrogen and the C—H bond of the methyl group. The relationship (15)

$$A_{\text{CH}_3}^{\text{H}} = \rho_{\text{N}}(B_0 + B_2 \cos^2 \theta)$$

where ρ_{N} = spin density on nitrogen, B_0 and B_2 are constants, and θ = dihedral angle, defined as the angle between the plane including the p -orbital on nitrogen and the N—C bond and the plane of the H—C and C—N bonds:



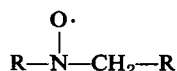
has much support in esr spectroscopy (1). Maximum coupling is observed when $\theta = 0$, and minimum or zero coupling when $\theta = 90^\circ$ (i.e., $B_0 \simeq 0$). Since it can be shown that $\cos^2 \theta = \frac{1}{2}$ for a freely rotating group, $A_{\text{H}} = \rho_{\text{N}}(B_2/2)$ for methyl substituted nitroxides. Taking $A_{\text{CH}_3}^{\text{H}} = 13$ gauss, $B_2\rho_{\text{N}} = 26$ (12); taking $A_{\text{N}} = 16$ gauss and $A_{\text{N}} = 35.6\rho_{\text{N}} + 0.9\rho_0$ (10,14), $\rho_{\text{N}} = 0.44$

* Although the oscillation of $\pm 30^\circ$ does not place each hydrogen in an identical "stereochemical" environment, it does place each hydrogen in an equivalent "magnetic" environment, i.e., the environment with respect to the p -orbital containing the unpaired electron.

since $\rho_N + \rho_0 = 1$; thus $B_2 \simeq 59$ and $A_H = \rho 59 \cos^2 \theta$ or $A_H \simeq 26 \cos^2 \theta$ for aliphatic nitroxides.

It is tempting to use this relationship directly to calculate the dihedral angle for the β -hydrogen in an alkyl nitroxide, and thus obtain the conformation of the group attached. The danger lies in assuming a static value for θ when in fact the coupling comes from an atom which oscillates about some "average" equilibrium position. However, if this caution is kept in mind, much can still be learned about the "approximate" stereochemistry of alkyl nitroxides from their esr spectra.

B. Nitroxides with β -Methylene Hydrogens



A variety of substituted methylene nitroxides have been obtained and are listed in Table 2. It should be noted that the N-hfsc is essentially the same as

TABLE 2
Dialkyl Nitroxides with β -Methylene Hydrogens

	A_N	$A_{\text{CH}_2}^H$	Solvent	Ref.
Ethyl				
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2-\text{N}-\text{CH}_2\text{CH}_3 \end{array}$	15.2	10.3	CCl_4	11
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2-\text{N}-\text{C}(\text{CH}_3)_3 \end{array}$	15.7	10.7	CH_2Cl_2	12
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2-\text{N}-\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_3 \end{array}$	15.1	10.7	CH_2Cl_2	12
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2-\text{N}-\text{C}\phi_3 \end{array}$	15.2	8.82	Dioxane	13
<i>n</i> -Propyl				
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2\text{CH}_2-\text{N}-\text{CH}_2\text{CH}_2\text{CH}_3 \end{array}$	14.5	9.8	CCl_4	11
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2\text{CH}_2-\text{N}-\text{CH}(\text{CH}_3)_2 \end{array}$	16.0	10.6	—	^a , 12
$\begin{array}{c} \text{O}\cdot \\ \\ \text{CH}_3\text{CH}_2\text{CH}_2-\text{N}-\text{C}\phi_3 \end{array}$	15.2	8.95	Dioxane	13

(Continued)

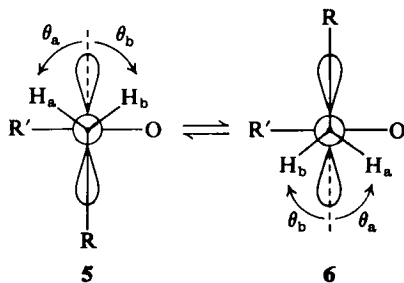
TABLE 2 (Continued)

	A_N	$A_{CH_2}^H$	Solvent	Ref.
Benzyl				
$\phi-CH_2-\overset{\overset{O\cdot}{ }}{N}-CH_2\phi$	14.9	8.7	CCl_4	11
$\phi-CH_2-\overset{\overset{O\cdot}{ }}{N}-C(CH_3)_2$	14.6	7.7	CH_2Cl_2	12
$\phi-CH_2-\overset{\overset{O\cdot}{ }}{N}-C(CH_3)_2CH_2C(CH_3)_3$	14.8	8.1	CH_2Cl_2	12
$\phi-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.2	7.8	Dioxane	13
Other				
$CH_3(CH_2)_3-\overset{\overset{O\cdot}{ }}{N}-(CH_2)_3CH_3$	14.5	10.0	CCl_4	11
$CH_3(CH_2)_3-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.1	8.9	Dioxane	13
$CH_3(CH_2)_5-\overset{\overset{O\cdot}{ }}{N}-(CH_2)_5CH_3$	14.5	10.0	CCl_4	11
$CH_3(CH_2)_5-\overset{\overset{O\cdot}{ }}{N}-C(CH_3)_3$	15.7	10.4	Ether	^a , 12
$(CH_3)_2CHCH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.1	9.7	Dioxane	13
$CH_3O-\overset{\overset{O}{ }}{C}-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.3	7.6	Dioxane	13
$HO-\overset{\overset{O}{ }}{C}-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	14.85	7.4	Dioxane	13
$CH_3O-\overset{\overset{O}{ }}{C}-CH_2-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.3	10.2	Dioxane	13
$HO-\overset{\overset{O}{ }}{C}-CH_2-NH-\overset{\overset{O}{ }}{C}-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.0	6.85, 7.5, 8.0	Dioxane	13
$HO-\overset{\overset{O}{ }}{C}-CH(CH_3)-NH-\overset{\overset{O}{ }}{C}-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.0	7.0, 7.5, 8.0	Dioxane	13
$CH_3O-\overset{\overset{O}{ }}{C}-CH(CH_2\phi)-NH-\overset{\overset{O}{ }}{C}-CH_2-\overset{\overset{O\cdot}{ }}{N}-C\phi_3$	15.0	8.3	Dioxane	13

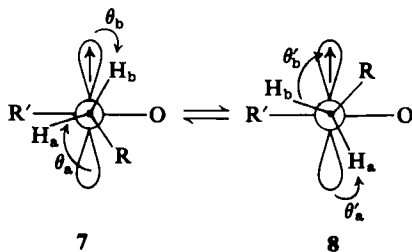
^a A. Rassat and H. Lemaire, *J. Chim. Phys.*, **61**, 1576 (1964).

for the methylene-substituted nitroxides. However, the methylene H-hfs is smaller than the methyl H-hfs for radicals of corresponding structure (~ 7 – 11 as compared to ~ 13 gauss). The same observation, namely, that methylene coupling is smaller than methyl coupling, has been reported for a large number of other radical systems and reasons for this occurrence have been thoroughly discussed (1).

It is generally agreed that, if the substituted methylene groups were freely rotating with respect to the plane of the N—O bond, the methylene H-hfsc would be essentially the same as the H-hfsc of methyl groups in nitroxides of corresponding structure (ignoring small possible influences from inductive effects on the hfs). The observation that methylene couplings are in fact smaller is attributed to the preference of the alkyl group for conformations wherein the average dihedral angle to the C—H bond is larger than the same angle for the C—H bond in freely rotating methyl groups (for methyl, $\theta_{av} = 45^\circ$). The obvious conformations which account for these observations are **5** and **6**, where the dihedral angles, θ_a and θ_b , are equal:



However, since the steric requirements of R' and O are different, it would be surprising to find **5** and **6** to be the correct conformation for all nitroxides with substituted methylene groups regardless of the bulk of R' . And yet, most examples known show equivalent coupling by the methylene hydrogens at room temperature. A better explanation is to suggest that the appropriate conformation for these nitroxides is a less symmetrical one, e.g., **7** or **8**.



Since **7** and **8** are mirror images in which H_a and H_b are interchanged,

$\theta_a = \theta'_b$ and $\theta_b = \theta'_a$, rapid oscillation of the methylene group will produce equivalent methylene hydrogen couplings.

Support can be found for this interpretation from studies on the effect of temperature on the spectra of certain nitroxides. Thus, although the esr spectra of ethyl or benzyl *t*-octyl nitroxides are normal at room temperature, i.e., the nitrogen 1:1:1 triplet is split into methylene 1:2:1 triplets, the spectra show anomalous line widths and line intensities at lower temperatures, e.g., -40° , such that the intensity "2" lines of the methylene triplets are much broader and of lower intensity than the intensity "1" lines of the methylene triplet. (The same type of spectrum is obtained for benzyl and glycyl trityl nitroxide at room temperature, Fig. 2).

At even lower temperatures (e.g., -100°) the spectrum for ethyl *t*-octyl nitroxide can be resolved into 12 lines. Two values for the methylene H-hfsc's can be extracted from the spectrum. These are 8.75 and 12.75 gauss. Spectra with regular sharp and broad line splitting patterns are said to exhibit *line width alternation* (53) (LWA) (1). The effect in this case is attributed to an interchange of two different coupling constants for the methylene protons at a rate which is between the fast exchange limit (where both methylene protons experience an equivalent magnetic environment through rapid, $\gg 10^7 \text{ sec}^{-1}$, interchange of coupling constants) and the slow exchange limit (where proton interchange is slow enough, $\ll 10^7 \text{ sec}^{-1}$, to give two H-hfsc's).

One can account for these results in terms of conformations 7 and 8, where the methylene H-hfsc's are unequal and a rapid jump occurs from one



Fig. 2. The esr spectra of (A) the nitroxide of tritylglycine methyl ester in dioxane and (B) tritylglycine in aqueous sodium hydroxide (pH 8) at room temperature. Courtesy of American Chemical Society, taken from *J. Org. Chem.*, **34**, 4072 (1969).

possible conformer to the other. For ethyl *t*-octyl nitroxide this rotation is rapid at room temperature, intermediate in rate at -40° , and slow at -100° . From this information the energy of activation for the jump was estimated to be 7.5 kcal/mole (12). At temperatures where LWA is observed, the substituted methylene group rotates from **7** at an intermediate rate ($\sim 10^{-7} \text{ sec}^{-1}$) to **8** wherein the equilibrium conformation has the same dihedral angle relationship to the C—H and C—R bonds as in **7**, but *the identities of H_a and H_b are interchanged*. At even lower temperatures this rotation is slow and the group is locked into conformation **7** or **8** on the esr time scale.

Other examples of LWA have been observed in this series of nitroxides as listed in Table 3. Unfortunately the spectra of alkyl trityl nitroxides were not studied as a function of temperature (13). Probably other examples of this phenomenon could be found through this approach. However, some tentative conclusions can be drawn on the basis of data on hand. The spectrum of benzyl trityl nitroxide showed LWA at room temperature, whereas LWA was

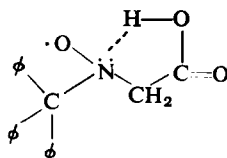
TABLE 3
Nitroxides Exhibiting Nonequivalent Methylene Coupling^a

	Temperature	$A_{\text{CH}_2}^{\text{H}}$
$\text{CH}_3\text{CH}_2-\text{N}(\text{O}\cdot)-t\text{-octyl}$	R.T. -40° -100°	10.7 LWA 8.75, 12.75
$\phi\text{CH}_2-\text{N}(\text{O}\cdot)-t\text{-octyl}$	R.T. -40° — -80°	8.1 LWA
$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2-\text{N}(\text{O}\cdot)-\text{C}\phi_3$	R.T.	LWA
$\phi\text{CH}_2-\text{N}(\text{O}\cdot)-\text{C}\phi_3$	R.T.	LWA
$\text{HOOCCH}_2-\text{N}(\text{O}\cdot)-\text{C}\phi_3$	R.T.	LWA
$\text{OOCCH}_2-\text{N}(\text{O}\cdot)-\text{C}\phi_3$ (?)	R.T.(pH 8/H ₂ O)	LWA
$\text{HOOCCH}_2\text{NHCCH}_2-\text{N}(\text{O}\cdot)-\text{C}\phi_3$	R.T.	6.85, 7.5, 8.0 with LWA
$\text{HOOCCH}(\text{CH}_3)\text{NHCCH}_2-\text{N}(\text{O}\cdot)-\text{C}\phi_3$	R.T.	7.0, 7.5, 8.0 with LWA

^a The *t*-octyl derivatives are reported by Chapelet-Letourneux et al. (12); the trityl derivatives are taken from Maender and Janzen (13), LWA = line width alternation in spectrum.

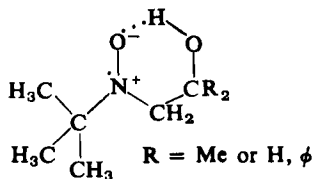
found for benzyl *t*-octyl nitroxide only below room temperatures (-40°). This indicates that the trityl group is more sterically hindering in nitroxides than is *t*-octyl. Furthermore, LWA was shown by the *sec*-butyl trityl nitroxide spectrum at room temperature, whereas the *n*-butyl trityl nitroxide spectrum was normal, indicating that *sec*-butyl is more sterically hindering than *n*-butyl. None of these conclusions comes as a surprise.

It is of interest, however, to note that the trityl glycine spectrum shows LWA, whereas the spectrum of trityl glycine nitroxide methyl ester is normal. The carboxyl proton appears to be necessary for LWA, possibly the result of intramolecular hydrogen-bonding in the nitroxide as in 9. That in aqueous



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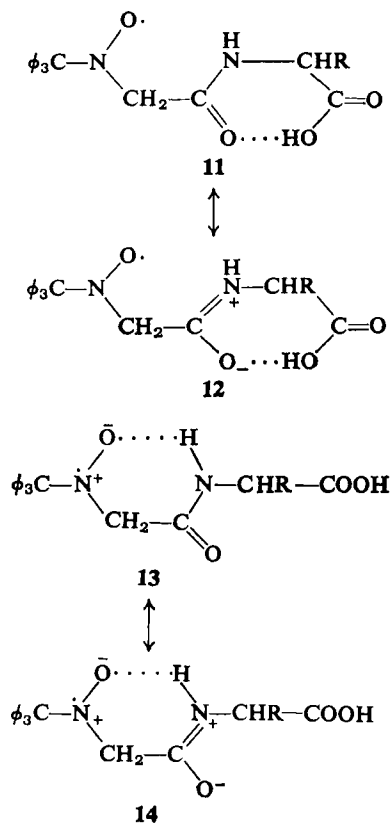
basic solution the trityl glycyI nitroxide spectrum shows extremely broad lines with marked LWA indicates severe restricted rotation of the methylene group, probably due to solvation of the carboxylate group. A number of additional examples of nitroxides with spectra displaying LWA at room temperature believed to be due to intramolecular hydrogen-bonding have recently been discovered in our laboratories.*



The spectra of two trityl peptide nitroxides show an additional interesting feature (13). Although the spectra of trityl glycyIglycyl and trityl glycyIalanyl nitroxides show LWA, additional splittings are resolved which can be analyzed for each spectrum in terms of overlapping peaks coming from three species with very similar methylene H-hfsc, (Table 3). It is suggested that possibly three structures exist for these nitroxides, varying only in the way the peptide part of the molecule is internally hydrogen-bonded; e.g., see 11-14.

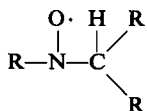
These preliminary investigations show that more attention needs to be

* Unpublished work of Dr. Irene G. Lopp.

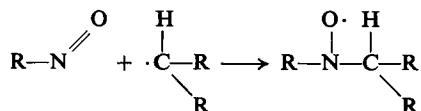


devoted to these types of studies. The nitroxide function as an intrinsic spin probe, i.e., as an integral part of a complicated molecule, may prove to have important applications in structure elucidation.

C. Nitroxides with β -Methine Hydrogens



A large number of nitroxides with this general structure have been made (a) by oxidation of the secondary amines of corresponding structure, (b) by radical addition to an alkyl or aryl nitroso compound (2,16,17):



A selection of such radicals is listed in Table 4, which demonstrates typical nitrogen and β -methine coupling constants. The main characteristic of the methine H-hfsc is the relatively small value, approximately 0–5 gauss. This

TABLE 4
Nitroxides with β -Methine Hydrogens

	A_N	A_{CH}^H	Ref.
Isopropyl			
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ (\text{CH}_3)_2\text{C}-\text{N}-\text{H} \end{array}$	12.7	12.1	12
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ (\text{CH}_3)_2\text{C}-\text{N}-\phi \end{array}$	11.1	2.8	^a , 12
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ (\text{CH}_3)_2\text{C}-\text{N}-\text{CH}_2\text{CH}_3 \end{array}$	16.0	4.8	^a , 12
$\begin{array}{c} \text{H} \quad \text{O} \cdot \quad \text{H} \\ \quad \quad \\ (\text{CH}_3)_2\text{C}-\text{N}-\text{C}(\text{CH}_3)_2 \end{array}$	14.7	4.5	^b , 11, 12
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ (\text{CH}_3)_2\text{C}-\text{N}-\text{C}(\text{CH}_3)_3 \end{array}$	16.8	1.8	^c , 12
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ (\text{CH}_3)_2\text{C}-\text{N}-\text{C}\phi_3 \end{array}$	14.7	0.4	13
α -Substituted benzyl			
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \phi-\text{C}-\text{N}-\text{C}(\text{CH}_3)_3 \\ \\ \text{CH}_3 \end{array}$	14.2	3.4	19
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \phi-\text{C}-\text{N}-\text{C}(\text{CH}_3)_3 \\ \\ \text{CH}_3-\text{CH}_2 \end{array}$	13.9	3.2	19
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \phi-\text{C}-\text{N}-\text{C}(\text{CH}_3)_3 \\ \\ \text{CH}_3(\text{CH}_2)_3 \end{array}$	14.0	3.1	19
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \phi-\text{C}-\text{N}-\text{C}(\text{CH}_3)_3 \\ \\ \phi-\text{CH}_2 \end{array}$	13.9	2.4	19
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \phi-\text{C}-\text{N}-\text{C}(\text{CH}_3)_3 \\ \\ \phi \end{array}$	13.7	2.0	19

TABLE 4 (Continued)

	A_N	A_{CH}^H	Ref.
α -Substituted benzyl (continued)			
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ (\text{CH}_3\text{CH}_2)_2\text{C}-\text{N}-\text{C}\phi_3 \end{array}$	13.91	1.77	13
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \text{HOOC}-\text{N}-\text{C}\phi_3 \\ \\ \text{CH}_3 \end{array}$	14.05	1.68	13
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \text{CH}_3\text{OOC}-\text{N}-\text{C}\phi_3 \\ \\ \text{CH}_3 \end{array}$	13.89	2.36	13
$\begin{array}{c} \text{H} \quad \text{O} \cdot \\ \quad \\ \text{CH}_3\text{OOC}-\text{N}-\text{C}\phi_3 \\ \\ \text{CH}_2\text{OH} \end{array}$	13.55	3.78	13

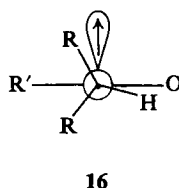
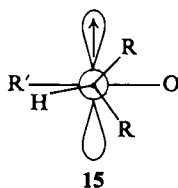
^a A. Rassat and H. Lemaire, *J. Chem. Phys.*, **61**, 1576 (1964).

^b G. Chapelet-Letourneux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, **1965**, 3283.

^c H. Lemaire, R. Ramasseul, and A. Rassat, *Mol. Phys.*, **8**, 557 (1964).

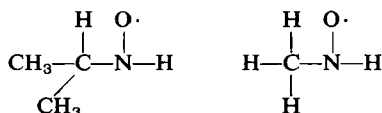
^d H. Lemaire and A. Rassat, *J. Chem. Phys.*, **61**, 1580 (1964).

fact is attributed to the dominance of the conformation wherein the average dihedral angle to the C—H bond is close to 90° ($A_H \simeq 0$ at $\theta = 90^\circ$). Of the



two possible conformations, **15** is more probable. The H-hfsc's vary with the bulk and nature of the group attached but not necessarily predictably (Table 4). Numerous other nitroxides are reported in which the β -methine hydrogen coupling is too small to detect (13) (less than the line width), e.g., in the trityl series (13), the cyclohexyl, 2-pentyl, and 2-octyl nitroxides.

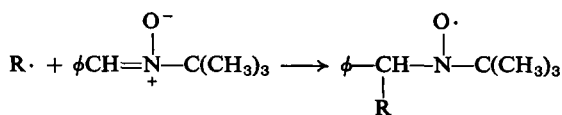
It is of interest to note that when $R' = \text{H}$, as in isopropyl hydronitroxide, the β -methine H-hfsc is unusually large (12.1 gauss, Table 4):



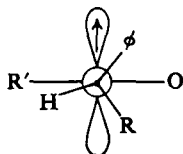
Since the methyl H-hfsc in methyl hydro nitroxide is 13.8 gauss (Table I), one concludes that the isopropyl group in isopropyl hydronitroxide is freely rotating on the esr time scale, an interesting but not entirely unexpected result.

Although a more detailed picture of the average conformation assumed by substituted nitroxides of this type cannot be obtained from a comparison of the β -methine H-hfsc's as a function of structure, preliminary inspection of spectra obtained from a series of nitroxides shows that the line widths of the spectrum may in fact provide some information of this type. Thus the spectrum of benzhydryl *t*-butyl nitroxide has unusually sharp lines, while *n*-butyl- α -benzyl *t*-butyl nitroxide has relatively broad (but symmetrical) lines. The line widths of the methyl and ethyl derivatives appear to fall in between. One interpretation of these observations is that the oscillation of the benzhydryl group about the nodal plane of the *nitrogen p*-orbital is very regular ("harmonic") owing to the symmetrical structure of the oscillator, whereas in the 1-phenyl-1-pentyl group this may not be true. Since only one proton gives splitting, line width alternation effects are not exhibited by these spectra. However, future studies on the temperature dependence of the line widths might be fruitful.

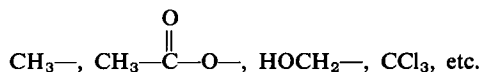
The small but reproducible difference in β -H-hfsc's for a series of differently substituted nitroxides has been used as a diagnostic tool for the *in situ* identification of reactive and short-lived free radicals in reacting systems (19). In our laboratories this approach has been developed into a general technique, called spin trapping (54), for the detection and identification of free radicals by the use of phenyl *t*-butyl nitron as a spin trap. Neutral radicals such as methyl, ethyl, *n*-butyl, phenyl, and benzyl add to the carbon atom of the nitron function to give *t*-butyl α -substituted benzyl nitroxides (spin adducts):



The β -H and N-hfsc's of the spin adduct are theoretically (and ideally) a unique set of parameters for each radical trapped. The reason is that the bulk of the trapped group will affect the conformation and hence the C—H dihedral angle differently for each radical trapped,



while the electronegativity of the group whether

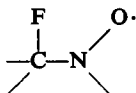


will affect the spin density distribution on the nitroxide function through an inductive influence on the dipolar bond. The conception of the spin-trapping technique was based entirely on stereochemical principles and has already shown considerable promise as a research tool in studies of free-radical reactions (19).

III. STEREOCHEMISTRY OF NITROXIDES WITH β -FLUORO AND β -CHLORO SUBSTITUENTS

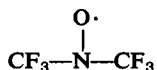
Radicals wherein fluorine replaces hydrogen have generated considerable interest among free-radical chemists for some time. Because fluorine has the same valence and not much larger atomic radius than hydrogen, the effect of a gross change in electronegativity on the system can be gauged by replacing hydrogen with fluorine. The fluorine atom has an additional attraction for esr chemists in that the hyperfine splitting expected in suitable systems is very large ($\sim 17,200$ gauss for a $2s$ electron), the nuclear spin value is a very convenient one ($I = \frac{1}{2}$, 100% abundance), and the unshared electron pairs provide a rich field for theoretical interpretations and speculations about the types of bonding and spin transfer mechanisms possible.

The development of the factors which determine the β -fluorine coupling as a function of dihedral angle has involved numerous nitroxides (Table 5)



and has uncovered some initially unexpected stereochemistry. Since the story is not complete at this time, it is best told historically.

