

**TOPICS IN
STEREOCHEMISTRY**

VOLUME 11

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TOPICS IN

STEREOCHEMISTRY

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VOLUME 11

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INTRODUCTION TO THE SERIES

During the last fifteen years 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 As a result, many of the details found in these texts are already inadequate or out of date, although the student of stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.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 for 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 intervals of one to two years. 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

April 1979

PREFACE

With Volume 11 of *Topics in Stereochemistry* we resume the annual publication schedule. There are four chapters, each of which examines some significant aspect of stereochemistry.

In the first chapter H. Aaron discusses intramolecular hydrogen bonding, as revealed in a dilute solution by infrared spectroscopy. It has long been known that hydrogen bonding can be detected and studied by this method. The hydroxyl group forms hydrogen bonds to many electronegative atoms, and since intramolecular hydrogen bonding does not suffer from the unfavorable entropy effects encountered in intermolecular bonding, such bonding tends to be relatively strong. The geometrical constraints required for hydrogen bonding are crucial and open to critical examination by this technique.

In the second chapter J. R. Boone and E. C. Ashby review the well studied topic of the reduction of cyclic ketones by complex metal hydrides. The versatility and usefulness of these reagents are well known. Their stereochemical behavior, once thought to be reasonably straightforward, has in fact proved to be quite intricate. The chapter considers the stereochemistry of reduction of a specific and important class of compounds, cyclic and bicyclic ketones, that are particularly well suited to such investigations.

The chemistry of small ring compounds has been of wide interest to chemists since the early investigations of Perkin. In Volume 8 of this series cyclobutane and its heterocyclic derivatives were discussed in some detail. In the third chapter of Volume 11 several ring systems, containing as many as six atoms are taken up. The emphasis is not so much on the ring systems themselves as on the use of vibrational and microwave spectroscopy for their study. T. B. Malloy, Jr., L. E. Bauman, and L. A. Carreira offer a very readable account for the non-specialist in this spectroscopic area of the kinds of problems and possible results.

In the fourth chapter of this volume the stereochemical aspects of six-membered rings containing phosphorus are examined by B. E. Maryanoff, R. O. Hutchins, and C. A. Maryanoff. Since the phosphorus atom can have as many as five substituents attached to it, and since these substituents may be various combinations of oxygen, nitrogen, sulfur, or occasionally other atoms, in addition to hydrogen or alkyl, there is a great variety of compounds to be considered. The structures and conformations of these compounds, frequently investigated by NMR spectroscopy, are thoroughly discussed. The stereochemistry of

substitution reactions at phosphorus and some of the biological aspects of these phosphorus compounds are then reviewed.

While the cyclohexane ring may be taken as the standard, simple, and ideal model for conformational analysis, phosphorus-containing six-membered rings are essentially at the other end of the spectrum. The different interactions (dipolar, van der Waals, resonance) that occur are substantially more complicated than in the hydrocarbon case, and while much of the observed behavior can be rationalized, if not necessarily predicted, our basic understanding of such systems is by far less advanced than that of cycloalkanes.

Norman L. Allinger
Ernest L. Eliel

Athens, Georgia
Chapel Hill, North Carolina
April 1979

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**TOPICS IN
STEREOCHEMISTRY**

VOLUME 11

Conformational Analysis of Intramolecular- Hydrogen-Bonded Compounds in Dilute Solution by Infrared Spectroscopy

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I. INTRODUCTION

Dilute-solution infrared (IR) spectroscopy is commonly used to prove the presence of an intramolecular hydrogen bond for configurational and conformational assignments. Properly applied, the method may also be used for more quantitative conformational analysis, because it can often define, simply and uniquely, the equilibrium position between intramolecular bonded and nonbonded conformations. An excellent review of intramolecular hydrogen bonding by IR spectroscopy and its applications in stereochemistry through 1964 has been published (1). Accordingly, this chapter focuses mainly on pertinent literature that has been published since 1964.

II. SPECTRAL CHARACTERISTICS OF THE INTRAMOLECULAR HYDROGEN BOND

To briefly summarize the aspects of the phenomenon which are most important to the stereochemist, intramolecular hydrogen bond formation occurs when a proton donor (usually OH, but also COOH, NH, and SH) is oriented toward and falls within the proximity [less than about 3.3 Å (2) or, perhaps, 3.4 Å (3), but variable] of an electron-rich proton-acceptor function, such as halogen, $-NR_2$, $-O-$, $C=C$, and $C=O$. Hydrogen bonding has usually been reported with OH as the proton donor, because the bonds formed by this common substituent are the most easily recognized and the most conveniently studied in the IR spectrum. Thus, in the vapor phase or in a dilute nonpolar solution in which intermolecular hydrogen bonding has been eliminated, the formation of an intramolecular hydrogen bond is seen (Fig. 1) as a broadening and a shift of ν_{OH} , the donor OH fundamental band, to a lower frequency compared to that of the corresponding nonbonded or so-called free OH species. The overtone OH band in the near IR is similarly affected (4a), although it may not be as useful as the one in the fundamental region, especially for quantitative applications (4b). The fundamental free OH band, which actually is still weakly associated with solvent even in a nonpolar medium (5), almost always falls above 3600 cm^{-1} in carbon tetrachloride solution, although certain exceptions are noted here. Hydrogen-bonded OH bands, on the other hand, almost always fall below 3600 cm^{-1} , except for some weak $OH \cdots \pi$ interactions. When an equilibrium exists between free OH and bonded OH species, the OH band of each is observed, as seen in Fig. 1. It should be noted, however, that due to the broadening of the bonded OH band, roughly in proportion to the magnitude of the ν_{OH} shift for any given compound, its size may appear misleadingly large relative to the actual molar concentration of bonded OH species in the equilibrium mixture.

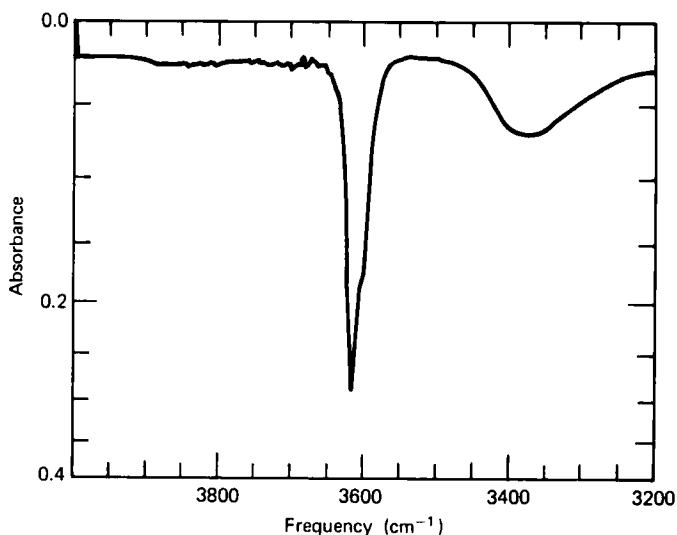


Fig. 1. 3 β -Granatanol (3) at $2.9 \times 10^{-3}M$ in CCl_4 , 2-cm cell path.

The magnitude of shift of the OH absorption ($\Delta\nu_{OH}$) between the free and bonded maxima is customarily taken as a measure of the strength of the hydrogen bond. The $\Delta\nu_{OH}$ value depends on a number of factors, and is apparently favored by the acidity of the donor OH, the basicity of the acceptor function, the proximity of the OH to the acceptor site, and the approach to linearity of the three-atom bridge (e.g., $O-H\cdots N$) that forms the hydrogen bond (1). Comparisons of $\Delta\nu_{OH}$ values between systems with different donor and/or acceptor functions are generally difficult, if not impossible, to assess. However, the $\Delta\nu_{OH}$ value is useful for correlating molecular geometries and for drawing comparisons between hydrogen bonded structures containing the same donor and acceptor function, as indicated below, for example, for $OH\cdots N$ bonded systems. Of course, the strength of a hydrogen bond is not necessarily related to the concentration of hydrogen-bonded species in an equilibrium mixture, since the latter may be significantly affected by entropy factors, as indicated in various examples mentioned here and by other conformational interactions that may be present.

III. THE EXPERIMENTAL METHOD

For these spectral studies a dual-beam IR spectrophotometer that gives good resolution in the OH region must be used. Thus, earlier studies were made with instruments equipped with lithium fluoride optics, whereas more recent work has almost invariably

been carried out on grating IR spectrophotometers, now commonly found in most laboratories. A nonpolar solvent that is essentially transparent in the OH region of the spectrum is required. Carbon tetrachloride, dried and kept dry by storage over 3 Å molecular sieves, is the preferred solvent, although carbon disulfide and tetrachloroethylene may also be used. The latter is especially useful (6) for compounds (e.g., some amino alcohols) that react with carbon tetrachloride or carbon disulfide, but must be passed over alumina and distilled to remove its ethanol stabilizer immediately before use. Chloroform (with the ethanol stabilizer removed) has also been used (7), but is not generally recommended, because weak intramolecular hydrogen bonding may not be revealed. In some cases, however, chloroform was reported to be the preferred solvent, because it eliminates residual weak dimeric association without affecting the intramolecular hydrogen bond (8). To eliminate intermolecular hydrogen bonding between the solute species, the spectral solution should be diluted until the extinction coefficient of the OH band (or the ratio of bonded to free OH absorbance maxima) does not change on further dilution. A 2.5 to $5.0 \times 10^{-3}M$ solution is generally suitable, and may be conveniently examined in a 1 or 2 cm quartz (IR grade or near-IR grade) cell, with a matched cell for the reference solvent blank (9). Commonly available cells of this type are essentially transparent down to about 2500 cm^{-1} . A mini-slide holder such as those available from the Wilks Scientific Corp. can be adapted to serve as an inexpensive cell holder if one does not care to purchase a more expensive type. For very insoluble compounds, or for detection of very small concentrations of an OH species, longer path cells (5 or 10 cm^{-1}) may be used, at least with carbon tetrachloride (10). Often the spectrum shows the presence of a little water, as a small band at 3702 cm^{-1} (11). This band can readily be balanced out by introducing a trace of water into the reference cell, most simply from water vapor present in the atmosphere, by removing some of the reference solvent with an eyedropper and then squirting it back into its cell. The process is repeated, if necessary, until a compensating amount of water has been absorbed in the reference solvent cell.

It may be necessary to distinguish the band of an intramolecular hydrogen bond from that of a carbonyl overtone, which falls in the same spectral region. For this purpose the most reliable method is to simply add a drop of D_2O to the solution and to the blank (12, 13). On standing, the OH is converted to an OD group, and both its free and bonded absorptions shift to lower frequencies by a factor of ca. 0.73 (14a). The position of the carbonyl overtone or of any other band that does not contain an exchangeable proton remains unaffected by this treatment.

For qualitative comparisons of intramolecular hydrogen-bonded systems, the ratio of the extinction coefficients (ϵ) of the bonded OH and free OH species is often taken, with each calculated as (14b)

$$\epsilon = \frac{1}{Cl} \log \frac{T_0}{T} \quad [1]$$

where C is the concentration (M), l is the cell thickness (cm), and T_0 and T are the intensities of the incident and transmitted light. For more quantitative applications, however, the integrated intensity (B) or area of the OH band is required, which is equal to (14b)

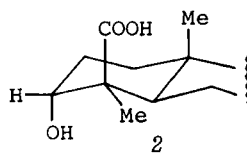
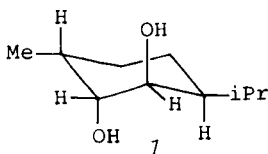
$$B = 2.303 \int \epsilon \, d\nu \quad [2]$$

Thus, for a given band ϵ is plotted against ν on linear graph paper, and the area is obtained in any one of several ways: by using a planimeter, by simple addition of the graph squares, or by cutting and weighing a photocopy of the curve. On more sophisticated spectrophotometers the area of a band may be integrated directly. Overlapping bands may be separated graphically. More recently, however, a commercial curve resolver (15) or a computer method (16) has been used for this purpose.

These methods can be used to determine the presence (or absence) of free and bonded OH absorption bands, the exact position and spectral characteristics of the bands, and the relative molar percentage of each species, if both are present, for use in structural and conformational assignments.

IV. SPECTROSCOPIC ANALYSIS OF THE FREE OH BAND

The dilute-solution IR data most useful for stereochemical assignments are provided by compounds that contain an intramolecular hydrogen bond. However, the presence of only a free OH band in the spectrum may also be important. Thus, the diaxial diol configuration of *p*-menthane-*trans*-2,3-diol (1) was assigned based on the presence of a single free OH band in dilute CCl_4



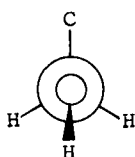
solution (17), and the stereochemistry of β -boswellic acid (2) was confirmed on similar grounds (18). Also, the area of the free OH band may be used to determine the number of OH groups in an unknown structure, through comparison to that of a suitable model compound (19).

The position, shape, and extinction coefficient of the free OH band may be useful for structural or conformational assignments. For example, the free OH band usually lies above 3600 cm^{-1} . However, if attached to a strong electronegative atom, as in hydroperoxides ($ROOH$) (20) or oximes (R_2NOH) (21), the free OH band usually falls below 3600 cm^{-1} , if not lower. Conversely, the opposite effect is observed in silanol systems (R_3SiOH), where unusually high-frequency OH absorptions are observed

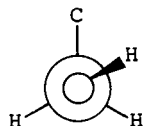
(3674 to 3686 cm^{-1}) (22). Cole and co-workers studied a series of triterpenoid alcohols, and found that primary hydroxyls absorb at ca. 3640, secondary at ca. 3630, and tertiary at ca. 3615 cm^{-1} in CCl_4 solution (7). These positions vary somewhat according to structure and stereochemistry (23), however, and alkyl substituents at the adjacent carbon will cause an increase in ν_{OH} (24). For example, some secondary alcohols with vicinal substituents absorb at 3642 to 3654 cm^{-1} (25). In carbon disulfide (5) or chloroform (7), however, the frequencies are lower by ca. 10 to 15 cm^{-1} . Phenolic OH, which usually absorbs in the same region as tertiary alcohols, is generally distinguished by its sharper band and larger extinction coefficient (26).

A spectral examination of the free OH band may distinguish an axial from an equatorial OH group, especially if both epimers are available for a direct comparison. Here an axial alcohol generally has a slightly higher (5 to 10 cm^{-1}) absorption frequency (7, 23, 27), larger extinction coefficient, and greater band symmetry than its equatorial epimer (9). The band symmetry has been characterized by the α/β ratio, corresponding to the half-band widths on the high (α) and low (β) frequency side of the OH band maximum (9, 15). Actually, the corresponding ratio at the one-quarter-band position, or the ratio of the band areas on each side of the ν_{max} position, can probably be more useful in characterizing the band symmetry, since the presence of a small asymmetrical component may not affect the α/β ratio, if taken at the half-band position.

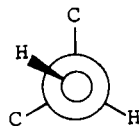
The distinctions between the axial and equatorial alcohols are apparently caused by a difference in the rotamer composition of each isomer (28, 29). Thus, based on a study of some simple aliphatic alcohols, the different conformers that are formed by rotation of the OH group about the C-O bond have been defined, and the ν_{OH} of each has been assigned as ca. 3640 cm^{-1} for type I, 3628 cm^{-1} for type II, and 3617 cm^{-1} for type III rotamer forms (28). For example, as defined, ethanol should exist as a



Type I

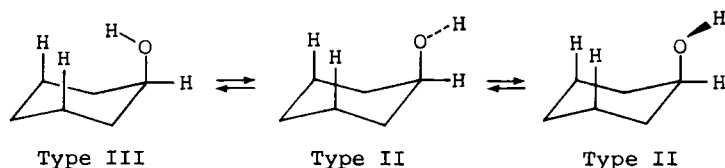


Type II



Type III

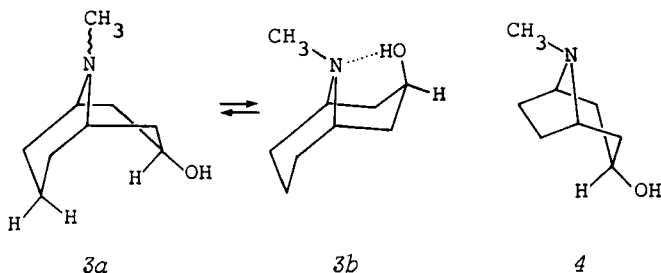
mixture of type I and type II rotamers; isopropyl alcohol, as a mixture of type II and type III forms. The apparent ν_{max} of the composite band, therefore, differs from that of the individual components, depending on the pattern of their overlap. Two explanations have been offered to account for the symmetry observed for the axial OH band. On the one hand the result has been attributed to a conformational homogeneity of the axial alcohols, as a result of a low concentration of the type III rotamer, because of steric interactions of the syn-axial hydrogens with the hydroxyl hydrogen (9). On the other hand Schleyer and co-workers



(15a) distinguished additional types of OH rotamers according to the substitution pattern at the β carbon atom, and suggested that two rotamer types are actually present in the axial alcohols, but that both have equal values of ν_{OH} . The results of a recent intermolecular-hydrogen-bonding study of *cis*- and *trans*-4-*t*-butylcyclohexanol (30) have been reported in support of the former explanation. An opposite effect has been noted for some epimeric tertiary aryl carbinols, however. Here, the axial-OH epimers gave the unsymmetrical band (31).

V. CONFIGURATIONAL ASSIGNMENTS OF HYDROGEN-BONDED COMPOUNDS

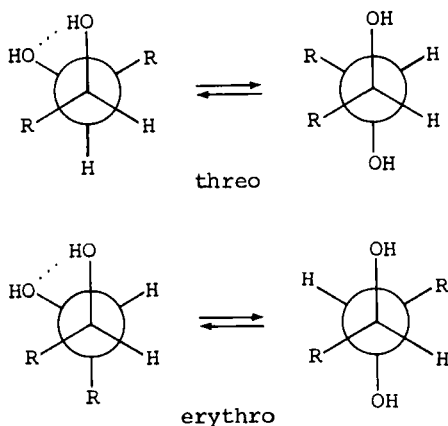
Probably the simplest useful application of dilute-solution IR spectroscopy has been configurational assignment, based on the presence in one isomer of an intramolecular hydrogen bond that is sterically impossible in the other. If available, however, both isomers should be examined to rule out any possible error arising from persistent intermolecular hydrogen bonding. In two of the earliest applications of this method intramolecular hydrogen bonding was reported for β -granatanol (3) (32) and Ψ -tropine (4) (33). For Ψ -tropine, however, the result was shown (34) to result from intermolecular hydrogen bonding in an insufficiently dilute solution. Nevertheless, Ψ -tropine is still



occasionally cited as an example of intramolecular hydrogen bonding (35). Reexamination of β -granatanol [suggested (1) as desirable in view of the Ψ -tropine error] has confirmed (9,36) the original report. This result establishes the configuration of both the α - and β -granatanol isomers, because hydrogen bonding is possible only in the β -isomer (3b). The equilibrium mixture of this compound has been assigned (9) as 15% boat (3b) and

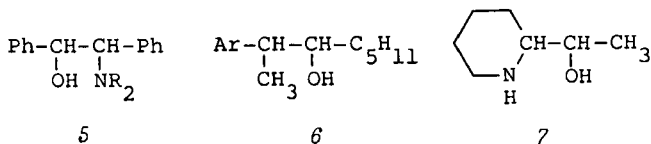
85% chair (3a) on the basis of IR data (Fig. 1). Examples of other stereochemical assignments that have been made in this way are given in succeeding sections.

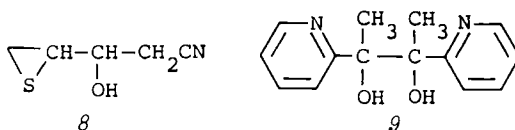
For two epimers, each containing an intramolecular hydrogen bond, the assignment of configuration can often be made by conformational analysis, by comparing the relative amounts of hydrogen bonding in each. For this purpose the ratio of bonded OH and free OH species is usually taken simply as the ratio of the extinction coefficients (ϵ_b/ϵ_f , respectively). The method has been applied to open-chain vicinal (i.e., 1,2-) diols and amino alcohols, as summarized in ref. 1. Here the threo (or *d,l*) isomer invariably shows more bonding (higher ϵ_b/ϵ_f ratio) than the erythro (or meso) isomer. This correlation is consistent with the assumption that the two bulkiest groups are relatively more favored in an anti-trans conformation, when the free OH (or bonded OH) rotamers of the two isomers are compared, as illustrated for the following RCHOHCHOHR diols:



In addition, for 1,2-diols and amino alcohols the $\Delta\nu_{OH}$ value is usually smaller in the erythro isomer, consistent with a longer hydrogen bridging distance arising from repulsion of the bulky groups that are gauche in the bonded conformation.

Recently the method has been used for the configurational assignment of the isomers of 5 (37), 6 (38), 7 (39), and 8 (8). For 6 no difference in $\Delta\nu_{OH}$ was observed for the two isomers. Compound 9 has also been studied, but interpretation of the spectral data is complicated because three different types of intramolecular hydrogen bond can be formed (40).





VI. SUMMARY OF INTRAMOLECULAR HYDROGEN-BONDING STUDIES

A. The OH...Halogen Hydrogen Bond

The splitting (or asymmetrical shape) of the OH band in 2-haloalkanols (41-43) is attributed to intramolecular OH...halogen hydrogen bonding (42,43). Higher ω -haloalkanols, however, apparently do not form an intramolecular hydrogen bond (44). For a series of 2-chloroalkanols $\Delta\nu_{\text{OH}}$ decreased in the order of tertiary > secondary > primary chlorine, and primary > secondary > tertiary hydroxyl (45). When the halogen is varied, the $\Delta\nu_{\text{OH}}$ values stand in the order I > Br > Cl > F for 2-haloethanols (45,46), and I > Br > Cl for 2-halocyclohexanols (47). This is the same order that had previously been observed for 2-halophenols (48). This order is consistent with a shortening of the hydrogen bridging distance with increasing size of the halogen atom.

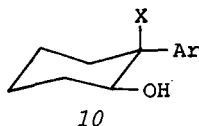
For the 2-halophenols it is generally agreed (48) that the relative strengths of the hydrogen bonds stand in the order Cl > Br > I, corresponding to a decreasing concentration of bonded (cis) species in the equilibrium mixtures (48a). Thus these relative bond strengths are exactly opposite to those suggested by their relative $\Delta\nu_{\text{OH}}$ values, based on the relationship between enthalpy (ΔH) and $\Delta\nu_{\text{OH}}$ postulated by Badger and Bauer for intermolecular bonded systems (49). It should be noted, however, that this criterion is customarily used to compare systems that contain the same donor and acceptor functions, respectively. The 2-fluorophenol analog shows a singlet OH band at 3591 cm^{-1} (48b), which, if attributable to a bonded OH, would have the smallest $\Delta\nu_{\text{OH}}$ value and be consistent with this series. The relative bond strength of the fluoro analog is uncertain, however, because there is disagreement over whether this band actually results from a bonded or free OH species, or even a mixture of the two (48).

For the 2-haloethanols the relative strengths of the hydrogen bonds were assigned as F > Cl > Br > I, based on the enthalpy difference (ΔH) calculated for the equilibrium between gauche (bonded) and trans (nonbonded) rotamer forms (46). In this case the fluoro analog also gave a singlet OH band, but this unsymmetrical band was graphically separated into two symmetrical bands, and the free OH species was assigned to the high-frequency component. The enthalpy values thus obtained were linearly related to a decrease in $\Delta\nu_{\text{OH}}$, and the assignments

correspond to those noted above for the 2-halophenol series.

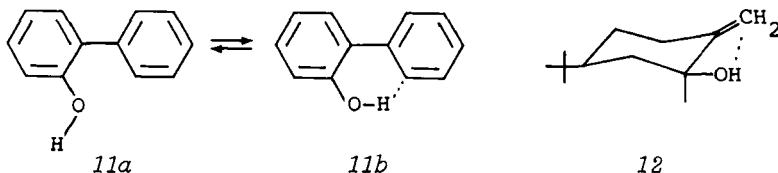
The *trans*-2-halocyclohexanols, on the other hand, have an inverse order of relative bond strengths ($I > Br > Cl$), based on the energy difference between diequatorial (bonded) and diaxial (nonbonded) conformers, in equilibrium in carbon disulfide solution (47). It should be noted, however, that when criteria defining the relative strengths of intramolecular hydrogen bonds are based simply on relative conformer populations in aliphatic systems, they are not necessarily valid, because the equilibrium position also depends on electrostatic and nonbonded steric (e.g., syn-axial) interactions of the substituent groups.

A spectral study of the mobile equilibrium of *trans*-2-bromo- and *trans*-2-iodocyclohexanols has shown that the diequatorial forms are largely but not completely hydrogen bonded (50), while only the chloro analogs of some anancomeric (51) (conformationally biased) 2-chloro, 2-bromo-, and 2-fluorocyclohexanols (10) contained no free OH (rotamer) (52). These results suggest that the $OH \cdots Cl$ species forms the strongest hydrogen bond in these compounds. A theoretical treatment of $OH \cdots$ halogen bonding based on the Schroeder-Lippincott potential function model has recently been presented (53), including an extensive tabulation of the earlier literature.



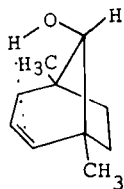
B. The $OH \cdots \pi$ Hydrogen Bond

Conformational studies of $OH \cdots \pi$ bonded substituted benzyl (54-57), β -phenethyl (58), olefinic (59, 60), acetylenic (61), and unsaturated terpene alcohols (62) have been reported. The position of the free OH/bonded OH equilibrium in 2-hydroxybiphenyl (11) has been assigned as 16 to 17% free OH (63). Conformational studies of substituted 2-hydroxybiphenyl systems have

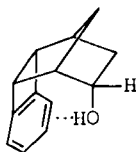


been carried out (64), and the magnitude of the $OH \cdots \pi$ shift was related to the degree of overlap of the bonding orbitals. These studies were then extended to a series of olefinic alcohols in which the $OH \cdots \pi$ shift was correlated with the square of an overlap integral, defined as a function of the geometrical parameters of the system (65).

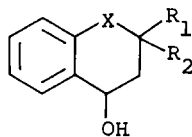
For anancomeric axial and equatorial allylic alcohols the equatorial OH isomer is generally observed as a doublet corresponding to bonded and free OH species (e.g., ν_{OH} 3605 and 3622 cm^{-1} , respectively, for 12) while the axial OH isomer is generally observed as a singlet (ν_{OH} 3618 cm^{-1}) (65). The latter was assigned as a bonded $\text{OH} \cdots \pi$ interaction, based on the favorable orbital overlap and on the fact that the free axial OH groups generally absorb about 10 cm^{-1} higher than their corresponding equatorial OH epimers. Usually, however, $\text{OH} \cdots \pi$ bonded systems exist in equilibrium between bonded and free OH species, corresponding to rotamer forms of the OH group. Thus the syn isomer of 1,5-dimethylbicyclo[3.3.1]non-2-en-9-ol (13) contains both free OH (3640 cm^{-1}) and $\text{OH} \cdots \pi$ bonded (3584 cm^{-1}) absorptions. The anti isomer shows only a free OH (3640 cm^{-1}). From these results the configurations of both isomers were assigned (66). In some compounds that contain an $\text{OH} \cdots \pi$ absorption, however, no free OH bands are observed [e.g., 14 (67) and the axial OH epimer of 12]. These results have been attributed to the strength of the intramolecular hydrogen bond, as well as to the unfavorable oxygen lone pair/ π -electron orbital/orbital repulsion that exists in the free OH rotamer form of these systems (67b).



13



14



15

Studies of tetralol, chromanol, thiochromanol, and tetrahydroquinolinol systems (e.g., 15) have been carried out (68), and OH conformations have been assigned as quasi-axial (singlet, ν_{OH} 3618 cm^{-1}) and quasi-equatorial (doublet, ν_{OH} 3622 and 3600 cm^{-1}) species. Although there has been some question as to whether the quasi-axial species exists in a free or bonded OH form, it is probably best assigned as a bonded $\text{OH} \cdots \pi$ species (68b). It has been concluded that 1-tetralol exists predominantly in the OH axial conformation (68b), to correct an earlier assignment. In 4-hydroxytetrahydroquinoline systems the influence of the nitrogen substituent on the $\text{OH} \cdots \pi$ interaction has been studied (68f).

Cyclopropylmethanol, which does not contain an olefinic group, also gives an IR doublet. While the explanation of this result has been a point of controversy, it is apparently the result of $\text{OH} \cdots \pi$ interaction (69a), since the σ electrons of the cyclopropane ring are known to exhibit characteristics of more mobile π electrons (69b).

C. The $\text{OH}\cdots\text{O}=\text{C}$ Hydrogen Bond

1. Hydroxyketones

A variety of structures in this category have been studied (13,18,70-77). Depending on the molecular geometry, two distinct acceptor sites of the hydrogen bond can be involved (13,72): the strongly bonding unpaired n electrons of the carbonyl oxygen atom, and the weakly bonding π -electron pair of the carbonyl group. Often, both of these species are present, in addition to the free OH, to produce a doublet or multiplet of bands in the OH region. In some cases a doublet is also observed (18) in the carbonyl region, corresponding to the strongly bonded and the free (or weakly bonded) carbonyl species, and this may be helpful in interpreting the ν_{OH} results.

When analyzing the OH bands in these spectra, however, one must be careful not to assign an intramolecular hydrogen bond to the carbonyl overtone absorption, which falls in the 3400 cm^{-1} region of the spectrum (Fig. 2). Some literature errors of this type have been cited (12b,13). Although the position, band width, and intensity may serve to distinguish the carbonyl overtone from an intramolecular hydrogen bond (13), the most reliable method is to simply add a drop of D_2O to the spectral solution, to convert the OH into an OD group, shifting its absorption to lower frequencies (12,13), as described in Sect. III.

For acyclic hydroxyketones, such as $\text{CH}_3\text{CO}(\text{CH}_2)_n\text{OH}$, the $\Delta\nu_{\text{OH}}$ values decrease in the order 1-hydroxy-2-propanone (135 cm^{-1}), 4-hydroxy-2-butanone (48 cm^{-1}), and 5-hydroxy-2-pentanone (31 cm^{-1}), corresponding to the increasing size of the hydrogen-bonded ring for $n = 1, 2$, and 3 , respectively (72). This trend is opposite to that which is seen in diols, methoxy alkanols, and amino alcohols, where the value of $\Delta\nu_{\text{OH}}$ increases in going from a five- to a six-atom bonding ring. For the hydroxyketones these results are apparently caused by a shift of the bonding site from the n -electrons to the π -electrons, due to the geometrical constraints of the system (13,72). The $\Delta\nu_{\text{OH}}$ values of these two types of hydrogen bonds correspond to those which are observed for $\text{OH}\cdots\text{O}$ (ether) and $\text{OH}\cdots\pi$ ($\text{C}=\text{C}$) systems, based on studies of model compounds of fixed geometry. Thus acyclic α -hydroxyketones tend to give symmetrical bands (Fig. 2) (13), as a result of $\text{OH}\cdots\text{O}$ absorption ($\Delta\nu_{\text{OH}} \sim 130\text{ cm}^{-1}$), while acyclic β -hydroxyketones generally give unsymmetrical (bonded) OH absorption bands. Joris and Schleyer consider the latter to be a composite of $\Delta\nu_{\text{OH}} \sim 30$ to 45 cm^{-1} ($\text{OH}\cdots\pi$) and a minor component of $\Delta\nu_{\text{OH}} \sim 90\text{ cm}^{-1}$ ($\text{OH}\cdots\text{O}$), plus free OH (13). That the $\text{OH}\cdots\text{O}$ interaction in the α -hydroxyketones is larger than that of the β -analogs is believed to be caused in part, by the greater acidity of the hydroxyl adjacent (α) to the carbonyl group, and in part, to a more favorable geometry which

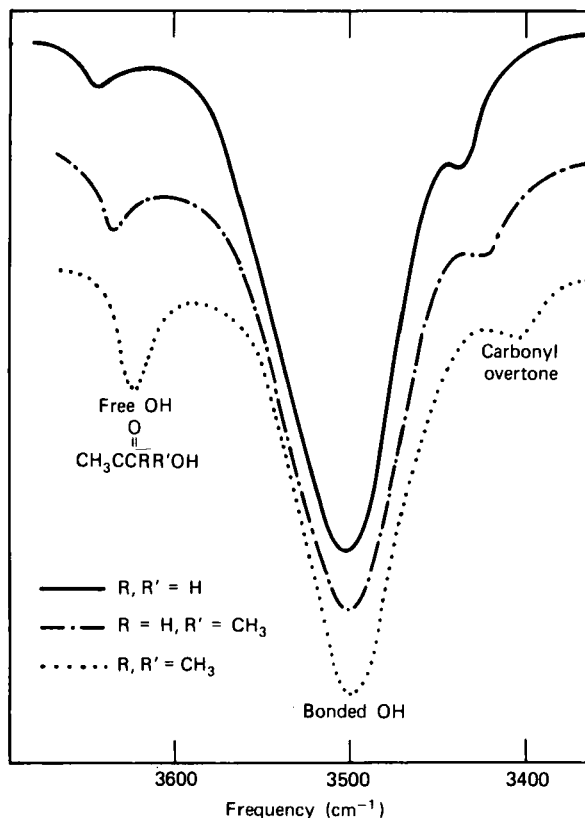


Fig. 2. Hydroxyl-region IR spectra of acyclic α -hydroxyketones.

permits a better overlap of the α -OH group with the unpaired n -electrons of the carbonyl oxygen.

A cyclic α -hydroxyketone may form a strong or weak intramolecular hydrogen bond, depending on its conformation. Thus an equatorial OH group (16) provides the correct geometry for strong intramolecular OH $\cdots$ O hydrogen bond formation, and for systems that are fixed in this conformation, all the molecules (within the detectable limits of the method) are intramolecularly hydrogen bonded and no free OH species is observed (72,73). For cyclic axial α -hydroxy (17) and β -hydroxyketones (18), however, only weak OH $\cdots$ π bond formation should be possible. Accordingly, most systems that are fixed in these conformations exist in an equilibrium between bonded and free OH rotamer forms (72,74), and give an unsymmetrical OH band, which may be separated into two symmetrical components corresponding to each conformer (e.g., 24a, 24b). Cyclic equatorial β -hydroxyketones (19), of course,

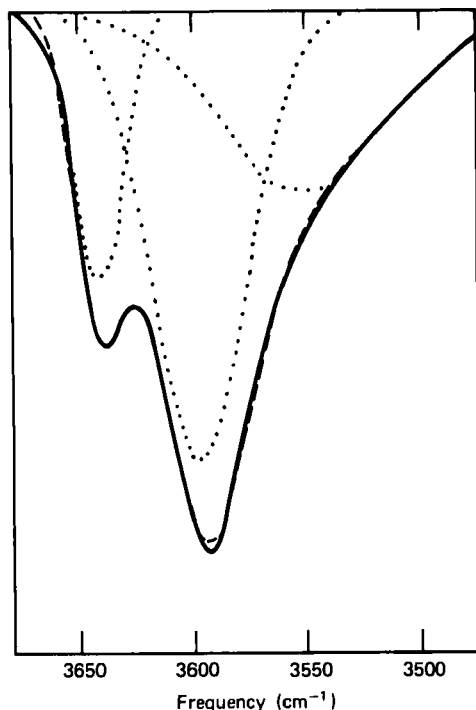
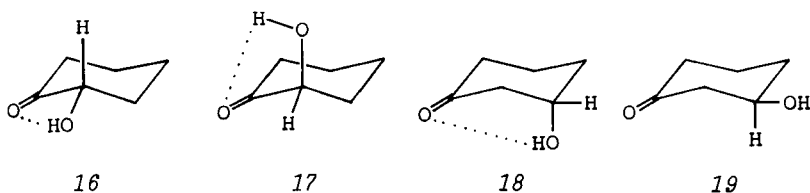
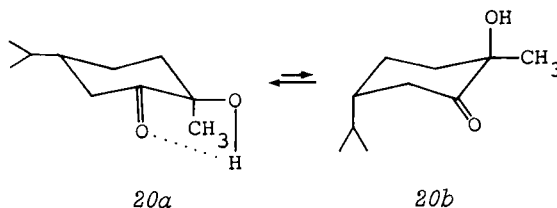


Fig. 3. Experimental OH absorption of 4-hydroxy-2-butanone, —; component bands calculated by computer ····; sum of the calculated components bands, ----.

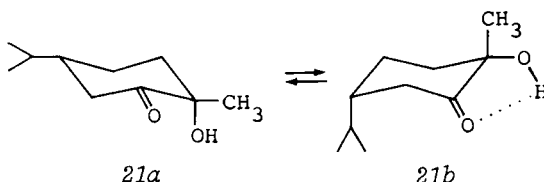
cannot form an intramolecular hydrogen bond, and only a free OH is observed.