The first report by Blackley (20) of the synthesis of bistrifluoromethyl nitroxide was very exciting because it showed that this radical is an unusually



stable molecule, comparable in stability to di-*t*-butyl nitroxide. The stability is largely due to the inertness of C—F bonds to radical reactions (e.g., F-atom abstraction or disproportionation). Other perfluoroalkyl nitroxides were shown to have similar stability in a subsequent paper (21). The N-hfsc's for

TABLE 5
Fluoroalkyl Nitroxides

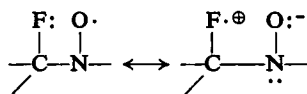
	A_N	A_N^p	Ref.
$\text{CF}_3-\text{N}(\text{O}\cdot)-\text{CF}_3^a$	9.3	8.2	20, 22
$\text{CF}_3-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3^a$	12.03	12.03	27, 28, 30
$\text{CF}_3-\text{N}(\text{O}\cdot)-\text{OC}(\text{CH}_3)_3$	22.8	5.9	24, 25
$\text{CF}_3-\text{N}(\text{O}\cdot)-\phi$	9.0	9.0	^b
$\text{CF}_3\text{CF}_2-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3^a$	11.25	21.16	27, 30
$\text{CF}_3\text{CF}_2\text{CF}_2-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3^a$	11.34	17.64	27, 30
$\phi\text{CF}_2-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3^a$	11.66	19.26	28
$\text{ClCF}_2\text{CF}_2-\text{N}(\text{O}\cdot)-\text{OC}(\text{CH}_3)_3$	21.8	9.5	24, 25
$\text{CH}_3\text{OOC}\text{CF}_2\text{CF}_2-\text{N}(\text{O}\cdot)-\text{CF}_2\text{CF}_2\text{COOCH}_3$	9.4	13.8	23
$(\text{CH}_3)_2\text{CF}-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3^a$	12.11	2.27	27, 30
$\phi\text{CHF}-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3$	12.1	45.4 ^{b, c}	31

^a At 25°, hfsc's as a function of temperature given in reference.

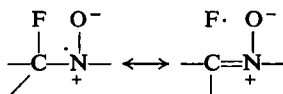
^b Unpublished work of Dr. B. R. Knauer in our laboratories.

^c $A_H = 1.18$ gauss.

these nitroxides are smaller than for dialkyl nitroxides (Table 5). This has been attributed to spin transfer from the N—O π -system to the fluorine orbitals by either (a) the involvement of the unshared electron pairs of the fluorine

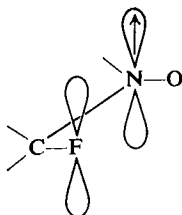


or (b) a hyperconjugation mechanism:

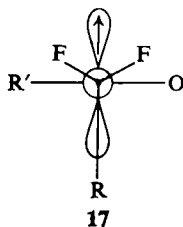


The effect of varying the temperature on the N- and F-hfsc in bistrifluoromethyl nitroxide has been carefully investigated (22). It was found that the N-hfsc decreased at the same time as the F-hfsc increased with a decrease in temperature. Spin transfer from the nitrogen atom to the fluorine orbitals seemed to be implied from the data.

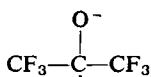
About the same time, Strom and Bluhm (23,24) reported that the β -F-hfsc was greater in a difluoromethylene nitroxide derivative than in a trifluoromethyl nitroxide. This observation came as a surprise because numerous examples of methylene *hydrogen* coupling were known wherein the coupling decreases, not increases, with substitution as previously discussed. It was tentatively proposed that the coupling in perfluoromethylene groups might be larger because of a 1,3- p - π spin transfer mechanism, which might be favored at larger dihedral angles and be at a maximum when this angle is 90° .



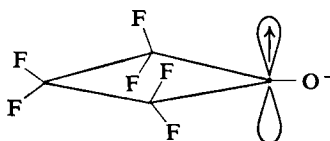
Implicit in this proposal was the assumption that the substituted perfluoromethylene group assumed essentially the same average conformation in these nitroxides as the substituted methylene groups were known to do (17). Al-



though it was next shown in our laboratories that the F-hfsc also increases in value when the dihedral angle decreases from 45° to 25 – 30° (26),



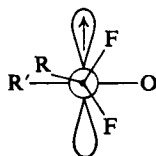
$$A_{\beta}^{\text{F}} = 24.7 \text{ gauss, } \theta_{\text{av}} = 45^{\circ}$$



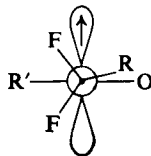
$$A_{\beta}^{\text{F}} = 82.9 \text{ gauss, } \theta = 27\text{--}30^{\circ}$$

(planar on esr time scale)

it was Klabunde's temperature study on trifluoromethyl, perfluoroethyl, and perfluoroisopropyl *t*-butyl nitroxides (27,28) which gave new insight into the conformational problem of perfluoroalkyl nitroxides. This work and subsequent studies in our laboratories (28,29) have provided results which support the proposal that *the average conformation for nitroxides with difluoromethylene groups is not the same as that of nitroxides of corresponding structure without fluorines* (i.e. it is not 17). The conformations which account for all



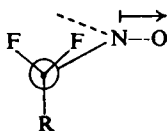
18



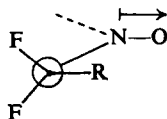
19

the observations are shown in 18 and 19. This proposal was also made by Underwood (30) as an alternative interpretation of Strom and Bluhm's earlier observations. By inspection of molecular models of, e.g., perfluoroethyl and α,α -difluorobenzyl *t*-butyl nitroxide, it is clear that 19 is a less crowded conformation than 18. Models also show that the eclipsing of the R group with the oxygen atom of the nitroxide function in 19 appears to present about the same problem as crowding of the R' group and the oxygen atom by the fluorine atoms in 17. The latter interaction is insignificant in the hydrogen analog (7) but becomes very severe in the chlorine analog (discussed later).

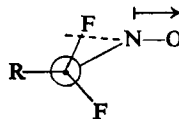
We have also argued that a dipole-dipole interaction of neighboring groups may contribute to the stability of the average conformation of these nitroxides (28). Thus, e.g., for α,α -difluorobenzyl *t*-butyl nitroxide, conformation 19 would be stabilized while 18 would be destabilized by this effect, all other factors remaining equal.



17a

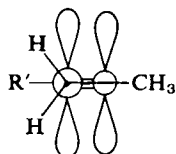


19a

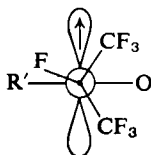
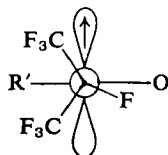


18a

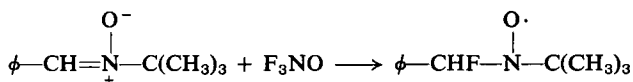
As has been noted by Underwood and co-workers (30), the preferred conformation for an ethyl group in acyclic aldehydes and ketones is analogous to **19**.



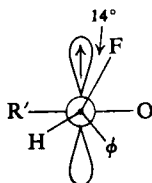
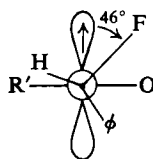
The work of Klabunde (27) and Underwood (30) also showed that the average conformation for a group with a "methine fluorine" is analogous to **15** or **16**. The F-hfsc in perfluoroisopropyl nitroxide is small and decreases with decrease in temperature, an expected result since the amplitude of the oscillations of the methine group would decrease with a decrease in temperature.

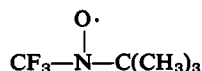
**20****21**

Despite of what appear to be reasonable arguments supporting conformation **19** for difluoromethylene and **20** (or **21**) for fluoromethine nitroxide derivatives, an example of a fluoronitroxide wherein the conformation could be deduced explicitly was not available until very recently (29). After many unsuccessful attempts we were able to obtain esr spectra for the mono fluorine atom spin adduct of phenyl *t*-butyl nitron by the use of trifluoramine oxide:



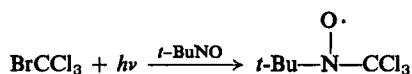
The radical appears to be quite stable in solution (in the absence of excess reagents) and gives the largest F-hfsc (45.6 gauss) known among fluoroalkyl nitroxides. The H-hfsc is unusually small (1.18 gauss). From the latter value the average C—H dihedral angle was calculated; $\theta_{\text{H}} = 74^\circ$. Then $\theta_{\text{F}} = 14^\circ$ as in **22** or 46° as in **23**. Since for trifluoromethyl *t*-butyl nitroxide,

**22****23**



where $\theta_{\text{av}} = 45^\circ$, $A_{\text{F}}^{\text{F}} = 12.03$ gauss, we concluded that conformation **22** was probably the correct one of the two. Molecular models, as well as the large F-hfsc obtained, both support conformation **22**. This nitroxide appears to provide the missing piece to the puzzle of the angular dependence of β -fluorine hyperfine coupling. If all the assumptions and rough calculations described here are allowed, the plot of β -fluorine coupling as a function of angle shows that $A_{\text{F}} \propto \cos^2\theta$, a trend predicted by both Extended Hückel (29) and INDO molecular orbital calculations (31,32). This plot also lends support to the assignments of conformation as discussed.

A similar approach has been used to provide information about the conformations assumed by β -chloroalkyl nitroxides (33) (Table 6). Trichloromethyl *t*-butyl nitroxide was made by nitroso-*t*-butane trapping of the trichloromethyl radical produced by photolysis of bromotrichloromethane:



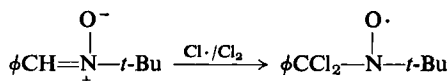
α,α -Dichlorobenzyl *t*-butyl nitroxide was made by the action of chlorine atoms (produced by photolysis of *t*-butyl hypochlorite in the gas phase) on phenyl *t*-butyl nitron:

TABLE 6
Chloroalkyl Nitroxides

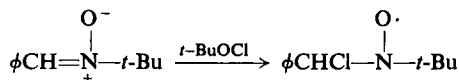
	A_{N}	A_{Cl}	Ref.
$\text{Cl}_3\text{C}-\text{N}(\text{O}\cdot)-\text{CCl}_3$	11.8	1.25	^a
$\text{Cl}_3\text{C}-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3$	12.4	2.3	33
$\phi\text{CCl}_2-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3$	13.2	3.3	33
$\phi\text{CHCl}-\text{N}(\text{O}\cdot)-\text{C}(\text{CH}_3)_3^{\text{b}}$	12.1	6.1	33

^a H. Sutcliffe and H. W. Wardale, *J. Amer. Chem. Soc.*, **89**, 5487 (1967).

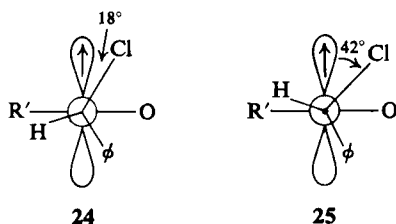
^b $A_{\text{H}} = 0.75$ gauss.



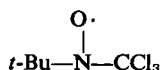
α -Chlorobenzyl *t*-butyl nitroxide was (at first accidentally) produced from phenyl *t*-butyl nitron and *t*-butyl hypochlorite in benzene:



The spectrum of this nitroxide is exciting. Not only is splitting from both chlorine isotopes (^{35}Cl , ^{37}Cl) observed, but the magnitude of the coupling is larger than that reported for the chlorine atom in *any* radical previously studied (6.05, 4.88 gauss). The H-hfsc is small (0.75 gauss). By similar calculations as used for the fluorobenzyl nitroxide, the following dihedral angles were found: $\theta_{\text{H}} = 78^\circ$ and $\theta_{\text{Cl}} = 18^\circ$ (as in **24**) or 42° (as in **25**). Again it was

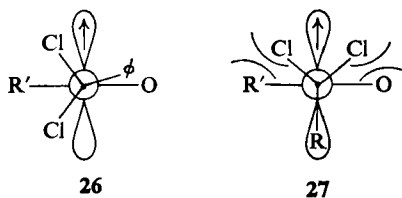


concluded that **24** is the more likely conformation, since the Cl-hfsc in tri-



chloromethyl *t*-butyl nitroxide, is 2.3 gauss. Since all the hyperfine splittings in the spectrum of **24** were unaffected by change of temperature in the 35–90° range, it is assumed that the chlorine atom is essentially locked in the conformation shown. Molecular models indicate that **24** is clearly the more stable conformation.

It is interesting to note that the β -chloro coupling in the dichlorobenzyl derivative fits into the following sequence of *t*-butyl nitroxides nicely, if it is assumed that conformation **26** is the most stable for this nitroxide: trichloro-

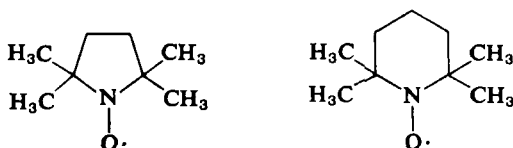


methyl, $A_{\text{Cl}} = 2.3$ gauss, $\theta_{\text{Cl}} = 45^\circ$; dichlorobenzyl $A_{\text{Cl}} = 3.3$ gauss, $\theta = 30^\circ$; monochlorobenzyl, $A_{\text{Cl}} = 6.1$ gauss, $\theta = 18^\circ$. The sequence shows that an increase in Cl-hfs occurs with a decrease in dihedral angle.

Conformation **26** is analogous to the one proposed for nitroxides with the difluoromethylene group **19** and is strongly supported by inspection of molecular models. Conformation **27**, which is analogous to **7** for nitroxides with methylene groups, is very unfavorable for chlorine atoms because of the large interactions between these atoms and R' and the oxygen atom of the nitroxide.

IV. ALICYCLIC NITROXIDES

The discussion of dialkyl nitroxide stereochemistry given to this point provides a good foundation for the understanding of the esr spectra of cyclic and bicyclic nitroxides. Although numerous stable tetramethyl pyrrolidine and piperidine nitroxide derivatives



have been under investigation for a long time (2,4,34–38), very little stereochemical information can be deduced from the esr spectra of these radicals. The results of both esr and 310-MHz nmr show, for example, that the tetramethylpiperidine nitroxide shown is either planar or in fast equilibrium between two chair conformations at room temperature (37). Unsubstituted or partially substituted cyclic nitroxides give spectra with considerably more stereochemical information, and they will be discussed here.

The earliest report of an unsubstituted cyclic nitroxide goes back to 1961 when Coppinger and Swalen (39) first detected nitroxides in the peroxide oxidation of secondary amines. The coupling constant of piperidine nitroxide was included in a table with other nitroxides without comment (15 lines, $A_{\text{N}} = 17.4$ and $A_{\text{H}}^{\text{H}} = 11.7$ gauss). Although Rassat and co-workers (40) also reported on the coupling constants of piperidine and morpholine ($A_{\text{N}} = 16.8$ and 16.8; $A_{\text{H}}^{\text{H}} = 22.6$ and 22.0 gauss, respectively), a careful study and analysis of the esr spectra of cyclic nitroxides did not appear until 1968 (41). During this time (1967–1968) we were engaged in a fairly extensive study of the esr spectra of alicyclic nitroxides as a function of ring size and substituent, including long-range γ -H coupling. Similar studies have since been described by other groups of workers. Our results, to the extent that they have not been published by others, will be given here (42).

The spectrum of a dialkyl nitroxide with two methylene groups attached to nitrogen is expected to show coupling from four *equivalent* β -hydrogens to give a quintet with a 1:4:6:4:1 intensity sequence. Examples of nitroxides where the β -H-hfsc becomes nonequivalent on the esr time scale have been described. Alicyclic nitroxides provide further examples of these types of nitroxides (Table 7).

Pyrrolidine (40-42), azacycloheptane (41,42), azacyclooctane (42), and

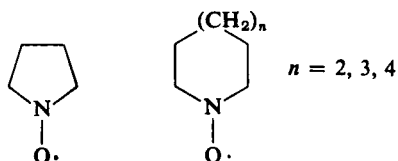
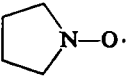
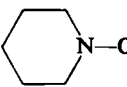
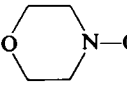
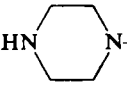
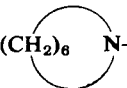
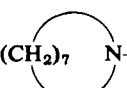
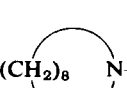
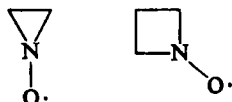


TABLE 7
Alicyclic Nitroxides

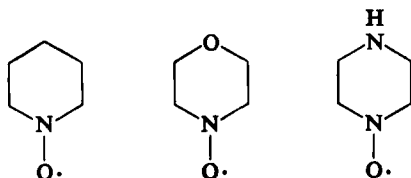
	A_N	A_β^H	A_γ^H	A_δ^H		Ref.
	16.6	22.3	0.47	—	R.T.	41
	18.0	12.3	—	0.75	R.T.	41
	16.85	26.3, 3.78	0.65	0.65	-100°	41
	18.1	12.5	—	—	R.T.	41
	16.80	26.4, 4.05	0.65	—	-100°	41
	18.2	25.0 (15.5, 95)	—	—	R.T.	44
	16.5	12.2	—	—	—	41
	13.2	13.8	—	—	—	42
	12.5	—	—	—	—	42

azacyclononane (42) nitroxides all give spectra consistent with equivalent magnetic environments for all four β -hydrogens. One can conclude that either the rings are planar on the esr time scale (pyrrolidine), or the axial-equatorial H-hfsc's are interchanging too rapidly to be distinguished from one another (azacycloheptane, -octane and -nonane, presumably through pseudo-rotations). The spectrum of pyrrolidine nitroxide shows no dependence on temperature. Although the spectra of the 7-, 8- and 9-membered rings have not been investigated at different temperatures (42), one can tentatively conclude from inspection of the individual line widths (42) that the β -hydrogens in the 7-membered ring are averaged "better" (narrower line widths) than in the 8- and 9-membered rings. Probably this is due to the highly flexible nature of the 7-membered ring. The broad line widths found in the spectra of the 8- and 9-membered rings may in fact be due to signals from the presence of more than one long-lived conformational species in solution. This possibility needs further investigation.

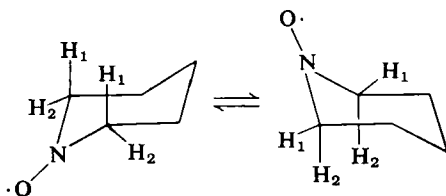
The production of the 3-membered alicyclic nitroxide has not been successful (42). The spectrum of an unsubstituted 4-membered alicyclic nitroxide also has not been reported to date.



The esr spectra of 6-membered rings are more interesting because, at room temperature, line width alternation is observed. The spectra of piperidine, morpholine, and piperazine nitroxides and some derivatives have been studied in detail (41-46). For piperidine nitroxide an "averaged" spectrum (where the β -H-hfsc is due to four equivalent protons) is obtained



at 110°, whereas at -103° a spectrum showing coupling from two pairs of β -hydrogens, two γ -hydrogens and one δ -hydrogen has been resolved (45, Fig. 1). Similarly, morpholine nitroxide gives an averaged spectrum at 110°, whereas at -100° splitting from two pairs of β -hydrogens and two γ -hydrogens is resolved. These results are interpreted in terms of a ring inversion which interchanges the axial and equatorial β -hydrogens at a rapid rate at above



room temperature, at an intermediate rate near room temperature, which makes the frequency of the interchange comparable to the esr frequency (LWA is observed), and at a slow rate at -100° where the spectrum of only one conformation is obtained. The spectrum of 4-*t*-butylpiperidine nitroxide, wherein the ring is expected to be locked in one conformation, gives coupling constants in good agreement with those obtained from piperidine nitroxide at low temperature (46).

From the line broadening, activation energies for the ring inversion have been obtained: 5.6 ± 0.5 and 8.6 ± 1 kcal/mole for piperidine and morpholine nitroxides, respectively (42). Two more recent calculations for piperidine nitroxide are 5.0 ± 0.1 (45) and 5.2 ± 0.4 (46) kcal/mole. These values are essentially the same as those found for cyclohexyl radical, 4.9 ± 0.5 kcal/mole (47), and for cyclohexanone, 4.9 kcal/mole (48) although the value for methylenecyclohexane is somewhat higher, 7.7 kcal/mole (49). These results provide further support for the notion that the behavior of a "radical function" is very similar to that of a nonradical function.

A study of certain substituted piperidine nitroxides has provided a fairly detailed picture of the stereochemistry of this system. 4-Methyl-, 4-*n*-propyl-, 4-isopropyl-, 4-*t*-butyl-, and 4-phenylpiperidine nitroxides have been studied in detail (43-64) (Table 8). A strong conformational preference is observed with these substituents. Thus for 4-methyl-, the ratio is 90:10 at 80° , and for 4-phenyl- it is 96:4 at 140° (45). Activation energies for ring inversion have been reported by two workers (45,46), although complete agreement has not been obtained: 6.3 ± 0.3 and 4.6 ± 0.2 (46) for the two conformers in 4-methyl-, 6.7 ± 0.5 and 4.6 ± 0.4 (46) for 4-isopropyl-, 8.8 ± 0.2 and 6.3 ± 0.2 (45) for 4-phenylpiperidine nitroxides. As has been pointed out (46) the conformational preferences of methyl and isopropyl as calculated from the piperidine nitroxide results are essentially the same as obtained from cyclohexane systems.

In all these discussions it has been assumed that the larger of the β -H-hfsc's is due to the axial hydrogens and the smaller due to the equatorial hydrogens. Furthermore, it is argued (45) or assumed that piperidine nitroxide exists in a chair conformation and that the ring interconversion is a chair to chair process. A value of 8° for the dihedral angle to the axial hydrogens in piperidine, 4-methyl- and 4-phenylpiperidine nitroxides and 7° for morpholine

TABLE 8
Substituted Alicyclic Nitroxides

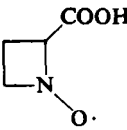
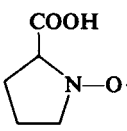
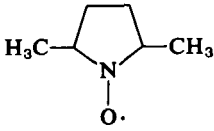
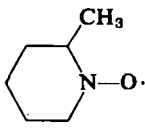
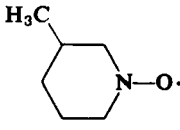
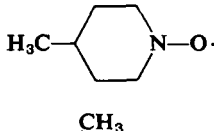
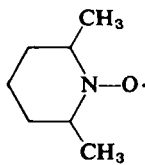
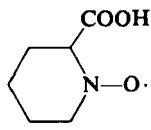
	A_N	A_B^H	A_γ^H	Method	Ref.
	16.23	20.07	0.94	a	42
	14.82	$\begin{cases} 16.88(1) \\ 20.02(1) \\ 20.32(1) \end{cases}$	$\begin{cases} 0.24(1) \\ 0.46(2) \end{cases}$	a	42
	18.9	23.4(2)	—	b	42
	16.8	$\begin{cases} 14.1(2) \\ 6.7(1) \end{cases}$	—	c	43
	16.1	$\begin{cases} 16.5(2) \\ 4.7(2) \end{cases}$	—	c	43
	18.1	$\begin{cases} 20.1(2) \\ 5.2(2) \end{cases}$	—	a	44, 46
	17.4	12.1	—	a	42
	16.3	$\begin{cases} 20.8(1) \\ 6.9(2) \end{cases}$	—	a	42

TABLE 8 (Continued)

	A_N	A_H^a	A_H^b	Method	Ref.
$\text{CH}_3\text{CH}_2\text{CH}_2\text{---}\langle\text{C}_6\text{H}_{10}\rangle\text{N---O}\cdot$	18.0	$\begin{cases} 20.5(2) \\ 4.7(2) \end{cases}$	—	^a	44
$(\text{CH}_3)_2\text{CH---}\langle\text{C}_6\text{H}_{10}\rangle\text{N---O}\cdot$	18.0	19.90(2)	—	^d	46
$(\text{CH}_3)_3\text{C---}\langle\text{C}_6\text{H}_{10}\rangle\text{N---O}\cdot$	18.0	$\begin{cases} 21.7(2) \\ 4.1(2) \end{cases}$	—	^a	44, 46
$\phi\text{---}\langle\text{C}_6\text{H}_{10}\rangle\text{N---O}\cdot$	16.80	$\begin{cases} 26.4(2) \\ 4.05(2) \end{cases}$	—	^d	45
$\text{CH}_3\text{---}\overset{\text{H}}{\underset{ }{\text{N}}}\text{---}\langle\text{C}_6\text{H}_{10}\rangle\text{N---O}\cdot$	18.1	$\begin{cases} 21.1(2) \\ 4.3(2) \end{cases}$	—	^a	44

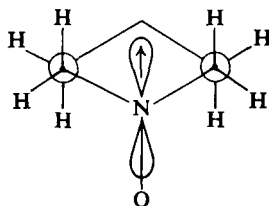
^a Aqueous base (NaOH) containing H_2O_2 ; note larger A_N (and hence A_H) due to polar protic solvent.