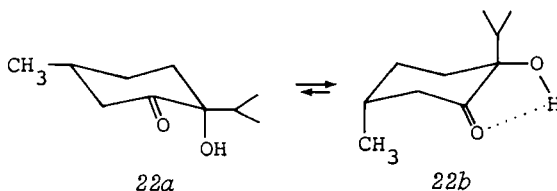
Conformational assignments that have been given on the basis of the spectral results include the 1-hydroxyisocarmen-thone (20) system, where only the bonded species (20a, ν_{OH} 3504 cm^{-1}) was observed, and no OH absorption corresponding either to a free OH rotamer form of 20a or to conformer 20b could be detected (73). Also, 1-hydroxycarmen-thone (21), which shows a



doublet at 3610 and 3502 cm^{-1} , was assigned as an equilibrium between *21a* and *21b*, respectively. However, the report (75) that

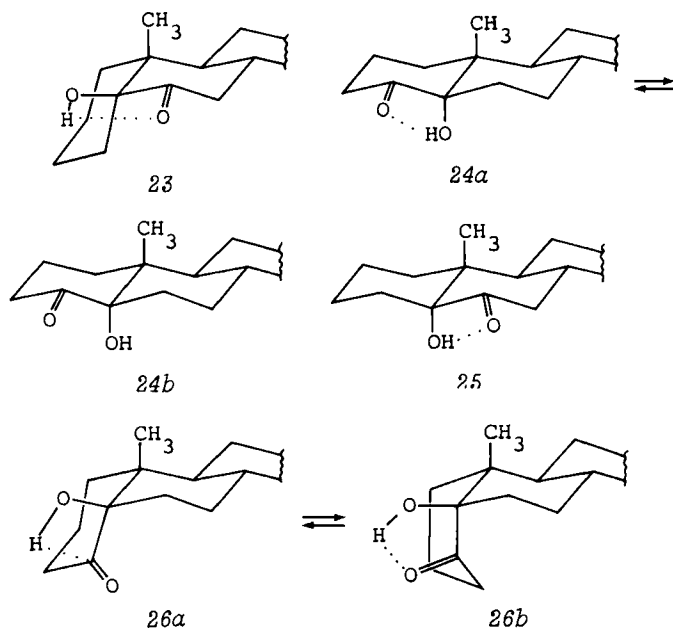


4-hydroxymenthone shows only a 3495 cm^{-1} band, assigned as *22b*, is inconsistent with the results for *21*.

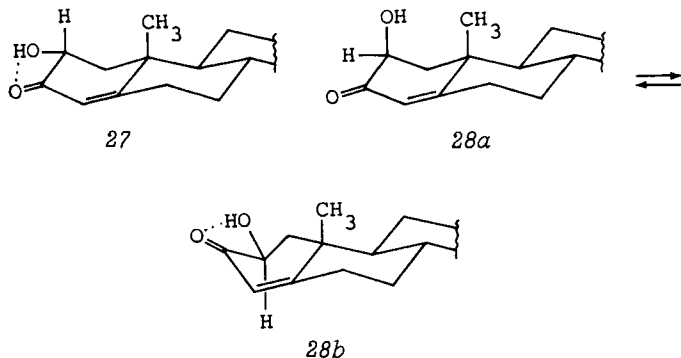


In the steroid series 5β -cholestan- 5β -ol-6-one (*23*) gives only a strongly bonded OH band ($\Delta\nu \sim 135\text{ cm}^{-1}$), whereas 5α -cholestan- 5α -ol-4-one (*24*) and the corresponding 6-one isomer (*25*) show both free OH (3614 cm^{-1}) and weakly bonded OH ($\Delta\nu$ 11 to 12 cm^{-1}) bands. In view of these results the fact that 5β -cholestan- 5β -ol-4-one (*26*) shows only an $\text{OH}\cdots\text{O}=\text{C}$ absorption at 3480 cm^{-1} (72) (and a significant $\nu_{\text{C}=\text{O}}$ shift) is not consistent with that expected for an axial α -hydroxyketone (*26a*). To account for these results a shift of ring A into a boat form (*26b*) has been suggested (78). Here the boat or, better, skew-boat (*79a*) would both be favored by the strong intramolecular hydrogen bond and also be formed in a cyclohexanone ring, in which the chair/boat energy difference is smaller than that in a cyclohexane ring (*79b*). It is not altogether clear, however, why *24* does not also form a similar species. Possibly the difference between a bowsprit-flagpole (*79a*) H/CH interaction in a *26* skew-boat vs. H/CH₃ in a *24* skew-boat may account for this difference, since the latter apparently results in a loss of rotational entropy of the CH₃ group.

In the epimeric 2-hydroxypregn-4-ene-3,20-diones both the 2α (*27*) and 2β (*28*) epimers show only $\text{OH}\cdots\text{O}$ bonding at $3497 \pm$

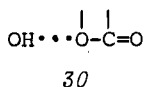
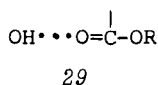


1 cm⁻¹, from which the 2 β isomer was assigned the half-boat conformation (28b) (74). In this case the energy difference between a boat and chair species in a cyclohexene ring is not large (79c), and the formation of the hydrogen bond in 28b plus the syn-axial Me/OH repulsion in 28a combine to produce the observed result.



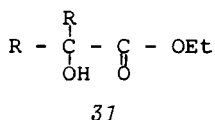
2. Hydroxyesters

The assignment of the OH bands in hydrogen-bonded hydroxyesters (80-87) is also complicated by the presence of multiple bonding sites, corresponding to a strong interaction with the carbonyl oxygen (29), and a weaker interaction with the alkyl oxygen atom.

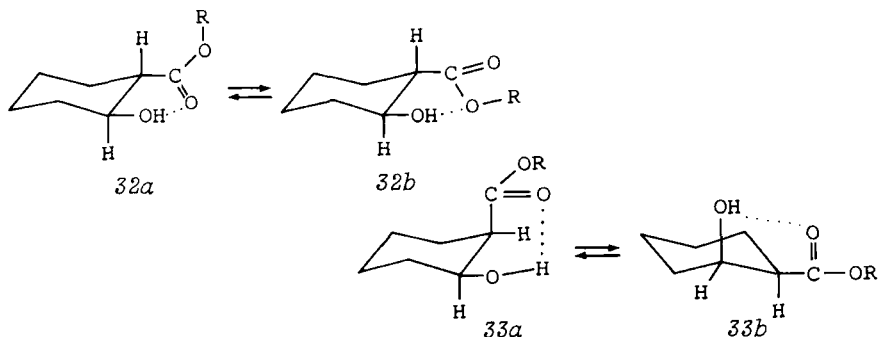


In addition the spectrum may contain bands resulting from the carbonyl overtone and from rotamer forms of the free OH (86). Although the presence of both *n*-electron and π -electron sites at the carbonyl group has also been recognized (82) (analogous to that in hydroxyketone systems described above), specific assignments of weak π -electron bonding in hydroxyesters do not appear to have been given. Conformational assignments of bonded OH absorptions in these compounds may be aided by examination of the C=O absorption. Thus, when the carbonyl oxygen is the proton acceptor (29), the C=O bond is lowered by 10 to 20 cm^{-1} , whereas with alkyl oxygen bonding (30) $\nu_{\text{C=O}}$ is raised by about 10 cm^{-1} over the usual value. When both types of bonds are present, a $\nu_{\text{C=O}}$ doublet (or unsymmetrical $\nu_{\text{C=O}}$ band caused by an unresolved doublet) is obtained (82-84).

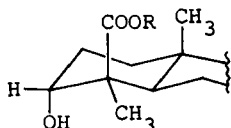
In α -hydroxyesters (e.g., 31) hydrogen bonds of both the 29 and 30 type are formed, but that with the carbonyl oxygen predominates and no free OH is observed (82,84,85). Higher



acyclic ω -hydroxy esters show decreasing amounts of bonded OH species through ethyl ϵ -hydroxycaproate. The latter shows only a small $\text{OH} \cdots \text{O} = \text{C}$ bond, which disappears completely for higher members of this series (82,85). In acyclic β -hydroxyesters (e.g., $\text{HOCH}_2\text{CH}_2\text{COOEt}$) hydrogen bonding to the carbonyl group also predominates, accompanied by a small proportion of free OH (82), and in some cases by the alkyl oxygen-bonded species (30) (85,86). For β -hydroxyester groups on a cyclohexane ring (32 and 33), the bonding pattern depends on their respective conformations (18,85,87). Thus diequatorial *trans*-hydroxyesters (32) contain both types of hydrogen bonds, but the $\text{OH} \cdots \text{O} = \text{C}$ type (32b) is preferred. *cis*-Hydroxyesters (33), on the other hand, mainly (if not exclusively) form the $\text{OH} \cdots \text{O} = \text{C}$ species, undoubt-

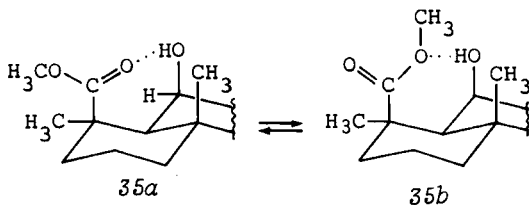


edly as an equilibrium mixture of *33a* and *33b*. In both *32* and *33* some free OH is also observed (85). A *trans*- β -hydroxyster system that is fixed in a diaxial configuration (*34*) cannot form an intramolecular hydrogen bond (18).

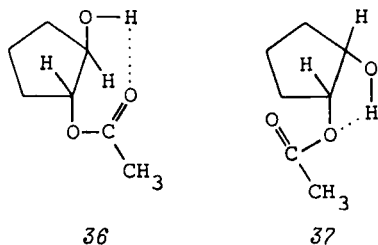


34

In the γ -hydroxycyclohexanecarboxylic acid esters (*cis* or *trans*) intramolecular hydrogen bonding does not normally occur (85). If the two substituents are fixed in a *syn*-axial configuration (*35*), however, both carbonyl- and alkyl oxygen-bonded species are observed, with only a trace of free OH (80). The OH equatorial epimer of this system also forms an intramolecular hydrogen bond, but almost entirely of the $\text{OH}\cdots\text{O}=\text{C}$ species, and in equilibrium with an appreciable amount of the free OH form.



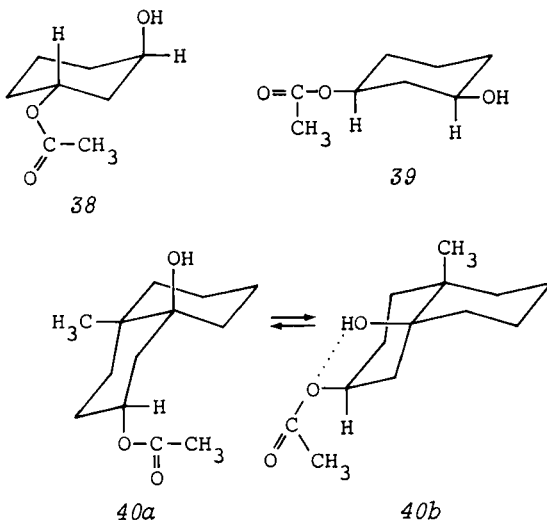
Hydroxyesters of the diol monoacetate type have also been studied (81,83). In the cyclopentane- and cyclohexane-1,2-diol monoacetate series, both the *cis* and *trans* isomers form intramolecular hydrogen bonds. For the *trans*-cyclopentane isomer intramolecular hydrogen bonding is sterically possible only between the OH and carbonyl oxygen (*36*), and this conformation is observed in equilibrium with free OH. In the *cis* isomer (*37*),



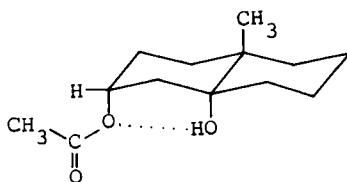
however, only a weak hydrogen bond to the ether oxygen is observed (3610 cm^{-1}), with no free OH (81). Earlier workers had

also reported (88) a weak absorption at 3542 cm^{-1} which though not observed in the more recent work, was interpreted to result from a trace of the $\text{OH}\cdots\text{O}=\text{C}$ species (81). In the cyclohexane series both the cis and trans isomers are reported to exist in equilibrium between $\text{OH}\cdots\text{O}=\text{C}=\text{O}$ (mainly) and $\text{OH}\cdots\text{O}=\text{C}$ forms, with no free OH in either isomer. In the case of the trans isomer, however, this result is not unequivocal, because it is based on the assignment of the strong 3627 cm^{-1} band as a bonded $\text{OH}\cdots\text{O}=\text{C}=\text{O}$ rather than a free OH form (81).

Simple cyclohexane-1,3-diol monoacetates (38,39) show no intramolecular hydrogen bonding. If the cis isomer is forced into a diaxial conformation, however, an $\text{OH}\cdots\text{O}=\text{C}=\text{O}$ interaction (40b) is observed (83). In a diaxial configuration (41) no free OH rotamer forms are observed (83). Therefore it should be possible to assign the position of the 40 equilibrium from the area

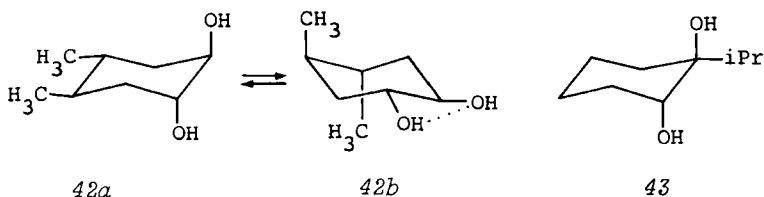


of the free OH. In these systems the six-membered hydrogen-bonded $\text{OH}\cdots\text{O}=\text{C}=\text{O}$ ring is preferred to an eight-membered $\text{OH}\cdots\text{O}=\text{C}$ ring, although for the same ring size the $\text{OH}\cdots\text{O}=\text{C}$ bond is presumably preferred.

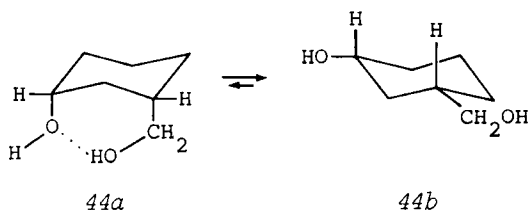


D. The OH...OH and OH...OR Hydrogen Bonds

An early classic study of intramolecular hydrogen bonding by IR methods was carried out by Kuhn (2) on cyclohexane- and cyclopentane-1,2-diols. Shortly thereafter Cole and Jefferies (89) studied donor-acceptor relationships in cyclohexane-1,2-diol systems, and concluded that a secondary equatorial OH forms hydrogen bonds in preference to a tertiary equatorial OH, but an axial OH forms hydrogen bonds in preference to an equatorial OH, whether secondary or tertiary. Spectral studies of additional cyclohexane-1,2-diols have since been reported (52,90). Thus in 42, for example, the presence of an intramolecular OH...OH bond established that the diaxial conformation 42*b* is present in the equilibrium mixture (90). It is of interest to note, however, that in 43 no hydrogen-bond formation was detected (89). Conformational differences in the isomers of the 1-, 2-, and 3-hydroxymethylcyclohexanols have been described (91). Only the 3-hydroxy isomers (cis and trans) are internally unbonded. The cis isomer must exist as 44*b*, therefore, because the diaxial conformer (44*a*) should show some hydrogen bonding, as has been observed in a steroid system (92). Transannular hydrogen-bond formation has been observed in some 1,4-dialkyl- and 4-phenylcycloheptane-1,4-diols (93).



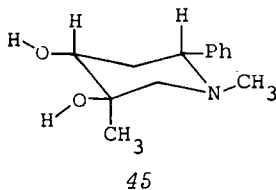
In the equilibrium between free OH and bonded OH...OH species in a series of α,ω -diols $[\text{HO}-(\text{CH}_2)_n-\text{OH}]$, values of ΔH^0 , ΔS^0 , and ΔG^0 were reported for $n = 2$ to 5. Here the enthalpy value (ΔH^0) increased linearly with increasing strength of the hydrogen bond ($\Delta\nu_{\text{OH}}$), and was largest, that is, most favorable for bonding, for butanediol ($n = 4$, $\Delta\nu_{\text{OH}}$ 160 cm^{-1}). However, the contribution of the entropy factor was such that the largest percentage of bonded species (ΔG^0) was observed for ethanediol (ca. 92% at 25°C). Although the general conclusions of this study are undoubtedly qualitatively correct, the quantitative assignments should be reconfirmed, because the conformer concentrations were assigned on the assumption that the absorbances resulting from free and bonded OH groups are equal. While this assumption may yield a reasonably good approximation for small values of $\Delta\nu_{\text{OH}}$ (e.g., 1,2-ethanediol, $\Delta\nu_{\text{OH}}$ 35 cm^{-1}), it is less valid for larger values. Thus for 1,3-propanediol ($\Delta\nu_{\text{OH}}$ 78 cm^{-1}) the equilibrium constant was assigned in favor of the bonded OH form, by 1.8 kJ/mol (ca. 67%). In an earlier study (95), however, the equilibrium had been assigned in favor of the free OH



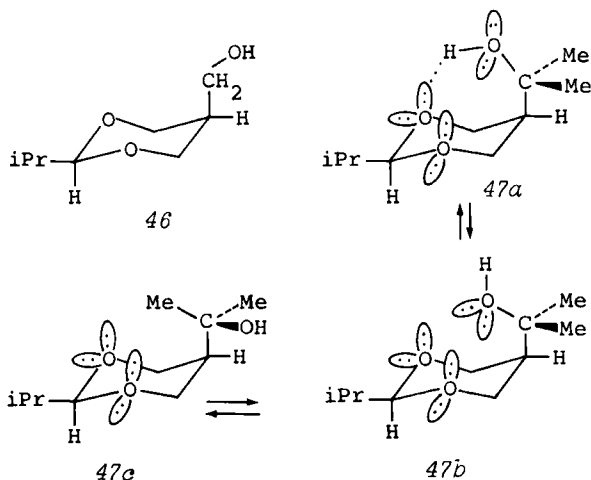
form, by 0.4 kJ/mol (ca. 54%), based on the extinction coefficient (but not the more reliable band area) of the free OH relative to that of propanol. Enthalpy values calculated in a related study on hydrogen bonding in butanediols (96) were faulted (94) for ignoring the corresponding mole equivalent of free OH that is present in all the bonded species.

Spectral studies of terpene (71), triterpene (97), and steroid diols (72, 98-100) have been carried out. Unsuccessful attempts were made to correlate the $\Delta\nu_{\text{OH}}$ values with deformations of the chair conformation in the sterol series (98). In the triterpene systems the presence of boat species was observed.

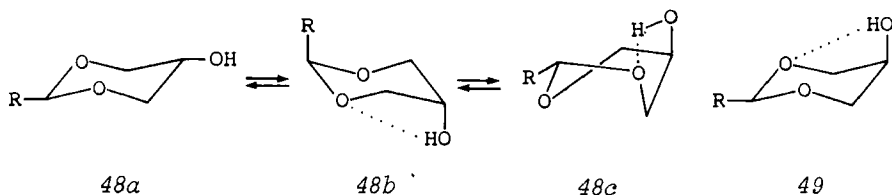
In recent studies of certain diol systems with small dihedral angles, the unexpected absence of intramolecular hydrogen bonding or the presence of an abnormally weak hydrogen bond has been recorded (101). In the case of a piperidine (45) and the corresponding tetrahydrothiopyran diol, however, the reported (102) absence of any intramolecular hydrogen bonding is inconsistent with the assigned structures.



Intramolecular $\text{OH}\cdots\text{O}$ hydrogen bonding has been studied for dioxane (103-107), dioxolan (104), tetrahydropyran (104, 108), tetrahydrofuran (109), and oxirane (110) systems. The unexpected absence (in 46) or very minor presence (47a) of intramolecular hydrogen bonding in 5-hoxymethyl-1,3-dioxane systems (103, 105, 111) has been attributed either to OH/O dipole/dipole repulsion (103) or to the anomeric effect (112), caused by interaction of the unpaired electron clouds. Accordingly, the predominant conformational species in 47 has been assigned as either 47b or 47c, with 47b being preferred (103). However, 47a should be favored over 47b because it not only has an (attractive) intramolecular hydrogen bond, but also contains one less (repulsive) anomeric interaction. Therefore, in the absence of intramolecular hydrogen bonding conformer 47c appears to be a more likely assignment.



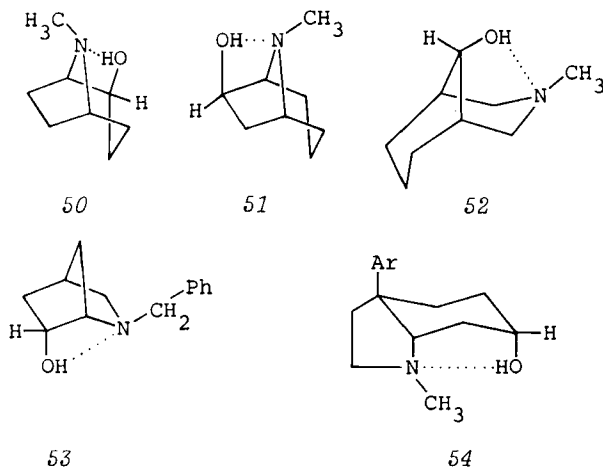
In both the *trans*-2-methyl- and *trans*-2-*t*-butyl-dioxan-5-ol isomers (48), the presence of an OH doublet (3629 and 3601 cm^{-1}) was attributed to a mixture of free and bonded OH species, assigned as a 48*a*-48*b* chair-chair equilibrium for the 2-methyl compound, and a 48*a*-48*c* chair-boat equilibrium for the 2-butyl analog (104). However, the 48*b* and 48*c* assignments are ques-



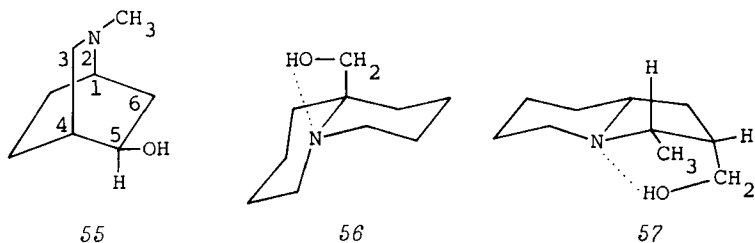
ionable on conformational grounds, in view of the $-\Delta G^0$ values of a 2-alkyl (≥ 4 kcal/mol) (113) and a 5-hydroxy (ca. 0.9 kcal/mol) (111) substituent on a dioxane ring in a nonpolar solvent. Since the corresponding *cis* isomers (49) show only a bonded OH at a somewhat lower frequency (3588 cm^{-1}), the 48 doublet is best assigned to the presence of two free OH rotamer forms, as discussed in Sect. IV.

E. The OH...N Hydrogen Bond

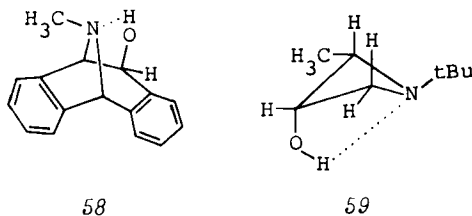
Configurations of epimeric amino alcohols that have been assigned on the basis of an OH...N hydrogen bond include 2 β -tropanol (50) (114), 6 β -tropanol (51) (115), 3-methyl 3-azabicyclo[3.3.1]nonan-9 β -ol (52) (34b), endo 2-benzyl 2-azabicyclo[2.2.1]heptan-6-ol (53) (116), 6-epimesambinol and its corresponding 9-phenyl analog (54) (117), and the *cis* isomers of 5- (55) and 6-hydroxy-2-methyl-2-azabicyclo[2.2.2]octane (118). Bridgehead nitrogen compounds related to quinolizidine, indoli-



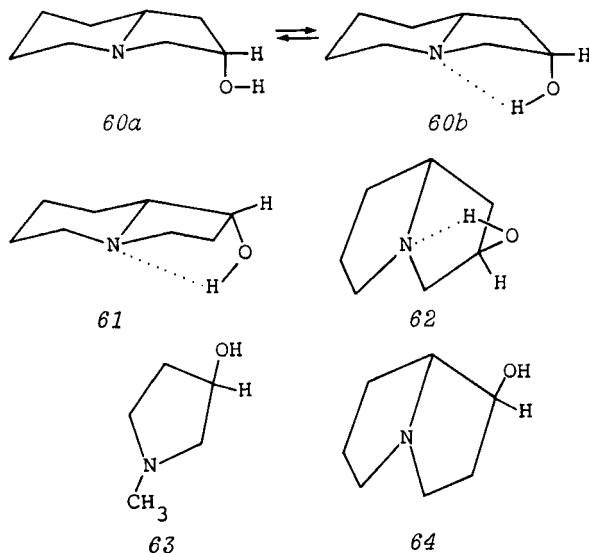
zidine, and pyrrolizidine systems that have been assigned in this way have been reviewed (119). More recently, the configurations of the four 4-phenylquinolizidin-1-ol isomers were assigned on the basis of their dilute-solution spectra (120). This system is further discussed below. Also, hydrogen bonding in hydroxymethyl derivatives of quinolizidine (e.g., 56) (121) and indolizidine systems (e.g., 57) (122) have been used for conformational assignments. The stereochemistry of two dibenzotropanol analogs



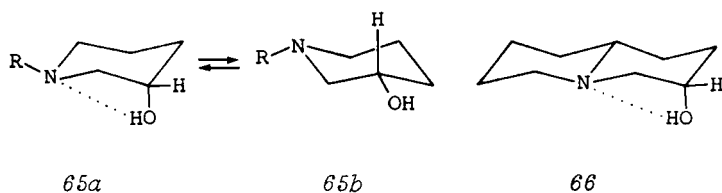
was assigned on the basis of the $\text{OH}\cdots\text{N}$ bond (ν_{OH} 3560 cm^{-1}) present in the syn-OH epimer (58) (123). The anti-OH epimer appears to exist in an $\text{OH}\cdots\pi$ conformation (ν_{OH} 3595 cm^{-1}). In the 1-*t*-butyl-2-methylazetidin-3-ol system the cis isomer (59) was assigned on the basis of a weak intramolecular hydrogen bond (ν_{OH} 3580 cm^{-1}), which is absent in the spectrum of the trans isomer (124).



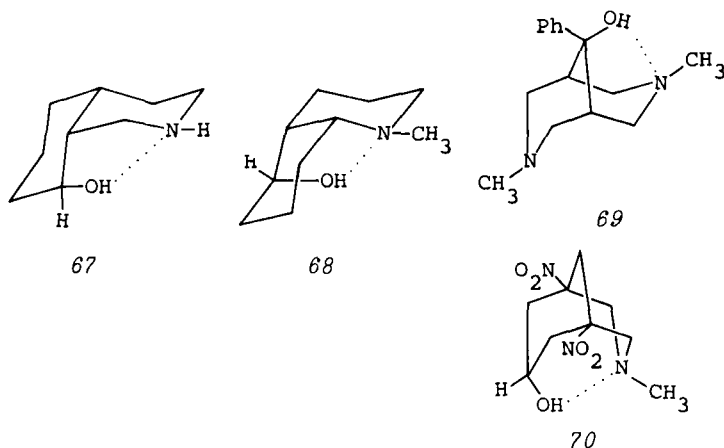
The relationship between the strength of the intramolecular hydrogen bond, expressed as $\Delta\nu_{\text{OH}}$, and the molecular geometry and/or intramolecular hydrogen bridging distance (see Sect. II) may be illustrated by comparison of a series of $\text{OH}\cdots\text{N}$ bonded compounds. Thus, in hydroxyl-substituted 5-membered-ring nitrogen systems 60-64 an intramolecular hydrogen to nitrogen ($\text{OH}\cdots\text{N}$) distance of $3.0 \pm 0.2 \text{ \AA}$ is obtained from Dreiding models, and this is about the limiting distance through which hydrogen bridging can operate in these systems. Accordingly, weak intramolecular hydrogen bonding ($\Delta\nu_{\text{OH}}$ 30 to 45 cm^{-1}) is seen (60-62) here, if at all (63, 64) (125). Moreover, for weakly bonded systems some free OH species is almost always observed, corresponding to rotamer forms of the OH group (e.g., 60a), although in some cases (e.g., 60 and 61), the equilibrium may greatly favor the bonded form.



In 3-hydroxypiperidine (65a) and related ring systems (e.g., 66) the $\text{OH}\cdots\text{N}$ bridge is more linear and shorter (about $2.4 \text{ \AA}$), and here moderately strong intramolecular hydrogen bonds are formed, which give $\Delta\nu_{\text{OH}}$ values in the 85 to 110 cm^{-1} range (9, 126). In compounds that contain the amino alcohol substituents in either a gauche (56) or syn-axial relationship (54, 67,



68), a near linear $\text{OH}\cdots\text{N}$ bridge with a hydrogen to nitrogen distance of ca. $1.9 \text{ \AA}$ is obtained from the models, and $\Delta\nu_{\text{OH}}$ values from ca. 240 cm^{-1} have been recorded (117,126). Some of the largest $\Delta\nu_{\text{OH}}$ values, however, are seen in substituted 4-piperidinol boat species (e.g., 3 and 69), where bridging distances as short as $1.6 \text{ \AA}$ may be measured from the models, and $\Delta\nu_{\text{OH}}$ values ranging from 240 cm^{-1} for 3(9) to ca. 400 cm^{-1} for 69 (35d) and others (127) have been observed. Finally, compound 70 has been prepared, in which an apparent hydrogen to amino nitrogen distance of ca. $0.4 \text{ \AA}$ is found from the model. Spectral data were reported only for a chloroform solution, however, as a broad band at $3100 \text{ to } 3450 \text{ cm}^{-1}$ (128).

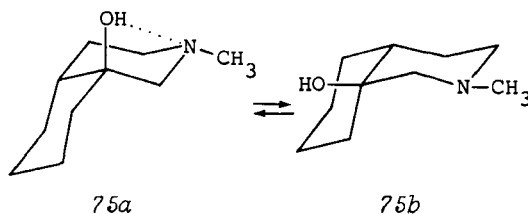
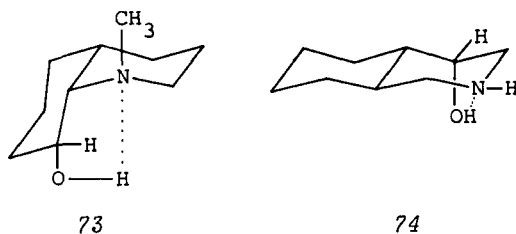
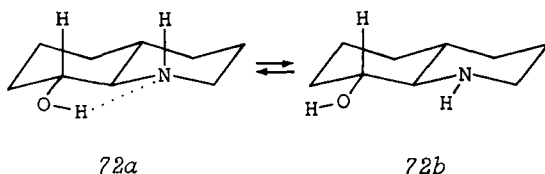
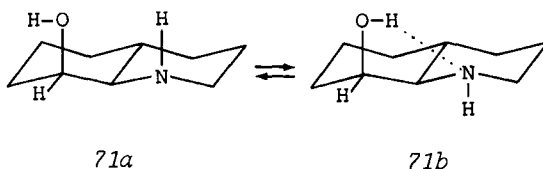


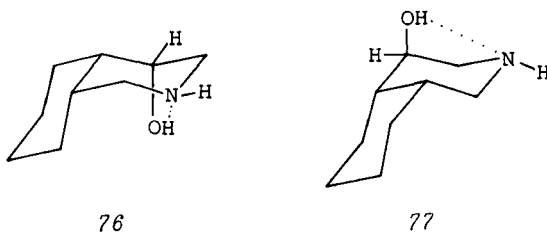
Such correlations have been used to show that an earlier assignment of a band of $\Delta\nu_{\text{OH}} 40 \text{ cm}^{-1}$ in a substituted 4-piperidinol to a hydrogen-bonded boat conformation actually results from a low-frequency rotamer form of the free OH group (25). By the same token the claim (129) of an intramolecular $\text{OH}\cdots\text{N}$ bonded boat conformation in the spectrum of *cis*-4-aminocyclohexanol ($\nu_{\text{OH}} 3450 \text{ cm}^{-1}$) should be reinvestigated, as suggested (1).

For $\text{OH}\cdots\text{N}$ bonded systems, the presence or absence of free OH rotamer forms may be related to the $\Delta\nu_{\text{OH}}$ value of the hydrogen bond. Thus, as noted above for weakly bonded compounds ($\Delta\nu_{\text{OH}} < 45 \text{ cm}^{-1}$), some free OH species (e.g., 60a) is invariably present. However, for the more strongly bonded 1- and 3-quinolizidinol (66) systems ($\Delta\nu_{\text{OH}} \sim 100 \text{ cm}^{-1}$), no free OH rotamer forms are observed (130). Therefore, in the conformational analysis of amino alcohols that contain an $\text{OH}\cdots\text{N}$ bonded species with $\Delta\nu_{\text{OH}} \geq 100 \text{ cm}^{-1}$, any free OH corresponding to a simple OH rotamer form of the bonded species is presumably small enough to be ignored. Any free OH observed in such spectra, therefore, is presumably caused by other molecular conformations (e.g., 65b).

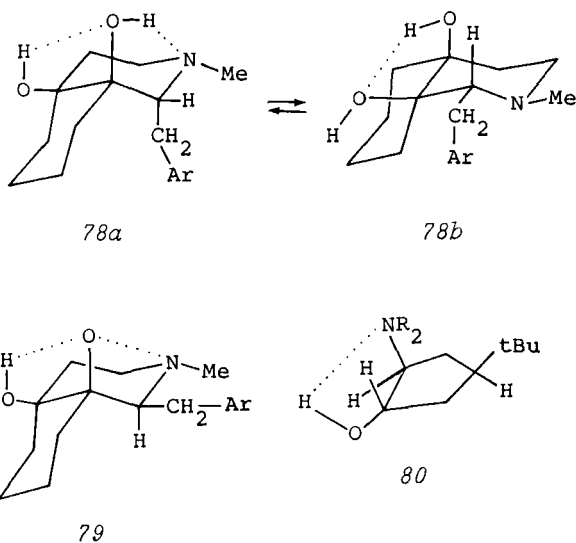
A number of IR studies of hydrogen bonding in substituted 3-piperidinol systems have been reported, and conformational assignments have been given (131-135). For the unsubstituted parent 3-hydroxypiperidine (65, $R = H$), the population of the four possible conformers in dilute carbon tetrachloride solution has been assigned (135). Conformational analyses of hydrogen-bonded hydroxyalkylpyridine (136) and hydroxyalkylpiperidine (39, 126, 136) systems have been presented.

Hydrogen bonding has been reported in decahydroquinoline (68, 71-73) and in tetra- and decahydroisoquinoline (67, 74-77) systems, and the conformational equilibria (e.g., 75) have been assigned (126, 135, 137-143). The *cis*-decahydroisoquinolin-4 α -(76) and -4 β -ol (77) epimers each form an intramolecular hydrogen bond. Their respective configurations, however, can be assigned on the basis of the smaller relative proportion of bonded $OH \cdots N$ species observed in 76, mainly caused by the unfavorable syn-axial CH_2/OH interactions that are present in this species (126, 142). Intramolecular hydrogen bonding also has been





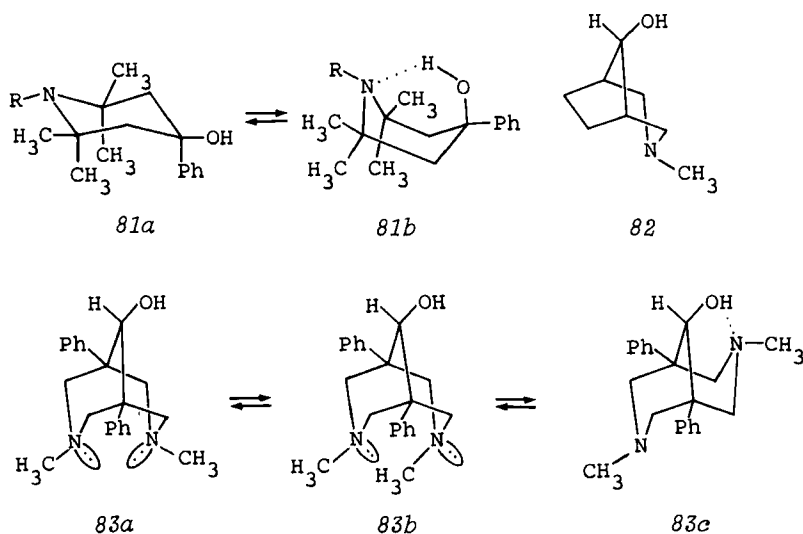
reported for isomers of a decahydroquinoline-9,10-diol system (144). Only in the case of the two 9,10-*cis* isomers, ν_{OH} 3434 and 3490 cm^{-1} , respectively, were the configurations not assigned. However, the fact that the former isomer also contains a free OH band ($\Delta\nu$ 3614 cm^{-1}), which is not observed in the latter, suggests that the configurations should be assigned as 78 and 79, respectively.