^b *p*-Nitroperbenzoic acid in dioxane.

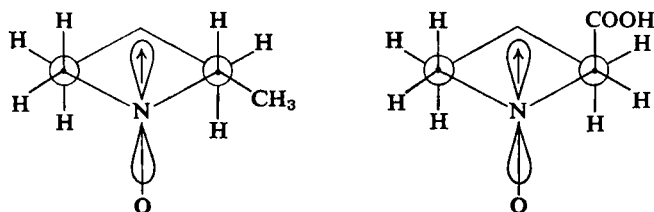
^c *p*-Nitroperbenzoic acid in methylene chloride.

^d Ultraviolet irradiation of the hydroxylamine derivative in methylene chloride.

nitroxides has been calculated (45) (by the use of an equation similar to $A_H = 26 \cos^2\theta$).

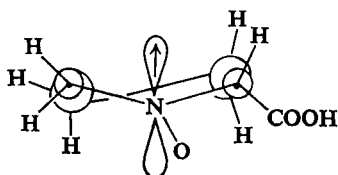


The substitution of a methyl group in the 2-position produces the result expected, assuming that the methyl group is equatorial in the most stable conformation.

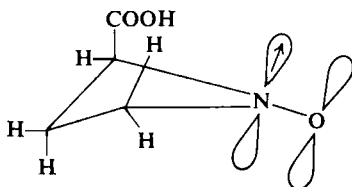


The 2-carboxypiperidine nitroxide (pipercolinic acid nitroxide) gives a sharp-lined spectrum which can be analyzed in terms of two coupling constants, 6.9 gauss for two protons, and 20.8 gauss for one proton. The large splitting is in the range for axial hydrogens (Table 8). Since coupling of this magnitude is seen for only *one* hydrogen, the carboxyl (or carboxylate) must be assigned to an axial position.

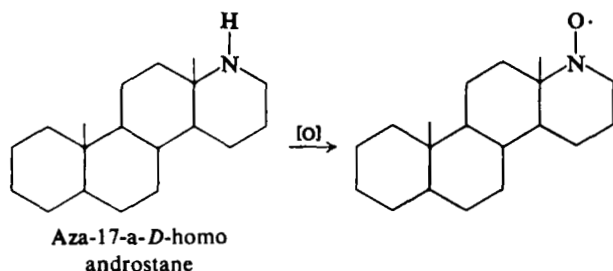
The 2-carboxypyrrolidine nitroxide (proline nitroxide) gave a sharp-lined spectrum with rich hyperfine splitting (42). Five different H-hfsc's were extracted from the spectrum (Table 8). Three of these are large in magnitude (16.88, 20.02, and 20.32 gauss), each due to one hydrogen, and are assigned to the β -positions. Since the two larger β -H-hfsc's (assigned to the quasi-axial hydrogens) are essentially equal, the dihedral angles to the quasi-axial hydrogens must be equal. However, since only three additional small splittings are obtained (assigned to γ -positions), the conformation of the ring must be slightly twisted although stable in this conformation at room temperature.



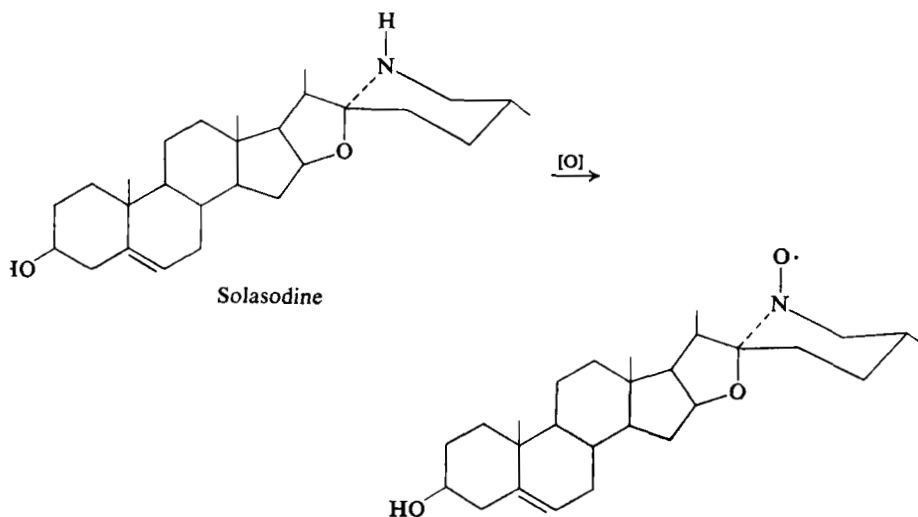
2-Carboxyazetidine surprisingly gives only two coupling constants, at room temperature, due to one proton each (20.07 and 0.94 gauss). The only reasonable explanation is that the carboxy group assumes a quasi-axial position and the quasi-equatorial hydrogens are at essentially 90° dihedral angles and do not give splitting. The remaining splitting can then be assigned to coupling from γ -hydrogen:



Two amine steroid derivatives were also oxidized by *p*-nitroperbenzoic acid in methylene chloride to the respective nitroxide by Rassat and co-workers (43):



The spectrum consisted of six doublets at 20°: $A_N = 16.9$, $A_{ax}^H = 19.7$, and $A_{eq}^H = 4.6$ gauss.

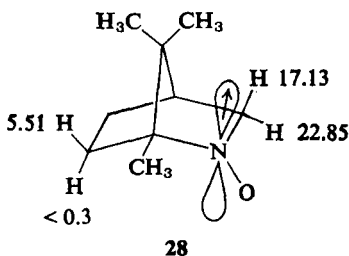


The spectrum of solasodine nitroxide was very similar: at 20°, $A_N = 14.8$, $A_{ax}^H = 19.8$, and $A_{eq}^H = 4.5$ gauss. Neither spectrum changed with temperature, although the magnitude of the axial hydrogen hfs did decrease with decrease in temperature.

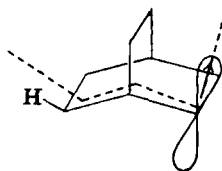
V. BICYCLIC NITROXIDES

The synthesis of two interesting bicyclic secondary amines by Gassman and Cryberg (50) prompted us to attempt the preparation of the corresponding nitroxides. 1,7,7-Trimethyl-2-azabicyclo[2.2.1]heptane was oxidized to

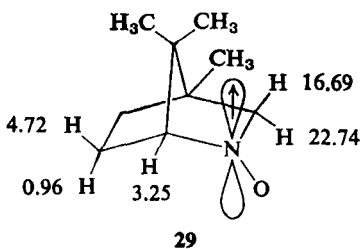
nitroxide **28** with *p*-nitroperbenzoic acid in aqueous NaOH. The esr spectrum



is due to splitting from nitrogen and three different protons, $A_N = 16.97$, $A_H = 22.85$, 17.13, and 5.51 gauss. The two larger values are undoubtedly due to β -hydrogens (as assigned in **28**). The smaller value is assigned to the *exo*- γ -hydrogen on the basis of numerous examples of long-range γ -hydrogen coupling now known from Russell's (51) work on bicyclic semidiones. Although the angular dependence of this coupling is not understood, the selectivity between endo and exo hydrogens appears to follow the W-plan rule known in nmr:

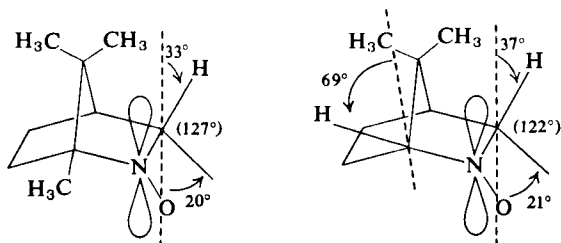


The oxidation of 1,7,7-trimethyl-3-azabicyclo [2.2.1]heptane produced a nitroxide assigned to structure (**29**). Five different coupling constants due to

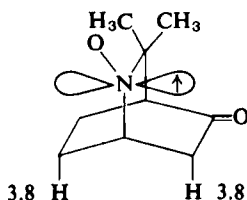


single protons were obtained: $A_N = 17.05$; $A_H = 22.74$, 16.69, 3.25, 4.72, and 0.96 gauss. The two large splittings are assigned to the exo and endo methylene hydrogens (as shown in **29**). The assignment of the 3.25 gauss coupling constant to the bridgehead hydrogen is based on analogies with other bicyclic radicals (semidiones), but is not unequivocal. The assignments of 4.72 and 0.96 gauss to the exo and endo hydrogens is based on the assignments made in **28**.

For rigid bicyclic systems it is probably safe to calculate a dihedral angle for the β -hydrogens. Using $A_H \simeq 26 \cos^2\theta$ the following angles can be calculated:



Sizeable long-range coupling has also been observed for the following stable nitroxide (52):



A triplet splitting due to two equivalent hydrogens is obtained ($A_H = 3.8$ gauss) in addition to nitrogen coupling ($A_N = 16.8$ gauss). By nmr the long-range coupling was shown to be positive. This field is an area of active interest.

In conclusion, it is fair to say that considerable stereochemical information can be obtained from esr spectra of nitroxides. The magnitude of the β -hydrogen coupling in acyclic nitroxides serves as an indication of the equilibrium conformation assumed by the group and can serve as a probe for structure elucidation in alicyclic and bicyclic nitroxide systems. The latter area is probably of most interest but is relatively unexplored at present.

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Conformational Analysis and Steric Effects in Metal Chelates

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I. INTRODUCTION

The interrelation of structure, energy, and reactivity of molecules has been recognized for a long time but has been difficult to interpret. Terms such as "strain" and "steric hindrance" evolved to characterize unusual kinetic or thermodynamic behavior, but they have frequently been associated with the stigma that, if all other explanations (e.g., electronic) failed to account for the reactivity, it must have come from such a cause. By implication, the explanation was inferred to be more meretricious than real. There is a special need, therefore, to quantify relatively small differences in structures such as conformational isomers.

In principle, the calculation can be done by solving the Schrodinger equation appropriate to the molecule, but this is so formidable even for simple molecules that alternative analyses are sought. The most common of the latter approaches is to assume that the molecule is held together by "classical" forces. Usually it is assumed that the structure is governed by a set of empirical, or semiempirical, energy functions. This set of functions is frequently termed "classical," although it has been asserted (1) that they are not deduced from classical physics but may well be considered an empirical representation of the Born-Oppenheimer approximation where the ground state of a molecule is a continuous function of the atomic coordinates. The first approach is then considered deductive, and the second inductive (1). Regardless of which attitude is adopted, the procedure appears to be extraordinarily powerful in predicting structure, and a substantial part of this chapter will consider its application to some inorganic chelates.

The chapter will also be concerned with chelate ring conformations, and it is pertinent therefore to define the term conformations as "nonsuperposable spatial arrangements of atoms or groups in a molecule with the same constitution and configuration which differ in their torsional angles" (2). One difficulty in such a definition is that biaryl enantiomers* are thereby

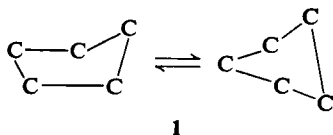
* We would like to suggest the term "catoptric" to describe a mirror image relationship instead of the word "enantiomeric"; see *Shorter Oxford Dictionary*, p., 277. "Catoptromers" are then defined as mirror image forms. This is much better than *antimer*, which merely describes one isomer as opposite to the other. Moreover, the word, or rather the prefix, already exists in the English language. Rarely is a nomenclature available or conceived which is so apt and yet has been overlooked for so long. [Editors' comment: This footnote represents the view of the authors, not that of the editors.]

considered conformers, and this offends some organic chemists. All definitions of conformation so far proposed appear to have some difficulty of this kind, and the only complete solution to date is to eliminate conformation and merely use configuration to describe spatial characteristics. Organic chemists appear reluctant to discard *conformation* because the word has useful connotations with respect to rearrangements and configurations about single bonds and in ring systems. Inorganic chemists on the whole have ignored these problems, or have partly followed the organic nomenclature. The truth is that inorganic nomenclature in this area is in a parlous state and some *definite* proposals are needed.

II. CHARACTERISTICS OF CHELATE RINGS

A. Organic Ring Systems

At the outset it is relevant to review briefly some features of organic ring systems in view of some radical differences which will appear in the common chelate systems. With respect to 3-membered rings such as epoxides, imines, and cyclopropanes, their existence is surprising when the stereochemical preference of the C—C—X angle ($X = C, N, O$) is considered (109.5°). The difficulty is augmented by the eclipsed nature of the nonbonded H...H interactions. The effect is seen in the total strain energy of cyclopropane (27.6 kcal/mole) relative to cyclohexane. A similar effect might be anticipated for cyclobutane, although the H atoms can be partly staggered by distorting the structure from a plane (total strain energy 26.4 kcal/mole relative to cyclohexane). In cyclopentane, however, the C—C—C angle is almost correct (108°) for unstrained bonding in the planar state, but all H atoms are eclipsed. A compromise is required which leads to a mobile, pseudo-rotating, half-chair conformation (**1**) with a total strain energy of 6.5 kcal/mole. Thus the

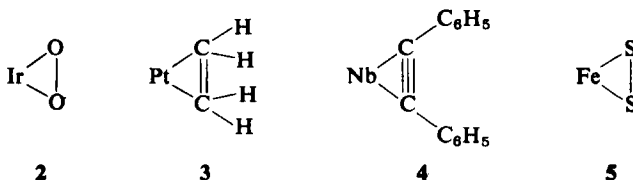


five-membered ring is considerably more stable than the three or four-membered one, but it is still less stable than cyclohexane. The latter can achieve a staggered relationship for adjacent nonbonded H atoms in the "chair" form and still retain the near tetrahedral angle for C—C—C.

B. Metal Chelate Rings

1. Three-Membered Rings

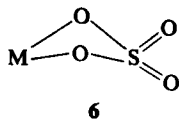
The same, or similar, factors apply in many chelate systems, along with added variety in coordination number, bonding angles, bond lengths, and the sizes of atoms and groups. Three-membered rings appear to be scarce in inorganic chemistry also, and it is really a matter of taste as to how they are viewed. The examples 2-4 (3-5) might be viewed as the metal bonded to



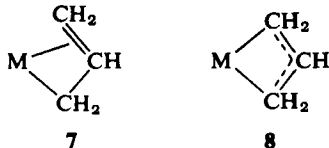
orbitals on both ligand atoms, or to an orbital composed from both ligand atoms. Oxygen therefore might be considered, in the extreme, as coordination of O_2^{2-} or of O_2 to different oxidation states of the metal. Different O—O distances are observed with different metals, and the reactivity also appears to change with the bond length.

2. Four-Membered Rings

Four-membered rings are likely to be more numerous, particularly chelates of oxy anions such as CO_3^{2-} , SO_4^{2-} , PO_4^{3-} , NO_3^- . They are also common in binuclear compounds. In at least one carbonato structure (6) there is a substantial distortion of the usual O—Co—O bond angle ($90^\circ \rightarrow 72^\circ$). Little is known about these types of structures, or about their relative reactivities. One interesting possibility is that for SO_4^{2-} and PO_4^{3-} the chelate may not be planar. A configuration of type 6 seems likely in contrast to the

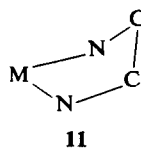
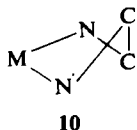
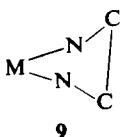


planar metal ion-carbonato configuration. Metal-allyl systems might also be classed as four-membered rings of two possible forms (7 or 8), both being planar, or close to planar (7,8).



3. Five-Membered Rings

a. Unsubstituted. By far the largest number of chelate ring systems are either five- or six-membered. Many, such as metal ion-oxalato rings, are planar and are therefore less interesting from the point of view of this chapter. In square planar and octahedral complexes, ligands such as 1,2-diaminoethane, containing four tetrahedral skeletal atoms, give rise to chelate rings with pronounced conformational characteristics. They differ from analogous five-membered carbocyclic systems in at least one particular, the metal ligand angle ($\sim 90^\circ$). A consequence of this difference is that the remainder of the chelate ring must pucker skew to prevent unreasonable distortion at the tetrahedral centers. Several structures can arise depending on the metal-ligand angle, bond length, and which heterocyclic atoms are present. For 1,2-diaminoethane the form usually found for cobalt(III) complexes (9,10) is close to that depicted by **9** and **10**, where the two C atoms are equidistant but on opposite sides of the N—M—N plane. In this condition two enantio-



meric forms of the half-chair chelate exist with C_2 symmetry. An alternative structure which appears to be much less common is the "envelope" conformation **11**. This form has a plane of symmetry (C_s), and the H atoms on carbon are eclipsed. In the half-chair conformers all the H atoms are more or less staggered relative to one another, and those on C are almost strictly "axial" or "equatorial" in the cyclohexane sense. The H atoms on the N centers have less pronounced axial equatorial character, but are nonetheless distinct. Another essential feature in which these systems differ from carbocyclic rings is that there are two axial substituents on the metal ion, either as bonded ions, or groups of atoms, or in the form of filled or partly filled d -orbitals. The metal ion also frequently has nonbonded electrons in orbitals which interact with the ligands, and both of these aspects will be discussed again with appropriate examples.

For the Co(III)-en chelate the metal-N distance is close to 1.95 Å and the N—C and C—C distances close to 1.5 Å, when corrections for the H atoms are made.* Characteristically the N—Co—N angle (θ) is 86° and the

* The crystal structures usually do not reveal H atoms, but on final refinement they are usually included at their calculated positions. This usually results in a shortening of the C—C and C—N bond lengths by 0.02–0.06 Å.

dihedral angle (ω) along the C—C bond is about 45° (). It is now

pertinent to explore what happens to the conformation when the M—N bond length changes, assuming that the other angles and bond distances remain constant. If the bond length is reduced to 1.75 Å, the stable conformation appears to be the envelope form. If the N—M—N angle is allowed to expand, then the half-chair form can also be stabilized for the shorter metal—ligand distance. When the metal—ligand bond distance is increased, the envelope form becomes even less stable, primarily because the ligand “bite” is now too large and the N—M—N angle must narrow to keep the intraligand angles undistorted. These changes may not occur, of course, if the ligand angles prefer to change. The means of evaluating such problems will be discussed later. For the moment, the analysis leads to possible ways of stabilizing the different extreme conformations by a judicious choice of metal ion and chelating agent.

For larger donating atoms in the ligand such as P or As, the M-donor bond lengthens relative to N, but so does the C-donor bond by about the same amount. Models indicate that there is no major change in the stability relationships for half-chair and envelope conformers except that the envelope is probably slightly more destabilized. However, for —S^- as a donor, there should be also a pronounced preference for the M—S—C angle to be smaller than the tetrahedral angle. This factor may lead to an even more puckered conformation, measured by an increase in the dihedral angle along the C—C bond. A similar but smaller effect might also be expected for —O^- as the donating atom.

It is apparent for tetrahedral complexes containing ethylenediamine that the chelate rings must be strained because the N—M—N angle will prefer to be close to 109° instead of 90° . Also, the ring will prefer to retain its puckered nature instead of distorting toward the planar state. Similarly, in trigonal bipyramidal complexes, chelation from the trigonal plane to the apical positions will be preferred over chelation within the trigonal plane for five- and six-membered rings.

The substitution of a planar divalent center such as >C=O in these five-membered chelates changes the conformational characteristics substantially. The carbon atoms of chelated α -amino acid anions, such as glycinate ion, appear to be no more than about 6° out of the N—M—O plane (11).

b. C-Substituted. Above are the broad features of five-membered rings themselves, and now the effects of substituents in place of H atoms may be examined. For chelates like ethylenediamine, two substitution sites exist, either at the two atoms most distant from the metal ion or at the ligating atoms.

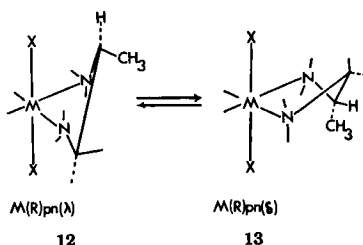
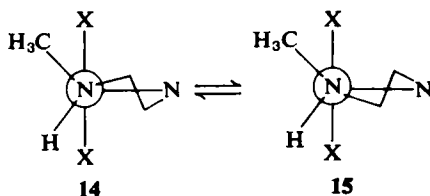


Fig. 1. Extreme half-chair conformations for metal (*R*)-propylenediamine chelate rings; **12**, $M(R)pn(\lambda)$; **13**, $M(R)pn(\delta)$.

Consider the substitution of a methyl group on the former site, to give (*R*)-1,2-diaminopropane (Fig. 1). There are now two conformations in equilibrium, λ (**12**) and δ (**13**), one with the methyl group axial and the other with it equatorial (12,13). It is expected, therefore (14), that the axial methyl group will interact more strongly with the axial group on the octahedral metal center than the equatorial one, and the λ conformation in this instance is significantly stabilized, >2 kcal/mole (14). If (*S*)-1,2-diaminopropane is considered, then the δ conformation is similarly stabilized over λ . The size of the substituent will obviously affect the conformational equilibrium also, and symmetrical disubstitution (e.g., (*R,R*)- or (*S,S*)-2,3-diaminobutane) should also increase the effect (15). However, if both methyl substituents are on the same C atom, then there will always be one axial and one equatorial substituent, or some intermediate compromise. The same is true for the chelated *meso*-2,3-diaminobutane, and we know little about these situations except that pmr studies indicate that the two methyl groups are different.

c. N-Substituted. Substitution on the ligating atoms, e.g., *N*-methyl-1,2-diaminoethane, produces similar results. In this instance the difference between the axial and equatorial positions is less pronounced ($\sim 20^\circ$) (**14**, **15**), but the substituents are now closer to the axial substituent on the metal ion. The nonbonded repulsion term therefore should be greater. Complexes of this type have stereochemical interest because the coordinated N center is asym-



metric, and the complexes are relatively inert to racemization in dilute acid solution. Several chelates of this type have been resolved in which the sole

source of asymmetry resides in one of these centers. It appears that racemization occurs only when a proton is removed and, moreover, that the rate of racemization is 10^2 to 10^6 times slower than H-exchange for Pt(II),(IV) and Co(III) complexes (16,17). The inertness of the proton attached to coordinated N contrasts sharply with rapid exchange observed with substituted ammonium ions under the same conditions. This aspect of inorganic stereochemistry was recognized only recently and its significance and implications are only now being uncovered. The point will be considered again later. For the moment, it is enough to say that the asymmetric N centers can be made to racemize in dilute base, and the stereoisomers and conformers can thus be equilibrated in this manner. Similar problems and compromises arise when the ligand is disubstituted on either, or both, N atoms.

4. Six-Membered Rings

a. Unsubstituted. Six-membered chelate rings which show pronounced conformational characteristics are moderately common. Examples include complexes of bidentate 1,3-diaminopropane, malonate ion, β -alanine, and 1,3-diarsenopropane or 1,3-diphosphinopropane with various substituents on the As or P atoms. Frequently these chelates are incorporated in fused-ring systems, and examples will be discussed later. The chelate systems are analogous to cyclohexane, and have similar conformational prospects, namely, chair (16), boat (17,18), and skew-boat (C_2) (19) as extreme forms. Fig. 2. In octahedral complexes the principal difference from cyclohexane arises from the valence angle about the metal, which is close to 90° . The structural analysis of Δ -[Co(trimethylenediamine)₃]-Br₃·H₂O indicates (18) that, in contrast to [Co(en)₃]³⁺, the N—Co—N angle is slightly greater than 90° (92 – 96°), and this presumably influences the Co—N—C angle which expands to 117.4° . The C—C—C angle (112°) is closer to the tetrahedral value.

The structural analysis also shows that all three rings are "distorted-chair" conformations (16). A similar result is found for the two trimethyl-

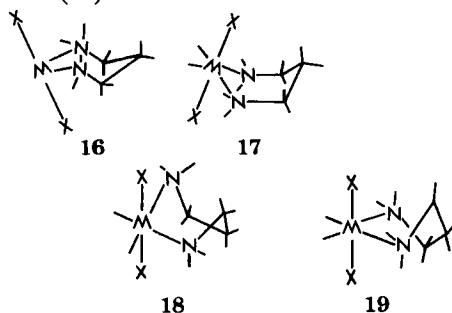
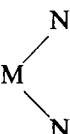


Fig. 2. The chair (16), boat (17,18), and skew-boat (19) conformations of metal ion-trimethylenediamine chelate.

enediamine rings in $[\text{Co}(\text{tn})_2\text{CO}_3]\text{ClO}_4$ (19). This is not necessarily expected, since the other main feature whereby the trimethylenediamine chelate differs from its cyclohexane analog lies in the presence of two axial substituents, one of which interacts strongly with the axial H atoms on the C centers (Fig. 2). The reason is that the two substituents on the metal prefer to be

perpendicular to the M  plane in the chelate. The interrelation between

metal-axial substituents and the chelate atoms is shown more clearly in Figure 2. It is conceivable that, if the axial-metal/chelate-axial interactions are substantial, the stable form for $[\text{Co}(\text{tn})_3]^{3+}$ may be the skew-boat form **18**. Here the axial-metal substituent axial-chelate substituent interactions are reduced, but some H...H eclipsing is introduced. It is not yet clear which is the stable form in these systems, and it may be that the tris chair configuration found for $[\text{Co}(\text{tn})_3]^{3+}$ (18) is required by lattice forces. In another complex of this nature where the structure is known, i.e., $[\text{Co}(\text{en})\text{mal}_2]^-$ (19), both malonate rings assume a flattened boat conformation folded toward each other. A cursory glance at the extreme boat forms in the trimethylenediamine chelate (**17** and **18**) is enough to show that these forms must constitute the least stable conformation. The nonbonded interaction between one H atom of the central methylene group and the H atom on the axial-metal substituent in **17** must be large, and a similar situation obtains in **18** between the H atoms on N and C. A further destabilizing influence in **17** and **18** is the eclipsing of the H atoms.

It is also true that little is known about the conformation of $[\text{Co}(\text{tn})_3]^{3+}$ in solution. For example, does the ion have D_3 symmetry, or are there two chelate rings of one conformation and one of another? In short, little is known yet about the stability relationships in these six-membered systems, nor have many crystal structures been reported. Another interesting structure in this respect is that of $[\text{Pt}(\text{S}_5)_3]^{2-}$, which has been shown to be tris chair (20).

b. N- and C-Substituted. The models, and the structure (18) of $[\text{Co}(\text{tn})_3]^{3+}$, indicate that the pitch for the two ends of the six-membered chelate are different; that at the metal end is less steep than that at the C end. Nevertheless, substituents on both C and N have substantially axial-equatorial character. That on C is not greatly different from the Co-pn type of system, but substituents on N are vastly different in orientation from those in the Co-Meen chelates. For chelated *N*-methyl-1,3-diaminopropane (Fig. 3), the $\text{N}_1\text{—CH}_3$ bond eclipses the M—N_2 bond in **20**, but in an alternative conformation (**21**) the N—CH_3 bond almost bisects the N—M—N angle

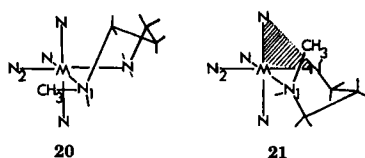
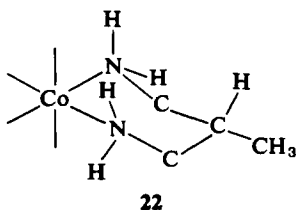


Fig. 3. Two diastereoisomeric forms of the chair conformation of the Co-*N*-methyl-trimethylenediamine ring. (**20** and **21** are different views of the same conformation to emphasize the orientation of CH₃ and H in the two conformers.)

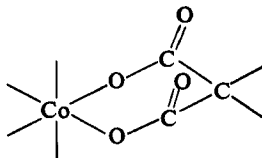
(hatched). This interaction should therefore act to stabilize **21**, but if the analogy with cyclohexane is valid, the equatorial form **20** will be preferred to the axial form **21**. At the moment it is not clear which interaction will dominate the issue since no equilibrium studies, or crystal structures, have been reported.

If the central methylene group in the Co-tn ring is substituted with a methyl group, the chelate ring has a plane of symmetry and, by analogy with cyclohexane, the chelate with CH₃ equatorial (**22**) should be favored. The



same argument holds for methyl substitution on C atoms adjacent to N, except that now the chelate is also asymmetric and additional isomeric forms are possible.

For chelates such as Co-malonato and Co- β -alaninato, where the sp^2 carbonyl group is incorporated in the ring, models indicate that $>C=O$ largely eclipses the axial H atom of the central methylene group in the chair conformer **23**. One crystal structure (21) indicates that this relationship holds in



23

the solid state, but the interaction should lead to some deformation of the chelate ring in solution; by how much is not yet clear.

III. ENERGY MINIMIZATION

A. Early Studies on Interactions Between Chelate Rings

An important factor in determining the conformations of chelate rings in the molecule or molecular ion which is of a more subtle nature, is the intramolecular interaction between the chelates. This problem was considered by Mathieu as early as 1944 and, using London dispersion forces (22) he did some calculations for the $[\text{Co}(\text{pn})_2(\text{NO}_2)_2]^+$ isomers. However, recent activity in this area was largely determined by a classical paper of Corey and Bailar's (14) which enumerated a number of the principles already outlined in this chapter. These authors considered primarily two simple systems, *trans*- $[\text{Co}(\text{en})_2\text{Cl}_2]^+$ and $[\text{Co}(\text{en})_3]^{3+}$. The configurations for the *trans* ion are shown in Figure 4 and they differ in that in one form, **24**, the chelate conformations are mirror images, whereas in the other form, **25**, they both have the same conformation. For the meso isomer the *cis*- NH_2 groups of opposing chelate rings have their H atoms eclipsed, whereas for the chiral form the interaction is more staggered. Corey used a hard H...H nonbonded potential function (23) to estimate the energy difference between the two forms as about 1 kcal/mole in favor of **25**. The same technique was also applied to the extreme forms of $[\text{Co}(\text{en})_3]^{3+}$; one where the chelates have their C—C axes almost parallel to the C_3 axis of the complex ion **27** ("lel" form), and the other where the C—C axes are oblique to the C_3 axis **28** ("ob" form). The perspective diagrams are given in Figure 5.

Using the Mason and Kreevoy H...H and H...C nonbonded functions (23), Corey calculated the energy difference between these extreme forms to be about 1.8 kcal/mole with "lel" more stable than "ob". The intermediate conformational forms had energies between these extremes. These values are mentioned here only because of what follows later in respect to energy calculations. Similarly, Corey and Bailar (14) estimated that the Co(III) (*R*)-1,2-diaminopropane chelate ring shown in Figure 1 was more than 2 kcal/mole more stable in the equatorial form, **12**, than in the axial

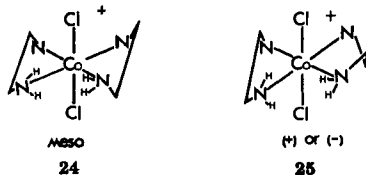


Fig. 4. Meso (**24**) and chiral (**25**) forms of the *trans*-[dichlorobis(ethylenediamine)cobalt(III)]⁺ ion.

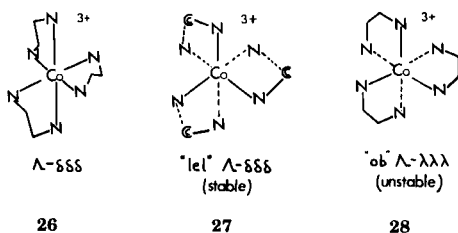


Fig. 5. The configuration (26) and conformation (27,28), of the $\Lambda(+)_589-[Co(en)_3]^{3+}$ ion (27 ($\delta\delta\delta$) and 28 ($\lambda\lambda\lambda$) viewed along the C_3 axis of the octahedron).

form 13, primarily because of the interaction of the axial methyl group with the ubiquitous axial substituent on cobalt. Some support for these values arose from the stabilities found for a series of complexes containing en and/or (*R*)-pn, and these constants will be discussed in detail in Sect. IV-B-1. A closer look at the H . . . H potential function showed that practically all the barrier in the ethane rotation is accounted for by this nonbonded repulsion, even though it is known that only a fraction of the barrier arises from this source (24). It is considered, therefore, that such a function is far too hard to represent the nonbonded potential, and that more realistic functions are required.

B. General Force Field Approach

1. Force Field

After a close examination of the Bailar and Corey type of calculations it was realized that a general force field was required, which in addition to nonbonded interactions, also included torsional potentials, bond stretching and bond bending functions, and other terms which might be appropriate for a particular molecule, e.g., dipole-interactions. Coupled with such a treatment there should be some means of cooperatively minimizing the calculated energy by continual adjustment of the atomic coordinates. Such procedures have now been developed. The total strain energy, U , is described (25) as the sum of the contributions in eq. [1] to the force field; $\sum U_{nb}$ is the sum of all the non-

$$U = \sum U_{nb} + \sum U_{\theta} + \sum U_{\phi} + \sum U_r \quad [1]$$

bonded energy terms, $\sum U_{\theta}$ is the sum of the contributions from valence angle deformations, $\sum U_{\phi}$ is the contribution from torsional effects, and $\sum U_r$ is the sum of the bond length stretching and compression energies. Other contributions, such as atom-dipole and dipole-dipole potentials, have not been considered so far for cases of the type discussed here.

Calculations of the type where one variable altered while the others remain constant have been pursued (26,27), and presumably comprehensive calculations of this sort map the energy surface in the volume where the coordinates are changed. However, what is desirable for our purposes is that one calculation find the energy minimum for the complete molecule in such a way that all the atoms are moved cooperatively in the search for the lowest minimum. A number of such procedures have recently been advanced, of which we will consider in detail one by Boyd (28) using a modified Newton-Raphson method (29). However, before describing this method, some description of the potential functions used in the force field is pertinent.

a. Nonbonded Interactions. The potential function for describing nonbonded interactions is usually one of two types:

$$U_{\text{nb}} = -A/r^6 + B/r^{12} \quad [2]$$

or

$$U_{\text{nb}} = -A/r^6 + Ce^{-ar} \quad [3]$$

where A , B , C , and a are parameters evaluated from experiment, and r is the distance between the nonbonded atoms. The "6-12" function is attributed to Lennard-Jones (30), and the "6-exponential" function is attributed to R. A. Buckingham (31). Both are composed of a London dispersion, or attractive, term which falls off rapidly with distance ($1/r^6$), and a repulsion term which falls off even more rapidly with the distance. The net result is that nonbonded atoms close together experience a strong repulsion which rapidly changes to a small attraction as the distance between them increases. The repulsive term accounts for the low compressibility of liquids on the one hand, and the attractive term for the existence of liquids on the other. The coefficients in eqs. [2] and [3] have been evaluated in many ways, but primarily from the virial coefficients for gases such as Ne, Ar, He, H_2 , N_2 , and CH_4 . Some of the H H functions which have been developed to examine nonbonded interactions in different situations are shown in Figure 6. Relative to these functions, the Mason and Kreevoy function (not shown) is by far the hardest since it minimizes at 4.34 Å, considerably in excess of the others, and vastly in excess of the van der Waals radii for two H atoms. In the calculations which follow, the potential functions shown in Figure 6 have been used to examine the sensitivity of the geometry, and to evaluate the energy difference between conformations. In these calculations, energy contributions beyond 1.2 times the sum of van der Waals radii have been ignored (32) as negligible. Nonbonded functions in general have been discussed recently in relation to calculations of the type considered here; for a more detailed treatment the reader is referred to this excellent review (33).

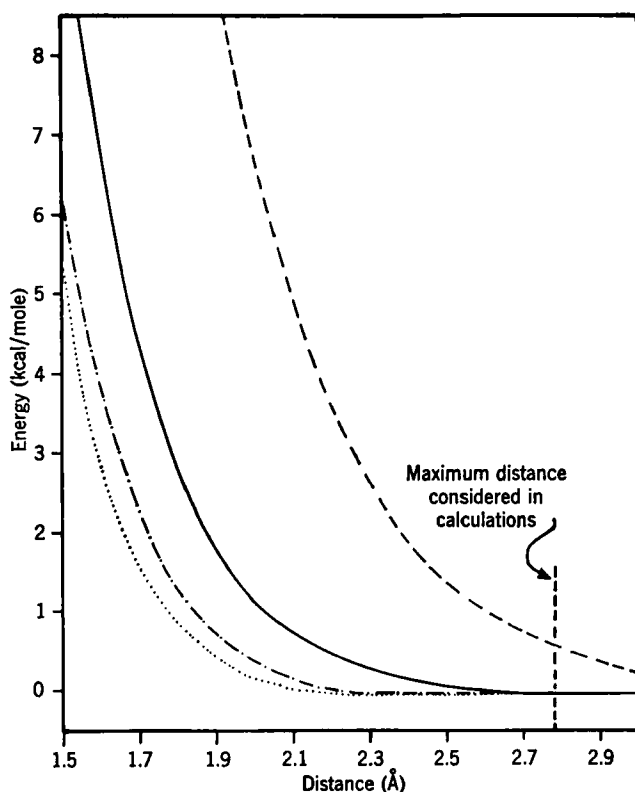


Fig. 6. Comparison of H . . . H nonbonded potential functions (25): — Bartell (37); — · — Scott, Scheraga (35); — — De Santis (82); Hill (34).

It can be seen from Figure 6 that the Hill function (34) is rather conservative and is close to that used by Scott and Scheraga (35). In terms of the reproduction of structure and thermodynamic and spectral properties of organic molecules, it appears that the functions used by Allinger (36), Bartell (37), De Coen (38) and Lifson (39) are all more or less satisfactory.

b. Bond Length Deformations. It is assumed that the atoms are held together by bonds which obey a Hooke's law function, namely,

$$U_r = 1/2 k_r (\Delta r)^2 \quad [4]$$

where k_r is the stretching force constant, and Δr is the difference between the normal unstrained and the distorted bond lengths. The force constant is rather large, and the parabolic nature of the function results in rather steep sides to the energy well about the undistorted value. Under these circum-

stances, corrections for anharmonicity in the potential function do not seem to be worthwhile since it is most unlikely that large deviations from the average bond distances will be observed.

The force constants for many types of bonds which are of interest to this discussion are known moderately well, e.g., C—C, C—N, C—O, M—N, M—O, and primary references containing such information are readily available (32).

c. Bond Angle Deformations. Again it is assumed that the motion is governed by a Hooke's law function, and that the energy required for deviation from the undistorted angle is given by the function

$$U_{\theta} = \frac{1}{2}k_{\theta}(\Delta\theta)^2 \quad [5]$$

where k_{θ} is the bending force constant, and $\Delta\theta$ is the angular displacement. The function assumes that the displacements will not be large ($\pm 10^\circ$), and it is clear that, for large displacements, anharmonicity corrections will be required, possibly even for distortions $\pm 5^\circ$ (33). Either of two situations will arise from gross distortions: the distortion will go over a potential barrier to a minimum, or dissociation of the bond will occur. Usually the energy contributions for bond bendings are considerably smaller than for bond stretching, and angle distortions can be expected more frequently than bond length deviations. Moreover, for large angle deformations the force constant will decrease relative to that near equilibrium, and the angle will therefore distort more readily. This occurs presumably because orbital overlap is less efficient at substantial distortions. An example of the effect is shown by the formation of cyclopropane. For saturated C—C—C, a bending function of the form $U_{\theta} \simeq 0.01(\Delta\theta)^2$ kcal/mole appears appropriate for small distortions. However, in the formation of cyclopropane, it appears that ~ 75 kcal/mole is required from this source alone. This value has to be compared with the actual strain energy difference between cyclopropane and the relatively unstrained cyclohexane (~ 27 kcal/mole). Clearly, the effect of such severe bending (some 50°) is grossly overestimated by the function.

d. Torsional Energies. The potential for rotation about a single bond can be represented by a function of the type

$$U_{\phi} = \frac{1}{2}U_0(1 + \cos n\Delta\phi) \quad [6]$$

where U_0 is the torsional energy barrier, $\Delta\phi$ is the displacement of the dihedral angle, and n is the periodicity. For ethane-type bonds, the function has a periodicity of 3, and molecules such as propane and butane appear to

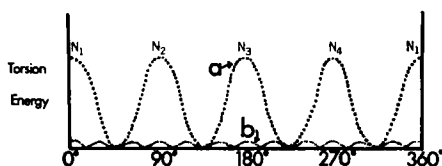
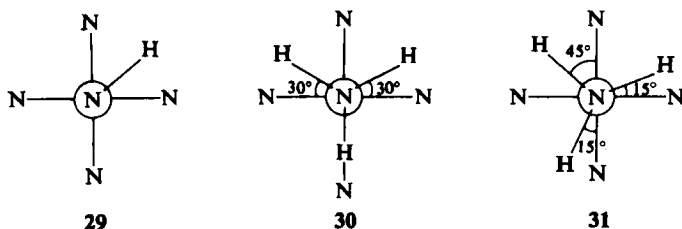


Fig. 7. Torsion energy for (a) a single N—H bond and (b) for NH_3 about a 4-fold octahedral axis, Co—N_4 .

have rotational barriers which conform to this assertion (24). Similarly, methylamine was used to estimate the barrier for rotation about the C—N axis (1.5 kcal/mole) in molecules like $\text{NH}_2\text{—CH}_2\text{—CH}_2\text{—NH}_2$, and the barrier for ethane was used to estimate the C—C barrier (2.4 kcal/mole). Both of these values have had the nonbonding contribution to the rotational barrier subtracted from them.

However, there appears to be little experimental information for rotational barriers about bonds joined to the metal ion for molecules like $[\text{Co}(\text{NH}_3)_6]^{3+}$ (83). Despite the lack of data, qualitative arguments suggest that this barrier must be small. For ethane with a 3-fold periodicity, the barrier is about 3 kcal/mole, but, nitromethane with a 6-fold periodicity, the barrier is only 0.006 kcal/mole, and the estimate for the 12-fold barrier is only 10^{-6} kcal/mole (24). The Co—NH_3 bond in $[\text{Co}(\text{NH}_3)_6]^{3+}$ has a periodicity of 12, and on this basis the barrier might be expected to be small. Qualitatively, if we consider the rotation of one N—H about the 4-fold axis (29) the potential barrier should appear as shown in Figure 7a. However, for a 3-fold rotor superimposed on the 4-fold rotor, the energies of the eclipsed (30) and staggered (31) forms approach each other, Figure 7b. Therefore, provided



the factors which give rise to barrier shape do not alter substantially, the 12-fold barrier must be considerably less than the 4-fold barrier. It seems likely, that relative to the 4-fold periodic function, the eclipsed conformation will be stabilized.

2. Minimization Method

In the Boyd approach (28), the gradient of the total potential energy, $\nabla U(r)$, where r represents the atomic coordinates of the trial geometry, is expanded in a Taylor series about a point near equilibrium:

$$\nabla U(r_0) = \nabla U(r) + F(r)\delta r \quad [7]$$

where r_0 represents the equilibrium coordinates, and $F(r)$ is the matrix of second derivatives, i.e.,

$$F_{\alpha\beta} = \frac{\partial^2 U}{\partial r_\alpha \partial r_\beta} \quad [8]$$

The solution of the set of equations

$$\partial U / \partial r_\alpha = 0 \quad [9]$$

represents the necessary but not sufficient condition that r_0 is an equilibrium conformation; thus $\nabla U(r_0) = 0$ and the equilibrium condition is obtained by solving a set of linear equations for r_0 of the form

$$r_0 = r + \delta r$$

and therefore

$$r_0 = r - F^{-1} \nabla U(r) \quad [10]$$

In this approach eq. [7] is approximate, since cross terms are neglected and the expression is truncated past second-order terms. Also eq. [10] is normally solved in terms of Cartesian coordinates, and the equations of transformation from internal atomic coordinates are approximated by assuming δr to be small. Thus the solution to eq. [10] is not exact, and the process of forming a set of linear equations is repeated using the new set of coordinates. After each iteration the coordinate shifts δr become smaller quantities until convergence is attained. The minimization is considered complete when the root-mean-square displacement is less than 0.01 Å.

In practice (25), the number of iterations depend on how accurately the expansion represents the minimized potential, and this depends on how accurately the initial coordinates represent the minimized geometry. Usually the problem either diverged or converged rapidly, but occasionally it oscillated. The divergence and oscillation occurred when the trial coordinates were distant from the minimized values and the number of parameters to be refined was large. The problems resulted from overcalculation of the displacement, and this was corrected by incorporating a dampening factor. The number of iterations increased thereby, but this was modified to some extent by decreasing the dampening factor as convergence progressed until it reached unity in the last few cycles.

IV. APPLICATION OF MINIMIZATION METHOD TO CHELATE RINGS

A. Structural Comparisons

1. General

It is necessary to digress a little to develop more background for the application of the calculations to specific problems. In 1920 Meisenheimer and his collaborators (40) studied the stereochemistry of the sarcosinato bis(ethylenediamine)cobalt(III) ion (Fig. 8).