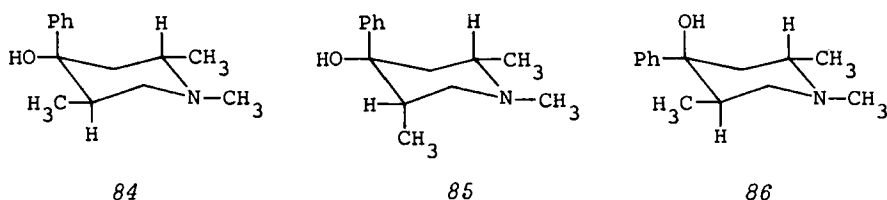
Intramolecular $\text{OH}\cdots\text{N}$ bonding studies of vicinal amino alcohols in substituted cyclohexane and cyclopentane derivatives have also been studied, and $\Delta\nu_{\text{OH}}$ values for the *cis* and *trans* isomers were reported (145). In the *trans*-substituted *t*-butylcyclopentane isomers (e.g., 80) an intramolecular hydrogen bond is observed (145c), which is not seen in *trans*-cyclopentane-1,2-diol (2).

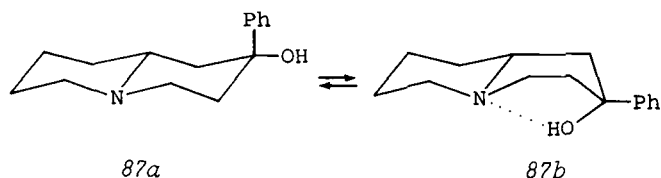
Boat conformers in substituted 4-piperidinol and related systems have been observed in the form of the intramolecular bonded species, as indicated for 3, 52, and 69. Although hydrogen bonding does aid the formation of the boat conformation, these

systems generally require, in addition, a destabilizing interaction in the free OH form, if a detectable concentration of the boat species is to be observed. Thus $\text{OH}\cdots\text{N}$ bonding is not observed in *N*-methyl 4-phenyl-4-piperidinol, but is observed in pentamethyl-4-phenyl-4-piperidinol (**81**) (146). The NH analog of **81** also exists in equilibrium between a chair (ν_{OH} 3604 cm^{-1} , carbon tetrachloride) and boat (ν_{OH} 3388 cm^{-1}) form (147), whose position (26% boat) is similar to that of the *N*-methyl analog (34% boat). Boat formation is also seen in β -granatanol (**3**) and **52** (but not in **4** or **82**), undoubtedly because of steric interaction of the 3,7 position of the double-chair form (e.g., **3a**). The related bispidanol systems **69** (35d) and **83** (148) also form intramolecular hydrogen bonds (147). For **83** the bonded conformation (**83c**) constitutes a majority (75%) of the molecular species, presumably due to anomeric or steric effects in the double-chair forms (**83a** and **83b**, respectively). Intramolecular hydrogen bonding caused by boat formation has been reported for the α -(**84**) and

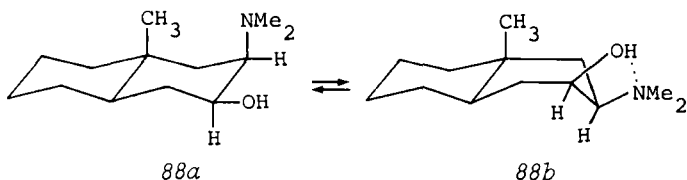


β -(**85**), but not the γ -(**86**), isomers of promedol (149), a result that is consistent with their configurational assignments. The formation of the boat conformation by **84** and **85** is somewhat analo-

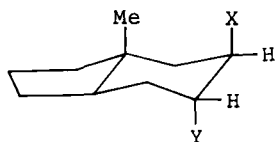
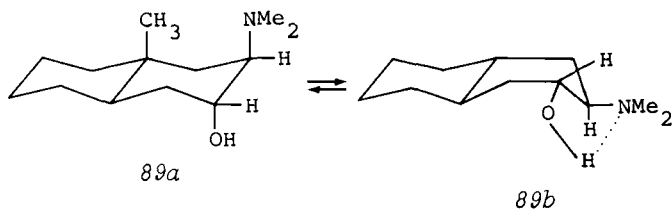




gous to that observed for the 2-phenylquinolizidin-2-ol isomer 87 (31, 150). In the latter 7% of the boat species (87b) has been assigned (150b).



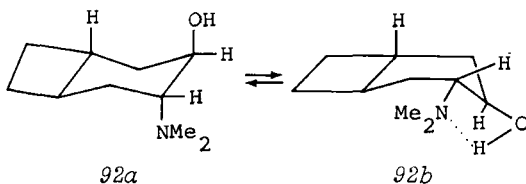
A boat conformation has been suggested for the substituted decalin 88, based on a study of hydrogen bonding in *cis*-2-dimethylaminocyclohexanol (151). Firmer evidence of boat formation, however, has been given for the *trans*-amino alcohol isomer 89,



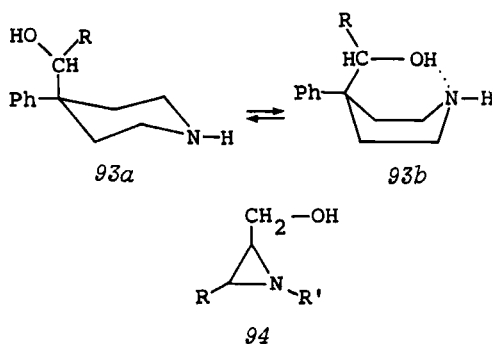
90: X = NMe₂, Y = OH

91: X = OH, Y = NMe₂

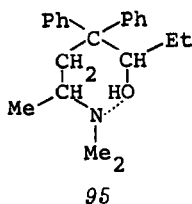
and also for the perhydroindane analogs 90 and 91 (152,153). Here the boat species was formed more readily in the perhydroindane than in the decalin series, and a significant amount (26%) (152) of bonded boat conformer was even observed when the bridgehead methyl of 91 was replaced by hydrogen. The trend carries over into the corresponding *trans*-fused cyclobutane



analog (92), where the majority of the molecular species apparently exists in the $\text{OH}\cdots\text{N}$ bonded form (153). On the other hand the correctness of the assignment (154) of an exclusive boat conformation to 93 ($\text{R} = \text{H}, \text{Me}, \text{or phenyl}$) is questionable on conformational grounds, especially since spectra of the corresponding *N*-methyl analogs in CCl_4 reveal no such species. The cause of the anomalous spectra of the 93 series is uncertain, therefore, but might result from solvent (CHCl_3) reaction or formation of a persistent dimer.

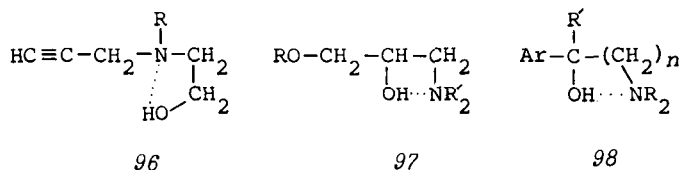


Assignments of some piperidin-3-ol alkaloid configurations have been made (155), in part, on the basis of their conformational analysis, as earlier applied to the carpaine alkaloids (156). Configurational assignments in solanum alkaloids have been based on their intramolecular hydrogen bonds (157). Dilute solution spectral study of some α -(hydroxymethyl)aziridines (94) has been reported (158).



Intramolecular hydrogen bonding has been studied in acyclic amino alcohols of the type $\text{R}_2\text{N}-(\text{CH}_2)_n-\text{OH}$ (159), and also in various C-substituted analogs (159a,d). In the series $\text{Et}_2\text{N}-(\text{CH}_2)_n-\text{OH}$ ($n = 2$ to 6) the largest value of $\Delta\nu_{\text{OH}}$ was recorded for $n = 4$ (159b,c). However, the percentage of bonded species decreased in the order of increasing value of n (corresponding to the increasing entropy loss of the bonded species), and was absent entirely for $n = 6$ (159b). Very strong hydrogen bonding with little or no free OH was recorded (159d) for the isomeric methadols (95), possibly due to the contribution of a *gem*-dialkyl (160) or Thorpe-Ziegler (79d) effect. The isomethadol isomers were also studied with similar results (159e).

Intramolecular $\text{OH}\cdots\text{N}$ hydrogen bonding was studied in a series of *N*-(2-hydroxyethyl)propynylamines (96), and the values of Δv_{OH} were correlated with the basicities (pK_b) and with certain substituent constants related to nitrogen substitution (159f). For a series of amino alcohols of the type 97 and the corresponding (RS) analog, both $\text{OH}\cdots\text{N}$ and $\text{OH}\cdots\text{O}$ or $\text{OH}\cdots\text{S}$ bonding were observed (159g). Attempts to correlate Δv_{OH} with the basicity of the amines (pK_b), however, were unsuccessful. A series of compounds of the type 98 were examined, and a linear correlation between an increase in the strength of the hydrogen bond (Δv_{OH}) and a decrease in basicity of the amino alcohol was obtained, which suggests that the formation of the intramolecular hydrogen bond causes the decrease in the basicity of the



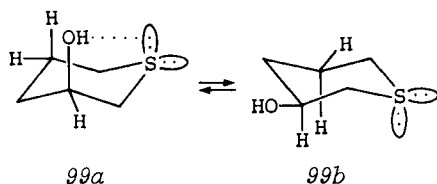
amine (159h). In flexible acyclic systems corresponding to structures such as 98, however, it is unlikely that the intramolecular hydrogen bond is responsible for the observed basicities of these compounds. Thus, although Δv_{OH} increases with the value of n in these systems, the percentage of molecular species in the bonded form becomes correspondingly smaller (due to the entropy effect) even in nonaqueous media. Intramolecular hydrogen bond formation, therefore, would have a vanishingly small effect on the basicity of the system. In an aqueous medium, moreover, the very strong intermolecular $\text{OH}\cdots\text{N}$ bonding with solvent most probably takes over almost exclusively, especially for values of $n > 2$. Finally, for epimeric amino alcohols that are conformationally fixed, the opposite correlation is invariably observed. That is, the epimer which is hydrogen bonded in nonaqueous solution is invariably the stronger base in aqueous solution (115,125,130,161).

F. The $\text{OH}\cdots\text{S}$ Hydrogen Bond

Intramolecular $\text{OH}\cdots\text{S}$ hydrogen bonding in the ω -ethylmercaptoalkanol $[\text{Et}-\text{S}-(\text{CH}_2)_n-\text{OH}]$ series has been studied, and the equilibrium position for the free and bonded OH species was compared to those of corresponding compounds containing an oxygen or nitrogen instead of sulfur as the proton-acceptor site (162). Although the Δv_{OH} values increase in the order $\text{O} < \text{S} < \text{N}$, the

equilibrium position stands in the order $S < O < N$, and is much lower in the sulfur analogs than in the other two. In addition, bonding is observed in the sulfur series only for $n = 2$ or 3 , compared to $n = 2$ to 5 for the oxygen and nitrogen analogs. On this basis it was concluded that the sulfur atom is much lower in intramolecular hydrogen bonding ability than the oxygen and nitrogen atoms, and that the $\Delta\nu_{OH}$ value cannot be used for comparing strengths of intramolecular hydrogen bonds when different proton-acceptor atoms are involved. A similar relationship was reported in Sect. VI-A for comparisons of intramolecular bonded $OH \cdots \text{halogen}$ systems.

A possible explanation of these results might be obtained from a reexamination of the data reported for tetrahydropyran-3-ol (163) and its corresponding thio (99) analog (164). Although

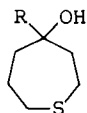


exact equilibrium concentrations were not assigned for the former (and should be reconfirmed using band areas in the latter), a comparison of their published spectra indicates that the percentage of bonded $OH \cdots O$ ($\Delta\nu_{OH}$ 16 cm^{-1}) species is apparently greater than that of the bonded $OH \cdots S$ ($\Delta\nu_{OH}$ 93 cm^{-1}) species in these two compounds. The equilibrium position of each, however, reflects the summation of all their conformational interactions. These include the relative strengths of their hydrogen bonds (attractive), their syn-axial H/OH interactions (repulsive, but probably comparable in each system), and their syn-axial C-H/O-electron pair and C-H/S-electron pair interactions (attractive, if applicable in this argument), respectively. Thus differences in equilibrium positions of either cyclic or acyclic carbinols containing different heteroatoms might depend more on their relative H/electron pair interactions than on the relative strengths of their intramolecular hydrogen bonds suggested on the basis of their $\Delta\nu_{OH}$ values, assuming that the latter is still a valid criterion, even when different proton acceptors are involved.

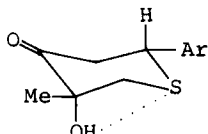
Transannular hydrogen-bond formation has been observed in equilibrium with free OH in the 4-hydroxythiacycloheptane series (165). For 100 the equilibrium position tends to shift in the direction of the bonded species as R changes in the order $H < Me < Ph$ (165a).

Configurational and conformational assignments of some 3-hydroxytetrahydrothiopyran-4-ones (101) had been given on the basis of their IR spectral data (166), and hydrogen-bonding

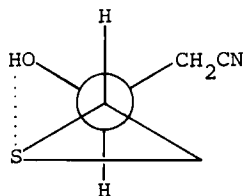
studies in some dithiane systems have been reported (167), as discussed in Sect. VII.



100

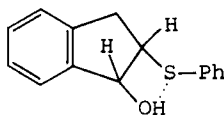


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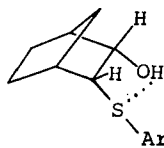


102

The configurations of threo (102) and erythro episulfide isomers of **8** have been assigned, as noted above (8). In the sulfenyl-substituted indanol (103) (168) and norborneol (104) (169) systems, only the cis isomers form an intramolecular hydrogen bond. In the latter system the corresponding $\text{OH}\cdots\text{O}\leftarrow\text{S}\rightarrow\text{O}$ bonded compounds were also reported.



103



104

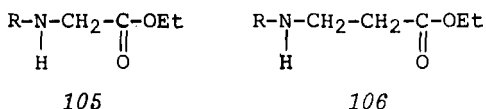
Intramolecular hydrogen bonding in aromatic sulfides, sulfoxides, and sulfones has been reported (170,171). For a series of ortho-substituted thiophenols and ortho-substituted phenols, the orders of frequency shifts were found to be $\text{OH}\cdots\text{S}$ ($\sim 145\text{ cm}^{-1}$) $>$ $\text{OH}\cdots\text{O} \rightleftharpoons \text{SH}\cdots\text{O}$ ($\sim 45\text{ cm}^{-1}$) $>$ $\text{SH}\cdots\text{S}$ ($\sim 19\text{ cm}^{-1}$). The relative bond strengths, calculated from the Schroeder-Lippincott potential function model of the hydrogen bond, were given as $\text{OH}\cdots\text{S} > \text{OH}\cdots\text{O} > \text{SH}\cdots\text{O} \rightleftharpoons \text{SH}\cdots\text{S}$ (172). It is not certain that these calculated assignments, which pertain only to aromatic systems, are actually in conflict with the results described above for $\text{OH}\cdots\text{S}$ vs. $\text{OH}\cdots\text{O}$ bonded equilibria in aliphatic systems. A better understanding and a more practical application of these results would be obtained, however, if actual equilibrium positions between free and bonded species were compared in the aromatic compounds.

G. Miscellaneous Hydrogen Bonds

Intramolecular hydrogen bonding by (donor) SH groups has been reviewed (173). In general, aliphatic SH groups form weak hydrogen bonds, which may be difficult to detect by IR methods. Thus, although bonding in ortho-substituted thiophenols has been

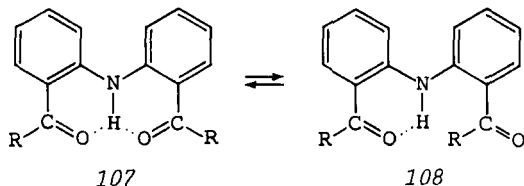
reported (174), no evidence of bonding in some substituted aliphatic thiols could be detected (175).

Intramolecular $\text{NH}\cdots\text{O}$ hydrogen bonding in ethyl α - (105) and β -aminoalkanoates (106) has been investigated (176) through measurement of the NH and C=O stretching absorptions, and compared to that in the corresponding mercapto analogs, (175b)



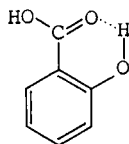
(which show no evidence of any hydrogen bonding) and the hydroxy analogs (82,86), which form an intramolecular hydrogen bond exclusively between the OH and C=O group. In the NH system the α -esters (105) gave no evidence of hydrogen-bond formation; in the β -esters (106), however, hydrogen bonding occurs, predominantly between the NH and C=O groups.

Intramolecular $\text{NH}\cdots\pi$ hydrogen bonding has been studied in *N*-benzylanilines, ArCH_2NHPh (177), and in *N*-(ω -phenylalkyl)aniline, $\text{Ar}(\text{CH}_2)_n\text{NHAr}$ (178), and compared to the corresponding $\text{OH}\cdots\pi$ and $\text{NH}\cdots\text{O}$ interactions in $\text{Ar}(\text{CH}_2)_n\text{OH}$ and *N*-(ω -phenoxyalkyl)anilines, $\text{ArO}(\text{CH}_2)_n\text{NH}\phi$ (179), respectively. Here, the $\text{NH}\cdots\text{O}$ and $\text{NH}\cdots\pi$ hydrogen bonding was observed for $n = 1$ to 5, with the $\text{OH}\cdots\pi$ bonding only for $n = 1$ to 3. For compounds of the type $\text{EtO}(\text{CH}_2)_n\text{CONHCH}_3$ the percentage of intramolecular $\text{NH}\cdots\text{OEt}$ bonding decreases in the order $n = 1 > 2 > 3$ (due to the entropy effect), while $\Delta\nu_{\text{OH}}$ increases in the reverse order (180). Thus for α -ethoxy *N*-methylacetamide ($n = 1$) a single band was observed, assigned as $\text{NH}\cdots\text{OEt}$, whereas for β -ethoxy-*N*-methylpropionamide an NH doublet at 3468 and 3409 cm^{-1} was observed, assigned as free NH and $\text{NH}\cdots\text{OEt}$, respectively. The 2-chloro-substituted *N*-methylacetamides, such as $\text{ClCH}_2\text{CONHCH}_3$, exist exclusively in an intramolecular $\text{NH}\cdots\text{Cl}$ bonded form ($\sim 3450\text{ cm}^{-1}$) (181). Intramolecular hydrogen bonding in some diacyldiphenylamines has been assigned (182) (based on the carbonyl absorption) as a bifurcated hydrogen-bonded species (107) in equilibrium with a singly bonded conformer.

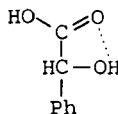


Intramolecular hydrogen bonding in hydroxy acids has been studied, but conformational assignments are often complicated by the presence of a multitude of bands. Thus in 2-hydroxy acids bands at ca. 3615 , 3560 , 3525 , and 3440 cm^{-1} were assigned, respectively, to the unassociated alcoholic OH, the alcoholic

OH bonded to the acid group in a dimer, the free OH of the carboxylic acid group, and the OH of the latter intramolecularly bonded to the alcoholic OH group (183). In α -hydroxyisobutyric acid, however, the corresponding bands were all assigned to monomeric species, with the strong band at 3575 cm^{-1} being assigned to the alcoholic OH intramolecularly bonded to the acid carbonyl group (184). Studies on γ -hydroxy acids have also been reported, but conformer percentages were not given, due to uncertainties in the band assignments (80). In salicylic (109) and mandelic (110) acids, on the other hand, the compounds exist exclusively as bonded species, apparently with the phenolic and alcoholic hydroxyls, respectively, bonded to the carbonyl oxygen of the carboxylic acid (184).



109

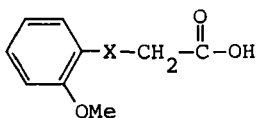


110

Dilute-solution spectra of α -, β -, and γ -alkoxy-substituted carboxylic acids have been recorded (185). For the α -substituted acids, intramolecular hydrogen bonding by the OH of the carboxylic acid group was observed as an equilibrium between free (ca. 3530 cm^{-1}) and $\text{COOH}\cdots\text{O}$ bonded species. In the β - and γ -substituted acids, however, no intramolecular hydrogen bonding was observed. In the α -hydroxy acids the presence of the intramolecularly bonded five-membered chelate ring may be confirmed by an unusually high-frequency exocyclic band (ca. 1782 cm^{-1}) (185b).

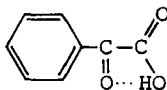
Intramolecular hydrogen bonding by the carboxylic acid OH group has been studied (186) in substituted *o*-methoxybenzoic acids. In general, an equilibrium between bonded and free carboxylic acid OH species was observed, and the frequency shift was correlated with the position and electronegativity of the substituent. However, when the carboxy group was flanked by the second substituent, intramolecular hydrogen bonding was completely suppressed. *o*-Methoxy-substituted phenoxyacetic (111) and phenylthioacetic acids (112) have been investigated (187). The former was found to exist as an equilibrium mixture, with free OH (ca. 3530 cm^{-1}), OH bonded to the α -phenoxy oxygen, and OH bonded to the methoxyl oxygen atom. In the latter, however, only a free OH and an $\text{OH}\cdots\text{OMe}$ species was observed. Intramolecular $\text{OH}\cdots\text{O}=\text{C}$ (π) bonding has been noted in phenylglyoxylic acid (113) (188).

Conformational equilibria have been observed (189a) between free OH and $\text{OH}\cdots\text{Fe}$ species in α -hydroxyalkylferrocene (114, $n = 1$), and also with an $\text{OH}\cdots\pi$ species in the β -hydroxyalkyl homolog ($n = 2$). These assignments are in agreement



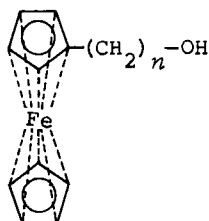
111, X = O

112, X = S

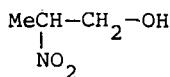


113

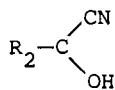
with those of another study (190), in disagreement with some earlier work. Intramolecular $\text{OH}\cdots\text{OH}$ and $\text{OH}\cdots\text{O}=\text{C}$ bonding in 1,1'-substituted ferrocene systems has also been described (189b). Spectral studies of intramolecular hydrogen bonding also have been reported, and conformational species assigned in nitro alkanols (e.g., 115) (191) and 1- (116) and 2-cyano alcohols (192).



114

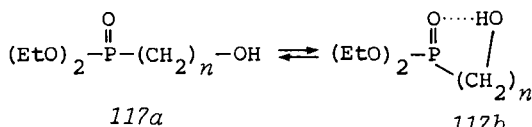


115



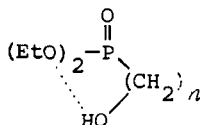
116

Conformational equilibria for α - and β -hydroxyphosphoryl compounds (117) have been reported (193). In this series a stronger intramolecular bond was observed for the β (six-membered chelate ring) than for the α (five-membered chelate ring) isomers in both the $\text{OH}\cdots\text{O}=\text{P}$ (117b) (3490 vs. 3590 cm^{-1}) and $\text{OH}\cdots\text{OR}$ (117c) (3600 vs. 3615 cm^{-1}) conformers (193a). This



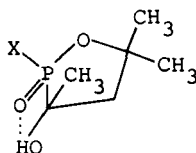
117a

117b



117c

result corrects the earlier opposite assignment of relative bond strengths in a related system which occurred because the study was not carried out at sufficient dilution to eliminate all intermolecular bonded species (193b). In another series persistent intermolecular bonded dimers were noted even in very dilute CCl_4 solutions (193c). In the substituted oxaphospholan-3-ol ring system a *cis* $\text{OH}/\text{P}=\text{O}$ isomer (e.g., 118) could be distinguished from its corresponding *trans* isomer on the basis of its intramolecular $\text{OH}\cdots\text{O}=\text{P}$ hydrogen bond (193d).



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VII. QUANTITATIVE APPLICATIONS

The relative intensities of spectral bands of individual conformers and/or of model compounds have been used to calculate the positions and thermodynamic parameters of conformational equilibria, as indicated in numerous examples cited above. The method is a general one that is not limited to dilute-solution spectral results, but assumes that a particular spectral band can be assigned to a specific conformation. Thus for an equilibrium between conformations C_1 and C_2 the integrated intensity or area (A) of a band that is specific for a particular conformer is given by $A = \alpha Cl$, where α is the integrated absorption coefficient, C is the concentration, and l is the cell length (194). The equilibrium constant (K) is then given by

$$K = \frac{C_2}{C_1} = \frac{A_2 \alpha_1}{A_1 \alpha_2} \quad [3]$$

If one assumes that $\alpha_1 = \alpha_2$ (46), then K is obtained directly from the ratio of the band areas. The standard free energy change is then given by

$$\Delta G^0 = -RT \ln K \quad [4]$$

In some cases the equilibrium position has been estimated simply from the ratio of the extinction coefficients of the band maxima (195). It is usually assumed, however, that $\alpha_1 \neq \alpha_2$. In this case the equilibrium constant cannot be determined unless an α_1/α_2 ratio is assigned. However, if one assumes that α_1/α_2 (also ΔS^0 and ΔH^0) remains constant over a given temperature range (196), then, by substituting for K (eq. [3]) into the van't Hoff equation

$$RT \ln K = -\Delta H^0 + T\Delta S^0 \quad [5]$$

the standard enthalpy (ΔH^0) may be obtained as the slope ($-\Delta H^0/R$) of the plot of $\ln A_2/A_1$ vs. $1/T$:

$$\ln \frac{A_2}{A_1} = \frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} + \ln \frac{\alpha_2}{\alpha_1} \quad [6]$$

Recently, Hartman et al. (194) have shown that the assumption of the temperature independence of α_1/α_2 , if correct, may be verified in a simple way. Taking the total concentration $C_T = C_1 + C_2$ and substituting $A = \alpha C l$ for each conformer, one obtains

$$C_T = \frac{A_1}{\alpha_1 l} + \frac{A_2}{\alpha_2 l} \quad [7]$$

or

$$A_1 = \frac{-\alpha_1}{\alpha_2} A_2 + \alpha_1 l C_T \quad [8]$$

If α_1/α_2 is indeed temperature independent, then a plot of A_1 vs. A_2 for a series of temperatures will generate a straight line with slope $-\alpha_1/\alpha_2$. The free energy and entropy change can then be calculated from eqs. [3], [4], and [6].

An alternative method of determining ΔS^0 (hence, ΔH^0 and ΔG^0) has been suggested by Mizushima and co-workers (197), based on the assignment of a third spectral band that is common to both conformers, and measurement of its intensity over the temperature range studied relative to that of each conformer band. It is assumed that the absorption coefficients of the common band and the specific conformer bands all change with temperature in the same way (198).

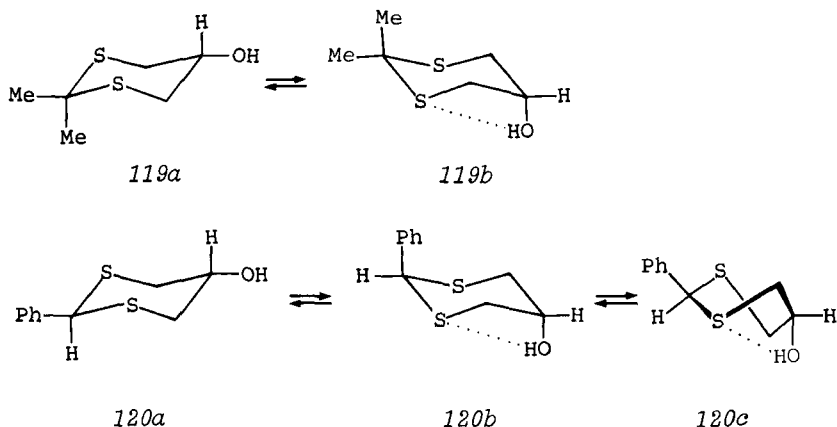
Some free OH-bonded OH...N equilibria have been studied (153) by the method of Hartman and, surprisingly, the α_1/α_2 ratio was found to be constant between 30 and 80°, even though the absorbance of each band maximum was used instead of the area in eq. [8]. The results thus obtained differed, generally markedly, from those determined for the same systems when α_1 was taken equal to α_2 , or when the extinction coefficient of the free OH band was compared to that of a model compound containing only free OH.

For the simplest application of the dilute-solution method, however, the position of the free OH-bonded OH equilibrium is probably best assigned from the integrated intensity (area) of the free OH band, in comparison to that of a 100% free OH reference model (9,126), or, alternatively, from that of the bonded OH band, in comparison to a fixed or conformationally biased [ananchomeric (51)] bonded reference model (134,152). Thus, although there is generally a large variation in the molar band areas of bonded OH species, a bonded OH reference model appears applicable to compounds having closely related structures. Except for qualitative purposes, the equilibrium position may not be reliable assigned from the ratio of free to bonded OH band areas, as has been done (76), because the area of the bonded OH is invariably larger than that of an equal percentage of free OH species. The equilibrium position also should not be assigned from the ratio of the bonded to free OH extinction coefficients, or from the an extinction coefficient in comparison to that of a reference OH model, because, as previously noted, extinction coefficients may vary considerably, even for axial and equatorial epimers, due to the difference in the position of band maxima of the various free OH rotamer forms that may be present (9). In contrast, free OH band areas are essentially equal for aliphatic secondary alcohols of similar structure, whether axial or equatorial, hence are apparently independent of the OH rotamer composition. Primary and tertiary alcohols, however, tend to have larger and smaller molar band areas, respectively, hence require their own appropriate reference models, if similarly studied.

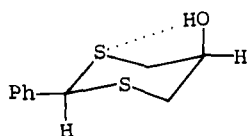
To assess other conformational factors in a hydrogen-bonded system, or to calculate the equilibrium position for the corresponding compound without its OH substituent (hence, without a hydrogen bond), the effect of the hydrogen bond on the position of the equilibrium must be taken into account. For example, one estimate of the effect of the hydrogen bond on the rotamer composition of unsaturated alcohols (e.g., benzyl and allyl alcohol) was given as about 0.5 kcal/mol (ΔH), based on a comparison to the equilibrium position in the corresponding saturated alcohols (56).

For more rigorous application to conformational analysis, however, the effect of the intramolecular hydrogen bond can perhaps best be taken into account by making a comparative conformational analysis of two similar systems (epimers, if possible), in order to cancel the free energy contribution of the intramolecular hydrogen bond, which is common to both. Alternatively, a value for the intramolecular hydrogen bond may be assigned from an analysis of the same or a closely related system, if all other conformational interactions may also be assigned or canceled.

These methods were used to assign the conformational equilibria of the 1,3-dithianes 119 and 120 as ca. 17 and 80% free OH species, respectively, based on the integrated inten-



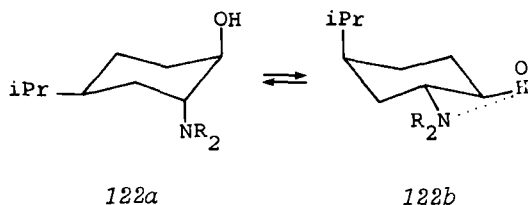
sity of the bonded OH in **121** as a 100% bonded OH reference (167). Taking the conformational free energy of the $\text{OH}\cdots\text{S}$ hydrogen



121

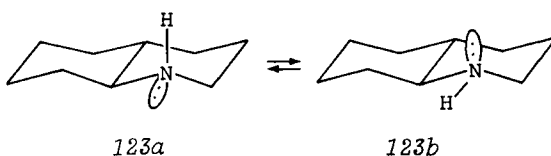
bond in **120b** from the **119** equilibrium, a $-\Delta G^\circ$ value of only 1.65 kcal/mol was obtained for the 2-phenyl group in **120**. In the same way, but on a less rigorous basis, the 2-phenyl group on a 1,3-dioxane ring was assigned a value of 1.7 kcal/mol. However, this result is in conflict with the more recent value (3.1 kcal/mol) determined by NMR (113). The reason for this discrepancy is uncertain, but may be caused in part, by the presence of a nonchair species, for example, **120c**, which is not present in the model OH systems. The presence of a twist-boat species in the 2-phenyl-1,3-dithiane systems has been suggested by NMR studies (199).

By the dilute-solution spectral method the conformational equilibria of some *trans*-2-aminocyclohexanols (**122**) were assigned (200). From the equilibrium position thus observed and the



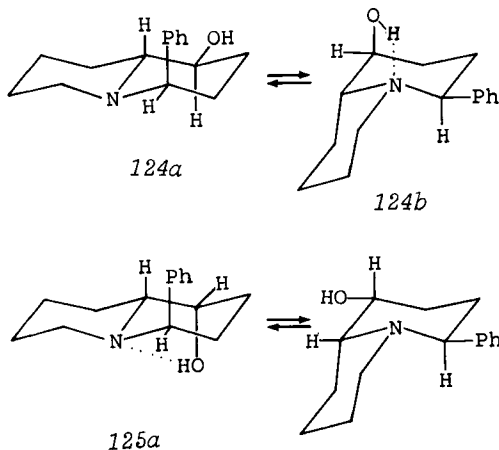
literature values of the conformational free energies of the individual substituents, the interaction of the vicinal equatorial R_2N/OH groups (in **122b**) was found to be attractive, equal to ca. 0.9 kcal/mol for OH/NH_2 , and 0.6 kcal/mol for OH/NMe_2 . Thus in this system the conformational contribution of the hydrogen bond is greater than the vicinal OH/NR_2 steric repulsion, to give, on balance, a net attractive interaction. By comparison, the corresponding OH/CH_3 interaction has been found to be repulsive by 0.4 kcal/mol (201).

More recently, the conformational equilibrium of the *trans*-8 α - (**72**) and *trans*-8 β -decahydroquinolinols (**71**) have each been compared to that of the parent decahydroquinoline (**123**). In this way all the conformational interactions were canceled, and the **123** equilibrium was calculated to be simply the average of that of **71** and **72**, equal to 0.5 kcal/mol in favor of the NH equatorial form (**123b**, 70%) at 33°C (136). A similar result has been



obtained from several other IR studies (196,202-205) not involving dilute-solution methods, where the equilibrium has also been assigned from the ratios of integrated intensities of various spectral bands, each assigned to a specific NH or N-electron pair conformation.

In another example (120) a conformational analysis was carried out on the two predominantly *cis*-fused isomers of 4-phenylquinolizidin-1-ol (**124** and **125**). Here as in the preceding



example, the two equilibria were each defined on the basis of the syn-axial and peri interactions in the products (124b and 125b) and the educts (124a and 125a), to give an equation for each system. By adding and, respectively, subtracting the two equations to cancel common terms, two new equations were obtained from which the free energy difference between the *cis*- and *trans*-quinolizidine ring fusion (defined as ΔG°) and the conformational free energy of their intramolecular hydrogen bonds (defined as $\Delta G^\circ_{\text{OH}\cdots\text{N}}$) were independently derived.

Tichý and co-workers studied the 3-piperidinol system (65) and concluded (134) that the conformational stabilization arising from intramolecular hydrogen bonding is stronger in the *N*-methyl than in the NH compound, based on a comparison of total axial OH (bonded plus nonbonded) and equatorial OH species in the two systems. Aaron and Ferguson (135), however, considered the equilibrium between the four possible conformers in each case, and defined a conformational difference between the bonded and nonbonded axial hydroxyl species in terms of their syn-axial substituent relationships. On this basis the conformational analysis of the hydrogen-bonded system was treated in a manner similar to that used for substituted cyclohexane systems. When the equilibrium position between any two conformers in the NH system was then calculated, the results were consistent with the assumption that the conformational free energy of the intramolecular hydrogen bond is essentially equal in both compounds ($\text{R} = \text{H}$ or Me), where $\Delta G^\circ_{\text{OH}\cdots\text{N}} \approx 0.55$ kcal/mol. This result, defined as the conformational free energy of a syn-axial OH/*N*-electron pair interaction ($\text{OH}\cdots\text{N}$) relative to that of the syn-axial H/*N*-electron pair, was in agreement with that calculated from the 124 and 125 equilibria. It is presumed to be applicable to the conformational analysis of $\text{OH}\cdots\text{N}$ hydrogen-bonded systems with similar geometry, having Δu_{OH} values of 90 to 100 cm^{-1} . For a group of $\text{OH}\cdots\text{N}$ bonded compounds in which entropy factors were assumed to be small, a roughly linear correlation of the conformational free energy of the hydrogen bond with Δu_{OH} has been reported as $\Delta G^\circ_{\text{OH}\cdots\text{N}} \approx 0.5$ kcal/mol per 100 cm^{-1} of Δu_{OH} (126). This correlation was based on the study of a limited number of compounds, however, and there is a large probable error in some of the results. Nevertheless, it may be helpful for estimating equilibrium positions in other related $\text{OH}\cdots\text{N}$ bonded systems if the $\Delta G^\circ_{\text{OH}\cdots\text{N}}$ values cannot be more rigorously assigned.