The ion contains two chiral centers, one about Co(III) and the other about the asymmetric N of the coordinated sarcosine. Meisenheimer and co-workers claimed to have isolated all four possible stereoisomers, but when this work was repeated very carefully only two forms were obtained (41). The second study (41) produced evidence from a number of sources that the sarcosinato ion was coordinated stereospecifically about one configuration of the Co(en)₂ moiety, and this conclusion was later proved by a structural analysis (42). In the stable form (33) the H atom is poised over the adjacent Co-en ring and the CH₃ group lies in the space between the two ethylenediamine rings. Calculations of nonbonded interactions from Dreiding models (41) indicated that in 32 the CH₃ group interacts substantially with the Co-en ring, and that this configuration is considerably destabilized (by about 10 kcal/mole if an undistorted geometry is assumed about the Co(III) ion and the Hill functions are used in the calculation). It was asserted that this situation would generally hold for similar systems, and the results were applied to the stereospecific synthesis of one of the diastereoisomers of the [Co(trien)-(sarcosinato)]²⁺ system (44) (trien = triethylenetetramine) (Fig. 9). Previous studies (45) had shown that [Co(trien)(OH)(OH₂)]²⁺ preferred the β configuration of the trien topology, as opposed to the α (38) or trans (39) structure, and it was assumed that this stability pattern would be preserved for

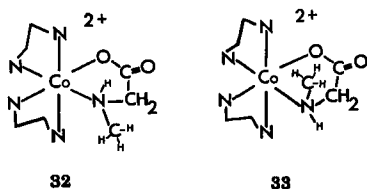
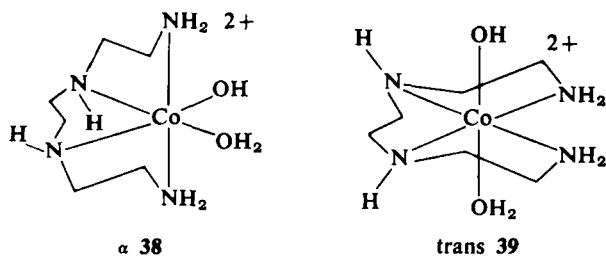


Fig. 8. The diastereoisomeric forms of the Λ -sarcosinatobis(ethylenediamine)cobalt(III)²⁺ ion: 32, Λ -S; 33, Λ -R.



the coordination of the sarcosinato ion. Under these circumstances, sarcosine could theoretically coordinate in several possible ways; with N or O trans to the apical chelate of trien (37, 34), with *R* or *S* configuration (43) about the asymmetric center of sarcosine (34, 35), or with *R* or *S* configuration about the asymmetric N center of trien which joins the two chelate rings in the same coordination plane (planar) (35, 36). In practice, it was found for more than twenty systems of the type β -[Co(trien)X₂]ⁿ⁺ that the stable conformation is that shown in Figure 9, with the H atom on the asymmetric trien N atom mentioned above directed toward the apical en chelate (34, 35, 37). Moreover, the results from the [Co(en)₂sar]²⁺ study would require 34 and 37 to be less stable than 35. In the former instances the CH₃ group is poised over a Co-en chelate ring and, for the β_1 structures (37), the same result is true regardless of the configuration about the asymmetric N atom of the sarcosine moiety. Only one [Co(trien)(sar)]²⁺ isomer was isolated by reaction of β -[Co(trien-(OH)(OH₂)]²⁺ with CH₃NHCH₂COO⁻ in aqueous solution, and the reaction mixture was composed exclusively of this isomer as far as the experiments could tell (44). Later, all ten isomers of [Co(trien)(glycinato)]²⁺, where

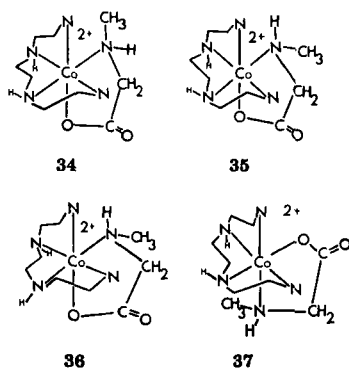
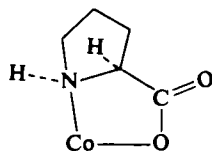


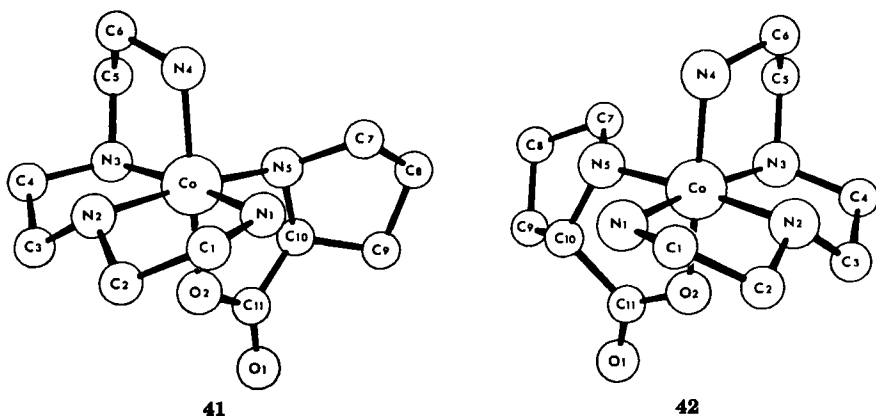
Fig. 9. Diastereoisomeric forms of the Δ -sarcosinato(triethylenetetramine) cobalt(III) ion: 34, Δ - β_2 -*R,R,R*; 35, Δ - β_2 -*R,R,S*; 36, Δ - β_2 -*R,S,S*; 37, Δ - β_1 -*R,R,S*; for the β_1 and β_2 nomenclature see (44).

the steric problem of the asymmetric CH_3 group is absent, were isolated and characterized (46) (four β_2 , four β_1 , and two α forms), and the properties of these ions (ir, visible spectra, rotatory dispersion, circular dichroism, pmr spectra, and X-ray structural analysis (47)) confirm the assignment of the $[\text{Co}(\text{trien})(\text{sar})]^{2+}$ structure as that given by 35. In all of these experiments, racemic $\beta\text{-}[\text{Co}(\text{trien})(\text{OH})(\text{OH}_2)]^{2+}$ or $[\text{Co}(\text{en})_2(\text{OH})(\text{OH}_2)]^{2+}$ was treated with the sarcosine anion. The result was, of course, a racemic product containing enantiomeric forms about Co of the stereospecifically formed ions containing (*R*-) and (*S*-)sarcosine, and excluding the other pairs of enantiomers. It was then of interest to design an experiment in which all these facts concerning the stability of stereoisomers of this type were used to direct a stereospecific synthesis to yield only one asymmetric chelate complex. The system chosen was the reaction of (*S*)-proline with $\beta\text{-}[\text{Co}(\text{trien})(\text{OH})(\text{OH}_2)]^{2+}$. Here the amino acid has two chiral centers which are coupled through the five-membered pyrrolidine ring system (40). On coordination, this ring per-



40

mits only one orientation of the proton on the N center, namely, that where it and the proton at the chiral C center are on the same side of the ring, (*S*)C—(*S*)N. This requirement allows coordination of the amino acid in only two possible ways in the β_2 form of the (Co-trien) moiety. These are the enantiomers 41 and 42 (Fig. 10). It is readily seen that 41 has the N proton



41

42

Fig. 10. Two possible diastereoisomers of (*S*)-proline in the β configuration of the Co(trien) moiety: 41, $\Delta\text{-}\beta_2\text{-}R,R,S$; 42, $\Lambda\text{-}\beta_2\text{-}S,S,S$.

poised over the apical chelate ring, whereas **42** has the pyrrolidine ring, interacting substantially with the apical chelate. The $[\text{Co}(\text{en})_2\text{sar}]^{2+}$ chemistry would therefore require **41** to be more stable than **42**, and the calculations of the nonbonded interactions from the Dreiding models indicated that the effect would be large (> 14 kcal/mole). Moreover, this effect might be expected to carry to the kinetics of coordination of the (*S*)-prolinato ion with $\beta\text{-}[\text{Co}(\text{trien})(\text{OH})(\text{OH}_2)]^{2+}$. Such steric repulsion should destabilize at least one transition state for the formation of the Λ isomer relative to that for the Δ isomer. In the experiment, however, roughly equal amounts of two isomers were formed, and their RD and CD curves indicated that these species had enantiomeric relationships of the ligands about the cobalt center (48). These, along with the visible and pmr spectra, indicated that they were both β_2 isomers, namely, **41** and **42**. It then became obvious that, if these species were as claimed, either the $\Lambda\text{-}\beta_2\text{-}S,S,S$ form was distorted, or the interaction of the pyrrolidine ring with one en ring of the trien moiety was substantial. Either situation was interesting, and the X-ray structural analysis was carried out for the salts $\Delta\text{-}\beta_2\text{-}(R,R,S)\text{-}[\text{Co}(\text{trien})(S\text{-Pro})]\text{I}_2 \cdot 2 \text{H}_2\text{O}$ and $\Lambda\text{-}\beta_2\text{-}(S,S,S)\text{-}[\text{Co}(\text{trien})(S\text{-Pro})]\text{ZnCl}_4$ (49). The computer drawn structures are given in Figures 10 and 11. There is a substantial distortion at the N_3CoN_5 angle (99.2° (0.4°)) for the $\Lambda\text{-}S,S,S$ isomer (**44**), which relieves the nonbonded interactions between the pyrrolidine ring and the apical chelate of the multidentate (Fig. 11). A smaller deviation from 90° appeared for the $\Delta\text{-}R,R,S$ isomer, **43** (94.2° (0.9°)). Other distortions from regularity were also observed at the $\text{CoN}(5)\text{C}(7)$ angles for the chelated amino acid anion, **41** (122.2° (1.7°)), **42** (125.3° (0.7°)), and this deviation from the regular tetrahedral angle occurs in all Co(III) chelated prolinato and sarcosinato complexes (50, 51). These results differ substantially, however, from those obtained with the $\text{Co}(\text{en})_2$ system (52). Reaction of $\text{trans-}[\text{Co}(\text{en})_2\text{Cl}_2]\text{Cl}$ with (*S*)-proline in basic meth-

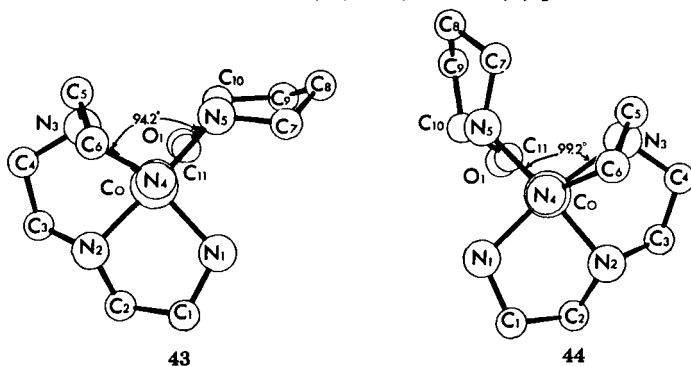


Fig. 11. Perspective view of $\beta_2\text{-}[\text{Co}(\text{trien})(S\text{-Pro})]^{2+}$ isomers from crystal structures as viewed down the trien apical chelate ring: **43**, $\Delta\text{-}\beta_2\text{-}R,R,S\text{-}[\text{Co}(\text{trien})(S\text{-Pro})]^{2+}$; **44**, $\Lambda\text{-}\beta_2\text{-}S,S,S\text{-}[\text{Co}(\text{trien})(S\text{-Pro})]^{2+}$.

anol solution appears to result in only the Δ -[Co(en)₂(S-Pro)]²⁺ isomer (similar to **41**). A similar result occurred with *N*-methyl-*R*-alanine (**52**) where only the Δ isomer is formed, and furthermore both the *N*- and *C*-methyl substituents were shown to be thermodynamically stable toward mutarotation in basic solution (**52**). This result also differs in degree from that obtained for the Co-trien system (**53**), and it may be that the asymmetric Co(en)₂ moiety induces more thermodynamic specificity toward asymmetric chelate rings than does the β -Co(trien) grouping. The difference could result from distortions built into the β -trien topology allowing fewer close contacts with the neighboring other chelate ring, and it will be of interest to test this proposal by minimization calculations.

2. β_2 -[Co(trien)(S-Pro)]²⁺ Isomers

Having observed the distortion in the crystal lattice, it was then of interest to see if the minimization technique reproduced the crystal structures (**54**). As a starting point, the structural coordinates were orthogonalized and reoriented on Co as the origin in such a way that there were no invariant internal coordinates. The force field described in Sect. III-B-1,2 was used, some 320 energy terms were considered, and 129 coordinates were varied cooperatively. The minimized structures drawn by computer control are given in Figure 12 (**25**). Nonbonded interactions greater than 0.5 kcal/mole are shown as dotted lines. First, the minimized structures reproduce the major distortions observed in the crystal structure (CoN(5)C(7): Δ -*R,R,S* 120.7°, Δ -*S,S,S* 122.2°; N₃CoN₅: Δ -*R,R,S* 92.4°, Δ -*S,S,S* 98.9°). Second, a comparison of the calcu-

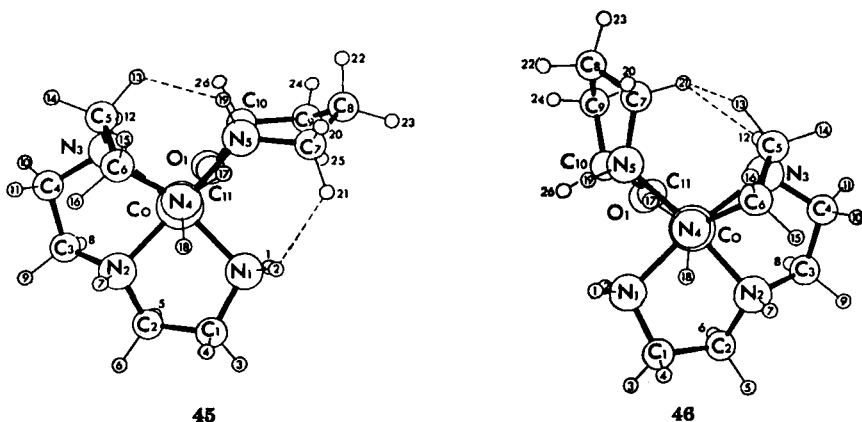


Fig. 12. Perspective diagram of minimized β_2 -[Co(trien)(S-Pro)]²⁺ isomers viewed down the trien apical chelate ring: **45**, Δ - β_2 -*R,R,S*-[Co(trien)(S-Pro)]²⁺; **46**, Δ - β_2 -*S,S,S*-[Co(trien)(S-Pro)]²⁺. Dashed lines indicate major nonbonded interactions (greater than 0.5 kcal/mole).

lated and observed atomic coordinates show that the detailed agreement is extraordinarily good for both structures (54). This agreement is demonstrated in Figures 13 to 17, which compare the crystal structures and minimized geometries from several different points of view: (a) deviations of the C atoms from the N—Co—N planes (Fig. 13), (b) torsion angles about C—C and C—N axes (Fig. 14); (c) variations in the N—Co—N angles (Fig. 15); and, to a lesser extent, by examining the proline geometry (Figs. 16, 17). A cursory glance at each of the figures is sufficient to show that the minimized treatment mimics closely the observed features of the coordination of the trien molecule, and includes substantial distortions induced by coordination of proline. The question which then arises is: How do we know that the coordination geometry is not accidentally similar in these two complex ions? This question is answered partly by considering the observed geometry for four different complexes of this type, the two $[\text{Co}(\text{trien})(\text{S-Pro})]^{2+}$ ions just discussed, and $[\text{Co}(\text{trien})\text{ClOH}_2]^{2+}$ (47) (55), and *sym*- $[\text{Co}(\text{trenen})\text{N}_3]^{2+}$ (48)

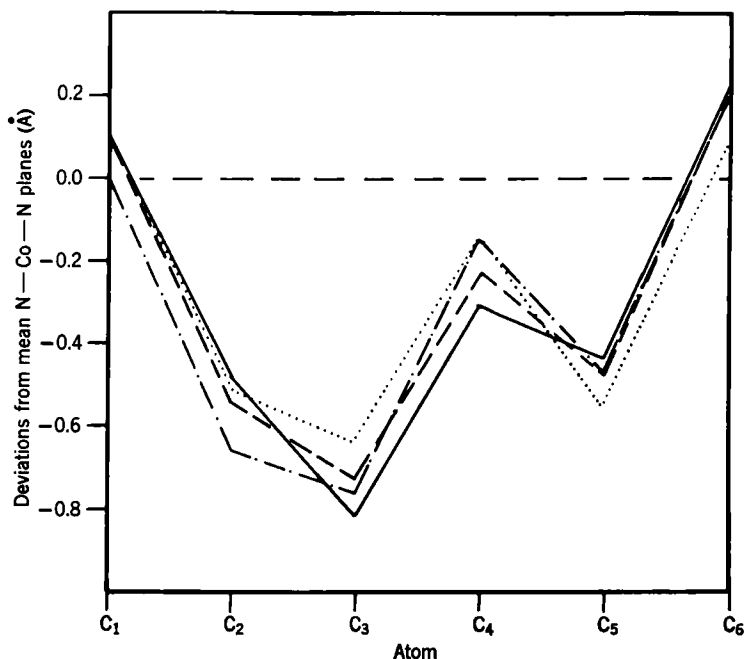


Fig. 13. Comparison of deviations of trien chelate ring carbon atoms from their respective N—Co—N planes: — calculated from minimized coordinates for $\Lambda\text{-}\beta_2\text{-S,S,S-}[\text{Co}(\text{trien})(\text{S-Pro})]^{2+}$; - - calculated from crystal structure coordinates for $\Lambda\text{-}\beta_2\text{-S,S,S-}[\text{Co}(\text{trien})(\text{S-Pro})]^{2+}$; - · - calculated from minimized coordinates for $\Delta\text{-}\beta_2\text{-R,R,S-}[\text{Co}(\text{trien})(\text{S-Pro})]^{2+}$; · · · calculated from crystal structure coordinates for $\Delta\text{-}\beta_2\text{-R,R,S-}[\text{Co}(\text{trien})(\text{S-Pro})]^{2+}$.

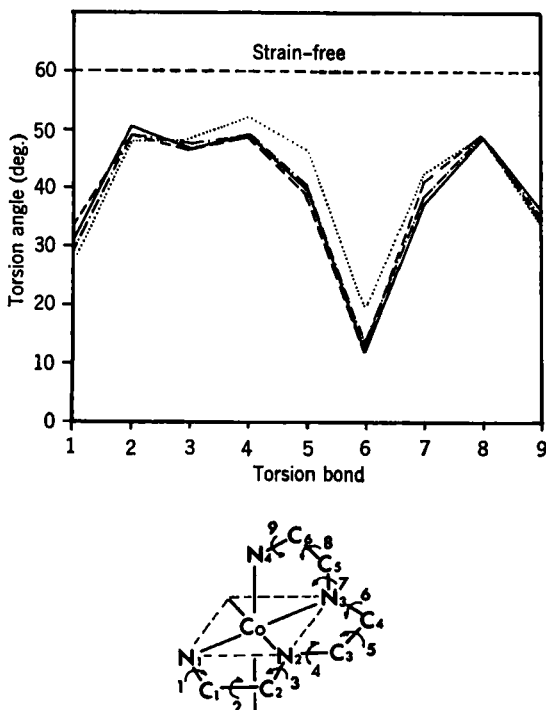


Fig. 14. Comparison of torsion angles for trien chelate rings: — Λ - β_2 -(S,S,S)-[Co(trien)(S-Pro)]²⁺ (minimized); — — Λ - β_2 -(S,S,S)-[Co(trien)(S-Pro)]²⁺ (crystal); - - - Δ - β_2 -(R,R,S)-[Co(trien)(S-Pro)]²⁺ (minimized); Δ - β_2 -(R,R,S)-[Co(trien)(S-Pro)]²⁺ (crystal).

(56) (Fig. 18). That the chloroaquo structure is relevant is immediately obvious, but the trenen structure has to be viewed as a substituted trien complex. It can be seen then that the right-hand side of **48** has the structural elements to duplicate the coordinated trien structure **46**, and the atomic coordinates for this part of the structure have been compared with those of the trien structures. The comparison is made in Figures 19, 20, and 21 by an analysis of the deviations of the C atoms from N—Co—N planes (Fig. 19), the torsion angles along the chelate chain (Fig. 20), and the angles between the successive planes, commencing with CoN₁C₁ and CoC₁C₂ and following the folding of the chelate chain in this way (Fig. 21). The three methods are included to avoid any particular bias arising from the choice of any one comparison. The results demonstrate the close agreement between the geometry of the coordinated trien moiety in all four compounds. Different lattice forces and space groups are involved, and clearly the similarity cannot therefore be

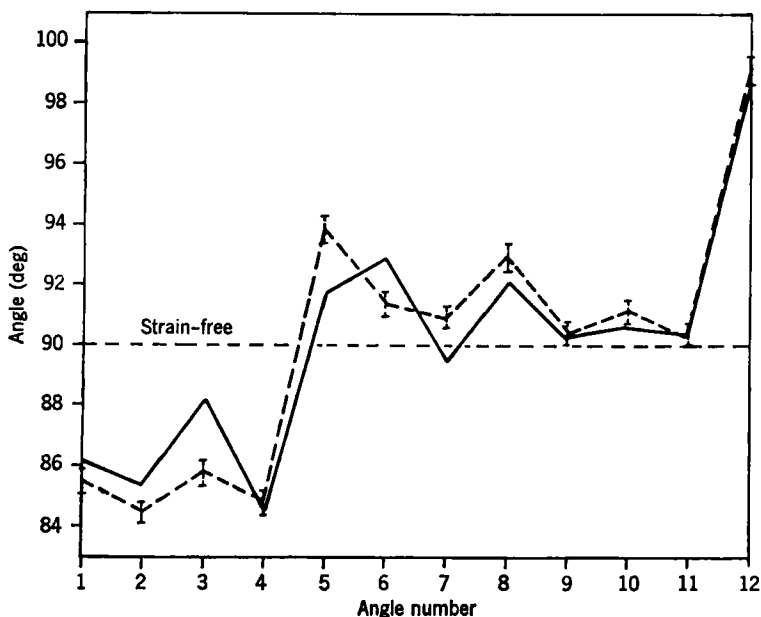


Fig. 15. Comparison of bond angles about cobalt ion for Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺; — calculated from minimized coordinates; - - calculated from crystal structure coordinates (with standard deviations). 1, N(1)—Co—N(2); 2, N(2)—Co—N(3); 3, N(3)—Co—N(4); 4, O(2)—Co—N(5); 5, N(1)—Co—N(4); 6, N(2)—Co—N(4); 7, N(1)—Co—N(5); 8, N(5)—Co—N(4); 9, N(1)—Co—O(2); 10, N(2)—Co—O(2); 11, N(3)—Co—O(2); 12, N(3)—Co—N(5).

an accident. It is inferred from this analysis that the trien chelate is comparatively rigid even in solution.

The minimized geometry within any given energy well should be independent of the starting coordinates, and there is no special reason, other than that of convenience for choosing the structural coordinates as the trial geometry. However, to test the technique for one structure, the most distorted prolinato chelate ring in **46** was moved ~ 0.7 Å to a position consistent with a relatively undistorted geometry about the Co(III) center. The new trial coordinates were inserted in the minimization calculation to give finally the same minimized structure, **46**. Such a process also checks for the presence of local minima.

The agreement suggests that the analysis of the rotational barriers about the Co—N bond is correct, and that dipole-dipole terms, etc., are either small or cancel. All the structural analyses show H-bonding between N—H protons and anions in the lattice, by which we infer that N—H bonding to H₂O

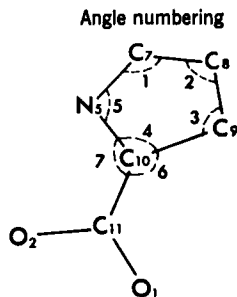
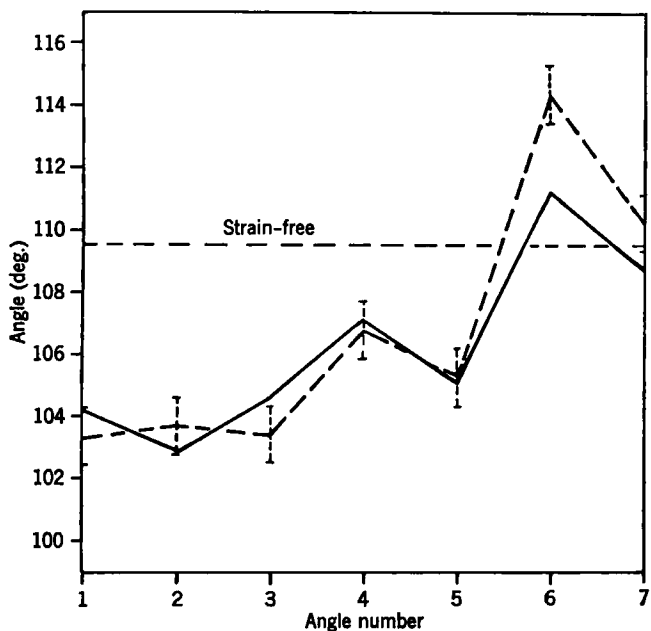


Fig. 16. Comparison of bond angles around pyrrolidine of proline: — calculated from minimized coordinates for Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺; - - - calculated from crystal structure coordinates for Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺ with standard deviations.

in aqueous solution is practically inescapable. A close analysis of the chelate rings indicates a variation from the C_2 half-chair form, through skew half-chair, to the skew-envelope form. Such a variation is not unexpected in such crowded systems, and the results are to be compared with the fairly regular geometry observed in the simple M-en rings (9,10). Numerous other comparisons with trends in the detailed geometry, such as variations in Co—N bond can be made (25), but these results are less certain than those

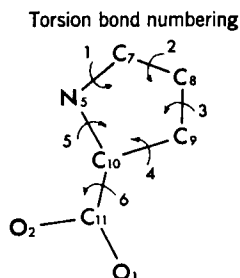
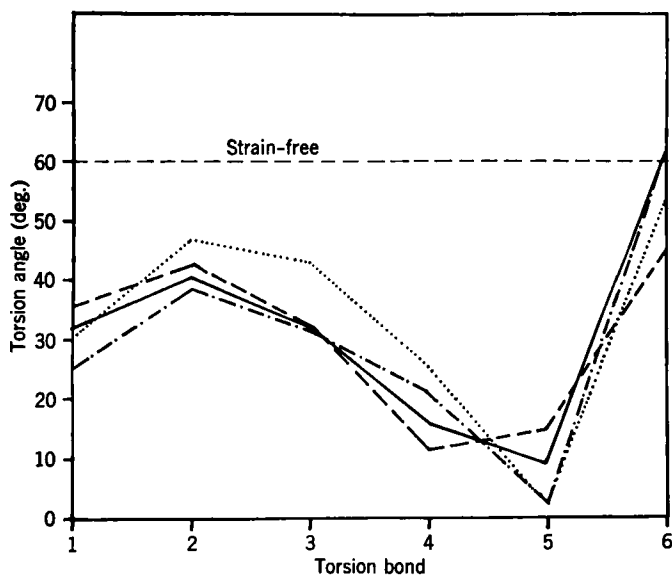


Fig. 17. Comparison of torsion angles for pyrrolidine ring of proline; — calculated from minimized coordinates for Λ - β_2 -(*S,S,S*)-Co(trien)(*S*-Pro)]²⁺; - - - calculated from crystal structure coordinates for Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺; — · — calculated from minimized coordinates for Δ - β_2 -(*R,R,S*)-[Co(trien)(*S*-Pro)]²⁺; calculated from crystal structure coordinates for Δ - β_2 -(*R,R,S*)-[Co(trien)(*S*-Pro)]²⁺.