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Reduction of Cyclic and Bicyclic Ketones by Complex Metal Hydrides

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I. INTRODUCTION

Complex metal hydrides, have gained widespread use as reducing agents for carbonyl compounds because of their availability and versatility. Studies of these reactions have generally centered in two areas: (1) functional group selectivity, that is, the selective reduction of one functional group in the presence of one or more other functional groups; and (2) stereoselective reduction of ketones, in particular, cyclic and bicyclic ketones, by complex metal hydrides. Most of the discussions concerning complex metal hydride reduction of organic substrates have centered on those factors that are thought to control the course of the stereochemistry. The one single case that best exemplifies the lack of understanding as to what factors control the stereochemistry of complex metal hydride reductions of ketones is that of 4-*t*-butylcyclohexanone. Several theories have been postulated to explain why most complex metal hydrides attack predominately the more hindered axial side of 4-*t*-butylcyclohexanone, but no one theory has been overwhelmingly satisfying.

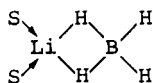
It is the intent of this chapter to briefly review the stereochemistry of complex metal hydride reduction of cyclic and bicyclic ketones, and to evaluate those theories that the authors believe are the most significant. First, the composition of several complex metal hydrides in solution and the mechanism of their reduction of ketones are discussed. It is quite clear that one must know something about the nature of the reagent in solution before using kinetic data and other information to construct a valid transition state. If it is not possible to construct a valid transition state, it is impossible to understand the reasons for the observed stereochemistry of the reactions in question. Second, some theories of stereochemical control involving these reactions are presented and discussed. Then the stereochemistry of reduction of several model ketones by different complex aluminohydrides is discussed in light of those theories of stereochemical control that are considered to be most significant.

II. COMPLEX METAL HYDRIDES: COMPOSITION IN SOLUTION AND MECHANISM OF KETONE REDUCTION

The composition of LiBH_4 , LiAlH_4 , and NaAlH_4 in diethyl

ether and tetrahydrofuran (THF) has been investigated (1,2) by means of conductance, molecular weight, IR, and NMR studies. Sodium borohydride presents a special problem in that it is often employed in alcoholic solvents when used as a reducing agent for ketones. The composition of NaBH_4 in these solvents is then complicated since the borohydride is not only strongly solvated by the alcohol but also reacts with the solvent to some extent to form alkoxy intermediates, $\text{NaB(OR)}_n\text{H}_{4-n}$.

Lithium borohydride appears to exist as contact ion pairs ($\text{Li}^+ \text{BH}_4^-$) or triple ions ($\text{Li}^+ \text{BH}_4^- \text{Li}^+$ and $\text{BH}_4^- \text{Li}^+ \text{BH}_4^-$) in THF. In diethyl ether aggregates larger than triple ions appear to exist. The equivalent conductance of LiBH_4 is dependent on concentration in THF, but independent of concentration in diethyl ether. These observations indicate that LiBH_4 association may be more covalent in nature in diethyl ether than in THF. These studies (1, 2) also indicate that the LiBH_4 contact ion pair (1) contains a disolvated lithium ion.



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On the other hand, lithium aluminum hydride in THF consists mainly of solvent-separated ion pairs. The solvated lithium ion appears to be four-coordinate, as determined by NMR, IR, and conductance studies. The fact that LiBH_4 is a contact ion pair in THF may be explained on the basis that the Li^+ and BH_4^- association is more covalent in character than that of Li^+ and AlH_4^- , thus compensating for any loss of solvation energy involving the lithium ion. In diethyl ether LiAlH_4 consists mainly of contact ion pairs in equilibrium with smaller amounts of higher aggregates. The addition of stoichiometric amounts of THF to a diethyl ether solution of LiAlH_4 results in an increase in the conductivity, indicating that solvation of Li^+ by THF is specific (1-3) in the mixed solvent at a molar ratio of THF to LiAlH_4 of 4:1.

Solutions of NaAlH_4 in THF consist of an equilibrium mixture of contact ion pairs and solvent-separated ion pairs. This conclusion is based on thermodynamic data obtained through conductance measurements as well as on a calculation of the center-to-center distance of the ion pair. The calculated distance is about midway between that found from crystallographic data for the solid and that obtained from a Dreiding model of the solvated ion pair. The indication is that there are about equal amounts of each type of ion pair.

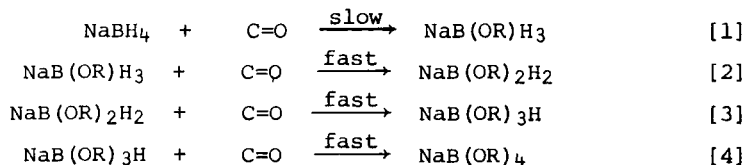
Tetrahydrofuran solutions of LiAlH_4 and NaAlH_4 in the concentration range of 10^{-5} to $10^{-1}M$ consist of more than 80% ion pairs. Below $10^{-5}M$ the fraction of free ion is 20% or more. Above $10^{-1}M$ the fraction of triple ions is 20% or more.

Studies (4-6) indicate that $\text{LiAl(OR)}_n\text{H}_{4-n}$ ($n = 1$ to 3) compounds are more stable to disproportionation in solution when the OR group is not a secondary alkoxy group. Ebullioscopic molecular weight studies (1, 2) of $\text{LiAlH}_n(\text{OCH}_3)_{4-n}$ show that the degree of association increases as the number of methoxy groups increases. This association occurs because of the ability of the methoxy group to form bridge bonds between the lithium and aluminum atoms. Association increases with increasing concentration of these compounds. When the methoxy group is replaced by the *t*-butoxy group, association is much less, presumably because of the increase in steric hindrance caused by the larger size of the *t*-butoxy group.

The association of alkoxy derivatives of LiBH_4 in THF (1, 2) is similar to that of the alkoxy derivatives of LiAlH_4 already mentioned. The secondary and tertiary alkoxy derivatives of NaBH_4 , $\text{NaB(OR)}_n\text{H}_{4-n}$ ($n = 1$ to 3), are more stable to disproportionation than primary ones in THF (7) and isopropyl alcohol (8-10). This may be explained on the basis that NaB(OR)_4 is not easily formed because of steric crowding about the boron atom when OR is secondary or tertiary. Steric hindrance of the secondary and tertiary OR groups about boron also reduces the possibility of an associated mixed-bridge intermediate necessary for disproportionation to take place. In the reduction of ketones by LiBH_4 and NaBH_4 , the presence of alkoxy intermediates is seemingly more significant than the presence of $\text{LiAl(OR)}_n\text{H}_{4-n}$ in LiAlH_4 reductions. The reason for this is that the alkoxy derivatives of the borohydrides are more reactive (7, 11) than the parent hydrides, LiBH_4 or NaBH_4 , while LiAlH_4 is more reactive (12, 13) than its alkoxy intermediates. Since most borohydride reductions of ketones are carried out in alcoholic solvents, the possibility arises of exchange of the alkoxy groups of $\text{NaB(OR)}_n\text{H}_{4-n}$ with the solvent. However, recent studies (14) show that no significant exchange occurs between NaB(OR)_4 and R'OH when R and R' are secondary, though it does occur when R and R' are primary. The significance of this discovery is discussed later.

Until recently little more than the reaction order for the mechanism of reduction of ketones by NaBH_4 was known, and not even that for LiAlH_4 reductions. A thorough knowledge of the mechanisms of these reactions should provide a better understanding of what factors may or may not influence stereochemical control in these reactions. Perhaps the single most intriguing question is what role, if any, the cation plays in these mechanisms.

Several kinetics studies have been conducted on the reduction of ketones by NaBH_4 in isopropyl alcohol (8, 10, 11, 14-26). These show the reaction to be second order: first order in ketone and first order in NaBH_4 . The transfer of the first hydrogen is the rate-controlling step, and the transfers of the other three hydrogens from the alkoxy intermediates are faster steps (7, 11):



Several Hammett studies have shown that reaction of NaBH_4 with substituted fluorenones (18, 19) and acetophenones (20) gives large positive ρ values: 2.65 and 3.06, respectively. This supports the concept of nucleophilic attack by BH_4^- at the carbonyl carbon. Correlation of the rates of reaction of several aliphatic ketones by Taft's equation shows that steric effects exhibit a significant role in the reaction (20). The kinetics of the reaction of the ketone and NaBH_4 does not distinguish among the following possibilities: (1) direct bimolecular reaction involving the ketone and borohydride ion, (2) complex formation followed by internal hydride transfer, (3) synchronous complex formation and hydride transfer.

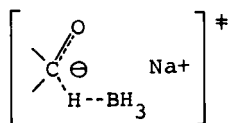
The rates of reduction of ketones by NaBH_4 show a small inverse isotope effect ($k_{\text{H}}/k_{\text{D}} = 0.7$) (21, 24, 27). This result may be interpreted to support either an early or a late transition state. The position of the transition state along the reaction coordinate and its effect on stereochemistry are discussed later.

The nature of the solvent and the cation have been shown to affect the rate of ketone reduction by borohydride ion. The reduction of ketones by borohydride ion has been reported by Brown to require the presence of an electrophilic agent, such as a protic solvent, or lithium or magnesium ion (17, 28-33). It has been reported that sodium borohydride does not reduce acetone in aprotic solvents such as acetonitrile, pyridine, dimethylformamide, and diglyme. Brown suggested that reported ketone reductions by NaBH_4 in these solvents actually occurred during the workup of the reaction mixture using aqueous hydrolysis. However, there still appears to be some confusion on this point. Although Brown published (17) in 1961 that NaBH_4 does not reduce acetone in aprotic solvents, there continue to be occasional reports (31, 32, 34-36) of reactions under such conditions. Presumably these reactions are a result of trace amounts of water or alcohols present in the solvent, or water introduced during workup of the reaction mixture.

Disappearance of the carbonyl group before quenching of the reaction mixture has been observed spectrophotometrically for the reduction of ketones by NaBH_4 (31, 32) and LiBH_4 (31, 32) in aprotic solvents. The inactivity of NaBH_4 in aprotic solvents observed by these workers may be a matter of degree, and with the proper temperature (36), solvent (36), and ketone (31, 32) the reaction may occur more easily. The reducing strength of NaBH_4 in refluxing toluene reportedly has been enhanced by the addition of crown ethers to complex the sodium ion (36).

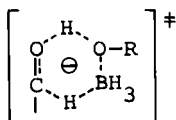
Three types of mechanisms or transition states have been proposed by workers in this area (14). All the transition states lead to an alkoxyborohydride product, but not the same alkoxyborohydride. The insight of Wigfield led to experiments that recently eliminated two of the three mechanisms.

The acyclic transition state 2 was originally suggested by Brown (11, 20, 30). The product $B(OR)H_3$ has been presented as having the OR group derived from either the alcoholic solvent (30) or the ketone (11, 20).



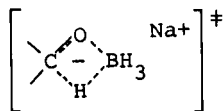
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Similar to 2 in some respects is the cyclic transition state 3 proposed by House (33). The role of the solvent is more explicitly shown. From 3, if correct, one might easily expect the reaction to be first order in ketone, BH_4 , and solvent. The product $B(OR)H_3$, however, would derive its OR groups solely from the alcoholic solvent, and a free alcohol would be produced as a result of reduction of the ketone.



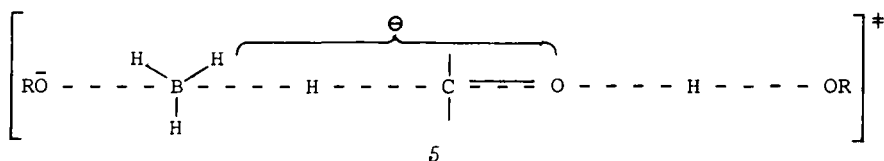
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The third suggested (20, 21, 34) transition state is represented by the four-centered transition state 4. The product $B(OR)H_3$ would derive the OR group only from the ketone.



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Recent studies (14, 26) by Wigfield show that $NaBH_4$ reduction of ketones is 1.5 order (26) in alcohol solvent and that the products of reduction are the free alcohol derived from the ketone and $B(OR)H_3$, in which the OR group is derived from the alcohol solvent (14). This, of course, eliminates the four-centered transition state 4, in which the OR group is derived from the ketone. Additionally, the cyclic transition state 3 as drawn would only be first order in solvent. Wigfield suggests the linear transition state 5 (26). The transition state 5 shows no participation by the Na^+ ion, since previously it had been shown



(17, 30) that Li^+ and Mg^{2+} , but not Na^+ , participate in the reduction. More recent evidence concerning the role of Na^+ in NaBH_4 reductions shows that removal of the Na^+ ion by the use of cryptates does not prevent reduction of ketones by NaBH_4 in methanol (28). Wigfield has used the linear acyclic transition state 5 to suggest a new concept in stereoselective reductions of cyclohexanones.

Equations [5] through [8] show how a 1.5-order reaction in alcohol solvent may be explained by assuming that RO^- arises from ionization of the solvent:

$$\text{rate} = k[\text{ketone}][\text{BH}_4^-][\text{ROH}][\text{RO}^-] \quad [5]$$



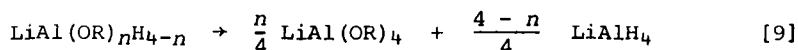
$$\text{RO}^- = K^{1/2} [\text{ROH}]^{1/2} \quad [7]$$

$$\text{rate} = kK^{1/2} [\text{ketone}][\text{BH}_4^-][\text{ROH}]^{3/2} \quad [8]$$

Although the cation in the NaBH_4 reduction of ketones in isopropyl alcohol does not participate in the reaction, interest in this point remains high because the cation may participate in other systems such as LiBH_4 in THF and LiAlH_4 in THF.

Kinetic studies of the reduction of a ketone by lithium aluminum hydride (37) or lithium tri-*t*-butoxyaluminumhydride [$\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$] (15, 23) in THF show the reaction to be first order in ketone and first order in hydride. The reaction of LiAlH_4 with ketones in diethyl ether has been reported (38) to be more complex, and it does not exhibit simple first-order kinetics in each reactant. Indications are that both monomeric and dimeric LiAlH_4 participate in the reaction. The degree to which the mechanistic information known about the metal borohydride (MBH_4) reduction of ketones can be applied to the metal aluminohydride (MALH_4) reduction is clearly uncertain.

The transfer of the second, third, and fourth hydrogens from aluminohydride ion to the ketone is slower (4, 12, 38) than the first step, although the opposite is true in the case of borohydride reduction. Additionally, it is known that many secondary alkoxyaluminumhydrides (products from ketone reduction) disproportionate rapidly to regenerate AlH_4^- (4, 5, 12):

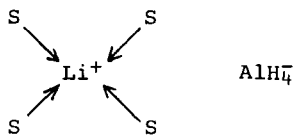


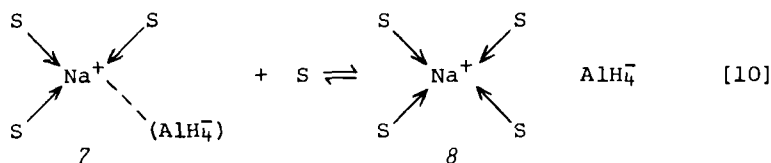
The stereochemical results of ketone reduction by NaBH_4 and LiBH_4 are affected by reactant ratio, and thus it has been concluded (10) that the stereoselectivity varies with reactant ratio. Such a conclusion seems reasonable, since under certain conditions a significant amount of reaction is occurring by the faster reacting alkoxyborohydride intermediates. On the other hand, because the stereochemical results of ketone reductions by LiAlH_4 are not significantly affected by reactant ratio, it has been suggested (4) that LiAlH_4 is the only significant reducing agent. However, to conclude, on the basis of stereochemical results alone, that no significant reaction of LiAlH_4 with ketones proceeds through alkoxyaluminumhydride intermediates may be a gross presumption. The major problem is that the stereoselectivity of the alkoxyaluminumhydride intermediates is no better understood than that of LiAlH_4 . For reasons that become apparent later in this discussion, it seems that significant reaction can occur by alkoxyaluminumhydride intermediates during the reduction of ketones by LiAlH_4 , and that it is simply not observable in the stereochemistry of the products.

It should also be pointed out that $\text{LiAl}(\text{OCH}_3)_3\text{H}$ and $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$, where the OR groups are primary and tertiary, respectively, are stable to disproportionation (4-6, 12). The percentage of the reduction occurring through $\text{LiAl}(\text{OR})_n\text{H}_{4-n}$ species may be significant, especially when the ketone/ LiAlH_4 ratio exceeds 1. In recent studies (38), in which a reagent was prepared from 1.5 to 1.7 mole *t*-butyl alcohol per mol LiAlH_4 , it was found that approximately 50% of the reduction of certain aromatic ketones occurs by reaction of $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$.

Mesityl phenyl ketone is reduced about 10 times faster by LiAlH_4 in THF than by NaAlH_4 in the same solvent (37). All indications are that reaction of MAlH_4 with ketones is not independent of the cation; if it were, equal rates of reaction of LiAlH_4 and NaAlH_4 would be expected. However, it is not entirely clear how the cation participates. The cation could possibly affect the reactivity of the ketone or the aluminumhydride ion, or both.

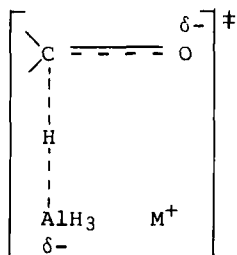
Under the conditions of these kinetic studies LiAlH_4 in THF (1×10^{-3} to $4 \times 10^{-2}M$, 25°) exists predominantly as solvent-separated ion pairs (1, 2) (6), whereas NaAlH_4 appears to be an approximately equal mixture of solvent-separated (8) and contact ion pairs (7) (eg. [10]). Under the reaction conditions a small fraction of each hydride is present as free ions and triple ions.





Because the reaction rate of the ketone with MAlH_4 depends on the nature of the cation M^+ , it is reasonable to assume that the transition state involves the presence of the cation and not just the free aluminohydride ion (33, 37, 40). The fact that the stereoselectivity of MAlH_4 reductions is also dependent (37, 40) on cation is further support for the presence of the cation in the transition state. Two possible mechanistic pathways for the reduction of mesityl phenyl ketone by MAlH_4 should be considered (37): (1) the cation does not complex the carbonyl oxygen; (2) the cation does complex the carbonyl oxygen. Since NaAlH_4 consists of both contact and solvent-separated ion pairs in THF to about the same degree, reaction through both types of ion pairs is possible. LiAlH_4 may be assumed to react through the solvent-separated ion pair, since this is by far the most abundant species present in THF solution at ambient temperature.

The first mechanism suggests a transition state *9* which involves nucleophilic attack by the M^+AlH_4^- ion pair on the carbonyl carbon without the cation complexing the carbonyl oxygen. If one compares the solvent-separated ion pair of NaAlH_4 (*8*) to the contact ion pair (*7*), it might be expected that *8* is the



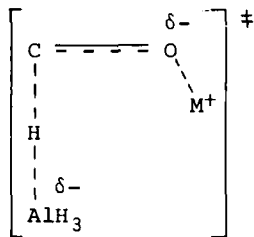
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better nucleophile, because the AlH_4^- is more insulated by intervening solvent molecules and further from the cation, hence it should be easier for AlH_4^- to release the negative hydride ion (H^-) to the carbonyl carbon atom. On the bases that *8* should react faster than *7*, and that *8* and *7* are present in about equal amount, it appears likely that *8* is the major reactive species. If the reactive species are the solvent-separated ion pairs of LiAlH_4 (*6*) and NaAlH_4 (*8*), then NaAlH_4 and LiAlH_4 would be expected to have similar reaction rates according to transition state *9*, since the expected difference between completely sol-

vated lithium and sodium ions should be small. However, LiAlH_4 (nearly all solvent-separated ion pairs) is ca. 11 times more reactive toward mesityl phenyl ketone than NaAlH_4 (about half solvent-separated ion pairs). It is also interesting to note that NR_4AlH_4 [NR_4^+ is tri(*n*-octyl)-*n*-propylammonium ion] reacts more slowly (39) with camphor than LiAlH_4 or NaAlH_4 . Although NR_4AlH_4 [when NR_4^+ is tetra (*n*-butyl) ammonium ion] is a contact ion pair (1,2) in solution, its experimentally observed center-to-center distance is greater than that of LiAlH_4 or NaAlH_4 . Therefore reaction rates ($\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$) cannot be correlated with the observed center-to-center distances of ion pairs ($\text{NR}_4\text{AlH}_4 > \text{LiAlH}_4 > \text{NaAlH}_4$).

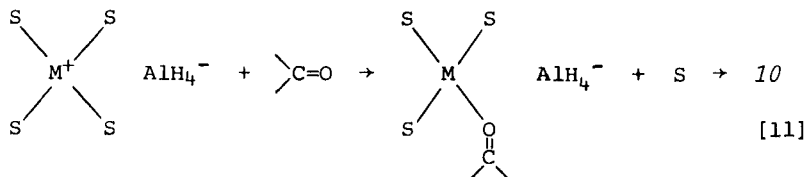
Reaction rates in THF ($\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$) may be correlated with the concentration of solvent-separated ion pairs (or free ions) in solution ($\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$), assuming that solvent-separated ion pairs or free ions are more reactive than contact ion pairs. However, this explanation of the rate differences based on transition state 9 meets with difficulty when the rates in THF are compared to those in diethyl ether. Lithium aluminum hydride in diethyl ether exists predominately as contact ion pairs, but it reacts ca. 30 times faster (38) with mesityl phenyl ketone than LiAlH_4 in THF (predominately solvent-separated ion pairs). This rate difference with solvent change is discussed below.

A second possible mechanism (10) involves attack by the M^+AlH_4^- ion pair on the carbonyl group, where the cation is bound to the carbonyl oxygen during reduction. This process may simply involve the displacement of one molecule of THF solvent attached



10

to M^+ by one molecule of ketone (eq. [11]).



In this case LiAlH_4 would be expected to react faster than NaAlH_4 , since Li^+ would associate more strongly than Na^+ with the carbonyl oxygen, hence would more strongly polarize and activate the C=O bond.

It has been shown (1,2) that ketones associate with lithium ions in THF solutions of lithium salts. It is further known (17,30) that LiBH_4 is more reactive than NaBH_4 toward ketones in aprotic solvents, and this difference in reactivity has been explained on the basis of the difference in the electrophilic nature of the lithium and sodium ions (17,31,32). Further evidence for complex formation between lithium ions and ketones is demonstrated by the substantial equilibrium constant (1.3 liters/mol) for complex formation between LiClO_4 and benzophenone in diethyl ether, as determined by UV studies (37). IR studies on acetone in THF and in diethyl ether show that increasing the LiClO_4 concentration broadens and shifts (1) the carbonyl absorption from 1725 to 1720 cm^{-1} . NMR studies of cyclohexanone (1.0M) in diethyl ether show that addition of LiClO_4 shifts the protons of cyclohexanone downfield from the ether triplet, by 8 Hz for the α protons, and 2Hz for the β and γ (37). Participation by the cation in the transition state is also indicated, not only by the difference in the reaction rates of MALH_4 with ketones ($\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$), but also by the dependence of the stereoselectivity of reduction of alicyclic ketones by MALH_4 compounds (39,40).

All these studies provide evidence of association of ketones with lithium salts in ethereal solvents, supporting transition state 10 which represents the reduction of ketone by LiAlH_4 as proceeding via a prior or synchronous association of the ketone with Li^+ with respect to transfer of the hydride ion.

If the ketone is associated with the lithium cation during reduction by LiAlH_4 in THF, then causing the ketone to compete against a solvating agent stronger than THF should reduce the rate of reaction. This is found to be the case (37). The rate of reduction of mesityl phenyl ketone by excess LiAlH_4 in the presence of *N,N,N',N'',N''',N'''*-hexamethyltriethylenetetraamine (complexes lithium cation) (41) is reduced by ca. one-half when the ratio of amine to lithium is 2:1. Similarly, if the ketone has to compete with a weaker solvating agent than THF, such as diethyl ether, the rate of reaction is expected to increase. Comparing the observed rate constants at 25°, it is seen that the reduction of mesityl phenyl ketone by LiAlH_4 ($k_{\text{THF}} = 4.8 \times 10^{-3}$, $k_{\text{ether}} = 0.26$ at $8.2 \times 10^{-3}M$; $k_{\text{THF}} = 11.7 \times 10^{-3}$, $k_{\text{ether}} = 0.40$ at $2.0 \times 10^{-2}M$) is ca. 30 to 50 times faster in diethyl ether than in THF. The reaction of LiAlH_4 with mesityl phenyl ketone appears to be more complex in diethyl ether (38) than in THF (37). In ether the LiAlH_4 monomer in equilibrium with LiAlH_4 dimer is the reactive species (eq. [12]). No such equilibrium was observed in THF (eq. [13]). For ketones other than

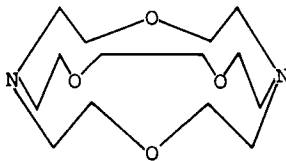
mesityl phenyl ketone the LiAlH_4 dimer in diethyl ether is also a reactive species (eq. [14]).

$$\text{rate in diethyl ether} = k[\text{LiAlH}_4]_2^{1/2}[\text{ketone}] \quad [12]$$

$$\text{rate in THF} = k[\text{LiAlH}_4] [\text{ketone}] \quad [13]$$

$$\begin{aligned} \text{rate in diethyl ether} = & (k_1[\text{LiAlH}_4]_2^{1/2} + \\ & k_2[\text{LiAlH}_4]_2) [\text{ketone}] \end{aligned} \quad [14]$$

It has been reported that the cation is indispensable (28,29) in the reaction of lithium aluminum hydride with cyclohexanones. No reaction was reported to occur when a cryptate such as 11 was used to complex the lithium ion. In the presence of a cryptate the Li^+ ion is supposedly no longer available to



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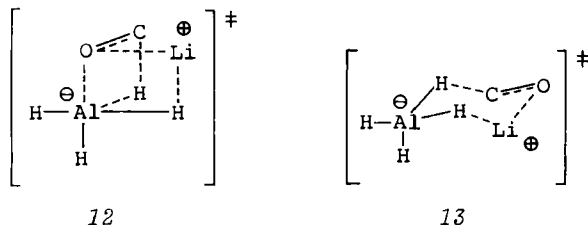
associate with the carbonyl oxygen atom, hence no reaction is observed. On the other hand another study (42) showed that aromatic ketones did react with LiAlH_4 in the presence of a cryptate, although isobutyraldehyde did not. However, LiAlH_4 alone gave only a 50% yield of isobutyl alcohol on reaction with isobutyraldehyde; perhaps enolization is a competing reaction. If the rate of reduction is slowed down by addition of the cryptate, it is easy to see how enolization could become the almost exclusive reaction. It is also important to consider that tetraalkylammonium aluminohydrides have been used successfully to reduce aliphatic ketones (39). It would appear that the tetraalkylammonium ion and a Li^+ ion complexed with a cryptate would behave similarly, that is, as a positive ion buried in the center of a cushion of organic substrate. The reactivity of NR_4AlH_4 cannot be attributed to any Na^+ ions remaining from its preparation from NaAlH_4 because NaAlH_4 and NR_4AlH_4 exhibit different stereoselectivities in their reactions with ketones. It is also known that crown ethers do not inhibit the reduction of ketones by aluminohydrides (39). In this connection it has also been reported (36) that crown ethers enhance the activity of NaBH_4 in the reduction of ketones in refluxing toluene. It would not be surprising if cryptates slowed the reaction, but inhibition of reduction by AlH_4^- would indeed be very surprising. These matters must be reexamined very carefully.

While polarization of the $\text{C}=\text{O}$ bond by M^+ gives an understandable explanation of rate differences between LiAlH_4 and NaAlH_4 , the effect on the reaction rate is more speculative in

the case of polarization of the aluminohydride ion by M^+ or charge separation in the $M^+AlH_4^-$ ion pair. It appears reasonable that the further away the cation is from the anion, the easier it will be for AlH_4^- to release H^- to the carbonyl carbon atom in the rate determining step. However, a rate enhancement caused by the polarization of AlH_4^- by the cation cannot be ruled out, based on present evidence. If the carbonyl oxygen atom is associated with the aluminum atom in the transition state, the polarization of AlH_4^- by the cation could be of major significance. Based on the evidence available to date, probably the most acceptable explanation of the cation effect on rate and stereoselectivity of AlH_4^- is polarization of the carbonyl group by specific complexation of the carbonyl oxygen atom, or simple electrostatic interactions between M^+ and $C=O$. If the mechanism of reduction involved only a nucleophilic attack by AlH_4^- or $M^+AlH_4^-$ at the carbonyl carbon, the rate and stereochemistry of the reduction would likely show little, if any, dependence on the cation, because it could be oriented away from the reaction center. However, reductions of several ketones by $MAlH_4$ show marked changes in rate and stereochemistry with changes in the cation (37,39).

It is assumed that the reactive species is the ion pair $M^+AlH_4^-$, because both M^+ and $MAlH_4^-$ are present in the transition state (37). If the ion pair is the attacking species, the attack by M^+ of the ion pair on the carbonyl oxygen may be prior to or synchronous with a rate-determining hydride transfer step. Since complexation of metal ions such as Li^+ with ketones is probably extremely rapid, it is reasonable that complex formation takes place prior to the rate-determining hydride transfer step. However, it is also possible that the attacking species is not the ion pair $M^+AlH_4^-$ but rather the free ions (37). In this case the carbonyl group associates with a free M^+ and is then attacked by a free AlH_4^- .

Structures 9 and 10 are not drawn as detailed transition states, but are intended only to reflect possible participation of the cation in the transition state. Transition state 10 can be represented in more detail by structures 12 and 13, which represent boat and chair conformations, respectively (37). Al-



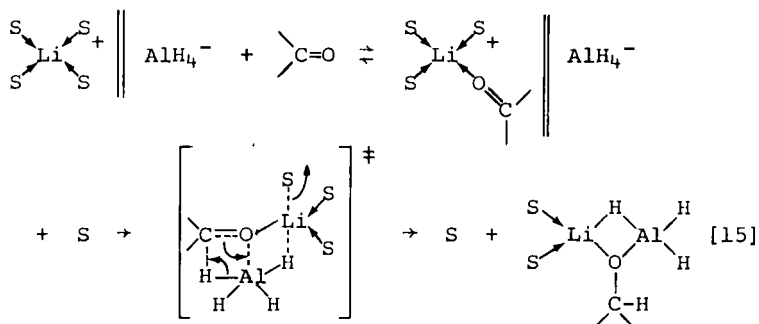
though the boat transition state 12 might seem less probable because the orbital on oxygen is not correctly oriented to overlap the back lobe of Al-H orbital involved in bond breaking,

at least two factors favor this transition state. First, interaction between aluminum and oxygen lowers the activation energy of the reaction and provides a pathway in which collapse of the transition state results directly in formation of the product $[\text{LiAl}(\text{OR})\text{H}_3]$ without the need of an intermediate step. The second point is that such a boat transition state can be validly suggested if one assumes pentavalent aluminum involving pseudorotation about the aluminum axis. The Li-H-Al interaction shown in 12 and 13 is reasonable also, on the basis that M-H-M bridge bond systems are well known and in addition would add stability to the transition state. Such an interaction should lower E_a and result in a more negative $\Delta S^\ddagger$, which is the case, as we see later. Although kinetic data do not allow for the drawing of such detailed transition states, these suggestions appear reasonable.

The enthalpy of activation for the reaction of LiAlH_4 with mesityl phenyl ketone (10.5 kcal) is considerably lower than that for the reaction of NaAlH_4 with mesityl phenyl ketone (18.1 kcal) (37). This may be explained by the difference in polarization of the carbonyl group due to complexation by the cation in the transition state. The lithium ion, because of its smaller size, should polarize the carbonyl group more than does sodium; thus the hydride ion is more easily transferred from the aluminum atom to the carbon atom in the case of lithium. The much more negative value for the entropy of activation for LiAlH_4 (-26.2 e.u.) than for NaAlH_4 (-5.4 e.u.) requires that the transition state for LiAlH_4 reduction be considerably more ordered than that for NaAlH_4 (37). Again, this observation is consistent with cation association with the oxygen of the carbonyl group in the transition state. The lithium cation would order to a much greater extent the ketone molecule as well as both primary and secondary solvent molecules than would the sodium cation. Such a large negative value is also consistent with a six-centered transition state such as those shown in structures 12 and 13. Since Li-H-Al bridge bonds should be considerably more stable than Na-H-Al bridge bonds, the large negative $\Delta S^\ddagger$ for the LiAlH_4 reaction compared with that for NaAlH_4 can also be attributed to some extent as to the restriction brought about in the transition state by this type of interaction.

Kinetic isotope studies for the reduction of mesityl phenyl ketone with LiAlH_4 in diethyl ether and in THF show a k_H/k_D value of about 1.3 (37,38). Interpretation of k_H/k_D is not straightforward because it represents both primary and secondary deuterium kinetic isotope effects (24,27,43,44). The small value of k_H/k_D may be explained by a small primary isotope effect which is not completely masked by inverse secondary effects. The small isotope effect would then be consistent with a rate-determining step involving transfer of the hydride from the aluminum to the carbonyl carbon. The small value of k_H/k_D , as well as other observations, is consistent with an early transition state.

Unfortunately, an exact interpretation of the magnitude of the kinetic isotope effect is not clear, not only because of the secondary isotope effect, but also because of the uncertainty of the Al-H-C angle in the transition state, and other factors. The following mechanism is consistent with known facts about the reduction of ketones by LiAlH_4 :



III. CONCEPTS OF STEREOCHEMICAL CONTROL OF KETONE REDUCTIONS BY COMPLEX METAL HYDRIDES

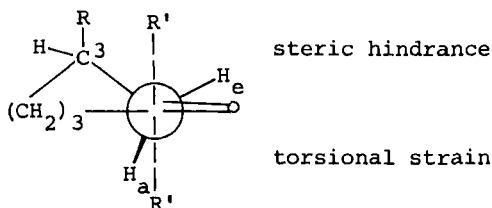
In recent years the area of stereoselective reduction of ketones by MBH_4 , MALH_4 , and their alkoxy derivatives has been investigated by several workers (33,45). Lithium aluminum hydride reduces 4-butylcyclohexanone predominantly by attacking (90%) the molecule from the more hindered axial side to give (46,47) the more stable equatorial alcohol. The more hindered ketone 3,3,5-trimethylcyclohexanone is attacked predominantly (55 to 75%) (4) from the less hindered equatorial side to give the less stable axial alcohol. These results were first explained by Dauben, who suggested the concept of "product development and steric approach control" (48). Dauben visualized the formation of an initial complex as the nucleophile approaches the π bond of the carbonyl group, followed by collapse of the complex to products. He further suggested that transfer of the hydride in the complex results in rehybridization of the carbonyl carbon atom from sp^2 to sp^3 . A late transition state in which hybridization is largely sp^3 allows the relative stabilities of the products to be reflected in the transition state. In the case of an unhindered ketone such as 4-butylcyclohexanone, Dauben suggests that the developing sp^3 hybridization is the controlling factor, hence that product development control is observed. On the other hand the C_3 axial methyl group of 3,3,5-trimethylcyclohexanone hinders the nucleophile in its axial approach, thus decreasing the ease of formation of this complex. This results in the favoring of equatorial attack, and steric approach control determines the stereochemistry of reduction. These and other results have been generalized (6,48), leading to the conclusion that reduction of unhindered ketones is governed by

product development control and that reduction of hindered ketones is governed by steric approach control. It is accepted that product development control would require a late transition state resembling the products, whereas steric approach control would require an early transition state resembling the reactants.

In 1968 Cherest and Felkin (49-52) suggested that there should be no fundamental difference between the mechanisms of hydride reduction of hindered and unhindered cyclohexanones and that the factors controlling the stereochemical results of these reductions should be the same in each case. They assumed the transition state to be reactantlike in all cases, and introduced the concept of torsional strain to explain the large degree of axial attack by hydrides on 4-*t*-butylcyclohexanone.

As shown by structure 14, equatorial attack on a cyclohexanone introduces torsional strain between the axial C-H bonds (H_a at C_2 and C_6 , and the forming C-R' bond at C_1 which partially eclipses them. Axial attack causes steric hindrance between the incoming hydride (R') and the axial substituents (R) at C_3 and C_5 . When R is hydrogen, as in 4-*t*-butylcyclohexanone, torsional strain is greater than steric hindrance, so the hydride

(axial attack)



(equatorial attack)

14

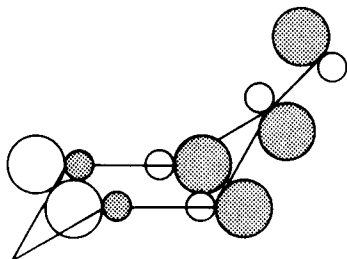
prefers to attack axially. When R is a methyl, as in 3,3,5-trimethylcyclohexanone, steric hindrance to axial attack is increased and equatorial attack is preferred.

Other theories of stereochemical control that have been proposed include: torsional strain between the C=O bond and the two equatorial C-H bonds (H_e in 14) (53) at C_2 and C_6 in 4-*t*-butylcyclohexanone, closeness of approach of the nucleophile to the carbonyl carbon in the transition state (54), and steric hindrance by the axial C_2 and C_6 hydrogens (55). Most of these theories have gained less acceptance than those of Dauben and Felkin. In light of the fact that $LiAl(O-t-Bu)_3H$ attacks the equatorial side of both 2,2-dimethyl-4-*t*-butylcyclohexanone and 4-*t*-butylcyclohexanone at the same rate, it may be concluded that steric hindrance to equatorial attack by the axial substituents at C_2 and C_6 is negligible (14,15).

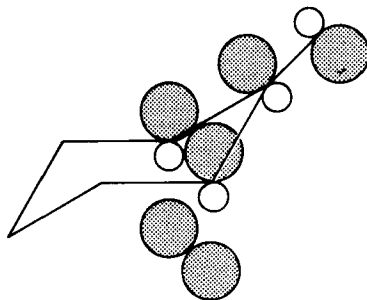
Recently Klein (56-58) Anh (59-61), Liotta (62), and ourselves (39) have presented new theories of stereochemical control for complex metal hydride reduction of ketones, based on orbital symmetry and unequal distortion of electron density about the carbonyl group. In these concepts of stereochemical

control the nucleophile's highest occupied molecular orbital (HOMO) is considered to interact with the ketone's lowest unoccupied molecular orbital (LUMO).

In orbital distortion theory there is an attempt to predict, at least qualitatively, the size and shape of the LUMO about the plane of the carbonyl group. The face of the carbonyl group at which the LUMO is most enlarged or distorted is regarded as the favored side of attack by a nucleophile. The LUMOs for a cyclohexanone arising from symmetrical β $\sigma^*-\pi^*$ interactions are represented (39) by 15 and 16. The LUMO of 15, resulting from β C-C $\sigma^*-\pi^*$ interactions, favors equatorial attack, whereas the LUMO of 16, resulting from β C-H $\sigma^*-\pi^*$ interaction, favors axial attack. The LUMO in 15 is distorted to the equatorial side because the π^* orbital overlaps with the large back lobes of the



15



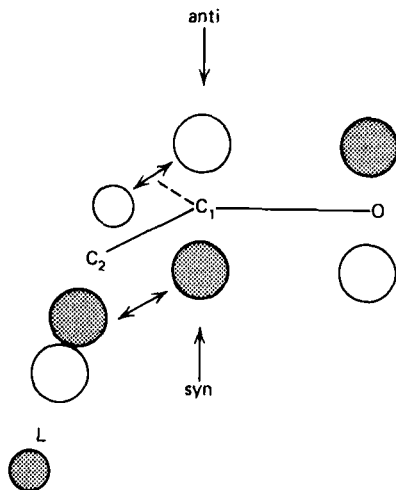
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σ^* orbitals of the β C₂-C₃ and C₅-C₆ bonds of the cyclohexanone ring. The distortion of the LUMO in 16 may be explained in a similar manner by using the σ^* orbitals of the axial C-H bonds at C₂ and C₆. If the σ orbitals of the β C-C bonds were used in 15, the LUMO would be distorted to the axial side because the β C-C σ orbitals would be larger between the carbon atoms (C₂-C₃ and C₅-C₆) and not larger outside them, as for the σ^* orbitals; thus π^* is distorted to the axial side and better overlaps the β C-C σ orbitals. The $\sigma^*-\pi^*$ interaction is considered more significant because σ^* is closer to π^* in energy than σ . The selection of which σ^* orbital is involved is another matter.

Axial attack by complex metal hydrides is usually observed for unhindered cyclohexanones, and the LUMO in 16 would explain the experimental results. However, the selection of the LUMO in 16 is really made after the experimental results are known. Although the β C-C orbitals are more polarizable (58), the axial C-H orbitals possess better geometry (39) for overlap with the C=O π^* orbitals. The C=O bond is a few degrees (3.3 to 12.7) (63,64) below the plane of the C-2 and C-6 equatorial C-H bonds, thus the axial C-H σ^* orbitals are more closely parallel

to the C-O π^* orbitals (i.e., more closely perpendicular to the plane of the carbonyl group) than to the β C-C orbitals. Using σ^* orbitals which more closely parallel the C-O π^* orbital has been more successful than any other method in predicting LUMO distortion in the direction of the experimentally observed direction of attack by complex metal hydrides with several model cyclohexanones, cyclopentanones, and bicyclic ketones (39). This is examined in more detail when each model is discussed.

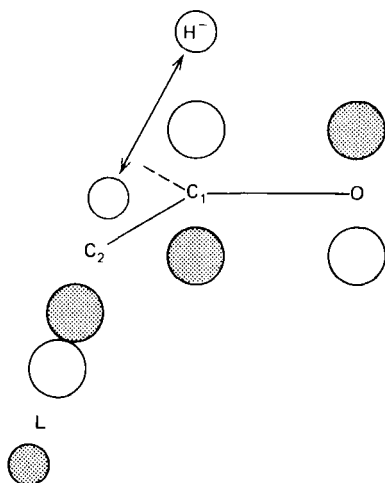
N. T. Anh has suggested (59) that orbital distortion causes the π -electron density to be greater on one face of the carbonyl group than on the other in ketones antisymmetric about the carbonyl group. Attack on the more positive face by a nucleophile is favored because of coulombic attraction. More recently Anh has pointed out (61) that this orbital distortion may be important only if the transition state is reached early. Even then the stabilization from orbital distortion does not exceed 2 kcal/mol, which is small compared with the 5 to 10 kcal/mol of extra stabilization produced by what Anh calls the "anti-periplanar effect" (61). The antiperiplanar effect arises when the forming C₁-H bond and the C₂-L (L is large substituent) bond are antiperiplanar (as in 17) because of good overlap between π^* and $\sigma^*_{C_2-L}$, leading to stabilization of π^* . Although the same favorable overlap between π^* and $\sigma^*_{C_2-L}$ occurs for synperiplanar attack, antiperiplanar attack is favored because: "(1) while anti attack with respect to L leads to an in-phase overlap between H⁻ and $\sigma^*_{C_2-L}$ (at C₂), syn attack leads to an out-of-phase overlap between H⁻ and $\sigma^*_{C_2-L}$ " (see 18 and 19), and



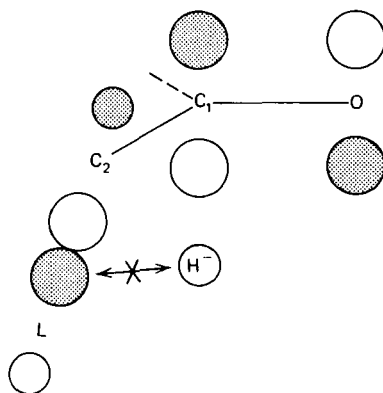
17

"(2) syn attack implies an eclipsing of C₁-H and C₂-L bonds" (61). For the three substituents at C₂-R₁, R₂, and R₃-the antiperiplanar effect would increase as the energy of the $\sigma^*_{C_R}$ de-

creases, thus the antiperiplanar effect follows the order $\text{Cl} > \text{CH}_3 > \text{H}$.

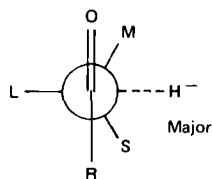


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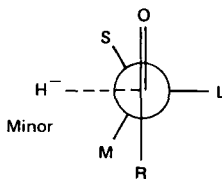


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Anh demonstrated the antiperiplanar effect by a detailed MO study of the transition state energies describing attack of H^- on the two faces of the carbonyl group, involving 12 conformations each for 2-chloropropanal and 2-methylbutanal. The most favorable transition state energies leading to the major and minor products were found to agree with the conformations predicted by Felkin (49), not with those suggested earlier by Cram (65), Cornforth (66), and Karabatsos (67). Of course, Felkin's models (20 and 21) are for asymmetric induction in nucleophilic additions to acyclic ketones, but they can be used to call attention to similar situations involving cyclic ketones (50).



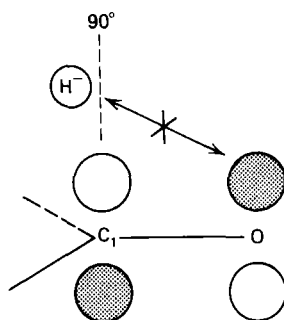
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21

Anh has quantitatively considered several very important points concerning complex metal hydride reduction of ketones, such as angle of attack and complexation of ketone by Li^+ , which prior to this time has only been a matter of speculation. Until recently it has always been assumed that the approach of the hydride to the carbonyl carbon occurs perpendicular to the plane of the carbonyl group. Recent MO calculations have shown (68) that the approach of H^- to formaldehyde takes place at an

angle of 126° with the $C=O$ bond at a distance of $2.5 \text{ \AA}$ (118° at $1.5 \text{ \AA}$). Anh likewise found approaches of H^- to $C=O$ to favor angles greater than 90° (99 to 103° being most favorable). An angle greater than 90° minimized the out-of phase overlap between the nucleophile and the oxygen atom (as in 22) because the nucleophile is further from the oxygen atom than it is at

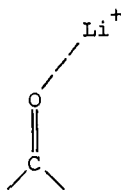


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90° . Anh's MO study favors a bond angle of 180° for $C=O \cdots Li^+$ (23), not 120° (24), as has been suggested (29,39) when a ketone is complexed by Li^+ . Additionally, the study suggests stronger interaction between the approaching H^- and Li^+ than



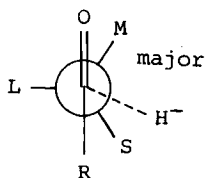
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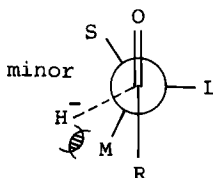
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the H^- and the carbonyl oxygen atom, even though Li^+ is further from H^- than the oxygen atom. This is because the atomic orbital of Li^+ is more diffuse. Thus complexation of the ketone by Li^+ favors nucleophilic attack more closely perpendicular to the carbonyl carbon.

Felkin's model of torsional strain for stereoselective reduction of acyclic ketones predicts that 20 is a more favorable transition state than 21. The suggested explanation is that R sterically interacts less with S (small) in 20 than with M (medium) in 21. However, an angle of attack of greater than 90° may allow a better explanation of why 20 is favored over 21. Steric hindrance involving S and the approaching nucleophile is smaller in 25 than the steric hindrance involving M and the approaching nucleophile in 26 (61).

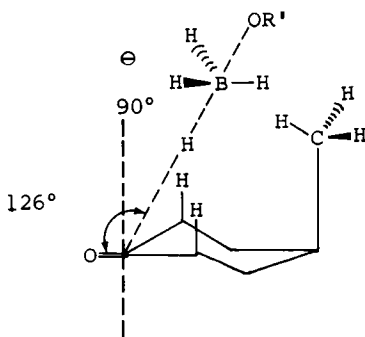


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If the angle of hydride approach to the carbonyl carbon is greater than 90° , then significant implications arise concerning present concepts of stereochemical control of complex metal hydride reduction of cyclohexanones. According to 14, when R' attacks axially it is pushed more strongly against R , and thus axial attack is more sterically hindered. Additionally, structure 14 shows that, as the angle of approach increases above 90° , R' attacking equatorially eclipses H_a even more, thus increasing torsional strain. Wigfield has suggested another possibility (26). Considering both the long transition state δ for $NaBH_4$ reductions and the larger angle of approach of the borohydride ion, he has suggested that the equatorial side of cyclohexanone may be sterically hindered by a C-4 axial substituent, as shown in 27.

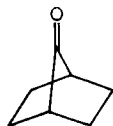


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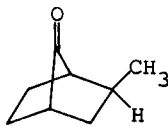
Two empirical procedures (69-71) have appeared for calculating the ratios of axial and equatorial attack on cyclohexanones. One method calculates the congestion (70,71), which is based on the surface area of cones of access, defined by each hindering atom, of the two faces of the carbonyl group. This method suggests the necessity of introducing a correction function for the torsional strain proposed by Felkin. The other model is useful specifically for predicting product ratios in the reduction of cyclohexanones by sodium borohydride, and weighs the contribution that various substituents on the ring make toward $\Delta H_a^\ddagger$ and $\Delta H_e^\ddagger$ (69). A third empirical model (72),

which is less definitive regarding the physical significance of the controlling parameters, has been presented for 2-substituted cyclopentanones. Time and space, however, do not allow any detailed discussion of these models for predicting product ratios.

Dauben and co-workers (48) suggested that steric approach control and product development control are important in determining the stereochemistry of complex metal hydride reduction of ketones. Steric approach control implies an early, reactantlike transition state in which the entering group approaches the least hindered side of the ketone, whereas product development control implies a late, productlike transition state in which the observed isomer ratio reflects the thermodynamic stability of the products. The concept of steric approach control is generally agreed to be a valid one. However, product development control has not gained this general acceptance, and several alternatives have been introduced to explaining the formation of the more thermodynamically stable product, such as Felkin's (49, 50) torsional strain, molecular orbital arguments (56-62), steric hindrance (26,55), and the antiperiplanar effect (61). Eliel (15,16), on the basis of competitive rate studies involving LiAlH_4 and 3,3,5-trimethylcyclohexanone, has suggested that product development control is not a major factor in stereochemical control. The axial C-3 methyl group retards the rate of axial attack compared with 4-*t*-butylcyclohexanone, whereas the rate of equatorial attack remains essentially the same. This observation is not consistent with that predicted by product development control, in that an axial methyl group would be expected to retard equatorial attack because of the compression of the forming axial OAlH_3^- against the axial methyl group. Since it is possible that changes in conformation of the transition state can take place in flexible systems such as cyclohexanones, we carried out a similar study, using a rigid system which also eliminated the possible complication of torsional effects (73,74). Studies showing equal rates of anti attack by LiAlH_4 on 7-norbornanone and on *exo*-2-methyl-7-



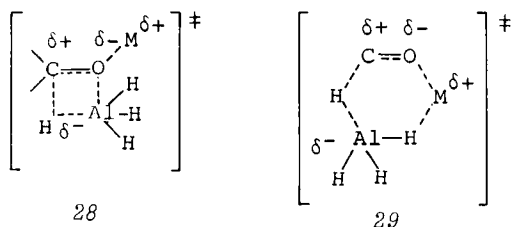
7-norbornanone

*exo*-2-methyl-7-norbornanone

norbornanone resulted in the conclusion that the concept of product development control is indeed questionable. It should be pointed out that, although the position of the transition state of complex metal hydride reduction of ketones along the reaction coordinate remains unproven, it is generally conceded that an early transition state is involved in most, if not all, cases.

It is obvious that some chemical property of 4-*t*-butylcyclohexanone directs the attack of complex metal hydrides to the axial side. Three of the several explanations for this observation involve electronic factors. Felkin's torsional strain (49-52) (single bond repulsions), Klein's orbital distortion (56), and Anh's antiperiplanar effect (61) are electronic in nature, not steric. Perhaps all of these are related. Anh's antiperiplanar effect includes torsional strain, and considers ketone MOs similar to those suggested by orbital distortion theory. Thus we use the term "antiperiplanar factors" to include all three of these concepts, since they do predict the same stereochemical results, and we do not feel that it is necessary to consider each theory separately for every single ketone.

In this connection we suggest that it is possible that there is something fundamentally different about a four-centered transition state (28) and a transition state that is not four-centered (29) that causes one side of a ketone to be preferentially favored over another. The profound difference in resulting stereochemistry between a four-centered and six-centered transition state has been demonstrated (75) for the alkylation of 4-*t*-butylcyclohexanone by $\text{Al}(\text{CH}_3)_3$. The four-centered transition state mechanism results in 20% axial attack, while the six-centered transition state mechanism results in 90% axial attack.



IV. STEREOCHEMISTRY OF REDUCTION OF MODEL KETONES BY COMPLEX METAL HYDRIDES

Table 1 lists results of the reduction of several model ketones by complex metal hydrides and their alkoxy derivatives, in several different solvents. Temperatures are not indicated, but almost all the reductions were carried out in the range 0 to 35°. Although temperature is important in stereochemical control, over the range 0 to 35° the effect is not that pronounced, especially for unhindered cyclohexanones. For example, the percentage of axial attack on 4-*t*-butylcyclohexanone varies about 1% over this temperature range (47). The variation in percentage of axial attack on 3,3,5-trimethylcyclohexanone is larger: 3 to 6% (47). These variations are well within the range of those caused by changes in other factors (39) such as concentration, ratio of reactants, order of addition of reactants, and method of determination of the ratio of isomers.

This means that small changes in stereochemical results are not significant, unless reported by the same workers under rigorously controlled conditions. The results reported in Table 1 are for reactions carried out with excess hydride. This table does not by any means include all work reported in the area, but has been obtained from selected papers as representative of general findings. The discussion is centered on the stereochemical results of model ketones by complex aluminohydrides.

A. 4-*t*-Butylcyclohexanone (I)

4-*t*-Butylcyclohexanone (I) should be a good model to represent the (noninverting) chair conformation of cyclohexanone. In this case the *t*-butyl group is locked in an equatorial position, and removed from any steric influence at the reaction center. In addition its inductive and field effects on the reaction center should be minimal. Therefore the data in Table 1 should represent accurately the ratio of axial and equatorial attack on the chair conformation of cyclohexanone. All the hydrides listed, except $\text{LiAl}(\text{OCH}_3)_3\text{H}$, give similar results in the reduction of I. A trend—namely, that the smaller the cation, the greater the percent of axial attack—can be suggested for the series LiAlH_4 , NaAlH_4 , and NR_4AlH_4 [NR_4^+ is tri(*n*-octyl)-*n*-propylammonium ion]. The small differences found are probably real, since these results are consistently reproducible under the same conditions for each reducing agent (39).

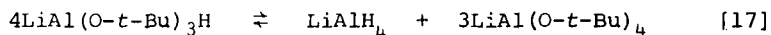
In I steric hindrance from the C_3 and C_5 axial hydrogens favors equatorial attack and the antiperiplanar factors (we let this term include torsional strain, orbital distortion, and Anh's antiperiplanar effect because they are closely related) favor axial attack. It should be pointed out that steric hindrance and antiperiplanar factors favor different directions of attack in I and many other cyclohexanones; however, this is not always the case. Since axial attack is dominant, the antiperiplanar factors caused by the axial C-H bonds at C_2 and C_6 are more significant than the steric hindrance by the axial C-H bonds at C_3 and C_5 . The ability of the smaller cation, Li^+ , to associate more strongly with the carbonyl oxygen atom than Na^+ or NR_4^+ could enhance the antiperiplanar factors and result in a slightly larger percentage of axial attack for Li^+ . The greater association of the carbonyl oxygen atom with Li^+ may possibly reduce the angle of attack (closer to 90°) (61), which would eliminate some of the steric hindrance by the C_3 and C_5 axial hydrogens, allowing slightly more axial attack. That the cation affects the stereochemistry is not that clear in the case of I; however, with other ketones the importance of the cation is clearly established.

Lithium trimethoxyaluminumhydride gives greater than 40% equatorial attack on I, whereas $\text{Li}(\text{O}-t\text{-Bu})_3\text{H}$ gives only 10%.

The common concepts of stereochemical control offer no satisfactory explanation for this observation. The difference, probably the result of some fundamental differences by which these two alkoxy hydrides react, demonstrates the desperate need to know more details about the mechanism of the reaction to explain the stereochemistry. It has been suggested (76) that the increased steric requirement of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ over $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ is caused by the greater association of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ compared with that of $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ in THF. However, the stereoselectivity in the reduction of I over a 100-fold change in concentration of hydride, using LiAlH_4 , $\text{LiAl}(\text{OCH}_3)_3\text{H}$, and $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$, including the concentration for which $\text{LiAl}(\text{OCH}_3)_3\text{H}$ should be monomeric, shows no change with concentration of hydride (39). This suggests either that reduction by $\text{LiAl}(\text{OCH}_3)_3\text{H}$ occurs through the same species at all concentrations or that the associated species have no greater steric requirement than the monomer. An alternative explanation is that reaction of $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ proceeds via $\text{Al}(\text{O}-t\text{-Bu})_2\text{H}$ as an intermediate (6,77):

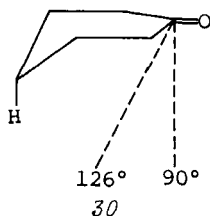


This does not seem likely, however, since it has been shown that $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ and $\text{Al}(\text{O}-t\text{-Bu})_2\text{H}$ have significantly different stereoselectivities (76) toward the same ketones. The possibility that reaction of $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ via LiAlH_4 produced by disproportionation (4,78) (eq.[17]) does not seem likely either, since LiAlH_4 reacts with certain substrates that $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ does not react with (79):



The equivalent molar conductance of $\text{LiAl}(\text{OCH}_3)_3\text{H}$ in THF (2.32 mhos/cm² at 0.1M) is much greater in THF than that of $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ (0.0124 mhos/cm² at 0.1M, indicating that the former is more solvated. The smaller extent of solvation of the lithium ion in $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ may possibly account for less effective steric bulk, hence more axial attack, than with $\text{LiAl}(\text{OCH}_3)_3\text{H}$. Of course, it is even possible that a different mechanism altogether is in effect for reduction of ketones by $\text{LiAl}(\text{OCH}_3)_3\text{H}$ compared with $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$, although this is not very likely.

Wigfield has suggested (26) that if the angle of approach to the carbonyl group is greater than 90° (e.g., 126°), steric interaction in equatorial attack from the C_4 axial substituent could become important (26,80) (see 27). Such an angle of attack, however, would also increase steric hindrance to axial attack. It seems that for this explanation to be important, a significant amount of ring flattening (30) would have to occur about carbon atoms $\text{C}_1, \text{C}_2, \text{C}_3, \text{C}_5$, and C_6 . The interaction of an



axial C_4 substituent with a nucleophile approaching the half-chair conformation of cyclohexanone at 90° has been discussed in some detail (75). In this connection we concluded some time ago that the axial C_4 hydrogen of I in a half-chair conformation cannot account for 90% axial attack in the reaction of $Al(CH_3)_3$ with I. However, the proposal by Wigfield is thought provoking, and should be considered further.

B. 3,3,5-Trimethylcyclohexanone (II)

3,3,5-Trimethylcyclohexanone (II) introduces a methyl group in the C_3 axial position, and this severely hinders axial attack on the cyclohexanone ring. The largest variability in the selectivity of the hydrides occurs with II (see Table 1), and equatorial attack predominates for all hydrides.

The importance of the cation in aluminohydride reduction of II is clearly shown in Table 1. A trend—the smaller the cation, the greater the percentage of equatorial attack—is clearly suggested in the series $LiAlH_4$, $NaAlH_4$, and NR_4AlH_4 . The trend, is however, exactly opposite to that observed in the case of I. It appears that regardless of what factors dominate the stereochemistry (steric hindrance or antiperiplanar factors), $LiAlH_4$ appears to experience these factors more than $NaAlH_4$ or NR_4AlH_4 , and is almost always the most selective (39) (i.e., the product ratio is furthest from 50:50). The behavior of $LiAlH_4$ toward II may be explained on the basis that $LiAlH_4$ is more solvated, and thus has a larger steric requirement than $NaAlH_4$ and NR_4AlH_4 . It might be noted that $LiAlH_4$ attacks II more from the least hindered equatorial side in THF than in diethyl ether, a more weakly solvating solvent. Also, if Li^+ is indeed associating with the carbonyl oxygen in the transition state, more order about the cation in the transition state is likely to increase the importance of steric factors. Thus $LiAlH_4$ presents the largest steric requirement in hindered ketones; in unhindered ketones, however, steric factors should be less important, and antiperiplanar factors, enhanced from association of the Li^+ with the carbonyl oxygen, should become the predominant factor.

The hydrides $ClMgAlH_4$ and $Mg(AlH_4)_2$ give results with II which are intermediate between those of $LiAlH_4$ and $NaAlH_4$. Although the Na^+ almost always gives results intermediate between Li^+ and NR_4^+ , the magnesium ion follows no such pattern. Since

the magnesium aluminohydrides give more axial attack on II than does LiAlH_4 , it appears that they experience antiperiplanar factors more than does LiAlH_4 . This is also the case with other ketones in Table 1. The magnesium aluminohydrides, probably more than any other aluminohydride, demonstrate the importance of the cation on stereoselectivity and have produced some very surprising results.

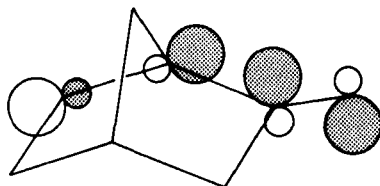
The importance of solvation, as suggested for the reactions $\text{LiAl}(\text{OCH}_3)_3\text{H}$ and $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ with I, is demonstrated with II when the solvent is changed from ether to THF. When THF is the solvent, a larger percentage of equatorial attack occurs on II than in the same reaction carried out in diethyl ether.

C. Camphor (III)

All the hydrides listed in Table 1 give predominately endo attack on camphor (III). The syn C7 methyl group severely blocks exo attack, and thus steric approach control is the expected result. LiBH_4 , ClMgAlH_4 , and $\text{Mg}(\text{AlH}_4)_2$ give less endo attack than the other hydrides.

Lithium borohydride gives results similar to LiAlH_4 for I, where antiperiplanar factors are believed to be the controlling elements in determining the direction of attack. When the reduction is controlled by steric hindrance, as in II and III, LiBH_4 gives more attack than LiAlH_4 from the more hindered side. This is consistent with the smaller size of the borohydride ion (81) compared with the aluminohydride ion and with the fact that LiBH_4 is less solvated (1,2) than LiAlH_4 in THF, and thus LiBH_4 possesses a smaller steric requirement. However, factors other than the size of the anion may be important. NaBH_4 in isopropyl alcohol and LiBH_4 in THF give similar results with II, but quite different results with III. In general the NaBH_4 results are more similar to those from NaAlH_4 and LiBH_4 , than to those from any of the other aluminohydrides. Lithium borohydride does not parallel its stereochemical results with any particular aluminohydride. Of course, there is likely to be a pronounced solvent effect in the case of NaBH_4 and LiBH_4 , the former being used in a protic solvent and the latter in an aprotic solvent.

It is not necessary to have a smaller anion, such as BH_4^- , to increase the percentage of exo attack relative to LiAlH_4 , because $\text{Mg}(\text{AlH}_4)_2$ gives considerably more exo attack than LiAlH_4 . Steric hindrance and antiperiplanar factors favor opposite sides of attack in I, II, and III. The antiperiplanar factors in III arise because of the interactions of the $\text{C}_1\text{-C}_6$ bond with the carbonyl π bond and the approaching nucleophile, and thus favor exo attack (31). Therefore increase in exo attack on III by ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ relative to LiAlH_4 could be caused by Mg^{2+} enhancing the antiperiplanar effect by complexing with the carbonyl oxygen. More is said about such



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possibilities later. It should be pointed out that III has a methyl group attached to a carbon adjacent to the carbonyl group and lying nearly in the carbonyl plane.

D. Norcamphor (IV)

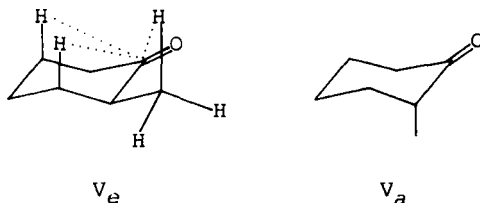
The results of the reduction of norcamphor (IV), listed in Table 1, show a definite trend in selectivity: $\text{LiAlH}_4 > \text{NaAlH}_4 > \text{NR}_4\text{AlH}_4$. Steric hindrance and antiperiplanar factors favor opposite sides of attack in I, II, and III, but not in IV, where both favor exo attack (31). It is likely that both steric hindrance and antiperiplanar factors are important in the stereochemistry of the reduction of IV. The differences in the stereoselectivities of LiAlH_4 , NaAlH_4 , NR_4AlH_4 may be explained by steric hindrance, as with II ($\text{Li}^+ > \text{Na}^+ > \text{NR}_4^+$), or by antiperiplanar factors, as with I ($\text{Li}^+ > \text{Na}^+ > \text{NR}_4^+$), or by some combination thereof. The stereochemistry of reduction of IV has generally been explained on the basis of steric hindrance by the endo hydrogens. The results in Table 1 suggest that other factors must be important, not necessarily because of the magnitude of the difference between LiAlH_4 and NaAlH_4 or NR_4AlH_4 , or between LiAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ or ClMgAlH_4 , but because NaAlH_4 and NR_4AlH_4 behave similarly to LiAlH_4 toward III while ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ do not, whereas toward IV, ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ behave similarly to LiAlH_4 while NaAlH_4 and NR_4AlH_4 do not. The pairs NaAlH_4 and NR_4AlH_4 , and ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ have swapped places relative to LiAlH_4 . The magnesium ion is indeed causing significant changes in the stereochemistry of the reduction of ketones by the aluminohydride ion. If the exact role of the cations in these reductions were better known, perhaps there would be less speculation about stereochemical control.

The alkoxyaluminumhydrides $\text{LiAl}(\text{OCH}_3)_3\text{H}$ and $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ give 98% and 93% exo attack on IV, respectively. The results are similar, but $\text{LiAl}(\text{OCH}_3)_3\text{H}$ appears to be the more selective reagent. The same trend occurs with III, except that endo attack is the major pathway. The pattern is that $\text{LiAl}(\text{OCH}_3)_3\text{H}$ always attacks the less hindered side of a ketone to a greater extent than does $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$. The borohydrides LiBH_4 and NaBH_4 give much more similar results with IV than with III.

A frequent observation is that with the more sterically hindered ketones, any change in solvent or cation that increases the solvation of the borohydride or the aluminohydride results in steric factors becoming more dominant in the stereochemical outcome of the reaction. (Compare the results of LiAlH_4 in ether and THF with II, LiAlH_4 and NaAlH_4 in THF with II, NaBH_4 and LiBH_4 with III, and LiAlH_4 and NaAlH_4 in THF with IV.)

E. 2-Methylcyclohexanone (*V*)

The flexibility of the ring system in this compound provides a unique case in the study of the stereochemistry of reduction. It is of interest to consider how a methyl group adjacent to the carbonyl group affects the stereochemistry of cyclohexanone reduction by complex metal hydrides. However, before an understanding of this reaction can be realized, one must consider the extent to which each of the two conformations of *V* (V_e or V_a) participate in the reaction. Unlike camphor



(III), which is rigid and cannot change conformation, *V* can easily flip from V_e to V_a and back to V_e . The conformation V_a is present to the extent of ca. 5% at ambient temperature (82). If the methyl group in *V* is replaced by an ethyl or isopropyl group, the percentage of the least stable conformer (analogous to V_a) present in the conformational equilibrium increases (ethyl ca. 12%, isopropyl ca. 30%) because of steric hindrance between the equatorial C_2 alkyl group and the carbonyl oxygen atom. This phenomenon is known as the 2-alkylketone effect (82). It is likely that 2-*t*-butylcyclohexanone resides predominately in the flexible (boat) conformation because of such an interaction. It should be pointed out that the flexible (boat) conformation was not considered along with V_a and V_e for the sake of simplicity. Of course, if the flexible (boat) conformer is present, reaction can occur via that conformer. However, in the case of *V* the two major conformers are V_e and V_a , and it is assumed that complex metal hydride reductions involve mainly these two conformers.

All the hydrides studied give more equatorial attack on *V* (see Table 1) than on *I*, if the reactive conformation is considered to be V_e . It has been suggested (83,84) that the hydrogen atoms of the methyl group introduce a third 1,3-diaxial interaction with respect to the incoming nucleophile

(see V_e) which, of course, retards axial attack. Reaction of V through the flexible forms (the various boat and twist-boat conformations) has also been suggested (85) to explain the greater degree of equatorial attack on V than on I. This increase in apparent equatorial attack has also been attributed (39,40,48,86,87) to reaction of the chair conformation with the axial methyl group (V_a). Axial attack on this conformation gives the same alcohol that results from equatorial attack on the conformer V_e , thus accounting for the increase in apparent equatorial attack on V over I.

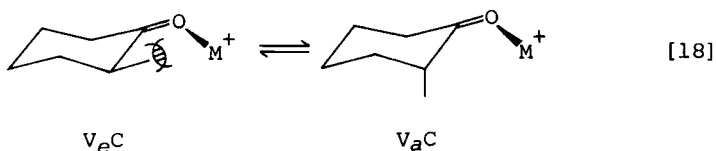
Reduction of *cis*-2-methyl-4-*t*-butylcyclohexanone (VI) by LiAlH_4 in THF (see Table 1) gives 17 to 19% equatorial attack compared to only 7 to 10% in a similar reaction involving I. This result provides good evidence that the equatorial C-2 methyl group does in fact retard axial attack by LiAlH_4 on a cyclohexanone. Reduction of V by LiAlH_4 in THF gives 22 to 25% equatorial attack, assuming V_e is the reactive conformation. This is slightly more equatorial attack than experienced by VI. The results involving V can be explained by two effects: (1) The equatorial C_2 methyl group retards axial attack on V; (2) V reacts through both conformations, V_a and V_e . If both conformations V_a (5%) and V_e (95%) had approximately the same rate of reaction, then 17 to 19% equatorial attack on V_e by LiAlH_4 (since VI gives 17 to 19% equatorial attack) plus nearly exclusive axial attack on V_a (only 5% present) would produce ca. 22 to 24% apparent equatorial attack on V, as experimentally observed.

The results tabulated in Table 1 for ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ similarly show that a third to a half of the *cis*-2-methylcyclohexanol produced must arise from the reaction of V_a . This result requires ca. 15 to 25% of the reaction to occur via V_a , although it is present to the extent of only about 5% in the equilibrium between conformers V_a and V_e . Thus with ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$, V_a appears to be more reactive than V_e , or the equilibrium concentration of V_a and V_e is different when complexed to magnesium compared to lithium. Two questions arise from a consideration of these results: (1) How does the equatorial C_2 methyl group of cyclohexanone actually retard axial attack? (2) Why is conformer V_a relatively more reactive than conformer V_e with the magnesium aluminohydrides than with LiAlH_4 ?

These results, indicating that the equatorial C_2 methyl group retards axial attack, may be explained by assuming that the C_2 methyl (1) partially blocks the axial approach of the aluminohydride ion from a direction perpendicular (or nearly perpendicular) to the plane of the carbonyl group; (2) blocks the aluminohydride ion from moving into an axial position after or during complexation of the oxygen atom by the cation; and/or (3) causes steric strain as the cation complexes to the oxygen atom, thus causing part of the reduction to occur via the flexible form. The first two reasons may seem to be the same, but

in fact are not. The first explanation is applicable to all approaching nucleophiles. The second suggests that if the mechanism does involve complexation of the carbonyl oxygen by the cation, then the effect of the equatorial C_2 methyl group is greater than it would be if no complexation occurred. The third possibility is included because it is felt that the flexible conformer, although a less likely intermediate, cannot be entirely ignored.

Conformer V_a may be considered more reactive than V_e because the axial methyl of V_a pushes against the axial C_6 hydrogen atom and the resulting outward thrust of the axial C_2 and C_6 bonds cause the ring to flatten. The flattening of the ring allows for easier axial attack on V_a than on V_e , which already has axial attack retarded by the equatorial methyl group. However, such an effect by itself should affect the stereochemistry and reaction rate of all aluminohydrides to about the same degree, since the effect is inherent in the ketone. Thus, if V_a is more reactive than V_e with one aluminohydride, it should be more reactive with all the aluminohydrides. This, however, is not the case, as pointed out earlier. A larger percentage of the reaction of V appears to occur through conformer V_a with the magnesium aluminohydrides than with $LiAlH_4$. It has been shown that the equilibrium constant for the complexation of 2-methylbenzophenone by $MgBr_2$ (88) in diethyl ether has a value of 4.1 liters/mol., and that the equilibrium constant for the complexation of benzophenone by $LiClO_4$ (37) in diethyl ether has a value of 1.3 liters/mol. This suggests that Mg^{2+} is a better complexing agent than Li^+ , in spite of the fact that 2-methylbenzophenone is a more sterically hindered ketone about the carbonyl group than benzophenone. If it is assumed that cation M^+ of $MAiH_4$ complexes with the carbonyl oxygen prior to or concurrent with reduction, the $MgCl^+$ or $MgAlH_4^+$, being larger than Li^+ , would interact more with the methyl group of V_e (V_eC), and thus force more of the reaction to proceed through the conformation V_a (V_aC).