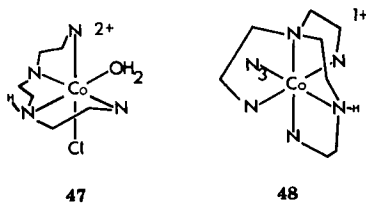


Fig. 18. Structures of β -[Co(trien)ClOH₂]²⁺ (47) (55), and *sym*-[Co(trenen)N₃]²⁺ (48) ions (56).

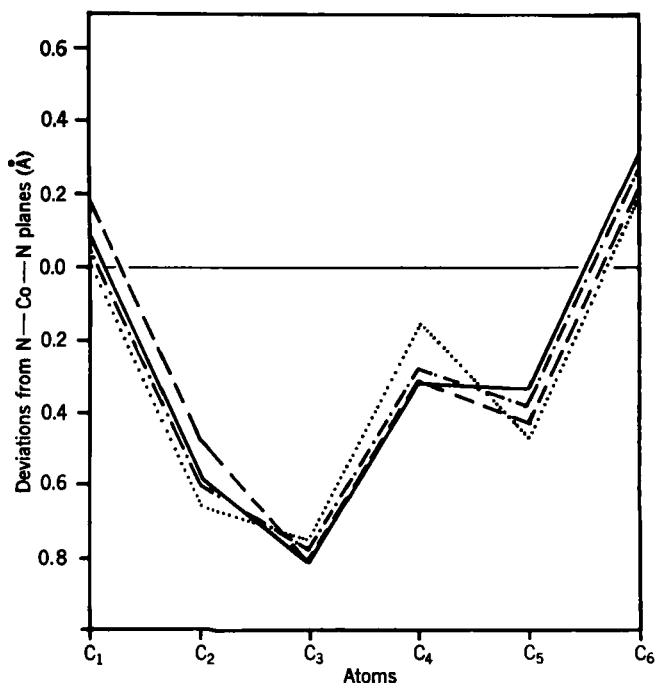


Fig. 19. Comparison of deviations of carbon atoms from their respective N—Co—N planes for β -trien chelate rings: — $\Lambda\text{-}\beta_2\text{-(S,S,S)-[Co(trien)(S-Pro)]}^{2+}$; - - - racemic- $\beta\text{-[Co(trien)ClOH}_2\text{]}^{2+}$; — · — $\Delta\text{-}\beta_2\text{-(R,R,S)-[Co(trien)(S-Pro)]}^{2+}$; · · · · $\text{sym-[Co(trenen)N}_3\text{]}^{2+}$.

given above. One comment, however, is justified, and that is the observation that in general there is a preference in these systems for distortion to occur about the angles associated with the metal ion, rather than in the intraligand bond angles and distances.

3. $[\text{Co}(\text{tetraen})\text{Cl}]^{2+}$ Isomers

A contrasting set of results arises from the $[\text{Co}(1,4,7,10,13\text{-pentaazatri-decane})\text{Cl}]^{2+}$ ions, $([\text{Co}(\text{tetraen})\text{Cl}]^{2+})$. The topological arrangements of the chelate are given in Figure 22. Isomer **49** has a plane of symmetry; **50** is asymmetric and can exist in two diastereoisomeric forms depending on the orientation of the proton at N(4); isomer **51** is also asymmetric but has no diastereoisomeric forms arising from inversion at N(3), but **52** has an asymmetric arrangement of the ligand about the cobalt center and also has four possible diastereoisomeric forms, for each arrangement, arising from the asymmetric centers at N(3) and N(4). The length of the chelate chain (N—C—

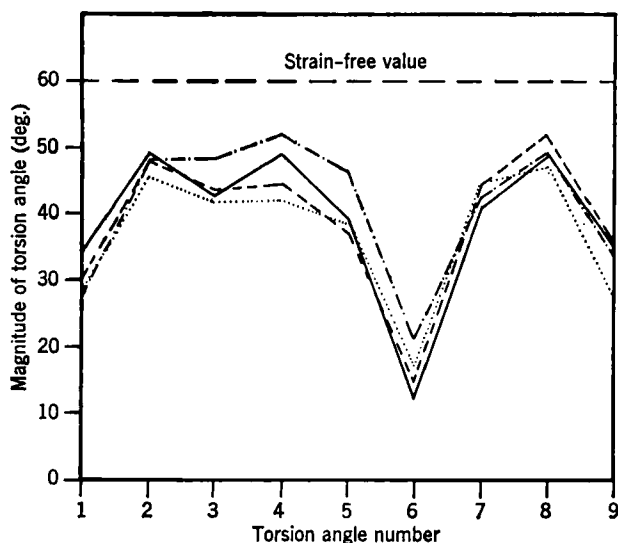


Fig. 20. Comparison of torsion angles for β -trien chelate rings: — Λ - β_2 -(S,S,S)-[Co(trien)(S-Pro)]²⁺; — — racemic- β -[Co(trien)ClOH₂]²⁺; — · — Δ - β_2 -(R,R,S)-[Co(trien)(S-Pro)]²⁺; · · · · sym-[Co(trenen)N₃]²⁺. Torsion angle numbering: 1, Co—N(1)—C(1)—C(2); 2, N(1)—C(1)—C(2)—N(2); 3, C(1)—C(2)—N(2)—Co; 4, Co—N(2)—C(3)—C(4); 5, N(2)—C(3)—C(4)—N(3); 6, C(3)—C(4)—N(3)—Co; 7, Co—N(3)—C(5)—C(6); 8, N(3)—C(5)—C(6)—N(4); 9, C(5)—C(6)—N(4)—Co.

C—N) does not allow inversion at the “angular” N atoms, i.e., where the chelate planes are orthogonal. Inversion at N which fuses two chelates can occur only when the two rings are in the same plane, and then conformational inversion of both rings is synchronous with inversion at the N center. These rearrangements are base-catalyzed, and are attributed to removal of the proton on the N atom by OH[−] ion. In most respects the complexes are closely related to the triethylenetetramine systems just discussed. A trivial nomenclature was adopted to name these complexes, which is also based on that used for the triethylenetetramine system. If the chelated ligand is observed from both ends, it has the characteristics of α,β or trans configurations. Thus the isomers in Figure 22 are, respectively, $\alpha\alpha$, $\alpha\beta$, $\beta\beta$, and β -trans. This system has the parochial merit that, if the nomenclature is remembered, the double label readily establishes the structure in the reader’s mind. If the octahedral numbering system (IUPAC) is used, the structure needs to be drawn before the geometry is readily visualized. Clearly, this area of inorganic nomenclature badly needs attention, especially now that macrocyclic ring systems are becoming more commonplace.

At the time of writing, isomer **49** and the two diastereoisomeric forms

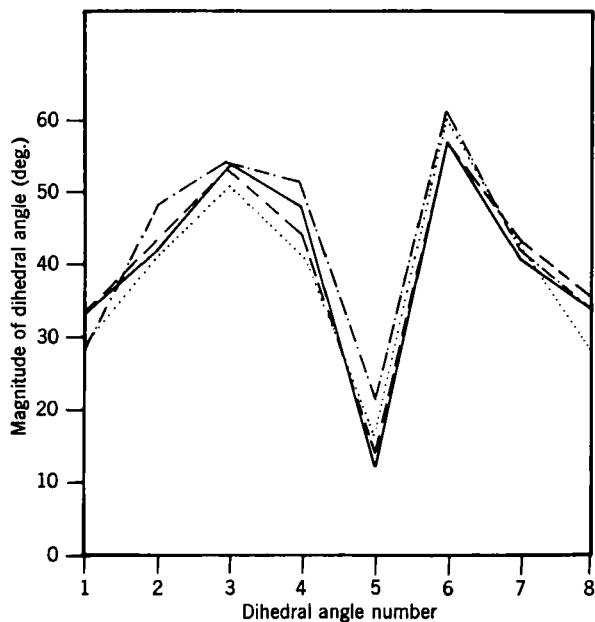


Fig. 21. Comparison of dihedral angles for β -trien chelate rings: — Λ - β_2 - S,S,S -[Co(trien)(S-Pro)]²⁺; — — racemic- β -[Co(trien)ClOH₂]²⁺; — · — Δ - β_2 -(R,R,S)-[Co(trien)(S-Pro)]²⁺; sym -[Co(trenen)N₃]²⁺. Dihedral angle numbering: 1, Co—C(1); 2, Co—C(2); 3, Co—N(2); 4, Co—C(3); 5, Co—C(4); 6, Co—N(3); 7, Co—C(5); 8, Co—C(6).

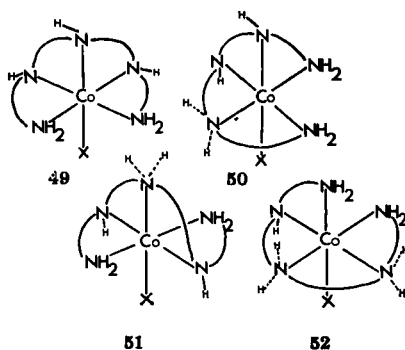


Fig. 22. Topological arrangements of the quinquedentate ligand tetraethylenepentamine (tetraen) about Co(III) in [Co(tetraen)Cl]²⁺ ions; 49, $\alpha\alpha$; 50, $\alpha\beta$; 51, $\beta\beta$; 52, β -trans.

of **50** have been characterized, chemically and by crystal structure analyses (32,57,58). It should be emphasized that the chiral N centers in these fixed-ring systems function like the chiral C atoms in carbocyclic compounds, and the N—H protons are kinetically inert in dilute acid or, at worst, exchange very slowly. Even so, the rate ratio of exchange to inversion at centers of this type is usually 10^4 to 10^6 , so that retention of configuration at these sites is effectively observed during proton exchange. Moreover, inversion is frequently slow at $\text{pH} < 9$ ($< 10^{-3}\text{sec}^{-1}$), and in the few instances where H exchange is effected by H_2O rather than by OH^- , the retention ratio is even larger, or the process occurs exclusively with retention (59,60).

With these properties in mind, it is conceivable that the diastereoisomers for the configuration **50** could be interconverted in neutral solution or dilute base. However, base hydrolysis of Cl^- intervenes, and by this method it is only possible to equilibrate these isomers as their hydroxo complexes. The equilibrium at 25° favors the form depicted by **50** by about 10:1 (58).

The isolated isomers, whose structures are shown in Figures 23 to 25 as drawn by computer control from the X-ray study (32,57), were compared with the structures computed by the application of the general force field (32,61). The comparison is given by the calculated and observed dihedral angles about the C—C bonds in Figures 23 to 25, and by the calculated and observed chain angles along the chelate rings in Figure 26. In general, the correlation between

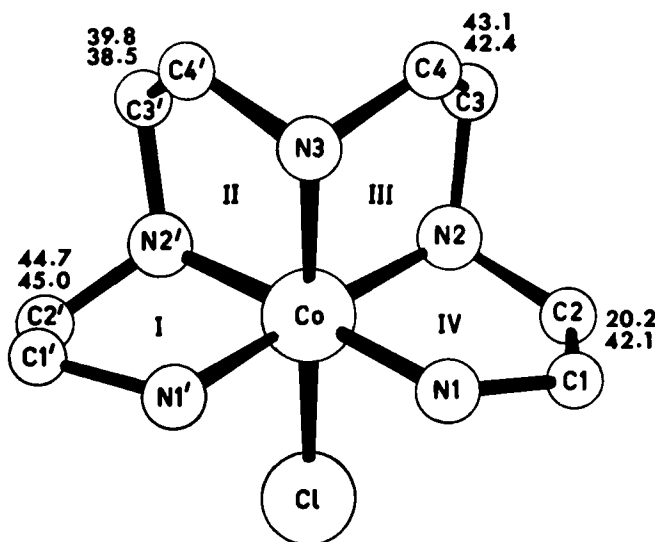


Fig. 23. Crystal structure of $\alpha\alpha\text{-[Co(tetraen)Cl]}^{2+}$ (**49**). A comparison of the torsion (dihedral) angle about the C—C and C—N bonds are given; (top figure) crystal structure; (bottom figure) minimized value.

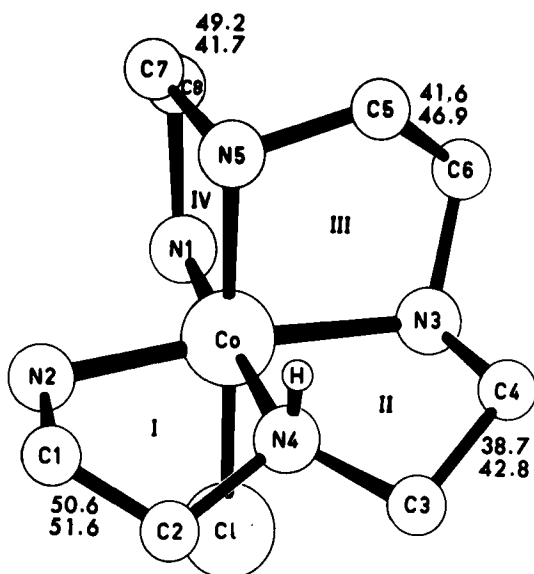


Fig. 24. Crystal structure of $\alpha\beta$ -[Co(tetraen)Cl] $^{2+}$ (50). A comparison of the torsion (dihedral) angle about the C—C and C—N bonds are given; (top figure) crystal structure; (bottom figure) minimized value.

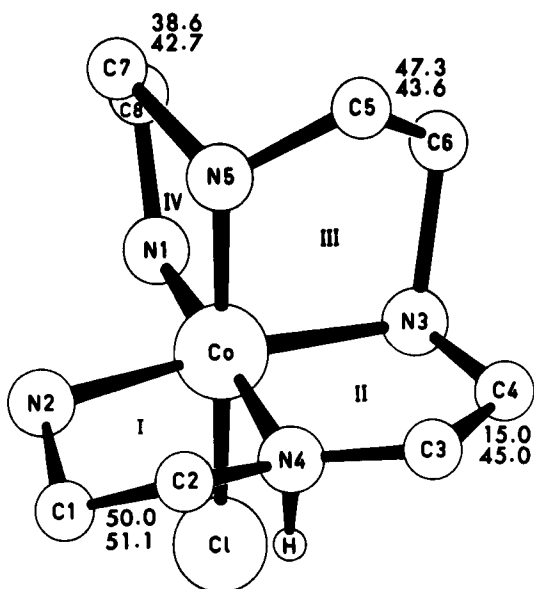


Fig. 25. Crystal structure of $\alpha\beta^1$ -[Co(tetraen)Cl] $^{2+}$ (50). A comparison of the torsion (dihedral) angle about the C—C and C—N bonds are given; (top figure) crystal structure; (bottom figure) minimized value.

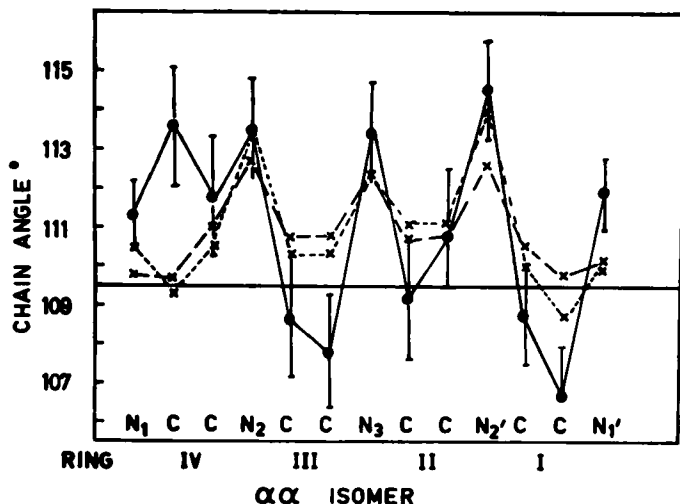


Fig. 26. Chain angles (32) for observed and minimized structures of **49**: ●—● observed; — — minimized (two sets of force constants used).

calculated and predicted geometry is good, except for some special comparisons. In isomer **49** there is a substantial difference between the calculated angle and the observed dihedral angle for C_1-C_2 ($\sim 22^\circ$) (Fig. 23). It has been traced to a packing force by which an oxygen atom from a perchlorate ion bisects a $H-C-H$ angle, and thus fixes the conformation. This interaction must also perturb the remainder of the structure, and it probably accounts for the overall poorer agreement relative to that observed in the trien systems. A similar distortion is also evident in the Δ -*R* form of isomer **50** (Fig. 24), for a similar reason, but a consistent picture appears for the Δ -*S* isomer of **50** in which there are no obvious packing interactions (Fig. 25). This series offers a valuable comparison, if only in that for those instances where disagreement between the calculated and observed structure is found, lattice forces appear responsible; where no such interaction occurs, agreement between the calculated and observed structures is uniformly good. Many examples of this type of behavior might occur, especially in the more flexible systems. Examples might include the different conformers of $[Co(en)_3]^{3+}$ or $[Cr(en)_3]^{3+}$ in different lattices (10), and the chair conformation in $[Co(tn_3)]^{3+}$ (18) relative to the distorted boat configurations in $[Co(en)mal_2]^-$ (19).

B. Energy Comparisons

Having established that the minimization procedure can reproduce the structure of these quite complicated, and in some instances distorted, molecules,

it is now relevant to check if it predicts the correct energy difference between isomeric forms.

1. Cobalt(III) *en-pn* Systems

Snow and Crossing (62) have recalculated the total strain energies for $\Delta\cdot[\text{Co(en)}_3]^{3+}$ ($\lambda\lambda\lambda$) and $\Lambda\cdot[\text{Co(en)}_3]^{3+}$ ($\delta\delta\delta$) using a force field similar to that described for the tetraen systems (Sect. IV-A-3); the energy difference stabilizing the $\Lambda\cdot\lambda\lambda\lambda$ form is only 0.58 kcal/mole. A similar conclusion was also reached by Gollogly and Hawkins (27). This is to be compared with about 1.8 kcal/mole calculated by Corey and Bailar. It is difficult at the moment to test these proposals because the evidence for the existence of the two forms in solution is fragmentary at best (63,64). The interpretation of some pmr and circular dichroism results led to a proposal that equal amounts of $\Lambda\cdot\lambda\lambda\lambda$ and $\Lambda\cdot\delta\lambda\lambda$ existed in solution, and this conclusion would be qualitatively consistent with the calculation, since the mixed species should be between the extremes in energy. It has been suggested also from a recent pmr study on $[\text{Ni(en)}_3]^{2+}$ that the free-energy difference between $\Lambda\cdot\lambda\lambda\lambda$ and $\Lambda\cdot\delta\delta\delta$ is 0.9 kcal/mole at 32° (65). These results have limited value at the moment, since the calculated energy represents a contribution to ΔH° and we have little or no information on ΔH° or ΔS° for the equilibria in these systems other than knowing that ΔG_{25}° is not large. Temperature variation studies for equilibration in the $[\text{Co(chxn)}_3]^{3+}$ (66) and $\beta_2\text{-}[\text{Co(trien)(gly)}]^{2+}$ (68) systems showed little change in the equilibrium constant over a 30–50° change. However, the ΔH° for the equilibrium $\Delta\text{-}\beta_2(R,R)\text{-}[\text{Co(trien)gly}]^{2+} \rightleftharpoons \Delta\text{-}\beta_2(R,S)\text{-}[\text{Co(trien)gly}]^{2+}$ has been measured calorimetrically as 1.1 ± 0.1 kcal/mole (67), which agrees well with the measured ΔG_{25}° of 1.2 ± 0.1 kcal/mole. This agreement augurs well for the future of the energy calculations described here, but many experimental measurements of this nature are required before their usefulness can be assured.

Some early measurements (71) of equilibria for some $\Lambda\text{-}[\text{Co(en)}_2(R)\text{pn}]^{3+}$ and $\Lambda\text{-}[\text{Co}(R)\text{pn}_3]^{3+}$ isomers are given in Table 1, along with the strain-energy differences calculated by Snow and Crossing (62). The results for the $\Delta\text{-}[\text{Co(en)}_2(R)\text{pn}(\delta\delta\lambda)]^{3+}\text{-}\Delta\text{-}[\text{Co(en)}_2(S)\text{pn}(\delta\delta\delta)]^{3+}$ pair (with an equatorial CH_3 group) are in good agreement, but that for the $\text{Co}(\text{pn})_3$ system (eq. [iv]) is not. One inference which might be drawn from the latter result is that $T\Delta S^\circ$ is not small relative to ΔH° . The calculations indicate that the energy differences result primarily from the torsional terms. Despite the lack of quantitative agreement, qualitatively the calculations predict which is the most stable isomer, and so do crude computations using regular stereo models and only nonbonded terms in the calculation. It becomes increasingly apparent that molecules undergo distortion to relieve these nonbonded interactions,

TABLE 1

Observed and Calculated Energy Differences for Cobalt(III) Complexes of Ethylenediamine and *R*-Propylenediamine at 25° (62)

1	2	ΔSE_{1-2} (kcal/mole) (62)	ΔG_{obs}° (63)
(i) $\Delta Co(en)_3(\lambda\lambda\lambda)$	$/ \Delta Co(en)_3(\delta\delta\delta)$	0.58	—
(ii) $\Delta Co(en)_2(-)pn(\delta\delta\lambda)$	$/ \Delta Co(en)_2(+)pn(\delta\delta\delta)$	0.41	0.45
	eq.		
(iii) $\Delta Co(en)_2(-)pn(\delta\delta\delta)$	$/ \Delta Co(en)_2(-)pn(\delta\delta\lambda)$	1.84	—
	axial		
(iv) $\Delta Co(-)pn_3(\lambda\lambda\lambda)$	$/ \Delta Co(+)pn_3(\delta\delta\delta)$	0.65	1.6
	eq.		
(v) $\Delta Co(en)(-)pn_2\delta\lambda\lambda$	$/ \Delta Co(en)(+)pn_2(\delta\delta\delta)$	0.75	1.2
	eq.		

primarily by alteration in valence and torsional angles. It follows, therefore, that provided the nonbonded interactions are appreciable, their evaluation in the regular geometry should give a rough guide to relative stability. Another factor which the calculations (62) in Table 1 demonstrate is the energy difference expected between the axial and equatorial orientation of the methyl group in the $Co(R)pn$ ring (Corey and Bailar value, > 2 kcal/mole). This value, to which all the energy terms except bond stretching contribute significantly, is sufficiently large to ensure that the rationalizations which have been applied to account for the stereochemistry of the C-substituted methyl-ethylenediamine systems are substantially correct. For example, it has been asserted for $Co(III)$, $Pt(II)$, and $Pd(II)-(R)pn$ rings (14,63,69,70), and for $Co(III)(-)$ 2,3-butanediamine rings (15), that the axial CH_3 -axial N-substituent interaction is sufficient to ensure that in solution the conformation of the ring is such that the CH_3 group remains substantially equatorial. The present calculations leave these arguments unchanged, although they require that for the propylenediamine systems the agreement between the Corey and Bailar calculations and the observed free-energy differences be fortuitous.

It is also relevant to point out some additional features of the $[Co(R)pn_3]^{3+}$ system. Isomerism arises not only from the configuration about the cobalt, from the chiral C centers, and from the conformations of the chelates, but also from the positions of the methyl groups in relation to one another. In this respect the complex has either C_3 symmetry (cis methyls), or C_1 symmetry (trans methyls). A separation of the two forms by fractional crystallization was claimed (72), but the properties of the supposed forms apart from solubility were remarkably similar. Even upper-layer Weissenberg photographs of single crystals of the dithionates were indistinguishable (73). However, the two isomers have now been separated chromatographically

(73) and they occur approximately in the ratio of 1:3. This is enough to show that there is no decided preference other than probability for one form over the other. The less abundant isomer was also the less soluble form and coincided with the form where the structure has been shown to be *cis* (9).