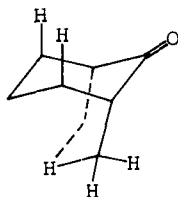
Actually, the solvated cations should be considered; however, Mg^{2+} would be expected to be more highly solvated than Li^+ , and the conclusions would remain the same. If complexation of the carbonyl group occurs during reduction, then the concentration of V_aC (and its transition state corresponding to axial attack) should increase relative to that of V_e , since the energy difference between V_aC and V_eC is less than that between V_a and V_e .

There is a question that should be asked at this point: Why does complexation not occur at the other side of the carbonyl group away from the methyl group in V_e ? The answer probably is that if complexation does occur in the manner shown in V_eC , it probably occurs predominantly at the side away from the methyl to avoid steric interactions. The net effect, however, would be that V_a would have two sites for complexation by M^+ and V_e only one; thus on the basis of concentration of active sites V_a would be twice as reactive as V_e . Of course, such an effect would be quite dependent on the complexing agent. The complexation of the carbonyl group has been suggested (61) to occur in such a way that the $C=O \cdots Li$ angle is 180° , then the increased effective bulk about the carbonyl oxygen is the same in the direction of both C_2 and C_6 carbon atoms. Even if the complexation angle is 120° , it may be valid to assume that the increased effective bulk about the carbonyl oxygen (75) is the same on both sides because the equilibrium is quite dynamic, with rapid exchange of solvent and ketone molecules about the complexing ions.

The reactivities of conformers V_a and V_e toward magnesium aluminohydrides may also be explained on the basis of antiperiplanar factors. Examination of conformations V_a and V_e suggests that V_a should be able to stabilize an induced positive charge at the carbonyl carbon better than V_e (58,59), because hyperconjugation should be greater for the more polarizable axial β C-C bond of V_a than for the axial β C-H bond of V_e . Thus this increased stabilization in V_a allows more of the reaction to proceed via V_a when $Mg(AlH_4)_2$ and $ClMgAlH_4$ are used than when $LiAlH_4$ is used (assuming that Mg^+ polarizes the carbonyl C-O bond more than Li^+). It should be pointed out that the axial methyl group of V_a would favor axial attack more than a hydrogen at the same position, because all the antiperiplanar factors (torsional strain, orbital distortion, and the antiperiplanar effect) are more important for the methyl group than for the hydrogen.

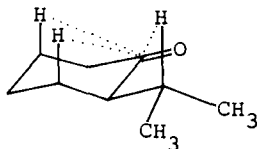
The reduction of *r*-2-*cis*-6-dimethyl-*cis*-4-*t*-butylcyclohexanone (VII) reinforces the evidence already present that a C_2 equatorial methyl group retards axial attack. Reduction of VII (see Table 1), by three different complex aluminohydrides gives 48 to 53% axial attack compared with 73 to 83% for VI and 87 to 93% for I. The effect of a C_2 axial methyl group is shown in the table for the reduction of *trans*-2-methyl-4-*t*-butylcyclohexanone (VIII). The methyl group does retard equatorial attack by complex aluminohydrides (4 to 8%) as compared to I (7 to 13%). If the amount of equatorial attack on VIII seems suprisingly higher than expected, consider 32, which shows that an axial C_2 methyl group may only approximate the steric hindrance of a C_3 or C_5 axial hydrogen.

The reductions of several other 2-alkylcyclohexanones are recorded in Table 1: 2-ethylcyclohexanone (IX), *cis*-2-ethyl-4-*t*-butylcyclohexanone (X), 2-isopropylcyclohexanone (XI), and *cis*-2-isopropyl-4-*t*-butylcyclohexanone (XII). Results for X and XII



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show that an equatorial C_2 ethyl or isopropyl group does not retard axial attack significantly more than does a methyl group (compare VI and I, X and I, and XII and I). This may be explained on the basis that conformers such as 33 participate significantly in the reaction of X and XII, where a methyl seldom interacts in a syn-diaxial fashion with the entering hydride. In the conformation 33 interference of axial approach by the hydride is no greater for ethyl or isopropyl than for methyl. Comparison of the results in Table 1 leads to the same conclusion about IX and XI as about V, namely, that a significant amount of the reaction of IX and XI occurs through a conformer with the alkyl group in an axial position.

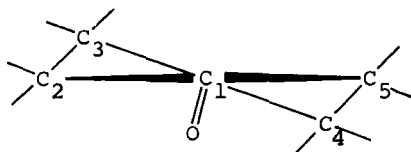


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Wigfield has concluded that both conformers V_a and V_e are involved in the reduction of V by $NaBH_4$ (87) in isopropyl alcohol, by using 2,2,4-trimethylcyclohexanone (assuming that no syn-diaxial methyl-methyl interaction may occur) instead of VI as a model for a cyclohexanone with an equatorial C_2 methyl group. He concluded that about half of the *cis*-2-methylcyclohexanol arises from axial attack on V_a by $NaBH_4$. Reaction of V through V_a probably is significant in accounting for the increase in apparent equatorial attack by $LiAl(OCH_3)_3H$ and $LiAl(O-t-Bu)_3H$ on V over that on I.

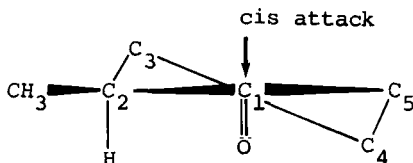
F. Cyclopentanones

The preferred conformation of cyclopentanone, the half-chair model, has a C_2 axis of symmetry (63), which allows equal attack from either side (34). Substituents distort the symmetry, causing one side to be attacked by hydride more easily than the other. Since 2-methylcyclopentanone (XIII) (see Table 1) is attacked by $LiAlH_4$ to the extent of 74 to 84% from a position *cis* to a methyl group, any steric hindrance from the



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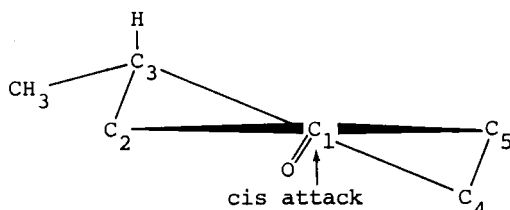
C₂ methyl group would seem to be minor. The methyl group is probably in a quasi-equatorial position (35), and steric hindrance is felt less than the antiperiplanar factors caused by the quasi-axial hydrogen at C₂ on the opposite side of the ring (45).



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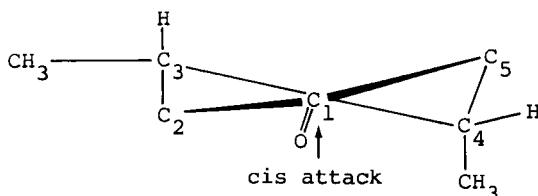
3-Methylcyclopentanone (XIV) (see Table 1) is attacked 60 to 73% by LiAlH₄ from a position trans to the methyl group. At first glance this may be ascribed to blocking of cis attack by steric hindrance of the C₃ methyl group, since the introduction of an axial C₃ methyl group on a cyclohexanone ring results in a large decrease in axial attack, from ca. 90% in 4-*t*-butylcyclohexanone to ca. 30% in 3,3,5-trimethylcyclohexanone. This latter observation involving cyclohexanones is clearly the result of steric hindrance. However, it must be remembered that the cyclohexanone chair conformation does not allow equal attack on both sides of the ring, while the half-chair conformation of cyclopentanone does. Therefore the C₃ methyl group of XIV only changes the preferred direction of attack from 50% to 60 to 73%. This effect is smaller than that observed for the C₂ methyl group of XIII (50% to 74 to 84%), whose stereochemistry of reduction is controlled not by steric hindrance, but probably by antiperiplanar factors. It is also reported that 3-*t*-butylcyclopentanone is attacked to approximately the same extent as XIV by LiAlH₄ [i.e., 60% trans attack (90)]. These results indicate that factors other than steric hindrance control the stereochemistry of reduction of XIV. The C₃ methyl group is probably in a quasi-equatorial position, offering little steric hindrance to cis attack (36).

The vicinal methyl groups of cis-3,4-dimethylcyclopentanone (XV) (see Table 1) probably twist in a manner to avoid eclipsing each other. One takes a quasi-axial position and the other a quasi-equatorial position (37). The quasi-axial methyl group can hinder cis attack at the carbonyl group, and thus it is not



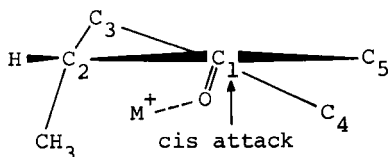
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surprising that LiAlH_4 attacks XV 90% from the trans side.



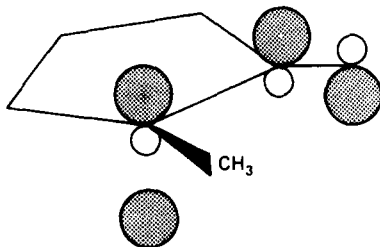
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The reduction of XIV and XV by ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ gives results similar to those for LiAlH_4 . With XIII, ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ give much more trans attack (35 and 55%, respectively) than does LiAlH_4 (16 to 26%). In fact, $\text{Mg}(\text{AlH}_4)_2$ gives more trans attack than $\text{LiAl}(\text{OCH}_3)_3\text{H}$ (55 vs. 44%) in THF. It appears that $\text{Mg}(\text{AlH}_4)_2$ experiences steric hindrance of the 2-methyl group more than $\text{LiAl}(\text{OCH}_3)_3\text{H}$, which is supposedly very sensitive to steric effects. Probably $\text{Mg}(\text{AlH}_4)_2$ attack on XIII occurs predominantly trans for reasons other than steric hindrance. In reductions of the cyclopentanones XIV and XV (where the methyl groups are not adjacent to the carbonyl groups) all the complex aluminohydrides behave similarly. Only when the methyl group is adjacent to the carbonyl group, as in XIII, III, and V, does a difference in stereochemical results occur between LiAlH_4 and ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$. It appears that complexation of the carbonyl group of XIII by Mg^{2+} pushes the methyl group from its quasi-equatorial position into a quasi-axial position (38), which increases steric hindrance to cis attack.



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The possible importance of antiperiplanar factors in the stereochemical control of hydride reduction of XIII has already been mentioned. Structure 39 shows how orbital distortion or the antiperiplanar effect could arise in compound XIII. Thus the set of antiperiplanar factors can also be applied to XIII as well as V. In both cases the methyl group becomes quasi-axial and, because it is more polarizable than a C-H bond, it enhances the antiperiplanar factors. If it is assumed that Mg^{2+} polarizes the carbonyl C=O bond more than Li^+ , which causes the antiperiplanar factors to be more significant, relatively more of XIII reacts through the conformer 39 than through 35 with ClMgAlH_4 and $\text{Mg}(\text{AlH}_4)_2$ than LiAlH_4 . It probably is of significance that such an explanation may also be applied to explain the differences in the stereochemical results of the reduction of III and V by LiAlH_4 and the magnesium aluminohydrides.



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V. SUMMARY

The mechanism of LiAlH_4 reduction of ketones is not known with a great degree of certainty; however, studies carried out in the past few years have provided much additional information about this reaction. The stereochemical results of complex aluminohydride reduction of ketones are dependent on the nature of the cation (39), and thus it may be concluded that the cation must be involved in the mechanism of reduction at least to some extent. It has also been demonstrated that solvent, temperature, and concentration are important factors in the stereochemical outcome of these reduction reactions. The stereochemistry of these reductions is probably best explained by steric approach control and antiperiplanar factors which are electronic in nature, although the concept of product development control cannot be completely eliminated as a controlling factor. Reaction of a flexible ketone through minor conformers that may be present in solution must sometimes be considered when explaining the stereochemistry of reduction. If the mechanism of ketone reduction by LiAlH_4 were known in more detail and with greater certainty, it might help to explain what factors are involved in the stereochemistry of reduction.

Table 1. Reduction of Model Ketones by Complex Metal Hydrides

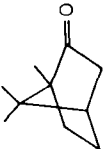
Hydride	Solvent	Ketone (percent axial, exo, or cis attack by the hydride on the ketone) (Ref.)			
					
			I	II	III
(1) NaBH ₄	2-propanol	87 (47), 83 (16)	42 (47,10), 48 (25), 38 (16,10)	14 (93)	
(2) LiBH ₄	THF	93 (39)	47 (39)	31 (39)	
(3) LiAlH ₄	Et ₂ O	92 (47), 92 (91), 90-91 (16)	45 (47), 37-42 (16)	--	
(4) LiAlH ₄	THF	90 (39), 92 (47), 93 (92)	20 (39), 23 (47)	9 (39), 8 (6)	
(5) NaAlH ₄	THF	87 (39)	41 (39)	12 (39)	
(6) NR ₄ AlH ₄	THF	85 (39)	45 (39)	12 (39)	
(7) ClMgAlH ₄	THF	90 (39), 93 (92)	29 (39)	19 (39)	
(8) Mg (AlH ₄) ₂	THF	87 (39), 91 (92)	39 (39)	26 (39)	
(9) LiAl (OCH ₃) ₃ H	Et ₂ O	--	25 (4)	--	
(10) LiAl (OCH ₃) ₃ H	THF	56 (39), 59 (16)	8 (4), 2 (16)	1 (6)	
(11) LiAl (O- <i>t</i> -C ₄ H ₉) ₃ H	Et ₂ O	--	27 (4)	--	
(12) LiAl (O- <i>t</i> -C ₄ H ₉) ₃ H	THF	89 (39), 90 (55), 90 (16)	12 (4), 12 (55), 4 (16)	7 (6), 5 (55)	

Table 1. (Cont.)

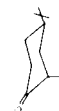
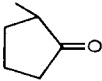
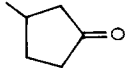
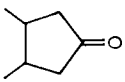
Ketone (percent axial, exo, or cis attack by the hydride on the ketone) (Ref.)						
IV	V	VI	VII	VIII	IX	X
						
(1)86 (93)	69 (93), 75 (16), 60 (10), 70 (25)	--	--	--	65 (25)	--
(2)82 (39)	71 (39)	--	--	--	--	--
(3)--	82 (48), 64 (94)	--	--	--	72 (96)	80 (96)
(4)91 (39), 89 (6)	76 (39), 75 (6), 78 (95)	81 (39), 83 (92)	53 (92)	96 (92)	67 (95)	--
(5)83 (39)	71 (39)	--	--	--	--	--
(6)74 (39)	74 (39)	--	--	--	--	--
(7)92 (39)	64 (39), 61 (92)	79 (39,92)	50 (92)	94 (92)	--	--
(8)87 (39)	52 (39), 59 (92)	73 (39,92)	48 (92)	92 (92)	--	--
(9)--	--	--	--	--	--	--
(10)98 (6)	37 (39), 31 (6)	--	--	--	--	--
(11)--	--	--	--	--	--	--
(12)93 (6)	64 (39), 70 (6), 63 (55)	--	--	--	--	--

Table 1. (Cont.)

Ketone (percent axial, exo, or cis attack by the hydride on the ketone) (Ref.)									
									
XI	XII	XIII	XIV	XV					
(1) --	--	--	--	--	--	--	--	--	--
(2) 60 (97)	--	--	--	--	--	--	--	--	--
(3) 71 (91)	80 (91)	76 (92), 74 (98)	40 (90)	--	--	--	--	--	--
(4) 63 (97,95)	--	84 (39), 75 (6), 79 (95), 80 (98)	27 (39)	10 (39)	--	--	--	--	--
(5) 70 (97)	--	--	--	--	--	--	--	--	--
(6) --	--	--	--	--	--	--	--	--	--
(7) --	--	65 (39)	25 (39)	10 (39)	--	--	--	--	--
(8) --	--	45 (39)	20 (39)	10 (39)	--	--	--	--	--
(9) --	--	--	--	--	--	--	--	--	--
(10) --	--	56 (6), 54 (98)	--	--	--	--	--	--	--
(11) --	--	--	--	--	--	--	--	--	--
(12) --	--	72 (6,98)	--	--	--	--	--	--	--

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Conformational Barriers and Interconversion Pathways in Some Small Ring Molecules

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I. INTRODUCTION

Tremendous advances have been made in the last 15 years or so in the determination of conformations and barriers associated with large-amplitude vibrations in molecules. Various experimental and theoretical techniques have been applied, including IR, Raman, and microwave spectroscopy as well as electron diffraction, NMR, and a variety of computational techniques. We do not address all of these, but rather consider a limited aspect, the advances made in the application of vibrational and rotational spectroscopy to large-amplitude vibrations in ring molecules. Omission of references to other techniques is not intended as a slight, but is done to concentrate on the areas mentioned.

These restrictions sharply limit the problems that are addressed. A further limitation is that we discuss spectra of samples in the gas phase at temperatures ranging from dry ice (185K) to ca. 450K. Despite these limitations useful information on molecular dynamics may be gained for a variety of ring molecules. The examples we give here disproportionately represent work done by the authors, but as much as anything, this represents the availability of the figures.

We hope to convey a sense of what is being measured and how the data are then used to extract information about the molecular dynamics. In particular we wish to indicate how these applications differ from some of the applications of vibrational spectroscopy to the determination of normal vibrational modes, and rotational spectroscopy to the determination of structural parameters.

The differences mentioned occur because of the large amplitudes of certain vibrational modes of some small-ring molecules. A nonlinear molecule has $3N - 6$ molecular vibrations. A four-membered ring molecule has one out-of-plane skeletal mode, usually referred to as the "ring-puckering" mode (Fig. 1). A five-membered ring has two out-of-plane skeletal vibrations, which may be represented by a ring-puckering and a ring-twisting mode (Fig. 2). In saturated rings these modes are usually the lowest frequency molecular vibrations and have unusually large amplitudes. In the first approximation they may be treated as independent of the remaining $3N - 7$ (or $3N - 8$) small-amplitude vibrations. The large-amplitude coordinates lead to interconversion of different ring conformations (Figs. 1 and 2). The determination of potential energy functions in these coordinates yields barriers to interconversion, energy differences between conformers, and interconversion pathways.

For illustrative purposes we compare some one-dimensional examples of potential energy functions appropriate to small-amplitude molecular vibrations to some one-dimensional potential functions appropriate to large-amplitude modes. The simplest example of a vibrational potential function is that for a diatomic molecule as a function of internuclear separation (1).

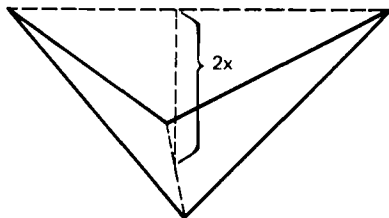
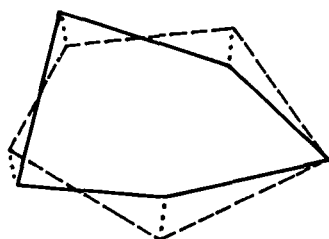
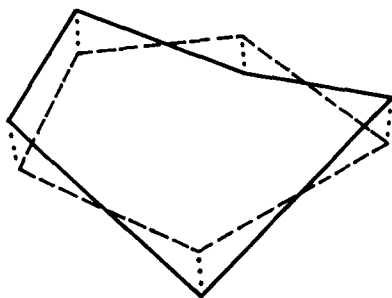


Fig. 1. One possible definition of a ring-puckering coordinate x for a four membered ring molecule. The coordinate is half the perpendicular distance between ring diagonals.



(a)



(b)

Fig. 2. Ring-twisting (a) and ring-puckering (b) vibrations for five-membered-ring molecules.

The familiar Morse curve (2) is an approximation to this shape which yields a closed form energy expression. The simplest approximation applicable to the lower energy states is the harmonic oscillator approximation, which corresponds to approximating the function by a parabola having the same curvature at the minimum. It may be thought of as expanding the potential energy in a Taylor series and truncating after the second-degree term(1):

$$V(r) = 1/2 k (r - r_e)^2 = 1/2 kx^2 \quad [1]$$

where $k = (d^2V/dx^2)$ is the Hooke's law force constant. Truncation after the quadratic term is a good approximation only if the amplitude of vibration is small, that is, if x is small.

The solutions to the Schrödinger equation for the harmonic oscillator are the Hermite functions, and the energy levels are given by

$$E_v = (v + 1/2) h\nu, v = 0, 1, 2, \dots \quad [2]$$

where ν is the frequency and h is Planck's constant. For room temperature IR or Raman experiments only transitions originating from the $\nu = 0$ state are ordinarily observed. The fundamental transition $0 \rightarrow 1$ may be used to calculate the force constant k in eq. [2]:

$$\nu = 1/2\pi \sqrt{\frac{k}{\mu}} \quad [3]$$

where the reduced mass $\mu = m_1 m_2 / (m_1 + m_2)$.

On the other hand the first overtone transition $0 \rightarrow 2$ may be observed, although it is not, strictly speaking, an allowed transition in the harmonic oscillator approximation. Due to anharmonicity the overtone frequency is not exactly twice that of the fundamental, and it may be necessary to carry the Taylor series expansion of the potential function to one more term before truncation:

$$V(x) = 1/2 k_2 x^2 + 1/6 k_3 x^3 \quad [4]$$

Normally the cubic term in the potential function is small enough that perturbation theory may be used to find an expression for the energy levels (1):

$$E = (\nu + 1/2) h c \omega_e - (\nu + 1/2)^2 h c \omega_e x_e + \dots \quad [5]$$

where ω_e is the harmonic frequency in reciprocal centimeters and $\omega_e x_e$ is the anharmonicity.

The value of the fundamental ($0 \rightarrow 1$) frequency and the overtone ($0 \rightarrow 2$) may be used to determine the two parameters in Eq. [4]. If more data are available, a least squares fit may be performed. Alternatively, the Morse function may be used. If high-temperature experiments or fluorescence experiments are performed, it may be possible to map the excited vibrational states and accurately determine the potential function.

For molecules larger than diatomic ones, multidimensional Taylor series expansion in the vibrational coordinates may be used. For a nonlinear molecule of N atoms, the harmonic oscillator approximation to the vibrational potential energy yields

$$V = 1/2 \sum_{i=1}^{3N-6} k_{ii} x_i^2 + \sum_{i \neq j}^{3N-6} k_{ij} x_i x_j \quad [6]$$

where x_i and x_j are vibrational coordinates and $k_{ij} = (\partial^2 V / \partial x_i \partial x_j)$. In general, even with the use of symmetry (3), there are more parameters in Eq. [6] than there are observed fundamental vibrational frequencies ($\leq 3N - 6$). To perform a normal coordinate transformation and simultaneously remove the cross

terms in the potential energy (Eq. [6]) and the kinetic energy, data from isotopic species and/or assumptions concerning some of the terms are necessary. When this is complete, one has determined the multidimensional equivalent of a parabolic approximation.

In treating large amplitude molecular vibrations it is usually not possible to make the harmonic approximation. The first approximation neglects cross terms between large- and small-amplitude modes. For a molecule with a single large-amplitude vibration the Taylor series expansion carried through the fourth degree yields

$$V(x) = ax^4 + bx^2 + cx^3 \quad [7]$$

where x is an out-of-plane ring vibration. In this equation $a = 1/4! (d^4 V/dx^4)$, $b = 1/2 (d^2 V/dx^2)$, and $c = 1/3! (d^3 V/dx^3)$. A linear term may always be excluded by choosing the origin to correspond to a maximum, a minimum, or an inflection point. With the restriction that $a \geq 0$, eq. [7] may represent several different types of molecular potential functions. Figure 3

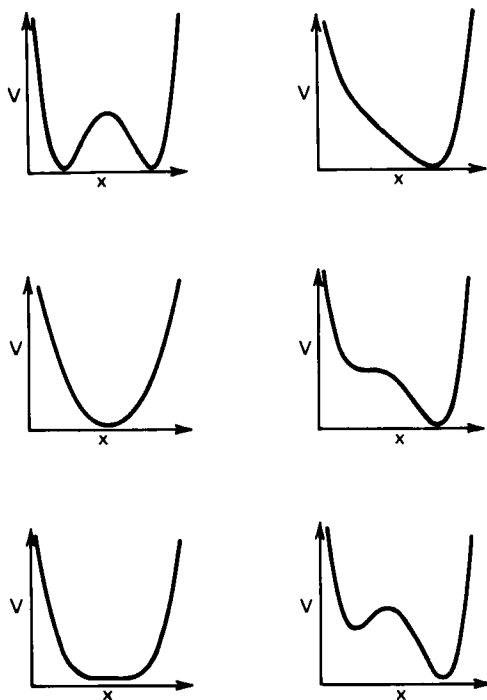


Fig. 3. Different types of one-dimensional potential functions are represented by Eq. [7]. These may be symmetric ($c=0$) or asymmetric ($c \neq 0$) and single-minimum or double-minimum functions.

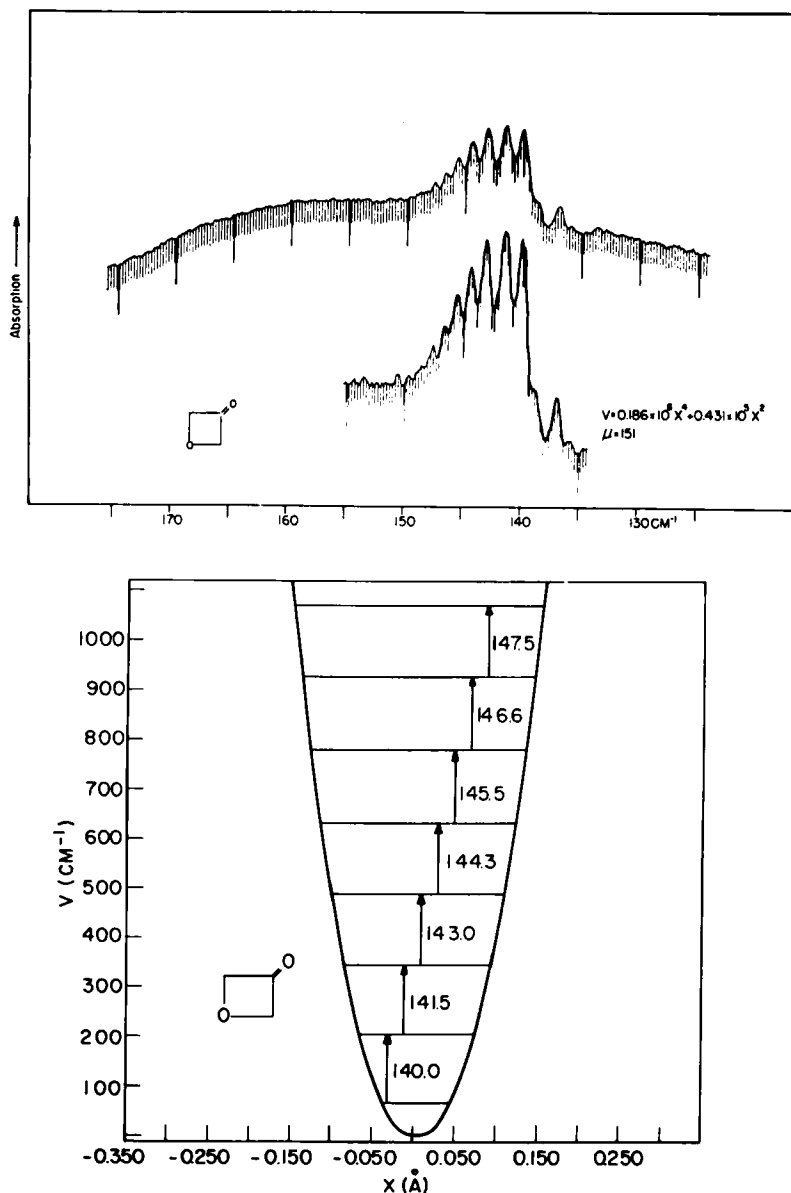


Fig. 4. Far-IR spectrum and ring-puckering potential function for 3-oxetanone. Pressure = 22 torrs, path length = 30 cm. The vertical lines on the spectrum are internal frequency markers. The spectrum is displayed with the absorption peaks upward, although some workers have presented their far-IR spectra with the transmission minima downward (see Fig. 5). (Reproduced with the permission of the American Institute of Physics from ref. 6).

indicates some of the different types of one-dimensional potential functions which may arise. Examples of each type of potential function appear in the literature (4,5).

In contrast to small-amplitude vibrations, the excited states of a large-amplitude mode may be appreciably populated at room temperature. For a purely harmonic oscillator the frequency of all the $\Delta v = 1$ transitions is given by $\nu(\text{eq. [2]})$. Consequently no dramatic effect on the spectrum is observed.

The far-IR spectrum of 3-oxetanone shows the effect of quartic anharmonicity (Fig. 4). In this case the $\Delta v = 1$ transitions increase in frequency with increasing quantum number. The individual Q -branch envelopes corresponding to the fundamental ($0 \rightarrow 1$) and "hot bands" ($1 \rightarrow 2$, $2 \rightarrow 3$, etc.) are clearly resolved in this spectrum. Figure 4 also indicates the potential function and the assignment of some of these transitions.

Equation [6] may also represent a symmetric double-minimum oscillator when $a > 0$, $b < 0$, and $c = 0$. Figure 5 shows the far-IR spectrum of silacyclobutane(7), the low-frequency Raman spectrum and the potential function and some of the assigned transitions. The extensive series of Q -branch transitions have been assigned to $\Delta v = 1$, $\Delta v = 2$, and $\Delta v = 3$ transitions, and used to derive a double-minimum potential function with a barrier of 440 cm^{-1} (1.26 kcal/mol, 5.26 kJ/mol). Examples of the other types of potential functions shown in Fig. 3, as applied to the interpretation of low-frequency spectra of ring molecules, are considered in Sect. III. In addition, extension to the treatment of molecules with two large-amplitude modes is considered.

II. EXPERIMENTAL CONSIDERATIONS

A. Far-IR Spectroscopy

In this section we are concerned primarily with the molecular properties that are measured as well as with some of the experimental details. Figures 4 and 5 show the assignment of some of the sharp features apparent in the far-IR spectra. In fact, we are observing an unresolved envelope of a manifold of vibration-rotation transitions.

A diagrammatic representation of vibration-rotation transitions for an oblate symmetric-top molecule is shown in Fig. 6. An oblate symmetric-top is one for which the smallest I_a and intermediate I_b moments of inertia are equal, with the largest moment I_c being unique:

$$I_a = I_b < I_c \quad [8]$$

The vibration-rotation energy levels are given by

$$E = E_{\text{vib}} + B_v J(J + 1) + (C_v - B_v) K^2 \quad [9]$$

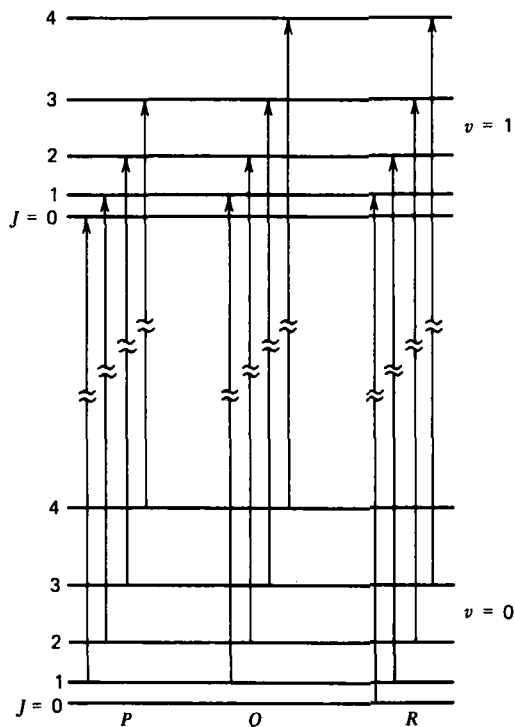


Fig.6. Some vibration-rotation transitions for an oblate symmetric-top molecule. The transitions all involve a change $\Delta v = +1$ in the vibrational quantum number. The transitions shown are termed *P*-branch ($\Delta J = -1$), *Q*-branch ($\Delta J = 0$), and *R*-branch ($\Delta J = +1$) transitions. In each case $\Delta K = 0$. These represent appropriate selection rules for a parallel band of a symmetric-top molecule.

where $J = 0, 1, 2, \dots$; $K = -J, -J + 1, \dots, J - 1, J$; J is the rotational angular momentum quantum number; and $K\hbar$ is the projection of the angular momentum along the inertial axis corresponding to the largest moment of inertia. The rotational constants B_v and C_v are defined:

$$B_v = \langle v | \frac{\hbar}{8} \pi^2 I_B | v \rangle \quad [10a]$$

and

$$C_v = \langle v | \frac{\hbar}{8} \pi^2 I_C | v \rangle \quad [10b]$$

where v represents the values of all the vibrational quantum numbers and $\langle v | O_p | v \rangle$ represents the quantum mechanical average.

For $\Delta v = +1$ transitions for a vibration whose dipole moment oscillates parallel to the unique, or *c*, axis, the frequencies are given by

$$\nu_P = \nu_{\text{vib}} + B_{v+1}J(J-1) - B_vJ(J+1) \quad [11a]$$

$$\nu_Q = \nu_{\text{vib}} + (B_{v+1} - B_v)J(J+1) \quad [11b]$$

$$\nu_R = \nu_{\text{vib}} + B_{v+1}(J+1)(J+2) - B_vJ(J+1) \quad [11c]$$

where *P*, *Q*, and *R* represent $\Delta J = -1$, 0, and $+1$, respectively. If $B_{v+1} \approx B_v$, then $\nu_Q \approx \nu_{\text{vib}}$, and the position of the *Q*-branch maximum corresponds to the position of the vibrational band origin. If B_v and B_{v+1} are known, corrections for the difference between the band origin and the *Q*-branch maxima may be made. For ring molecules these corrections are of the order of a few tenths of reciprocal centimeters, except in unfavorable cases.

For ring molecules all three moments of inertia may be different, and it is not possible to write a closed expression for the frequencies (eqs. [11a], [11b], and [11c]). The resolution available is usually not great enough to resolve individual transitions within the *P* and *R* branches, much less within the *Q*-branch. However, three general types of vibration-rotation bands may arise, classified as *a*-, *b*-, or *c*-type bands. Figure 7 indicates an example of each type. The bands are classified as *a*, *b*, or *c* depending on whether the dipole moment oscillates parallel to the principal inertial axis corresponding to the smallest, intermediate, or largest amount of inertia.

The character of the far-IR spectra shown in Figs. 4 and 5 should now be clearer. The generalized background is the result of overlapped *P* and *R*-branch transitions associated with the different vibrational transitions. The sharp features are

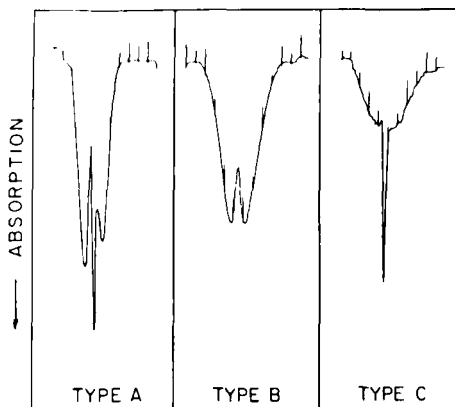


Fig. 7. Examples of *a*, *b*, and *c* type vibration-rotation bands in a IR spectrum. (Courtesy of C. J. Wurrey.)

the Q -branch transitions of c -type bands. this usually allows us to approximate the position of the band origins within a few tenths of a reciprocal centimeter.

For four-membered rings with no out-of-plane atoms except hydrogen atoms, the axis perpendicular to the ring plane is the c axis. This can give rise to c -type bands for ring-puckering transitions. When the b axis is perpendicular to the ring plane or when $I_b \approx I_c$, the overlapped bands may yield an envelope from which it is difficult or impossible to estimate band origins. 1,1-Difluorocyclobutane is an example of such a molecule (9). From Fig. 7 it is seen that overlapped a -type transitions should yield observable Q -branch structure. To our knowledge no ring-puckering spectra have been reported for pure a -type band contours. However, the dipole moment need not oscillate parallel to an inertial axis during a vibration, and vibration-rotation selection rules applicable to more than one band type may be appropriate. This gives rise to "hybrid" bands when the oscillating dipole moment has components along more than one axis. Particularly common in ring-puckering spectra are the occurrence of a - c -hybrid bands.

All of this indicates some of the problems that may arise in using far-IR spectra to determine the position of the energy levels for ring-puckering vibrations. The most favorable case arises when the bands are c -type for a near oblate rotor ($I_c > I_b \approx I_a$), in which case prominent Q -branch transitions are expected on less pronounced P and R envelopes.

The experimental problems involved with obtaining good far-IR spectra are quite severe. Pioneering work on the application of far-IR spectroscopy to the out-of-plane vibrations of ring molecules was done primarily in two laboratories—that of R. C. Lord at MIT, and that of Herbert L. Strauss at Berkeley—by these men and their co-workers.

Sources of radiation are generally quite weak in the far-IR region, simultaneously producing intense shorter wave-length radiation which must be eliminated. The pure rotational spectrum of water vapor is exceptionally intense, and due to the comparatively long optical path length between the source and detector, atmospheric absorption is a serious problem. Secondly, trace amounts of water can obscure the normally weak absorption by the sample. In addition efficient low-noise far-IR detectors are scarce.

Two different approaches have been taken to solve some of these severe problems. Both grating far-IR spectrophotometers and interferometers have been constructed in various laboratories. Both types of instruments have been marketed commercially. In principle the interferometer has significant advantages over the grating spectrometer, but high quality spectra have been obtained with both types of instrument. It has only been in the last few years, with the advent of commercially available, rapid-scanning interferometric spectrometers, that the potential of this technique has begun to be widely exploited.

The problem of absorption of the far-IR radiation by atmospheric water vapor has been approached in two ways. The first way is to seal the spectrometer compartment and purge it with a source of dry air or nitrogen. Typically, the boiloff from liquid nitrogen has been used. Readers acquainted with the use of mid-IR spectroscopy are aware of the problems with the vibration-rotation spectra of water and CO_2 in the mid-IR. These can cause interference unless removed by purging. The problem in the far-IR is considerably more significant. The pure rotational spectrum of water in the far-IR is many times more intense than the vibration-rotation spectrum in the mid-IR. Consequently, the demands on a purge system are much more severe. A second, and ultimately better, technique is to evacuate the spectrometer. The vacuum attained does not have to be a high vacuum, ca. 100 mtorr being sufficient. The remaining water vapor absorption is such that it may be ratioed out on a double-beam grating spectrometer or ratioed out by comparison with the background in an interferometric spectrometer.

The only remaining problem is removal of water from the sample. For samples with intense far-IR spectra this is less of a problem than for those with weak spectra. For intense spectra, pressures of a few torrs and path lengths of ca. 10 to 30 cm are sufficient. Polyethylene is used as the window material. For samples with weak far-IR absorption full vapor pressure of the sample may be used with path lengths as long as 40 m. The sample cells in this case are multiple-reflection cells with mirrors at each end. The number of traversals of the cell, and thus the path-length, is determined by adjusting the orientation of the mirrors. For the cyclopentene molecule, 0.05% water in the sample would lead to full-scale water lines at ca. 100 cm^{-1} under the conditions required to obtain the spectrum (10). Consequently, scrupulous drying of the sample and sample-handling equipment is essential.

Finally, the obtainable signal to noise ratio may be severely limited by the detector. Rapid-scanning interferometers with room-temperature detectors rely on extensive signal averaging to obtain reasonable signal to noise ratios. Although expensive to operate, liquid helium-cooled bolometers have given good results.

Despite all these difficulties, far-IR spectroscopy is a viable technique in the study of the out-of-plane modes of ring molecules. However, the application requires considerably more effort than do the normal uses of mid-IR spectroscopy.

B. Raman Spectroscopy

Around 1970, argon ion lasers became available with output powers greater than 1 W at 488.0 nm and 514.5 nm. Coupled with good double monochromators available from several manufacturers, these allow the observation of many ring-puckering spectra at low-frequency shifts from the exciting line. Many of the same considerations concerning band types and

vibration-rotation selection rules that are a factor in locating the band origins in far-IR spectra are applicable. Figure 8 indicates two drastically different band types in the Raman

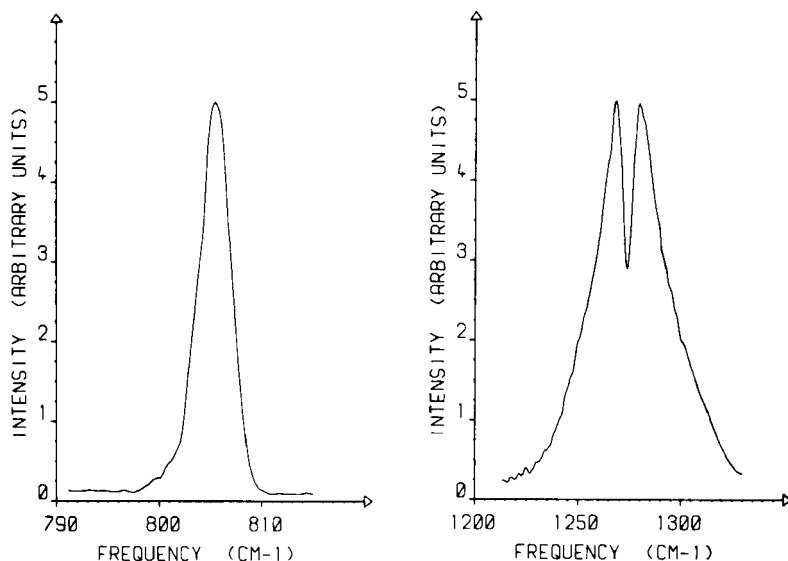


Fig. 8. Examples of a totally symmetric and nontotally symmetric vibration-rotation band in a Raman spectrum.

spectrum of a gaseous sample. The first is a totally symmetric vibrational mode consisting of a highly intense, sharp Q branch ($\Delta J = 0$). The accompanying O ($\Delta J = -2$) and S ($\Delta J = +2$) branch envelopes are significantly weaker and are not evident in Fig. 8. The second band, however, results from a nontotally symmetric mode and exhibits no sharp features.

The sharpness of the Q branches of totally symmetric Raman bands makes them desirable for complex overlapped ring-puckering spectra. However, with the exception of molecules having C_s symmetry where the symmetry plane is perpendicular to the ring (e.g., chlorocyclobutane) (11) and the trivial case of C_1 symmetry, the ring-puckering vibration is not totally symmetric. If, however, there is substantial electrical anharmonicity, the $\Delta v = 2$ transitions, which start from and terminate on energy levels of the same symmetry, are allowed. These "overtone" or "double-jump" transitions are totally symmetric, and consequently have sharp Q branches whose maxima occur close to the band origins. The prominent features in the low-frequency Raman spectrum of silacyclobutane (Fig. 5) are the totally symmetric $\Delta v = 2$ transitions. The sharpness of the Q -branch transitions for $\Delta v = 2$ transitions and the application of Raman spectroscopy to ring molecules have been most widely utilized by J. R. Durig and co-workers at the University of South Carolina (12).

The resolution of ring-puckering motions attainable in Raman spectroscopy has typically been 1 to 5 cm^{-1} , less than that for far-IR studies (ca. 0.10 to 1 cm^{-1}). The two techniques have proven to be complementary, and on several occasions Raman data have allowed determination of potential functions when interpretable far-IR spectra proved difficult or impossible to obtain.

The primary reason for the lower resolution obtainable from Raman spectroscopy lies in the weakness of the Raman effect and the necessity of using a double monochromator, with consequent lower throughput, to eliminate stray light. One approach is to use high-power lasers. Some spectra have been obtained with laser powers as high as 10 W at the laser head. The limitation here is the sample. Not all samples can be subjected to powers this high without decomposing, particularly if condensation occurs on the windows. Multipass cavities in which the laser is reflected and refocused a number of times (16 to 20) in the sample have been used to increase the signal. The windows on the cell, usually quartz, are mounted at the Brewster angle to minimize reflection losses, since a number of traversals are made. In addition the Raman signal may be almost doubled by placing a spherical mirror 180° from the monochromator entrance slits on the other side of the sample, and refocusing the scattered light back into the sample and then on the entrance slits of the monochromator.

Because of the compact size of the sample cells (ca. 1 cm diameter $\times$ 4.0 cm) it has proven convenient to heat liquid samples to obtain a higher vapor pressure and consequently a stronger Raman signal. The most common and most successful technique has been to blow warm air on the sample cell, which has a reservoir containing excess sample. The main problem is making sure that the windows are heated to avoid condensation and subsequent destruction of the sample. Temperatures used have ranged up to 150°C. Many spectra of gas-phase samples have been obtained in this fashion which would not have been possible otherwise. Although heated multiple-reflection cells have been used in far-IR spectroscopy (13), this is much less convenient than with Raman spectroscopy.

C. Mid-IR and Mid-Raman Spectroscopy

Mid-IR and mid-Raman spectroscopy deal with the higher frequency regions ($\sim$ 300 to 4000 cm^{-1}) corresponding to the fundamentals of the small-amplitude vibrations. In principle these vibrations may have different selection rules depending on the difference in symmetry between the planar and nonplanar ring conformation(s). This may allow determination of the planarity or nonplanarity of the ring molecule. In practice this is a very poor approach if the barriers at the planar conformation are ca. 1 to 2 kcal/mol or less. Even though, in

principle, selection rules may differ, the "allowed" modes for the lower symmetry may be extremely weak. When mistakes are made in applying these techniques to molecules with large-amplitude modes, it is almost always in incorrectly choosing the higher symmetry.

Ueda and Shimanouchi in 1967 pointed out the occurrence of difference-band progressions involving the ring-puckering vibrations and CH stretching modes in the mid-IR spectra of a number of ring molecules (14). The band progressions were compared with the known energy separations for some molecules that had been studied in the far-IR. For others, for which far-IR data

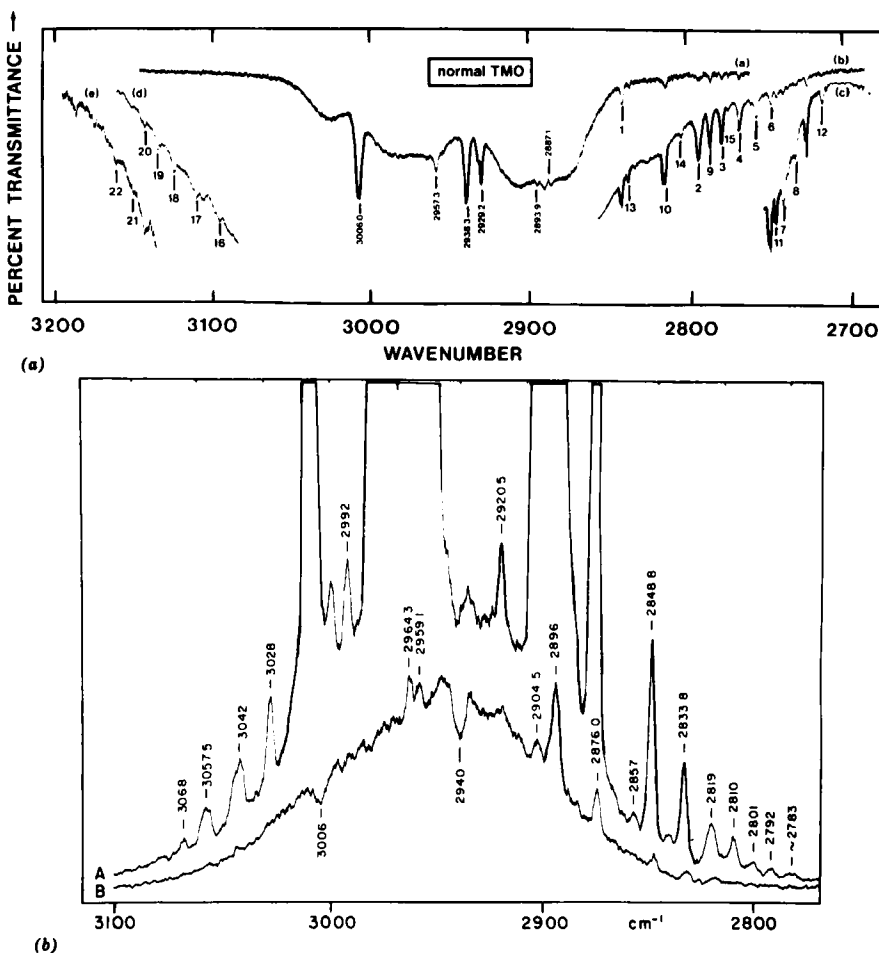


Fig. 9. Ring-puckering combination and difference-band progressions in the CH stretching region of the mid-IR (a) and mid-Raman (b) spectra of trimethylene oxide.

(Reproduced with the permission of the American Institute of Physics, from ref.29.)

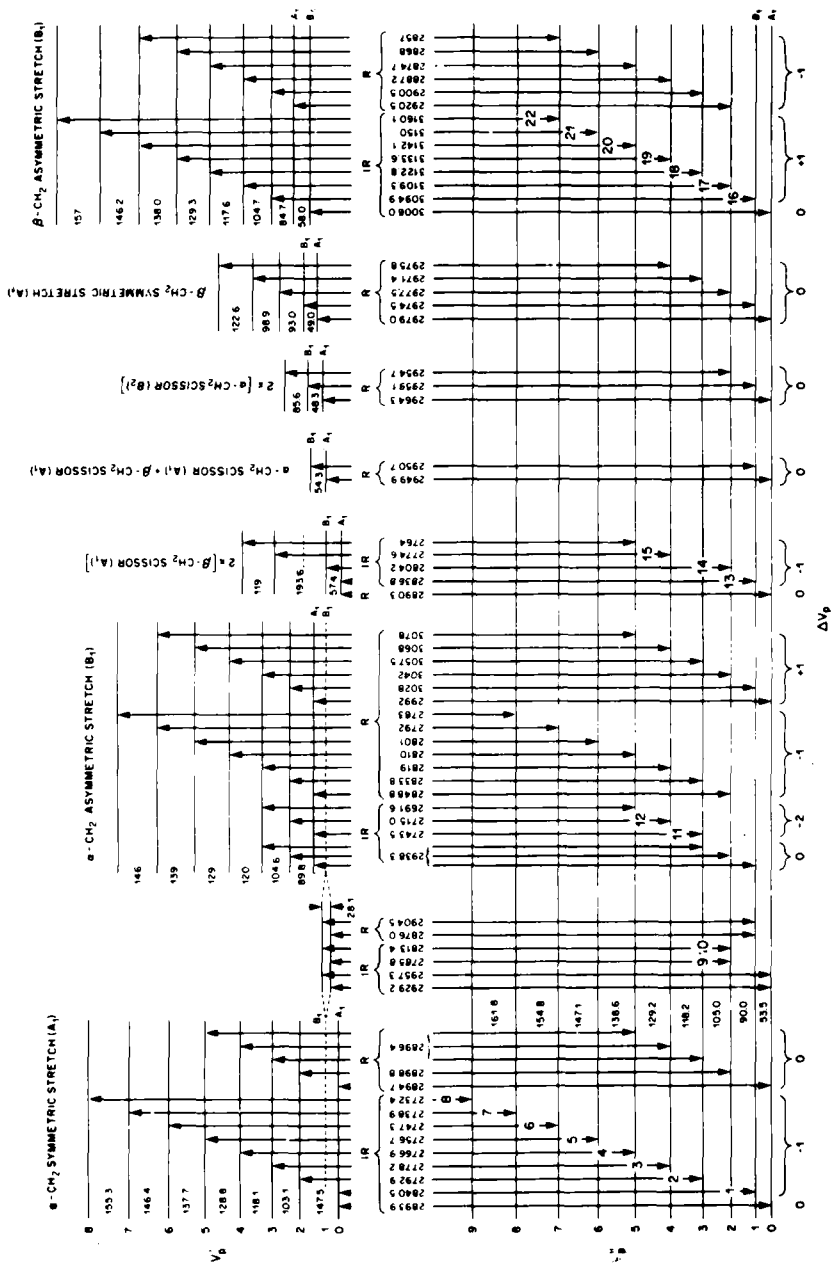


Fig. 10. Assignment of some of the transitions in the mid-IR and mid-Raman spectra of trimethylene oxide. (Reproduced with the permission of the American Institute of Physics, from ref. 29.)

were not available, the ring-puckering potential functions were approximately determined from the difference-band progressions. Since then numerous band progressions involving ring-puckering vibrations have been reported (15-29). Similarly, band progressions have been observed in the fundamental region of the Raman spectra of ring molecules (29-33).

Extensive studies of the far-IR, low-frequency Raman, mid-IR and mid-Raman spectra of trimethylene oxide and several of its deuterated analogues have been reported by Wieser and co-workers (27,29-31,34-36). Figure 9 indicates the rather extensive ring-puckering structure observed near the CH-stretching region for trimethylene oxide in the mid-IR and mid-Raman spectra. The assignment of the various transitions for trimethylene oxide is shown in Fig. 10. Combination and difference-bands progressions involving ring-puckering and other small-amplitude modes have been observed. The transitions shown in Fig. 10 are transitions between vibrational levels. Each one of these transitions has its own associated rotational structure (e.g. Fig. 6), and the discussion of band types appropriate to far-IR and low-frequency Raman spectra applies. However, the band types now depend on the types corresponding to the direct product of the symmetry species of the ring-puckering vibration and the particular reference vibration in question.

In dealing with combination- or difference-band progressions, it is possible to describe the transitions by changes in two quantum numbers. For any single progression only the change in a reference-band quantum number v_R , that is, the small-amplitude vibration, and a ring-puckering quantum number v_p are involved. The fundamental transition of the small-amplitude mode is described by $\Delta v_R = +1$, $\Delta v_p = 0$, where it is understood that the quantum numbers corresponding to the other modes do not change. For combination-band progressions in the mid-IR or Raman spectra, $\Delta v_R = +1$ and $\Delta v_p = +1$. In Fig. 10 the IR transitions marked 16 to 22 are combination bands, and follow the above selection rules. Difference-band progressions originate from excited states of the ring-puckering vibration. In this case $\Delta v_R = +1$ and $\Delta v_p = -1$. IR bands 1 through 8, among others, in Fig. 10 are examples of difference-band progressions.

Combination- and/or difference-band progressions may arise from anharmonic cross terms in the potential function. The most likely are terms of the form $x^2 q_R^2$, where x is the ring-puckering and q_R is the coordinate corresponding to the reference vibration. As may be seen from Fig. 10, the ring-puckering intervals in the excited state of the reference transition differ slightly from those in the ground state. This is caused by the dependence of vibrational averaging over the small-amplitude modes on the quantum state of these modes.

Due to the effects mentioned in the preceding paragraph, as well as the possible occurrence of other progressions or weak bands interleaved with the ring-puckering progressions, it is sometimes difficult to arrive at an unambiguous assignment.

This is particularly true if the vibrational spacings for the ring-puckering are not known in advance from direct observation in the far-IR or Raman spectrum, or if only one progression, the combination or the difference progression, is observed from a particular reference band. However, combination- and difference-band progressions may yield data when the large-amplitude modes are inactive or are too weak to be observed in the Raman or far-IR spectra. The pseudorotational mode in cyclopentane is an example of such a case (22).

D. Microwave Spectroscopy

After the end of World War II applications of microwave spectroscopy to the study of molecular rotational spectra were possible because of the development of various components for microwave radar. The application of microwave spectroscopy to the analysis of ring-puckering in molecules was first done by Gwinn and co-workers at the University of California at Berkeley in the early 1960s. This group was responsible for many of the theoretical advances that allowed interpretation of the spectra (37-40).

With the development of reliable backward-wave-oscillator sources it became possible to scan an entire frequency band in the microwave spectrum of 3-thietanone (4-1) obtained in the R-band region (26.5 to 40.0 GHz) (Fig. 11). For comparison to IR

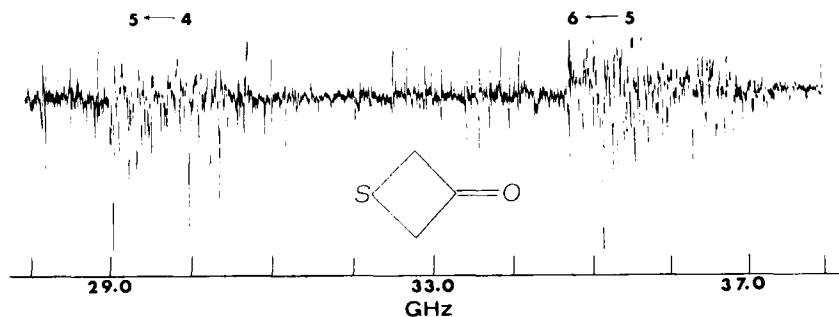


Fig. 11. Microwave spectrum of 3-thietanone in the R-band region (26.5 to 40.0 GHz). Pressure = 80 mtorr, path length = 6 ft, Stark field = 2000 V/cm. Zero field lines are down, Stark lobes are up. (Reproduced with the permission of Academic Press Inc. New York,) (ref.41.)

and far-IR spectra it should be noted that this frequency range corresponds to ca. 0.9 to 1.3 cm^{-1} . For a period in the late 1960s and early 1970s microwave spectrometers were commercially available. Most of these found their way to university research laboratories, and when widespread industrial and government laboratory markets failed to materialize, marketing was discontinued. Most of the components of these spectrometers are still

available, and it is still possible to assemble a microwave system.

Usually transitions between rotational levels associated with a particular vibrational state are observed in a microwave study. In Fig. 6 this would correspond to keeping v constant and causing transitions between levels with different rotational quantum numbers. Because of the Boltzmann population of excited states of the large-amplitude motions, a number of vibrational satellites, that is, rotational transitions from vibrationally excited states, may be observed. These are shifted in frequency from the ground-state lines because of the differences in averaging the rotational constants over the different vibrational states (eq. [10]).

For a small-amplitude vibration the variation of rotational constants with vibrational quantum number is expected to be linear:

$$\beta_v = \beta^{(e)} + \sum_{i=1}^{3N-6} \alpha_i (v_i + 1/2) \quad [12]$$

where β is the A , B , or C rotational constant. Due to the large-amplitude nature of ring-puckering vibrations as well as the anharmonic nature of the potential functions, the variation of the rotational constants with ring-puckering vibrational state may deviate from the linear behavior predicted by eq. [12].

The expected results may be classified according to the type of potential function. For a molecule with a single-minimum potential function the vibrational energy spacings are, in general, small (ca. 50 to 150 cm^{-1}), but they are still large compared with rotational energy spacings. Consequently, vibrational and rotational motions may be separated, and rigid rotor spectra are observed in the microwave with different effective rotational constants for the different vibrational states. The variation of the A rotational constant for 3-thietanone is shown in Fig. 12. The variation, while regular, shows a definite curvature as opposed to the linear behavior indicated by eq. [12].

For a ring molecule with a symmetric double-minimum potential function, several cases may be distinguished. For a very low barrier, that is, one of the order of the ring-puckering zero-point energy, the resulting microwave spectrum is similar to that described for the single-minimum potential function (38). Rigid rotor spectra are observed and, with the exception of the lowest few levels, there is a regular variation of rotational constants with vibrational state. The ring-puckering spectrum observed in the far-IR or Raman spectrum and the variation of rotational constants from the microwave spectrum are exceptionally sensitive to the presence of even a small barrier. For cyclobutanone (42-44) the barrier of 7.6 cm^{-1} (ca. 0.02 kcal/mol) is well below the zero-point energy of 16.8 cm^{-1} . Figure 13 indicates the variation of the A rotational constant. The irregularity is indicative of a small

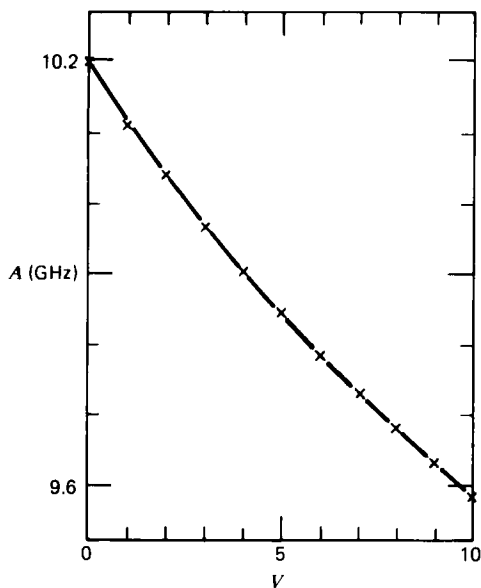


Fig. 12. Variation of the A rotational constant for 3-thietanone with ring-puckering vibrational state. (From data in Ref. 41.)

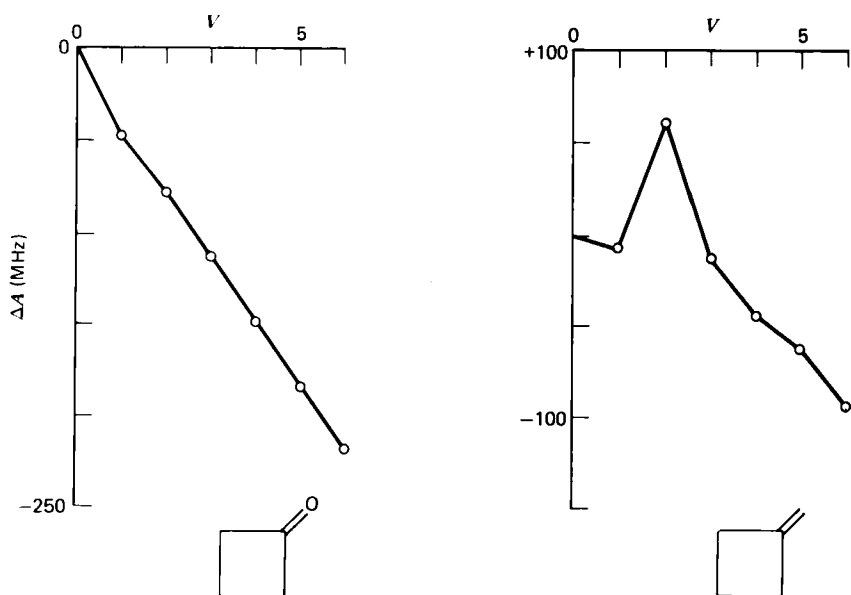


Fig. 13 Variation of the A rotational constants with ring-puckering vibrational state for cyclobutanone and methylenecyclobutane. (From data in Ref. 44 and 45.)

barrier, illustrating the exceptional sensitivity to the details of the potential function. The presence of this small barrier is also indicated by the pattern of transition frequencies in the far-IR spectrum(43).

If a barrier to planarity is intermediate (ca. 100 to 500 cm^{-1}), the ring-puckering levels below the barrier begin to coalesce into closely spaced doublets. This can lead to vibrational energy spacings that are on the order of rotational energy spacings. For these doublets, vibration and rotation cannot be treated separately. Nonrigid rotor spectra arise, and the vibrational dependence of rotational constants may be quite irregular. The latter is illustrated for methylenecyclobutane in Fig. 13 (45). For this molecule the 0-1 vibrational spacing is ca. 1 cm^{-1} , which corresponds to typical rotational energy spacings. Nonrigid rotor spectra were observed for these two states. Similarly, for trimethylene sulfide the 0-1 vibrational splitting is ca. 0.27 cm^{-1} , leading to large vibration-

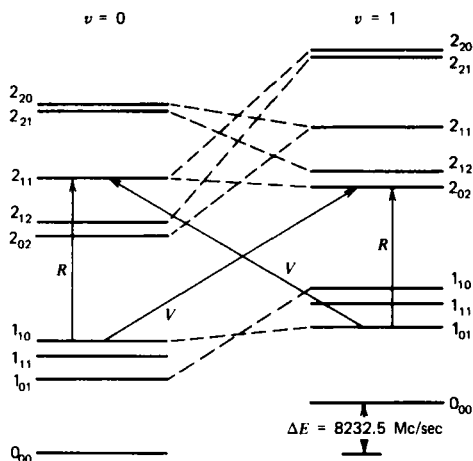


Fig. 14. Vibration-rotation energy levels for trimethylene sulfide. The dashed lines indicate the symmetry-allowed interactions between rotational states in the $v = 0$ and $v = 1$ vibrational states. These interactions cause the levels to shift from their unperturbed positions, and nonrigid rotor spectra result. (Reproduced with the permission of the American Institute of Physics, from ref. 40.)

rotation interactions (40). This is illustrated in Fig. 14. A similar zig-zag dependence of rotational constants is also observed for this molecule.

When the barrier to planarity is very large for a symmetric double-minimum potential function, the levels are doubly degenerate pairs that split as the top of the barrier is approached. As long as the rotational spectra are studied in

vibrational levels that are low in energy with respect to the barrier height, rigid rotor spectra and a regular variation of rotational constants with respect to barrier height are to be expected. These cases may be distinguished from the single-minimum results, since the values of the rotational constants are indicative of a nonplanar ring.

For molecules with asymmetric potential functions, the single-minimum and low-barrier double-minimum cases are similar to those described for symmetric cases. For intermediate to high barriers the levels are no longer pairs, but correspond, below the barrier, to specific conformations. Rigid rotor spectra are expected in all cases.

III. EXAMPLES OF APPLICATIONS

A. One-Dimensional Potential Functions

Several examples of ring molecules with symmetric potential functions have been given in the preceding sections. Several one-dimensional potential functions have been used. For single-minimum potential functions the simplest function having positive anharmonicity is

$$V(x) = ax^4 + bx^2 \quad [13]$$

where $a > 0$, $b \geq 0$.

This may also represent a double-minimum oscillator when $a > 0$, $b < 0$. Another double-minimum function is represented by

$$V(x) = bx^2 + ce^{-dx^2} \quad [14]$$

which is a harmonic oscillator with a Gaussian barrier. Some workers have included a quartic term for shaping the walls at large amplitude, resulting in

$$V(x) = ax^4 + bx^2 + ce^{-dx^2}. \quad [15]$$

By far, eq. [13] has been the most widely used. When it proves adequate, it is the most desirable, since it contains only two adjustable parameters, as opposed to three in eq. [14] and four in eq. [15].

The use of eqs. [13] through [15] requires knowledge of the reduced mass of the molecule for the vibrational motion represented by the coordinate x (Fig. 1). This is complicated by the fact that, due to the large amplitude of vibration, this reduced mass may be a function of x . The ramifications of this have been discussed by several authors (Appendix I). For the purpose of determining barrier heights the use of a constant reduced-mass Hamiltonian is quite adequate. In fitting spectroscopic data a Hamiltonian in a reduced or dimensionless

coordinate is all that is required. Only if a dihedral angle corresponding to a potential minimum is desired, is it necessary to know the reduced mass. One coordinate that has been used yields a Schrödinger equation:

$$A\left(-\frac{d^2}{dz^2} + Z^4 + BZ^2 = \lambda\right)\psi \quad [16]$$

where $Z = (2\mu a/\hbar^2)^{1/6}x$ and the vibrational energy is given by $A\lambda$. The value of a is that appearing in eq. [13], μ is the reduced mass, and $\hbar$ is Planck's constant divided by 2π . The relation between this and the other reduced coordinates that have been used is described in Appendix II. Reduced equations cor-

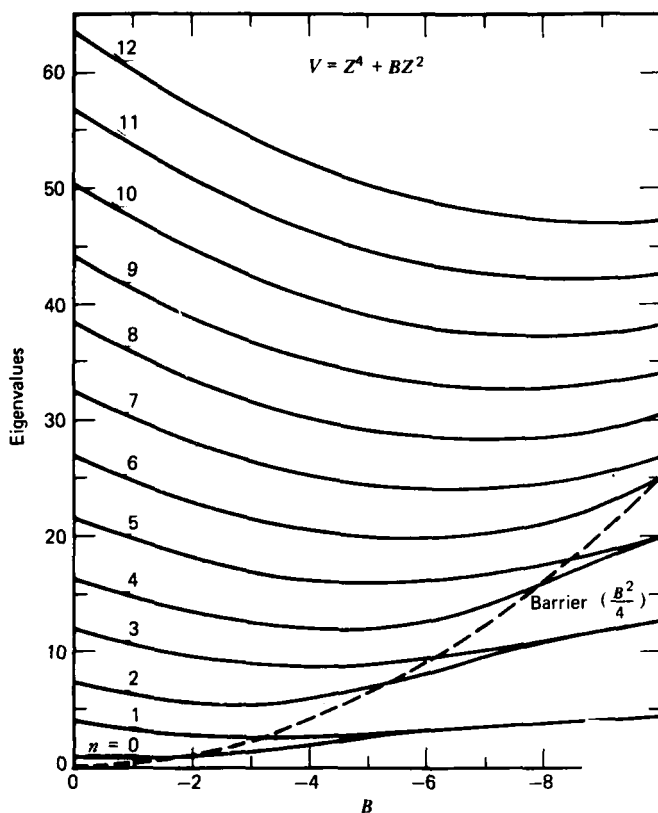


Fig. 15. Eigenvalues of the dimensionless Schrödinger equation (eq. [16]). The eigenvalues for the dimensionless potential $V = Z^4 + BZ^2$ are shown for $B < 0$. The barrier height is shown as a dashed line (barrier = $B^2/4$ for $B < 0$). (Reproduced with the permission of the American Institute of Physics from ref. 10.)

responding to the potential functions given in eqs. [14] and [15] may also be described.

Equation [16], as it stands, cannot be solved in closed form, but must be solved numerically. Several discussions of the linear variation method applied to the solution appear in the literature (38,40,46-50). Figure 15 indicates the variation of the dimensionless eigenvalues λ as a function of B .

1. 3-Thietanone

3-Thietanone, mentioned earlier, is an example of a ring molecule having a symmetric, single-minimum potential function. The microwave spectrum in the R-band region is shown in Fig. 11. Figure 16 indicates the far-IR spectrum and the associated potential function (51). In this case the c-type Q-branch transitions are severely degraded due to a combination of two factors. First, in 3-thietanone $A \gg B \approx C$, and c-type bands inherently do not have prominent Q branches in this limit. Second, the rotational constants change rather markedly with vibrational state and degrade the Q branch further. The band origins occur ca. 0.3 to 0.4 cm^{-1} to the low-frequency side of the Q-branch maxima and were so corrected in the far-IR study. The observed frequencies were then fitted by a least squares adjustment of the two parameters appearing in eq. [16], A and B , yielding a good fit. The potential function, in the dimensionless coordinate Z , is given by

$$V(\text{cm}^{-1}) = 9.90 (Z^4 + 6.17Z^2) \quad [17]$$

The procedure followed to fit the variation of the rotational constants with vibrational state is that used successfully by Gwinn and co-workers (38-40). The rotational constants are expanded in power series in the rotational constants, and averaged over the vibrational state:

$$\beta_v = \beta(0) + \beta(2) \langle v | Z^2 | v \rangle + \beta(4) \langle v | Z^4 | v \rangle \quad [18]$$

where β_v is the A , B , or C rotational constant, and $\beta(0)$, $\beta(2)$, and $\beta(4)$ are empirical parameters determined by fitting the data. The potential constant B in eq. [16] depends on the microwave data in the sense that the expectation values of Z^2 and Z^4 depend on the vibrational state and consequently on the vibrational wave functions. The rotational constants, however, do not depend on A , which is simply a scale factor, and are better determined by relating eigenvalue differences $\lambda_{v+1} - \lambda_v$ to frequencies $A(\lambda_{v+1} - \lambda_v)$ measured in the far-IR spectrum. The procedure used for 3-thietanone was to simultaneously fit the far-IR frequencies and the microwave rotational constants by a least

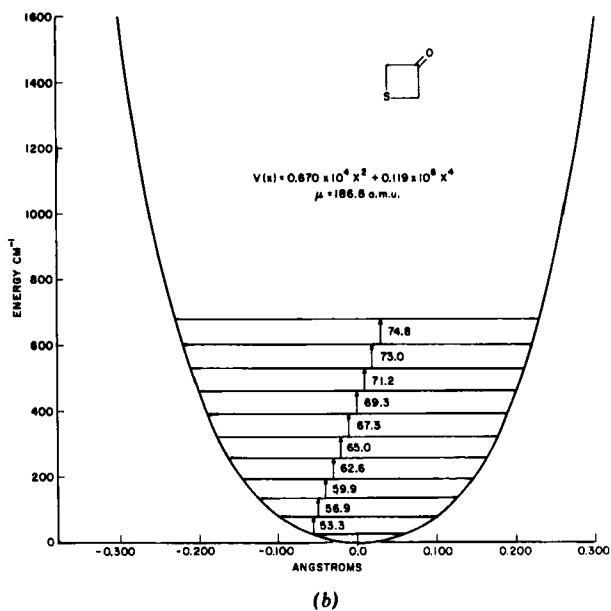
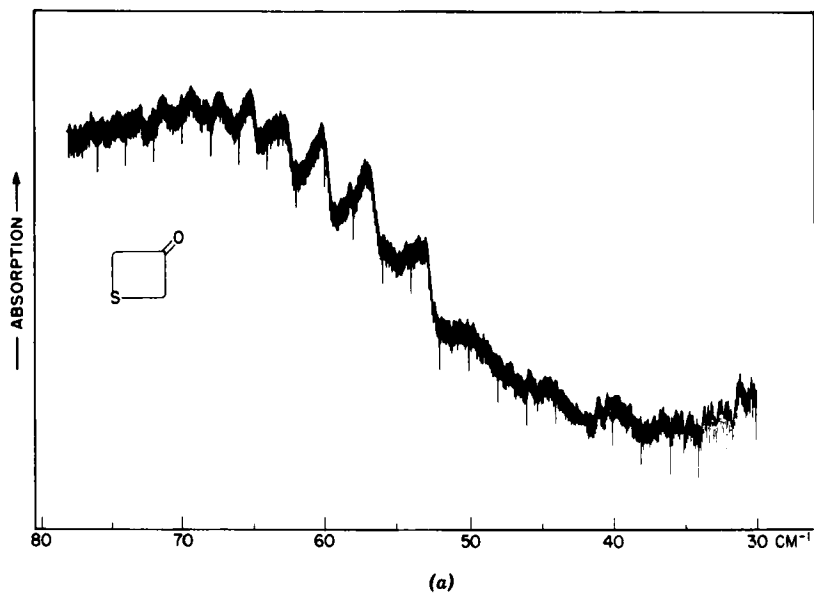


Fig. 16. Far-IR spectrum (a) and ring-puckering potential function (b) for 3-thietanone. Pressure ca. 1 torr, path length = 20 m. (Reproduced with the permission of Academic Press, New York, from ref.51.)

squares adjustment of A and B, the potential function parameters in eq. [16], and the rotational constant-expansion coefficients in eq. [18]. The potential function compares favorably with that determined by fitting the far-IR data alone (eq. [12]). The ability to fit both microwave and far-IR data with the same potential function is gratifying.