2. Other Bidentate Chelates

Additional evidence for the view expressed above comes from equilibria established for the Λ - and Δ -[Co((-)-1,2-*trans*-cyclohexanediamine)₃]³⁺ ions (66) and for the Λ - and Δ -[Co((-)-2,3-butanediamine)₃]³⁺ ions (15). In the former example the conformations of the chelate are fixed by the cyclohexane ring in both enantiomers, and conformational inversion is not possible. Here the equilibrium constant, $\Delta/\Lambda = 21.7$ at 25°, is not greatly different from that observed for the (*R*)pn system. Also, Woldbye (15) has been unable to find any evidence for the Λ form of the (-)-2,3-diaminobutane cobalt(III) complex, which indicates Δ/Λ greater than 50. In the Δ - isomer both methyl groups are equatorial, whereas in the Λ form the interactions between the axial methyls and the axial substituents on cobalt will be double that for the Co(*R*)pn chelate.

The octahedral cobalt(III) complex containing three molecules of (-)-*trans*-1,2-cyclopentanediamine has also been prepared, and a preliminary structural report has appeared (74). The molecule was first recorded by Jaeger (75), but it was suggested (76,63) later that its existence was doubtful. Dreiding models indicate that the tris chelate must contain ligands which are considerably distorted, and the structure shows this to be so (74). It follows that strain energy calculations on the Λ and Δ isomers of this complex, and also for the *trans*-1,2-cyclohexanediamine system, should be most interesting (62). Both sets of isomers have relatively rigid chelate conformations, but one chelate system is grossly strained whereas the other is relatively strain-free.

3. β_2 -[Co(*trien*)(*S-Pro*)]²⁺ Isomers

For the triethylenetetramine (*S*)-proline chelates an examination of the magnitude of the terms which contribute to total strain energy is revealing. Calculations have been carried out for four isomers of the β_2 -[Co(*trien*)(*S-Pro*)]²⁺ ion (25), namely, Δ - β_2 -*R,R,S* (41), Λ - β_2 -*S,S,S* (42), Δ - β_2 -*R,S,S*, and Λ - β_2 -*S,R,S*. X-ray structural analysis has been carried out on the first two, but the remaining species have not been isolated. The latter isomers are those diastereoisomeric forms of the isolated ions having the "planar" N center of the *trien* residue in the inverted configuration. There is no evidence for the existence of the last two species, either in the preparative mixture or

TABLE 2
Minimized Energy Terms for β_2 -[Co(trien)(S-Pro)]²⁺ Isomers (kcal/mole)

	$\Delta\text{-}\beta_2\text{-}R,R,S$	$\Lambda\text{-}\beta_2\text{-}S,S,S$	$\Delta\text{-}\beta_2\text{-}R,S,S$	$\Lambda\text{-}\beta_2\text{-}S,R,S$
Bond length deformations, $\sum U(r_{ij})_r$	1.2	1.3	1.5	1.5
Nonbonded interactions, $\sum U(r_{ij})_{nb}$	4.7	4.9	5.4	5.8
Valence angle deformations, $\sum U(\theta_{ijk})$	7.5	8.9	9.4	11.1
Torsional strain, $\sum U(\phi_{ijkl})$	10.3	10.2	10.2	10.5
Total strain energy, U	23.7	25.3	26.5	28.9
Energy differences (relative to $\Delta\text{-}\beta_2\text{-}R,R,S$)	0	1.6	2.8	5.2

when the relevant proton is removed with OH^- (48). The contributions from each term considered in the force field are given in Table 2. Overall $\Delta\text{-}\beta_2\text{-}R,R,S$ was calculated as 1.6 kcal/mole more stable than $\Lambda\text{-}\beta_2\text{-}S,S,S$, and their diastereoisomeric counterparts as 2.8 and 3.6 kcal/mole, respectively, less stable. The latter values agree with their absence in the preparative experiments. Attempts to equilibrate $\Delta\text{-}\beta_2\text{-}(R,R,S)\text{-[Co(trien)(S-Pro)]}^{2+}$ and $\Delta\text{-}\beta_2\text{-}(R,R,R)\text{-[Co(trien)(R-Pro)]}^{2+}$ (the latter is equivalent energetically to **42**) by exchanging the protons on both the proline-N and asymmetric-C atom were not successful (48); unfortunately, cleavage of the amino acid chelate ring occurred before mutarotation, and it was attributed to the fact that both asymmetric centers, N and C, must be deprotonated at the same instant before inversion can take place. The reason for this requirement is that the relevant protons must be cis relative to the proline ring when proline is chelated (**40**). Models show that the proline ring size is not large enough to permit the trans arrangement. The dissociation constant for the dual deprotonated species must be small, $< 10^{-30}$, since the coordinated N—H proton has $pK_a > 14$, and the carbon proton is even less acidic. This aspect of the chemistry merits some discussion, because isomers containing either asymmetric N(16) or C(77) centers of this nature have been readily equilibrated in base. However, the $\Delta\text{-}\beta_2\text{-}R,R,S(S)$ and $R,R,R(R)$ isomers have been equilibrated (78) using charcoal, and they give a free-energy difference of 1.3 kcal/mole in favour of the $\Delta\text{-}\beta_2\text{-}R,R,S$ isomer at 25°. In this process the charcoal generates a little of the labile Co(II) ion, and electron transfer between this and the Co(III) ion is fast in the presence of the charcoal (79). The agreement between the calculated and observed energy difference may be fortuitous but, in company

with the many results on other systems, the calculation correctly predicts the most stable species. A calculation using a regular geometry from Dreiding models, and only nonbonded contributions (Hill), overcalculates this energy difference to the extent of about 13 kcal/mole. In the present calculations the analysis shows that the torsion terms are largest, but they largely cancel in all the structures. For the isolated isomers, the contribution of the nonbonded interactions differ by only 0.2 kcal/mole, and the energy difference is due almost entirely to the bond angle bending terms. As expected, the differences in the bond length deformation contributions are very small.

4. $[Co(tetraen)Cl]^{2+}$ Isomers

Similar calculations for the $\Lambda\text{-}\alpha\beta\text{-}R$ and $\Lambda\text{-}\alpha\beta\text{-}S$ $[Co(tetraen)Cl]^{2+}$ isomers (Figs. 24, 25) give energy differences of about 2 kcal/mole, and these are relatively insensitive to force field variations (61). The values are consistent with the measured ΔG° value for the hydroxo complex. A calculation of the same type on the hydroxo complexes would not be expected to differ significantly from that for the chloro species.

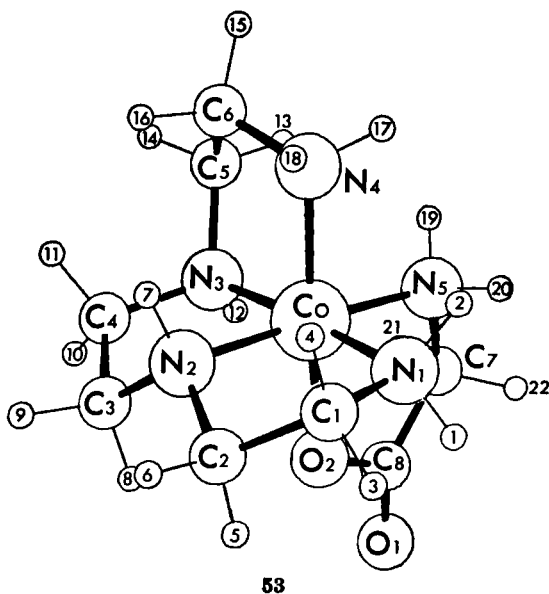
One general, important aspect of these calculations is the magnitude of the total strain energies involved for each system. By comparison with calculations based solely on the nonbonded interactions (using moderate potential functions), these energies are small. It follows that the energy differences are correspondingly larger relative to the total strain energy and are therefore probably more meaningful.

5. $\beta_2\text{-}[Co(trien)gly]^{2+}$ Isomers

Table 3 shows the results of the force field calculations for the two diastereoisomeric forms of $\Delta\text{-}\beta_2\text{-}[Co(trien)(gly)]^{2+}$ (**53**) (Fig. 27), **54** (Fig. 28). Here the equilibrium constant has been measured, $\Delta G_{25}^\circ = 1.2 \pm 0.1$ kcal/

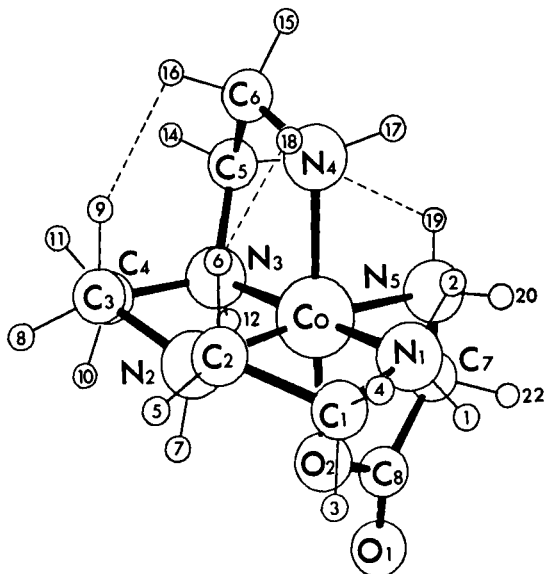
TABLE 3
Minimized Energy Terms for $\beta_2\text{-}[Co(trien)(gly)]^{2+}$ Isomers
(kcal/mole)

	$\Delta\text{-}\beta_2\text{-}R,R$	$\Delta\text{-}\beta_2\text{-}R,S$
Bond length deformations, $\sum U(r_{ij})_r$	0.6	0.8
Nonbonded interactions, $\sum U(r_{ij})_{nb}$	2.9	3.6
Valence angle deformations, $\sum U(\theta_{ijk})$	3.4	5.1
Torsional strain, $\sum U(\phi_{ijkl})$	5.3	5.4
Total strain energy, U	12.2	14.9
Energy difference (relative to $\Delta\text{-}\beta_2\text{-}R,R$)	0	2.7



53

Fig. 27. Perspective view of $\Delta\text{-}\beta_2\text{-(R,R)-[Co(trien)(gly)]}^{2+}$ ion (53) drawn from minimized coordinates (25).



54

Fig. 28. Perspective view of $\Delta\text{-}\beta_2\text{-(R,S)-[Co(trien)(gly)]}^{2+}$ ion (54) drawn from minimized coordinates (25). (Dashed lines indicate the nonbonded interactions greater than 0.5 kcal/mole).

mole, and the calculated value is appreciably smaller than for the proline systems. Using essentially the same force field, the energy difference for the $\Delta\text{-}R,R \rightleftharpoons \Delta\text{-}R,S$ equilibrium was calculated as 2.7 kcal/mole (25), and the predicted structures **53** and **54** are shown in Figures 27 and 28, along with the major nonbonded interactions. The same pattern in the energy distribution occurs with these isomers as with the proline complexes. The dominant term contributing to energy difference is due to bond angle deformations, although the difference between the nonbonded contributions is a little larger, 0.7 kcal/mole. Torsion and bond stretching terms approximately cancel in the two structures. With these isomers, the two chelate rings in the same coordination plane have their conformations (δ or λ) fixed by the configuration about the common asymmetric N center, but the apical chelate has theoretically the possibility of existing in either a λ or a δ form. A very recent crystal structure (80) of racemic ($\Delta R,R + \Delta S,S$)- β_2 -[Co(trien)gly]Cl₂ has indeed confirmed the presence of the λ and δ apical rings; both the ($\delta\delta\lambda + \lambda\lambda\delta$) and ($\lambda\delta\lambda + \delta\lambda\delta$) conformations occurred in the asymmetric unit. This finding differs from other crystal structural results which for the $\Delta\text{-}R,R$ isomers have exclusively demonstrated the presence of the $\delta\delta\lambda$ conformer. For the $\Delta\text{-}R,S$ isomer, where only one structure is available, $\Delta\text{-}(R,S)\text{-}\beta_1\text{-[Co(trien)(gly)]I}_2$ (47), calculations were carried out for the $\delta\lambda\delta$ and $\lambda\lambda\delta$ forms, and the results showed that the latter was about 3 kcal/mole less stable than the former. This result is consistent with the structural result, and for the majority of these trien complexes it is likely that a distinct conformational preference will occur in solution (81). It is also pertinent to point out that the calculated geometries of the trien portion of the glycine complexes are very similar to those found in the crystal structures. The starting geometries for these calculations were composed from the analogous proline structures (49), and from a portion of the [Co(trenen)N₃]²⁺ (56) structure. This means that the initial coordinates differed considerably from the final minimized coordinates.

6. $\beta_2\text{-[Co(trien)(sar)]}^{2+}$ Isomers

The stereospecificity generated by the chelation of the sarcosine ion (44) has been discussed in Sect. IV-A-1, and it is now relevant to calculate the energy differences between the most likely isomers, **34**, **35**, and **36** (Fig. 9). The observation of stereospecificity for the R,R,S form (**35**), implies that the other two configurations are at least 2 kcal/mole less stable, and it is known that equilibration between the three forms can be achieved in dilute base.

The starting coordinates were obtained (25) from the glycine isomers, assuming a tetrahedral arrangement for the CH₃ group about the asymmetric N center. The minimized geometries (**55,56,57**) drawn by computer control are given in Figures 29 to 31, where the nonbonded interactions greater than

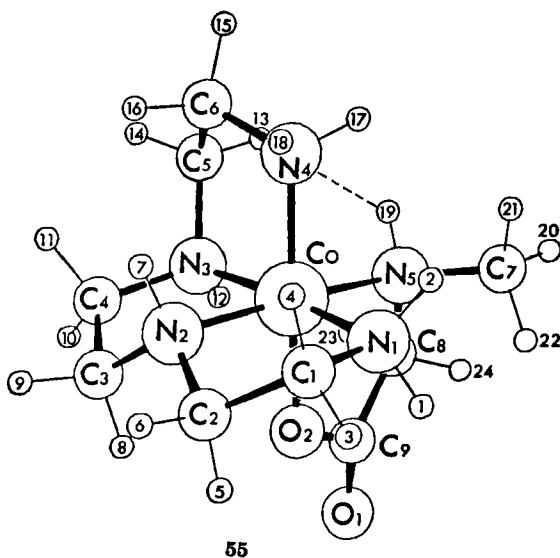


Fig. 29. Perspective view of $\Delta\text{-}\beta_2\text{-(R,R,S)-[Co(trien)(sar)]}^{2+}$ ion (55) drawn from minimized coordinates. (Dashed line indicates a nonbonded interaction greater than 0.5 kcal/mole).

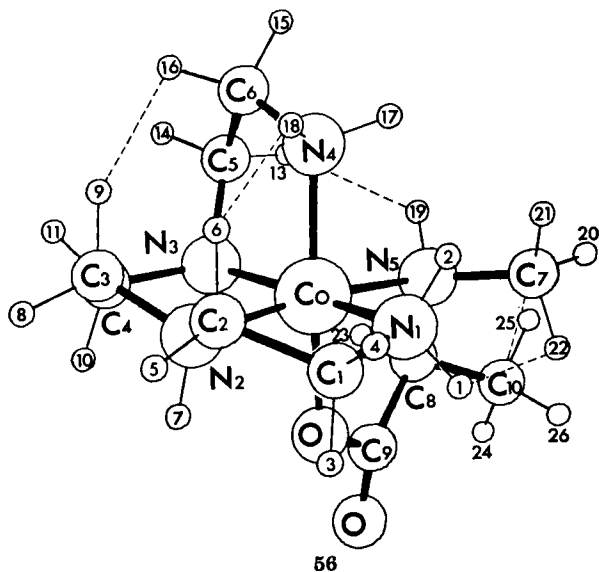


Fig. 30. Perspective view of $\Delta\text{-}\beta_2\text{-(R,S,S)-[Co(trien)(sar)]}^{2+}$ ion (56) drawn from minimized coordinates. (Dashed lines indicate nonbonded interactions greater than 0.5 kcal/mole).



0.5 kcal/mole are shown by dashed lines. For the Δ -*R,R,S* isomers (**55**) the most significant feature is that the Co—N(5)—C(7) bond angle alters from the tetrahedral value to 117.0°, which is consistent with other structures containing substituents in this position. For the other minimized structures (**56** and **57**), considerable distortion and increases in nonbonded contributions occur; the energy terms for these structures are given in Table 4. From these

	$\Delta\text{-}\beta_2\text{-}R,R,S$	$\Delta\text{-}\beta_2\text{-}R,R,R$	$\Delta\text{-}\beta_2\text{-}R,S,S$
Bond length deformations, $\sum U(r_{ij})_r$	1.1	1.4	1.4
Nonbonded interactions, $\sum U(r_{ij})_{nb}$	4.6	5.5	5.4
Valence angle deformations, $\sum U(\theta_{ijk})$	4.3	5.4	6.2
Torsional strain, $\sum U(\phi_{ijkl})$	5.2	6.2	5.9
Total strain energy, U	15.2	18.5	18.9
Energy difference (relative to $\Delta\text{-}\beta_2\text{-}R,R,S$)	0	3.3	3.7

values, the $\Delta\text{-}\beta_2\text{-}R,R,R$ (**57**) and $\Delta\text{-}\beta_2\text{-}R,S,S$ (**56**) isomers appear to be at least 3 kcal/mole less stable than the $\Delta\text{-}\beta_2\text{-}R,R,S$ isomer (**55**), and this is consistent with the apparent stereospecificity (44). These results are to be compared with the energy difference between the $\Delta\text{-}R,R,S$ and $\Delta\text{-}R,R,R$ forms, calculated from the nonbonded interactions (Hill) only, of about 8 kcal/mole (44). The Hill potential function thus overestimates the energy difference, but in the correct direction, and angular distortions take place to reduce the nonbonded interactions considerably. The same result is obtained here as that found for the energy contributions in the other isomeric complexes, namely, that bond stretching, torsional terms, and nonbonding interactions make the smallest contributions to the energy differences.

C. Variations in Force Field

The comparisons given in the preceding section have been carried out with a force field chosen critically from values which appear in the literature and which appear to work successfully for organic systems (25,32,33). It is of interest to examine some variations in the force field to see how sensitive the structures and energies are to the basic input data. This point is of considerable interest, since several types of potential functions have been used in the past, and accurate force constants are not yet available for some bond length, bond angle, and torsional functions. It is important to the success of the method that variations of these values, within reasonable limits, make little or no change in the minimized coordinates, or energy difference, between the various structures.

1. Nonbonded Interactions

In the systems examined here, the H...H nonbonded interactions make important contributions to the total energy of the molecular ion. It is therefore sensible to test the validity of the calculations by varying the functions which describe them, from "soft" (Hill (34), Scott and Scheraga (35)), through moderate (Bartell (37), Liquori (38)), to "hard" (De Santis (82), Mason and Kreevoy (23)), interactions. The energies of the various functions chosen are depicted in Figure 6, plotted in the Buckingham form. These expressions were applied to the $\Delta\text{-}\beta_2\text{-}R,R,S$ and $\Delta\text{-}\beta_2\text{-}S,S,S$ [Co(trien)-(S-Pro)]²⁺ ions (**41** and **42**). Using the "soft" Scott and Scheraga function, which is not greatly different from that devised by Hill, the calculated energy differences were not greatly different, 1.3 kcal/mole, from that found using the Bartell function, 1.6 kcal/mole. However, the total energies differed considerably, 14.1 (**41**), and 15.4 (**42**), compared with 23.7 and 25.3 kcal/mole, respectively. The striking feature of the Scott and Scheraga calculation,

however, was that the contribution to the nonbonding term was attractive. For Bartell-type calculations, the nonbonding contribution is always repulsive. Since the molecules develop the pronounced angular distortions in order to relieve such nonbonded interactions, it seems unlikely that a function which makes these interactions attractive in the minimized geometry is correct. Although the process works to minimize the total energy, it does not function to minimize the nonbonded contributions, and it would be expected, therefore, that a compromise among all the terms would result. The calculations indicate that, primarily, a compromise between angular distortions and nonbonded interactions occurs. The effect of this variation on molecular geometry was small, the maximum change in any bond angle was less than 1° , and the variation in the chelate conformations was not significant. The use of the "hard" De Santis function (82) gave a vastly different picture. The nonbonded contribution completely dominated the calculation so that the total energy increased enormously and the other terms were almost insignificant. Moreover, it diverged rapidly in a few cycles of the calculation, and it was concluded therefore that this function was far too "hard" to be realistic. From these investigations it appeared that functions similar to the Bartell potential are appropriate, that the energy differences and geometries are not particularly sensitive to the choice of function, but that the "total energies" are sensitive to such a choice. The total energies are, of course, arbitrary anyway. In view of the history of the Hill function in calculations of this sort, we note that it falls in the "soft" category and yet appears to overestimate the energy differences between isomers when no account is taken of other contributions to the force field.

2. Bond Angle Force Constants

The comparison of crystal structures **43**, **44**, and minimized geometries **45**, **46**, for the Δ -(*R,R,S*)- and Λ -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺ isomers indicates that the intrachelate bond angles do not change much and that most of the distortions occur at those angles which involve the metal center, i.e., N—Co—N and Co—N—C. Therefore, only these most sensitive areas were examined (25). A reduction in the N—Co—N force constant from 0.68 to 0.40 (10^5 dynes cm⁻¹) had a negligible effect on the minimized geometry of both isomers, except that the N(3)—Co—N(5) bond angle for the Λ -*S,S,S* form **46** increased from 98.9° to 101.3° ($99.2(4)^\circ$ in **44**). Likewise a change in the Co—N—C force constant from 0.40 to 0.20 only significantly affected the most distorted bond angles; i.e., for the Λ -*S,S,S* isomer (**46**), Co—N(5)—C(7) increased from 122.2° to 126.0° ($125.3(7)^\circ$ in **44**). The changes in the force constants also had little effect on the energy differences between the ions (less than 0.3 kcal/mole). It is apparent that neither the

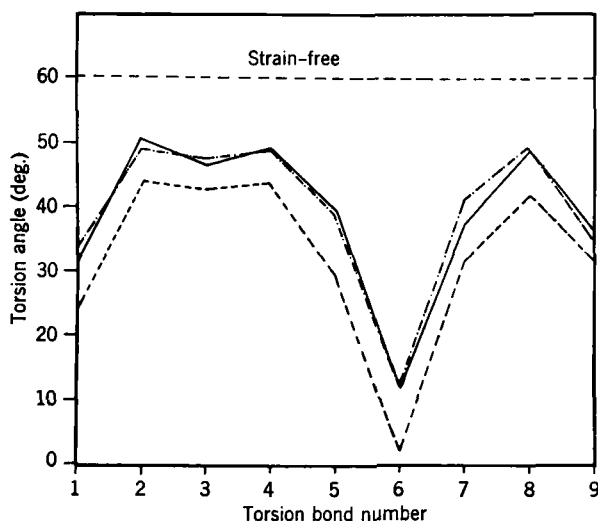


Fig. 32. Comparison of torsion angles for β -trien chelate rings: — Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺ (minimization including torsion terms); - - Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺ (minimization excluding torsion terms); - · - Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺ (crystal structure). Torsion angle numbers: 1, Co—N(1)—C(1)—C(2); 2, N(1)—C(1)—C(2)—N(2); 3, C(1)—C(2)—N(2)—Co; 4, Co—N(2)—C(3)—C(4); 5, N(2)—C(3)—C(4)—N(3); 6, C(3)—C(4)—N(3)—Co; 7, Co—N(3)—C(5)—C(6); 8, N(3)—C(5)—C(6)—N(4); 9, C(5)—C(6)—N(4)—Co.

minimized structure nor the energy difference between the different structures is very sensitive to the bending force constants, and that the values used, which were obtained from the normal coordinate analyses of model systems, appear adequate. When the angular distortion is large, the simple Hooke's law function is almost certainly inaccurate; future refinements may come from corrections in this area (36). At the moment, however, it would appear that more comparisons of structure with calculated geometry are desirable to establish the general validity, and usefulness, of the method.

3. Torsional Terms

A test of the effect of torsion terms was made by comparing the Λ - β_2 -(*R,R,S*) and Λ - β_2 -(*S,S,S*)-[Co(trien)(*S*-Pro)]²⁺ structures (41 and 42), obtained by including and excluding torsional contributions in the minimization calculations. From the calculation including only nonbonded, valence angle deformation and bond stretching terms, new torsion angles were computed, and they were compared with those obtained by including the torsional contributions in the calculation (Fig. 32). The comparison immediately demonstrates the importance of these torsional terms in predicting the

structure. In the absence of such terms, the calculated torsional angles tend to come out about 10° too small, which is not surprising since their inclusion would tend to minimize the total strain and make the torsional angles larger (more staggered). However, the energy difference between the two structures was not great.

4. Bond Stretching Force Constants

These values are known rather well for most bonds and, since they contribute little to either the total energy, or the energy difference, they have not been examined further.

V. ISOMER EQUILIBRATION

A. Kinetically Inert Complexes

In the preceding discussion the equilibration of some isomers has been mentioned, but this problem in general merits additional attention. Two possibilities are available: either the ligand configuration is preserved and mutarotation occurs about the metal ion; or vice versa. The trisdiamine complexes of Co(III) have frequently been equilibrated on charcoal, whereby some of the kinetically labile Co(II) species are produced and electron transfer on the surface of the catalyst is fast. Equilibrium is thereby achieved through the labile Co(II) species generated, e.g.,



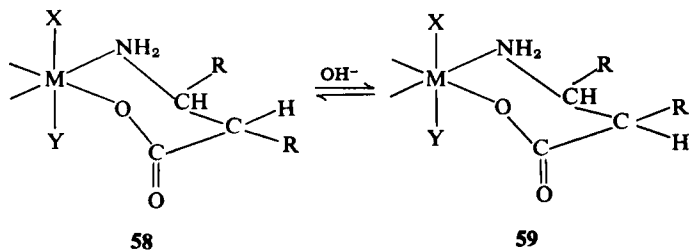
which cannot be established without the charcoal catalyst. It appears certain that the trace of Co(II) on the surface of the catalyst does not appreciably affect the activities of the two Co(III) ions in solution. In this way the equilibration of $\Lambda_{(ob)}$ and $\Delta_{(lel)}$ -[Co((-)trans-1,2-cyclohexanediamine)₃]³⁺ ions was achieved (66). The preliminary results at three temperatures are given in Table 5.

The argument above concerning the effect of the catalyst on the equilibria is also relevant to the equilibria discussed previously, effected by traces of OH⁻, e.g., $\Delta\text{-(R,R)-[Co(trien)(gly)]}^{2+} \rightleftharpoons \Delta\text{-(R,S)-[Co(trien)(gly)]}^{2+}$. Here the ligand N—H protons are abstracted by OH⁻, and a mutarotation at the chiral N center results. Likewise, mutarotation at chiral C centers for chelated α -amino acid anions (77,84,85) is established by such a mechanism, unless there is some complicating issue such as loss of ligand. Equilibration through proton exchange at similar N and C centers should occur for many organic ligands. For example, mutarotation at the α -C atom of chelated

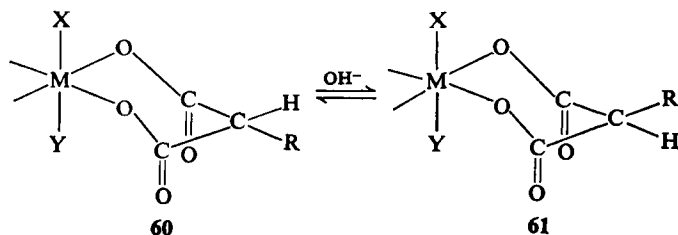
TABLE 5
 Temperature Dependence of Equilibrium Constants for $\Delta_{(\text{ob})}$ and $\Delta_{(\text{del})}$
 $[\text{Co}(-)(\text{chxn})_3]\text{Cl}_3$ in 1 *M* NaCl
 (50 mg in 25 ml)

Temperature	$K = \Delta/\Delta$
25.0	$\left. \begin{array}{c} 0.045 \\ 0.045 \\ 0.049 \end{array} \right\} 0.046 \pm 0.003$
50.0	$\left. \begin{array}{c} 0.046 \\ 0.049 \\ 0.047 \\ 0.049 \\ 0.048 \end{array} \right\} 0.048 \pm 0.001$
80.1	$\left. \begin{array}{c} 0.052 \\ 0.052 \\ 0.054 \\ 0.053 \end{array} \right\} 0.053 \pm 0.001$

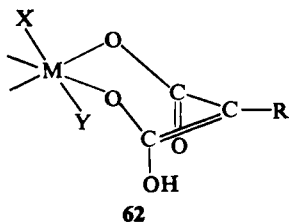
β -amino acid anions should be achieved by such a route, but it is expected that the β -C would not equilibrate this way.



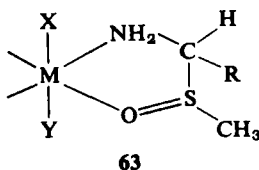
Analogous properties are expected for chelated malonate ion. Moreover, in



this instance H^+ also equilibrates the system via the intermediate **62** (86). An



interesting ligand type in this context is **63**. In such a species the conformational



character should be pronounced, and OH^- should induce H exchange at the saturated C center as well as at N.

So far, no catalyst has been found to induce proton exchange at the saturated C atoms in the ethylenediamine type of complexes, although this may be possible with hydride-type catalysts (87), provided the complex ion is not reduced completely to a labile Co(II) species.

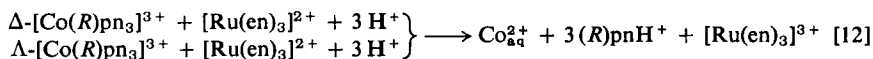
There is evidence that isomers of systems such as $[Pt(pn)_3]^{4+}$ and $[Rh(pn)_3]^{3+}$ can be equilibrated (88,89) through an intermediate involving a hydride complex. This may be the result of the strong labilizing effect of coordinated H^- which allows the trans ligand to dissociate and the complex to rearrange. However, tests for equilibration have not been carried out for these systems, and the reported work needs to be repeated.

Chromium(III) complexes have been equilibrated via traces of the Cr(II) species in the presence of charcoal as a catalyst for the electron transfer processes. Also, it is now evident that the robust Cr(III) species can be equilibrated by generating small amounts of Cr(II) electrolytically in the presence of charcoal (90). Possibly the electrode surface could also function as a catalyst to hasten electron transfer between the Cr(II) and Cr(III) species. In all these instances the equilibrium concentrations of isomers can be frozen under suitable conditions, and it remains for the investigator to separate them.

In the few simple equilibria which have been examined with some care, it was found that the temperature dependence of K is rather small, and the measurement of ΔH° by this method is therefore inaccurate, apart from the fact that it also assumes ΔH° to be constant. So far as we are aware, there are no accurate measurements of ΔH° for systems of this type, although studies

are in progress. For equilibria which are established by a rate law dependent on OH^- or H^+ , calorimetric measurements on the two components seem to be feasible. Here the rate of attainment of equilibrium can be chosen to give optimum accuracy provided the isomer is sufficiently soluble.

For robust trisdiamines of Co(III) and Cr(III), ΔH° might be measured calorimetrically with a strong reducing agent, such as $\text{Cr(II)}_{\text{aq}}^{2+}$ or $[\text{Ru(en)}_3]^{2+}$. The overall reaction in acid solution should produce common products from



the isomeric forms (e.g., see Eq. [12]), and ΔH° is thereby measured directly. It is required that the reactions occur reasonably quickly (10–30 min) so that ΔH° can be measured with reasonable accuracy. The solubility also needs to be adequate in order that the temperature change will be reasonably large. Side, or subsequent, reactions should also be absent, or considerably slower. Unfortunately, combustion seems to be an impracticable method for such measurements. The chances of generating the nonvolatile oxides in the same state from the different isomers are not great, but reproducible heterogeneous reactions would be acceptable.

B. Labile Equilibria

It is not strictly meaningful to compare various equilibria involving a metal ion and a series of related ligands and their resultant complexes, since no common standard state is available for the comparison. However, for a series of ligand isomers such as *meso*-2,3-diaminobutane, *racemic*-2,3-diaminobutane, and isobutylenediamine, the stability constants for complexes with Ni^{2+} and Cu^{2+} have been used to argue for the existence of steric effects. For the coordinated *meso*- and isobutylenediamines, one methyl group should always be in the axial position, and the stabilities of their complexes should therefore be lower than those of the racemic isomer, if this effect is dominant in the formation reaction. Within a factor of 10 for each stability constant this trend is usually observed. For example, for Ni^{2+} the differences for β_3 show that the tris-(*meso*) complex is about 10^4 times, and the tris-(*ibn*) complex about 10^5 times, less stable than tris-(*racemic bn*). These comparisons have been discussed in detail elsewhere (14,15) and are not considered further here; two other examples will suffice to illustrate the point.

For bidentate chelating agents a more striking comparison for the influence of steric effects occurs for the chelation of oxalate, malonate, succinate, and adipate with Cu^{2+} ion. A comparison of the K_1 values with the chelate ring size is given in Table 6 (91,92). Clearly, there is little effect for the change from five- to six-membered systems, but the stability falls drastically

TABLE 6

Stability Constants for the Chelation of Dicarboxylate Anions with Cu^{2+} (25° , $\mu = 0.1$) (91,92)

Acid anion	Log stability constant	Ring size
$(\text{COO})_2^{2-}$	6.3	5
$\text{CH}_2(\text{COO})_2^{2-}$	5.0	6
$(\text{CH}_2)_2(\text{COO})_2^{2-}$	2.6	7
$(\text{CH}_2)_3(\text{COO})_2^{2-}$	2.3	8

for the seven- and eight-membered systems. By analogy with comparable organic rings it seems reasonable to argue that this effect is due to the steric strain which arises in the formation of the higher-membered rings.

For the potentially sexadentate ligands such as the *N,N*-tetracetic acid series, shown in Table 7, an even more striking set of results exists. For the chelation to Ca^{2+} , a change in stability constant of about 10^6 is observed as the size of the central chelate ring changes from five- to nine-members. In this set of data there is also evidence for the coordination of another Ca^{2+} ion in the seven-, eight-, and nine-membered systems. Even if the log K value does not refer to a sexadentate chelate, the steric argument is still valid. It means that the chelating agent may prefer to be doubly tridentate (NOO) in order to relieve the steric problems arising from the formation of a large sexadentate chelate.

It seems likely that these drastic differences result largely from steric sources, since the correlation follows closely that expected by analogy with the saturated organic ring systems. However, it is not required that this be so, and the energy term due to steric interaction may be either larger or smaller than the K values imply.

TABLE 7

Stability Constants for the Chelation of *N,N*-Tetracarboxylate Anions with Ca^{2+} (20° , $\mu = 0.1$ (KCl)) (93)

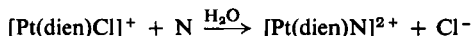
Acid anion	log K	Central ring size
$(\text{OOC})_2\text{N}(\text{CH}_2)_2\text{N}(\text{COO})_2^{4-}$	10.59	5
$(\text{OOC})_2\text{N}(\text{CH}_2)_3\text{N}(\text{COO})_2^{4-}$	7.12	6
$(\text{OOC})\text{N}(\text{CH}_2)_4\text{N}(\text{COO})_2^{4-}$	5.05	7
$(\text{OOC})_2\text{N}(\text{CH}_2)_5\text{N}(\text{COO})_2^{4-}$	4.60	8
$(\text{OOC})_2\text{N}(\text{CH}_2)_6\text{N}(\text{COO})_2^{4-}$	4.40	9

VI. KINETIC EFFECTS

If there are differences between the initial and transition states of a reaction in terms of nonbonding compressional energy, and other effects are unimportant, kinetic steric effects will be observed. If the compressional energy is greater in the transition state than in the initial state, the reaction is retarded; if steric strain is reduced in the transition state, the reaction will be accelerated (94). Both effects, of course, must be measured against some standard situation. Thus, in a series of analogous compounds in which steric crowding is increased, a marked retardation of a reaction should be characteristic of a bond-making process and marked acceleration of a bond-breaking process. Authenticated examples of these effects are uncommon for reactions of coordination compounds (95), but two examples, which appear to be well founded, are given in the next sections to illustrate the effect.

A. Platinum(II) Complexes

In the substitution of Pt(II) square planar complexes by various nucleophiles N,



a rate law of the form $k_{\text{obs}} = k_1 + k_2[\text{N}]$ is usually observed (96–98). A large amount of evidence supports the associative mechanism, given in Figure 33, for the substitution process. The term first-order in N involves the direct addition of the nucleophile, while the term independent of N involves the initial addition of solvent by the same associative path to give the analogous product with solvent coordinated, followed by rapid reaction of the species

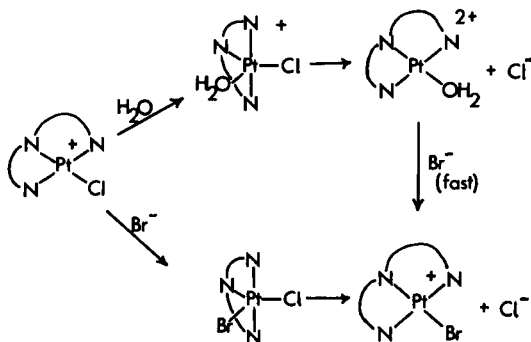
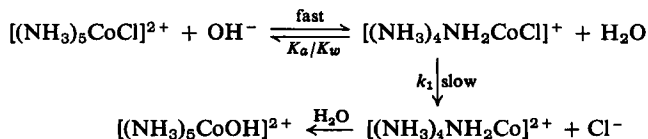


Fig. 33. Proposed mechanism for substitution in Pt(II) amine complexes.

so formed with the nucleophile, N. However, when the tridentate diethylene-triamine ligand is substituted at nitrogen either as $[\text{Pt}(\text{Et}_4\text{dien})\text{Cl}]^+$ or as $[\text{Pt}(\text{MeEt}_4\text{dien})\text{Cl}]^+$, the kinetic pattern changes dramatically. For practically all the nucleophiles examined, the k_2 term involving the nucleophile vanishes and only the first-order term k_1 is observed. Moreover, the rates fall sharply relative to that observed for the unsubstituted system. For example, aquation of $[\text{Pt}(\text{dien})\text{Cl}]^+$ is some 10^4 times faster than that for $[\text{Pt}(\text{Et}_4\text{dien})\text{Cl}]^+$. Similarly, the entry of Br^- into these two complexes follows a first-order rate law with $k_1 = 10^{-4}\text{sec}^{-1}$ at 25° for the dien complex, while $k_1 = 8.5 \times 10^{-6}\text{sec}^{-1}$ at 80° for the Et_4dien complex. The entry of Br^- into $[\text{Pt}(\text{Et}_4\text{dien})\text{H}_2\text{O}]^{2+}$ has a rate constant of $6 M^{-1}\text{sec}^{-1}$ at 25° . These dramatic changes in rate and rate law are attributed to steric hindrance for the entering nucleophile by the substituents on the coordinated N atoms. Apparently both rate constants are affected, one much more than the other, and there is some evidence to suggest that the mechanisms may be different. One proposal is that the sterically crowded complexes are "pseudo-octahedral," since their reaction pattern is more like that of aquation and anation in octahedral ions. There are still some unusual features to these reactions, in that OH^- and $\text{S}_2\text{O}_3^{2-}$ show both first- and second-order paths in the rate law with the Et_4dien complex, but there are many anionic and neutral nucleophiles for which the second-order term is insignificant. Also, it appears certain that the two-term rate law is not the complete rate law, that electrophilic species at least can be involved in the associative path, and that possibly both 5- and 6-coordinate intermediates can intervene. However, the bulk of evidence supports the proposal that steric effects dominate the issue (99).

B. Cobalt(III) Complexes

Another class of reaction which appears to be moderately well understood is that of base hydrolysis in cobalt(III) amine complexes. Considerable evidence has accumulated to support a dissociative mechanism for the conjugate base of the amine complex ($S_N1\text{CB}$ mechanism).



The rate law observed for this example is

$$-v_{[(\text{Co}(\text{NH}_3)_5\text{Cl}^{2+})]} = k_1 \frac{K_a}{K_w} [\text{Co}(\text{NH}_3)_5\text{Cl}^{2+}][\text{OH}^-]$$

and this rate law is always observed for cobalt(III) complexes with weakly

acidic N protons, $pK_a \gg 14$. The principal feature of the reaction is the presence of the intermediate of reduced coordination number, which has been characterized by its competition for different nucleophiles in solution including isotopic forms of water, various anions, neutral molecules, and coordinated nucleophiles, and by the stereochemical course of the reactions and by deuterium-exchange studies on reactants and products of the hydrolysis reaction (100). For this dissociative process, steric crowding in an analogous set of complexes should lead to an acceleration in the rate of base hydrolysis by relief of steric strain as the Co(III)—Cl bond is lengthened, and the intermediate of reduced coordination number should also be relatively stabilized by the same effect. These proposals have recently been examined for the hydrolysis of a set of amine complexes of the type $[(RNH_2)_5CoCl]^{2+}$ ($R = H, CH_3$ to $i\text{-C}_4H_9$) (Table 8) (101). The sterically hindered species containing five secondary amine ligands showed a dramatically faster rate of hydrolysis than either the $[Co(NH_3)_5Cl]^{2+}$ or *trans*- $[Co(NH_3)_4(NH_2CH_3)Cl]^{2+}$ ions (Table 8). Calculations of the nonbonded interactions for a minimized geometry by the conservative Hill function indicated that, for a regular octahedron with normal bond distances and bond angles, the complex $[Co(CH_3NH_2)_5Cl]^{2+}$ is less stable by some 25–30 kcal/mole than $[Co(NH_3)_5Cl]^{2+}$. While these values might be reduced by as much as 70% with suitable angular distortions, the significance of the calculations is that the nonbonded interactions will lead to deformations, and therefore reduced stability, in the reactant ground state and, by a closely corresponding amount, for the deprotonated reactant. The possibility that the rate differences arose from other sources, such as variations in the equilibrium constant for the N—H protons, inductive effects of the alkyl substituents and variations in activity effects, was eliminated.

TABLE 8
Rate Constants^a for Base Hydrolysis of $[CoA_5Cl]^{2+}$ at 25°

A	pH	$10^2 k_{(ob)} \text{ (sec}^{-1}\text{)}$	$k_{OH} \text{ (M}^{-1} \text{sec}^{-1}\text{)}$
NH ₃	12–14		0.25 (102)
<i>cis</i> -NH ₃ , <i>trans</i> -CH ₃ NH ₂	14	6.4	0.64
CH ₃ NH ₂	8.03	0.40	3,800
	8.74	1.9	3,400
	9.11	3.9	3,100
	10.18	47.5 ^b	3,100 ^b
	8.70	3.9 ^c	7,700 ^c
<i>n</i> -C ₃ H ₇ NH ₂	7.49	0.35	11,000
<i>i</i> -C ₄ H ₉ NH ₂	7.45	5.3 ^c	150,000 ^c

^a $\mu = 1.0$; 0.1 M Tris-HClO₄ buffer.

^b Diethanolamine-HClO₄ buffer.

^c Measured in 0.1 M Tris-HClO₄; $\mu \sim 0.05$.

In addition to a relative stabilization of the transition state by lengthening the Co—Cl bond, it is axiomatic that the 5-coordinated intermediate will also be stabilized for the substituted alkylamines relative to $[(\text{NH}_3)_4(\text{NH}_2)\text{Co}]^{2+}$, and some evidence arose from the competition properties of the two intermediates. Whereas N_3^- and NCS^- (0.5 *M*) capture about one-third of the alkylamine intermediate, they sequester only about 5% of $[\text{Co}(\text{NH}_3)_4(\text{NH}_2)]^{2+}$ in competition with H_2O . In general, for both deprotonated intermediates, the anions are better competitors than H_2O , molecule for molecule, and the inference from the experiment is that the hindered ion has a longer lifetime and seeks the better nucleophile.

These experiments suggest interesting possibilities for amine-type ligands intermediate between the simple amines mentioned above and those described by Sacconi (103) for stabilizing 5-coordinate compounds, e.g., $\text{N}(\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2)_3$. There is an excellent possibility that a molecule a little less crowded than the fully methylated triaminotriethylamine will allow a 6-coordinate complex to react to give a relatively stable 5-coordinate intermediate. Such molecules should not differ greatly from the situation realized for the dissociation of the *t*-butyl halides. In such circumstances, aquation may intervene before the base hydrolysis reaction for substituted Co(III) amine complexes, and $S_N1(\text{lim})$ kinetics will be observed. Such complexes may help to define more clearly the role water plays in the unhindered systems, a subject which still appears controversial. Moreover, the possibility exists that the 5-coordinate intermediate may even be stable enough to be isolated under favorable circumstances.

C. Steric Factors and Stereochemical Course

One example is sufficient to show the possible effects of conformation and steric interactions on the course of substitution reactions in octahedral complexes. The chelated ligand 1,4,8,11-tetrazaundecane, abbreviated 2,3,2-tet,* has some interesting features (104,105). Two trans isomers of $[\text{Co}(2,3,2\text{-tet})\text{Cl}_2]^+$ have been identified, the *meso-trans*-(*RS*)- $[\text{Co}(2,3,2\text{-tet})\text{Cl}_2]^+$ and the racemate - *trans*-(*R,R* + *S,S*)- $[\text{Co}(2,3,2\text{-tet})\text{Cl}_2]^+$ (104). The *meso* isomer presumably adopts the chair conformation for the six-membered ring (64), but the *R,R* and *S,S* forms probably have this ring in a skew-boat form (65). Possibly this factor accounts for the *meso* being the most stable isomer.

* Concerning the trivial nomenclature of these multidentate systems with varying chain lengths and types between the ligand atoms, it is perhaps timely to revive the simple system devised by Lions and used by Dwyer and Lions (108) for the complicated sexadentate ligands. Applied to the system above, it becomes ETE. With suitable nomenclature for the ligating atoms a more complete description arises, i.e., $\text{N}_4(\text{ETE})$. For trien, the nomenclature would be $\text{N}_4(\text{EEE})$.

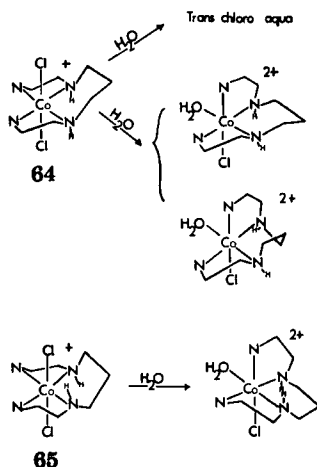


Fig. 34. The stereochemistry and possible products for the aquation of the *trans*- $[Co(2,3,2-tet)Cl_2]^+$ ion.

Moreover, in the course of aquation, either spontaneous or induced by Hg^{2+} , the meso isomer gives only the meso-*trans* chloroaquo product, whereas the *R,R* and *S,S* forms give both *cis- β* and *trans* forms (Fig. 34). These results may also be rationalized by steric effects. For the meso isomer, if the six-membered chair ring is retained in the possible *cis- β* product, both five-membered rings must be distorted into the envelope form if the geometry about the Co center remains close to octahedral. Alternatively, if the boat form of the six-membered ring is preferred in the *cis- β* product, the axial interaction with the apical five-membered chelate would be pronounced. It is only when the *trans* configuration is retained that these problems are avoided.

The contrary is true for the *R,R* and *S,S* isomers. Here the skew-boat form of the six-membered ring in the *trans* isomer would form the chair form in the *cis- β* chloroaquo product. The skew-boat conformation is not possible without a major distortion of the molecule, and the boat form interacts strongly with the substituent on cobalt. Perhaps the *cis- β* isomer is stabilized by the formation of the chair conformation relative to the skew-boat form in the *trans* isomer. In all these systems the orientation of the *R* and *S* centers is preserved in the acid solution; for the dichloro systems proton exchange must occur before inversion is possible. In this way the two *trans* isomers and the β isomer may be interconverted. One fact which emerges from these results is that the β -(*R,R*)-chloroaquo product is more stable than the *trans*-(*R,R*) form (105). This result negates the assertion (106), often made, that increased chain length in these systems stabilizes *trans* complexes. Clearly, the problems are more complicated than this, and each isomer system will require a careful

investigation. This complexity was also observed in the $[\text{Co}(\text{trien})\text{X}_2]^+$ complexes, for which the isomer stability varied with the group X (107).

The *R,R* or *S,S* α isomers cannot exist with a chair conformation for the central ring, and the boat form must also be considerably destabilized. The only feasible conformation appears to be the skew-boat. Also, the α -configuration is not possible with *R* and *S* conformations about the two chiral secondary N centers.

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