The experimental results on 3-thietanone indicate that the out-of-plane mode is anharmonic and large in amplitude. The fact that it was possible to determine the vibrational spacings to such a high vibrational quantum number ($v = 10$) is a result of the high population of the excited states at room temperature and the increased intensity of high v transitions for molecules having a substantial quartic anharmonicity. Similarly, the high population of the excited states allowed observation of the rotational spectra originating from a number of these states at room temperature.

At this stage the interpretation of the experimental data is finished. However, as shown by Gwinn and co-workers for several ring molecules, it is possible to determine something more of the dynamics of the ring vibration by a model calculation (38). The model error may be quite large, and only qualitative agreement with experimental data is expected. In the model used for the ring-puckering vibration, the methylene groups are assumed to share a common bisector with the adjacent C-C-S angle, and maintain a constant HCH angle. The carbonyl group is assumed to bisect the C-C-C angle. All bond distances were assumed to remain constant. With these restrictions there are two extremes that may describe the ring-puckering vibration. These are shown in Fig. 17. The ring may bend by fixing the C-C-C and C-S-C angles and moving the sulfur atom, or the C-C-S angles may be fixed and the ring bent by moving the methylene groups. These two models lead to the same reduced mass for infinitesimal displacements. However, if we calculate the moments of inertia and then the rotational constants as a function of x , half the perpendicular distance between ring diagonals, it is different for the two models. The predicted variation of the rotational-constant variation as well as those calculated for the two models (Fig. 17) is shown in Fig. 17. The best fit is obtained for a model for which the C-S distance changes ca. 5 times as much as the change in the C-C distance. For this model the two C-C-S angles, which have force constants somewhat greater than the C-S-C angle bending, but considerably less than the C-C-C angle bending (sp^2 hybridization), change by greater amounts than those of the other two angles. That the C-C distance changes at all is probably caused by the small C-S-C bending force constant somewhat balancing the effect of the large C-C-C force constant. The model calculation does not yield a perfect fit to the rotational-constant variation, but it does lead to a result that is quite physically reasonable;

$$\begin{array}{c} \text{O} \\ || \\ \text{C-C-C} \end{array}$$

this is, the C-C-C angle, which is the most highly strained,

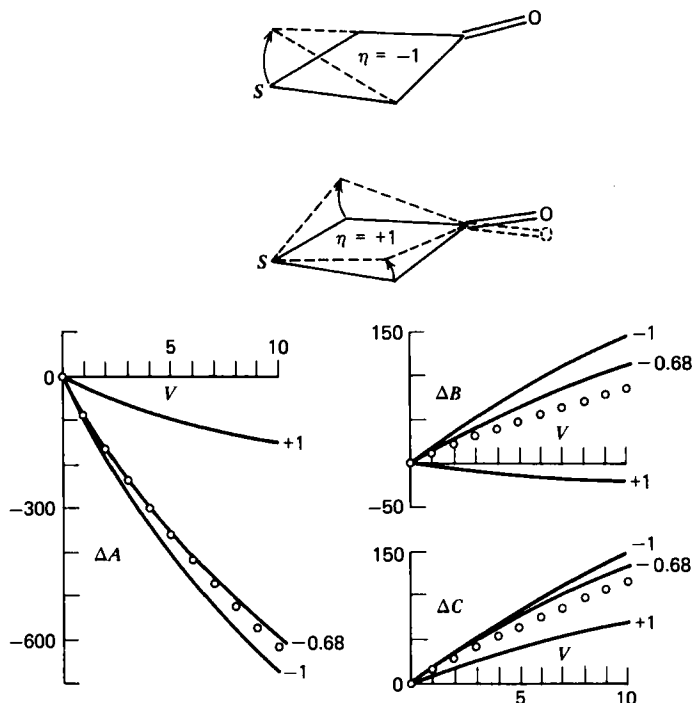


Fig. 17. Two limiting models for the ring-puckering vibration in 3-thietanone. Here $\eta = -1$ corresponds to fixing the nonbonded C-C distance, and $\eta = +1$ corresponds to fixing the nonbonded C-S distance. For $\eta = 0$ the change in the nonbonded C-C and C-S distances are equal. The observed rotational-constant variation with ring-puckering state is shown along with that calculated for $\eta = -0.68$, which gives the best fit. (Reproduced with the permission of Academic Press, New York, from ref. 41.)

does not decrease to any great extent during the vibration.

For four-membered-ring molecules the ring-puckering potential functions represent a delicate balance between two rather large effects. In general, ring angles in these cases are smaller than their unstrained values. Since ring angles are maximized at the planar conformation, angle strain favors this conformation. On the other hand torsional interactions between adjacent groups tend to favor staggered conformations about the ring bonds, corresponding to nonplanar ring conformations.

2. 1,2-Dimethylenecyclobutane

In the molecule 1,2-dimethylenecyclobutane there is an additional factor. A planar carbon skeleton is favored by the delocalization of the π electrons. The microwave spectrum was

assigned in the ground state and four excited states of the ring-puckering vibration (52). The rigid rotor fits are found to be quite adequate. The rotational constants A , B , and C in the ring-puckering vibrational states are shown in Fig. 18. The variation, while exhibiting curvature, is smooth, as opposed to that

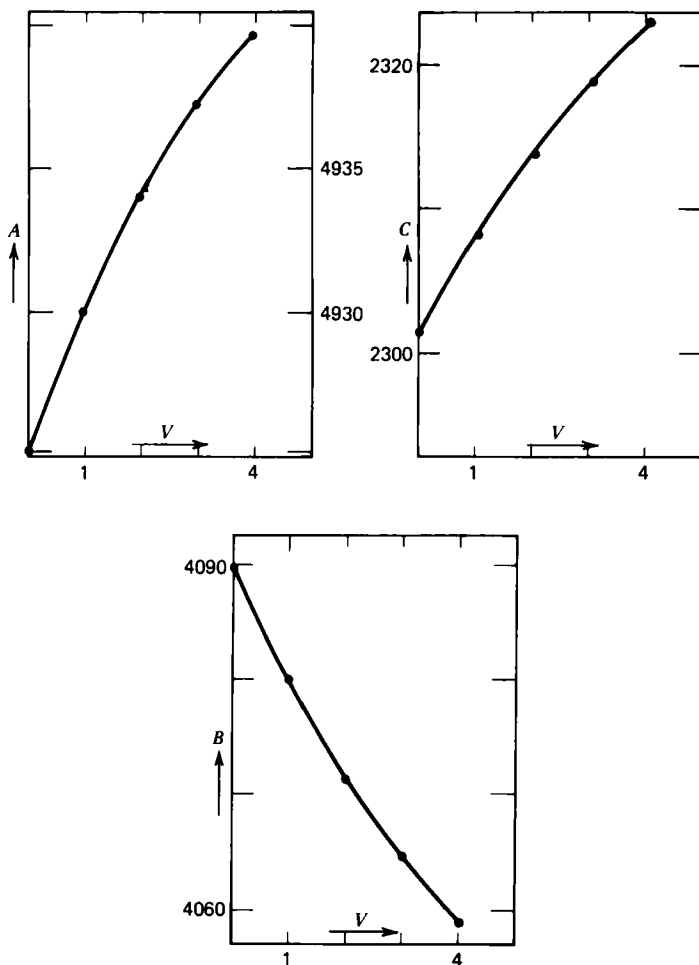


Fig. 18. Rotational constants (MHz) vs. ring-puckering vibrational state for 1,2-dimethylenecyclobutane. (Reproduced with the permission of Academic Press, New York, from ref. 52.)

shown for cyclobutanone in Fig. 13. Consequently, we may state that the potential function definitely has a single minimum and that all six carbon atoms are coplanar. Figure 13 indicates that even a barrier as small as 0.02 kcal/mol is detectable by this technique.

3. 2,5-Dihydrofuran

As shown in Fig. 2, a five-membered-ring molecule has two out-of-plane ring vibrations. For a five-membered-ring molecule with an endocyclic double bond, such as 2,5-dihydrofuran, one of these modes, the twisting about the C=C double bond, is higher in frequency. The other mode, the ring-puckering, is low in frequency and large in amplitude. The first approximation is to neglect the coupling of the ring-puckering with all the other modes, including the ring-twisting. Such five-membered-ring molecules have been termed pseudo-four-membered-ring molecules, and the ring-puckering treated as outlined above. The far-IR spectrum of 2,5-dihydrofuran was first reported by Ueda and Shimanouchi in 1967 (46), and fitted with a single-minimum, one-dimensional potential function of the form of eq. [13]. Higher resolution spectra obtained by Carreira and Lord (6) showed the existence of a satellite series of ring-puckering transitions shifted to higher frequency (Fig. 19). These are the ring-puckering transitions originating from the first excited state of the ring-twisting vibration. The fact that they are shifted in frequency from the ground-state transitions indicates the presence of an anharmonic coupling term in the potential function. However, it is possible to derive an effective one-dimensional ring-puckering potential for the two series of transitions separately. The potentials in the reduced coordinate of eq. [16] are given by

Ground state of twisting:

$$V(\text{cm}^{-1}) = 24.6 (Z^4 + 2.93 Z^2) \quad [19a]$$

Excited state of twisting:

$$V(\text{cm}^{-1}) = 24.9 (Z^4 + 2.99 Z^2) \quad [19b]$$

The potential function for the ground-state series is also shown in Fig. 19. Later Carreira, Mills, and Person used a two-dimensional Schrödinger equation with constant effective masses to simultaneously fit both series of ring-puckering transitions and the ring-twisting from the Raman spectrum (53). This two-dimensional equation is given by

$$\frac{\hbar^2}{2\mu_1} \frac{\partial^2 \psi}{\partial x^2} - \frac{\hbar^2}{2\mu_2} \frac{\partial^2 \psi}{\partial y^2} + (a_1 x^4 + b_1 x^2 + a_2 y^4 + b_2 y^2 + a_{12} x^2 y^2) \psi = E \psi \quad [20]$$

where x is the ring-puckering coordinate, y is the ring-twisting coordinate, and μ_1 and μ_2 are the associated reduced masses. Odd power terms are not present because of symmetry, and the $x^2 y^2$ cross term is the lowest degree cross term allowed by symmetry. Recently, Malloy and Carreira have shown that effective one-dimensional potential functions for 2,5-dihydrofuran, along with the fundamental frequency of the twisting vibration, may be used to estimate the coefficient of the cross term in eq. [20] (54). For the ground state of the twisting mode the effective potential in dimensioned coordinates is given by

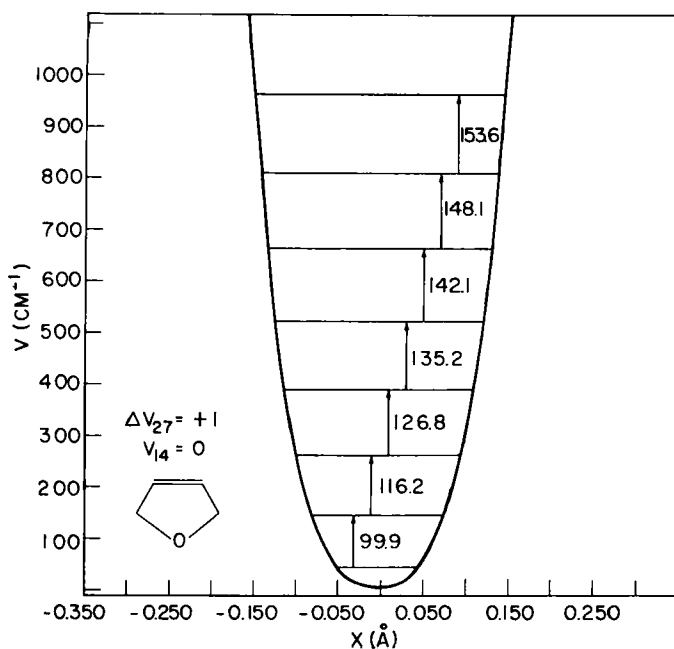
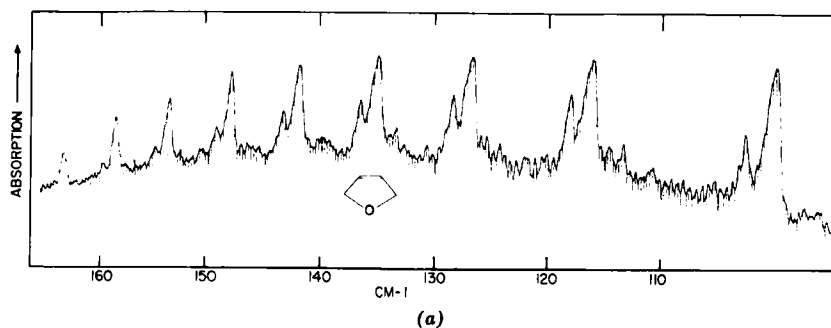


Fig. 19. Far-IR spectrum (a) and ring-puckering potential function (b) for 2,5-dihydrofuran. Pressure = 60 torrs, path length = 30 cm, resolution ca. 0.2 cm^{-1} . The satellite series of ring-puckering transitions originating from the first excited state of the ring-twisting mode is visibly shifted to higher frequencies. The potential function is for the ground-state series. (Reproduced with the permission of the American Institute of Physics, from ref. 6.)

$$V_0(x) = a(0)x^4 + b(0)x^2 \quad [21]$$

and the potential function in the first excited state is given by

$$V_{1,i}(x) = a(1)x^4 + b(1)x^2 \quad [22]$$

In these equations the effective potential constants may be related to those in eq. [20] by

$$a(i) = a_1 + a_{12}^2 \sum_{v_2 \neq i} \frac{\langle i | y^2 | v_2 \rangle^2}{E_i - E_{v_2}} \quad [23a]$$

and

$$b(i) = b_1 + a_{12} \langle i | y^2 | i \rangle \quad [23b]$$

For 2,5-dihydrofuran and related molecules the wavefunctions required to calculate the matrix elements of y^2 may be approximated as a harmonic oscillator with the appropriate twisting frequency and the value of a_{12} , a_1 , and b_1 thus determined from the preceding equations.

All these refinements on the initial study of 2,5-dihydrofuran have led to a more complete understanding of the out-of-plane ring motions. They have shown that the approximations made still lead to a single-minimum potential function with a substantial anharmonicity. They have also shown that some care must be taken in reaching conclusions on the precise values of potential constants (eq. [19a] and [19b]) subject to interactions with other modes.

4. Analogues of Bicyclo[3.1.0]hexane

Like unsaturated five-membered-ring molecules, analogues of bicyclo[3.1.0]hexane may be considered to be pseudo-four-membered-ring molecules. A six-membered-ring molecule has three out-of-plane ring vibrations. For bicyclo[3.1.0]hexane analogues these may be characterized as a rocking motion of the three-membered ring, a twisting vibration of the five-membered ring, and a ring-puckering vibration of the five-membered ring. These are illustrated in Fig. 20. The rocking and twisting modes are essentially harmonic, while the ring puckering is quite anharmonic.

The potential function appropriate for the ring-puckering is the given in eq. [7], where the cubic term indicates the lower symmetry of the molecule. In the dimensionless coordinate z the Schrödinger equation is given by

$$A \left(-\frac{d^2}{dz^2} + z^4 + Bz^2 + Cz^3 \right) = \lambda \psi \quad [24]$$

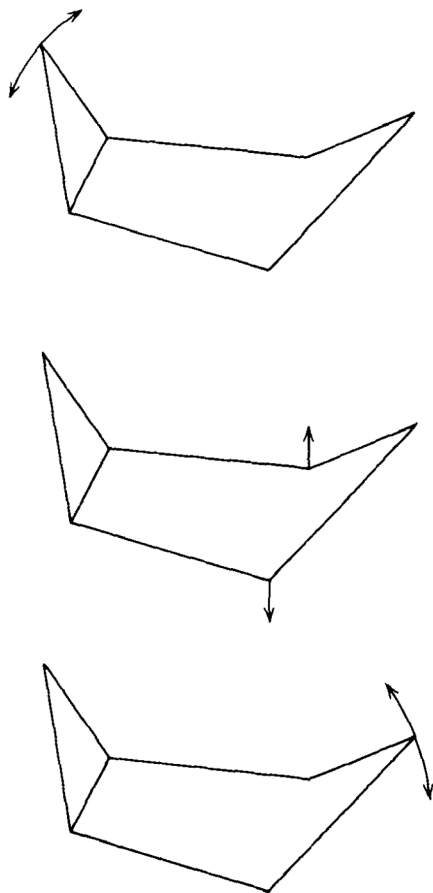


Fig. 20. Rocking of the three-membered ring; ring-twisting and ring-puckering vibrations for analogues of bicyclo[3.1.0]hexane.

The potential function represents a variety of shapes of potential functions, some of which are indicated in Fig. 3. For bicyclo[3.1.0]hexane and its 3-oxa, 6-oxa, and 3,6-dioxa analogues, these potential functions have a single minimum (23,55, 56). Figure 21 indicates the far-IR spectrum of 3,6-dioxabicyclo[3.1.0]hexane and the ring-puckering potential function. The nine transitions decrease in frequency, reaching a minimum with the $5 \rightarrow 6$ transition, and then begin to increase in frequency. The correspondence between the observed and calculated frequencies is quite good, the phenomenon of the transitions reversing direction after the $5 \rightarrow 6$ transition being quite well reproduced. The potential function derived from fitting the data is also shown in Fig. 21.

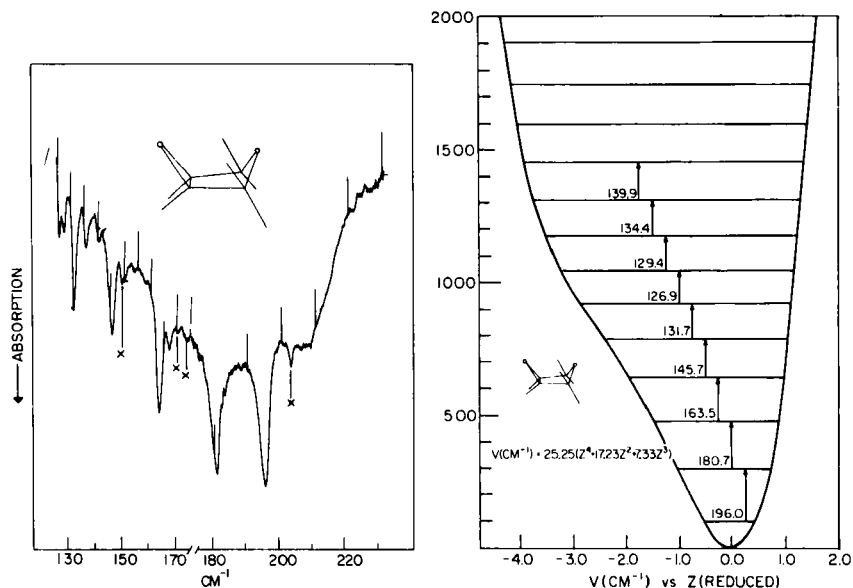


Fig. 21. Far-IR spectrum and ring-puckering potential function for 3,6-dioxabicyclo[3.1.0]hexane. Pressure ca. 1 torr, path length = 20 m; x marks pure rotational transitions of residual water vapor in the sample. (Reproduced with the permission of Academic Press, New York, from ref. 55.)

One major difference between the asymmetric and symmetric potential functions lies in the identification of the conformation corresponding to the origin. For a symmetric function the planar conformation lies at the origin. For symmetric single-minimum functions the planar ring conformation corresponds to the minimum energy. For a symmetric double-minimum potential function the planar ring conformation corresponds to the maximum in the potential function, which occurs at the origin. The two equivalent minima correspond to puckering the ring above and below the plane, respectively. The precise angle corresponding to the minimum may be determined only if the reduced mass is known or if this angle is obtainable from some other experimental technique.

For a molecule having an asymmetric potential function, the situation is not as clear-cut. It is always possible to define the puckering coordinate in a fashion similar to that done for four-membered rings, as shown in Fig. 20 for bicyclo[3.1.0]hexane. However, the planar ring conformation does not necessarily correspond to a point on the potential function where the first derivative is zero, and consequently a linear term may be required to describe the potential function as well as quadratic, cubic, or quartic terms. On the other hand we may always elimi-

nate the linear term by translating the origin to a minimum in the potential energy. This leads to an equation of the form of eq. [7] and a reduced Schrödinger equation of the form of eq. [24]. However, since we do not know the distance or even the direction of the translation required, we do not know the position of the planar ring conformation on the potential curve, nor do we know the identity of the conformer corresponding to the minimum. Consequently, fitting the low-frequency vibrational data allows us to determine the potential function in the reduced coordinate, but does not allow direct correlation between the reduced coordinate and the conformation.

This is a simple matter to rectify in the case of 3,6-dioxabicyclo[3.1.0]hexane. The dipole moment is dominated by the presence of the two oxygen atoms. In the boat conformer the two oxygen atoms are on one side of a plane formed by the four carbon atoms, and a large dipole moment is expected. In the chair conformer a small dipole moment is expected. The dipole moment, measured by a heterodyne-beat method in benzene solution, is 2.50 D (55). Analysis of the Stark effect in the microwave spectrum yielded a value of 2.48 ± 0.04 D (57).

The microwave data, however, also yield additional information indicative of the preference for the boat conformation. Lafferty and Cresswell calculated the moments of inertia and corresponding rotational constants for a number of postulated structures for 3,6-dioxabicyclo[3.1.0]hexane (57). This was done by transferring structural parameters from dimethyl ether and ethylene oxide (58,59), fixing the angle between the planes defined by $C_1C_2C_4C_5$ and the oxirane ring at 116° , and then varying the position of the oxygen atom in position 3 for a grid of boat and chair conformers. This admittedly crude procedure yielded quite good agreement between the observed rotational constants and those calculated for a boat conformer, as shown in Fig. 22.

Similar agreement was found for bicyclo[3.1.0]hexane and its 6-oxa and 3-oxa analogues (60-62). This was of some importance, since total dipole-moment measurements of these three compounds are not indicative of the conformation. For the oxygen-containing analogues, however, the direction of the dipole moment is indicative of the conformation. For 3,6-dioxabicyclo[3.1.0]hexane it was possible to predict the dipole-moment components in the principal inertial axis system by assuming a group dipole of 1.90 D (from ethylene oxide) for the oxirane ring directed along the C_1OC_5 bisector, and a group moment of 1.30 D (from dimethyl ether) directed along the C_2OC_4 bisector. Then, as the rotational constants were calculated for a grid of values, it was possible to calculate the components of the dipole-moment vector in the principal axis system. The results are shown in Fig. 22. The agreement, in both the magnitude and the direction of the dipole moment, is good evidence for the preference for a boat conformation. The direction of the dipole-moment vector in the principal axis system for 6-oxa- and 3-oxabicyclo[3.1.0]hexane is also consistent with the boat conformation (60,61).

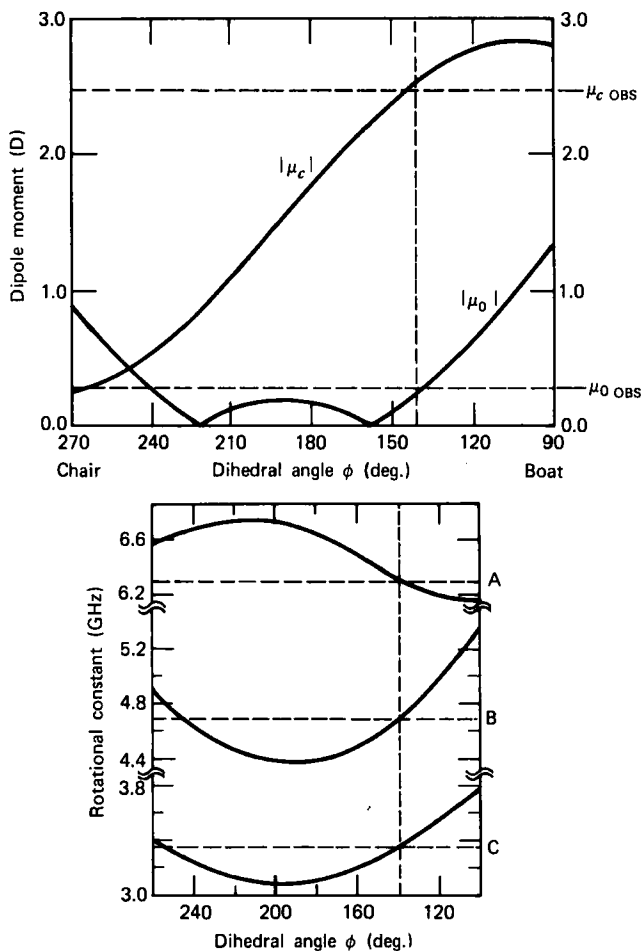


Fig. 22. Model calculations for the rotational constants and dipole-moment components for 3,6-dioxabicyclo[3.1.0]hexane. Here ϕ is the angle between the $C_1C_2C_4C_5$ plane and the $C_2O_3C_4$ plane. Values of ϕ less than 180° correspond to boat conformations; values of ϕ greater than 180° correspond to chair conformations. The solid lines are the model calculations; the dashed horizontal lines are the experimental values. (Reproduced with the permission of Academic Press, New York, from ref. 57.)

Figure 23 shows projection diagrams that indicate the reason for the preference of the boat conformation for these molecules. The boat form leads to a staggering of the bridgehead hydrogens with the adjacent methylene groups, whereas the chair conformation leads to an eclipsed configuration.

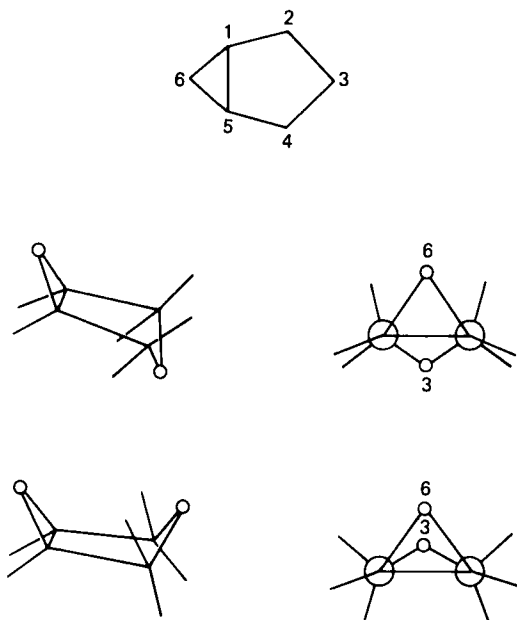


Fig. 23. Projection diagrams for boat and chair conformations of 3,6-dioxabicyclo[3.1.0]hexane. For the boat conformation the preferred staggered configuration about the C_1C_2 and C_5C_4 bonds is obtained. (Reproduced with the permission of Academic Press, New York, from ref. 55).

A few more comments should be made about these molecules. Examination of Fig. 21 shows a single minimum in the potential function, corresponding to the boat conformation. Since no chair conformation corresponds to a minimum in the potential energy, it is meaningless to speak of the difference in energy between the boat and chair conformations. The potential energy function given in eq. [29] is quite well characterized. The data extend to levels well above the second inflection point in the curve. The potential functions for the other analogues of bicyclo[3.1.0]hexane are not as well determined but, conservatively speaking, extrapolations of the shapes of the curves should be accurate to at least 1 kcal/mol (350 cm^{-1}) above the last observed transition. Although there is no indication of a second minimum in these potential functions, if there is one present, (1) the barrier between the two minima is at least 3 to 5 kcal/mol, (2) the second minimum is at least 2 to 3 kcal/mol above the ground state. These statements are conservative.

5. Trimethylene Oxide

It is not possible to discuss experimental studies of ring molecules without mentioning trimethylene oxide, the most thoroughly studied four-membered-ring molecule, and the first for which a quantitative potential function was determined from spectroscopic data. Interestingly enough, the potential function for this molecule indicates the extremely delicate balance between angle strain and torsional interactions, the potential function having a small barrier at the origin. This is shown in Fig. 24, which shows that the barrier is below the lowest energy level. This small barrier (ca. 0.04 kcal/mol), has a significant effect on the spectra of trimethylene oxide. Particularly, the 0-1 transition in the far-IR spectrum and the 0-2 transition in the Raman spectrum are unusually low in frequency compared to the other transitions. Fitting these data with the Schrödinger equation given by eq. [16] requires a small negative coefficient for the quadratic term in the Hamiltonian. The barrier that results also has an effect on the microwave spectrum. The variation of the rotational constants with vibrational state is shown

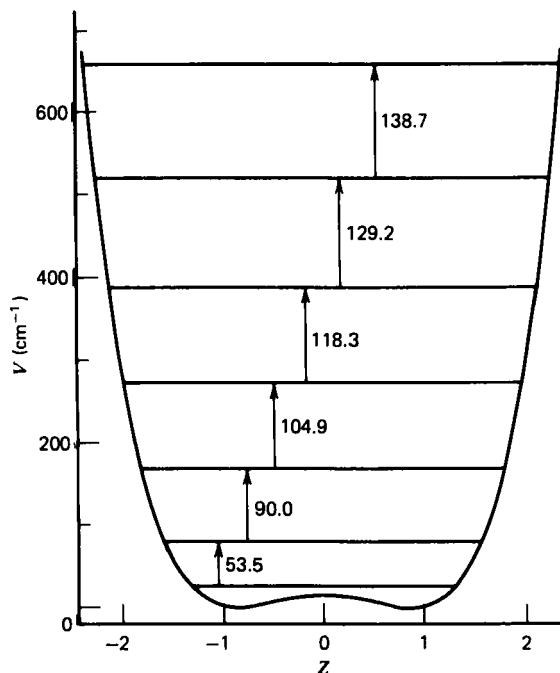


Fig. 24. Ring-puckering potential function for trimethylene oxide. The barrier is less than the ring-puckering zero-point energy. (From data in ref. 36.)

in Fig. 25. This should be compared to the variation of the rotational constants for 1,2-dimethylenecyclobutane, which has a single-minimum potential function (Fig. 18). It should be emphasized that the same potential function which reproduces the observed far-IR and Raman transitions also reproduces the rotational-constant variation when the expansions given by eq. [18] are used (38).

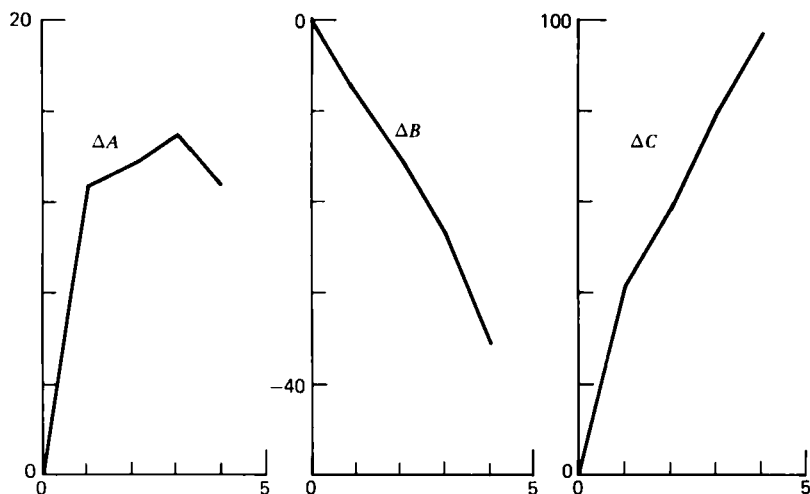


Fig. 25. Variation of the rotational constants with vibrational state in trimethylene oxide. The effect of the small barrier is quite evident. (Reproduced with the permission of the American Institute of Physics, from ref. 37.)

As mentioned, trimethylene oxide has been the most thoroughly studied ring molecule. Far-IR, low-frequency Raman, microwave, mid-IR, and mid-Raman studies of trimethylene oxide and several isotopically substituted analogues have been reported (14,16,27,29-31,34-39,63-66). Such extensive data make possible the examination of some of the assumptions made in deriving ring-puckering potential functions from spectroscopic data. As much as anything it gives an indication of the degree of reliability of the potential functions for other molecules for which such extensive data are not available. It should be emphasized that it is the absolute variation which is important, not the percentage, in this unusual case.

It has been found that the ring-puckering potential functions are not precisely isotopically invariant. If the dimensioned potential function (eq. [13]) is invariant, the relation between the potential constants in eq. [16] should be given by

$$\frac{A_1}{A_2} = \left(\frac{\mu_2}{\mu_1} \right)^{2/3} \quad [25a]$$

and

$$\frac{B_1}{B_2} = \left(\frac{\mu_1}{\mu_2} \right)^{1/3} \quad [25b]$$

where 1 and 2 refer to the different isotopic species, and μ_1 and μ_2 refer to the reduced masses. These equations do not hold precisely. Errors may arise in calculating the reduced masses, and eqs. [25a] and [25b] may be combined, yielding

$$\frac{A_1}{A_2} = \left(\frac{B_2}{B_1} \right)^2 \quad [26]$$

which eliminates this possible source of error. However, even this equation does not hold. The barrier heights derived from fitting each isotopic species individually vary from 15.1 cm^{-1} for normal trimethylene oxide to a low of 11.2 cm^{-1} for trimethylene oxide- d_6 (36). Possible sources of this discrepancy include (1) failure to correct Q -branch maxima for shifts from the vibrational band origins, (2) failure to take into account the change in reduced mass during the course of a ring-puckering vibration, and (3) failure to include the effect of the interaction with other vibrational modes of the molecule.

Workers have concerned themselves with the first of these three sources of error. Jokisaari and Kauppinen obtained the spectrum of normal trimethylene oxide under higher resolution conditions and used the rotational constants from the microwave study to show that the band origins were shifted from 0.1 cm^{-1} to 0.4 cm^{-1} from the Q -branch maxima (66). They then fitted the data with a constant reduced-mass Hamiltonian including an adjustable sixth power term in the potential function. The barrier they derived was $15.23 \pm 0.05 \text{ cm}^{-1}$, where the estimated uncertainty is obtained from the least squares treatment of the data. This estimated uncertainty, $\pm 0.05 \text{ cm}^{-1}$, does not include the effect of model error mentioned in points (2) and (3). However, it does show that for trimethylene oxide correction of the frequencies for shifts from the band origins does not account for the discrepancies on the order of the variation in the barrier heights among isotopic species.

Of the two remaining sources of error, failure to include the interaction of the ring-puckering with the small-amplitude modes is the most important. The effect of the variation of the reduced mass is discussed in Appendix I. There are several categories of interactions with small-amplitude modes. If a small-amplitude vibration is of the same symmetry species as the ring-puckering vibration, harmonic cross terms such as those described

in eq. [6] may occur. CH_2 rocking vibrations are the most likely to fall in this category, because of their symmetry and low frequency. These interaction terms may be removed by a "normal coordinate" transformation, but the result is that the *effective one-dimensional ring-puckering coordinate may differ for isotopic species*. Particularly, it may involve differing degrees of CH_2 or CD_2 rocking motions. If this is the case, then at this stage we expect different effective potential functions for isotopic species, since they would describe different motions.

Figure 19 shows the effect of the anharmonic interaction of two modes for 2,5-dihydrofuran via a x^2y^2 -type cross term (eq. [20]). The only reason that it is observable in the spectrum is that the thermal population of the ring-twisting mode (y) is high due to the low frequency of this vibration. If the frequency is high, satellite transitions may not be observed in the far-IR spectrum, but it may be possible to find combination- and difference-band progressions in the mid-IR or mid-Raman spectra. Figure 9 indicates such band progressions for trimethylene oxide, and these have been discussed in some detail. Some indication that such terms contribute to the effective potential functions may be seen by examining Table 1. It is seen that the quartic terms in the dimensioned potential functions vary only slightly among the isotopic species. On the other hand the variation of

Table 1 Potential Function
Constants for Trimethylene Oxide^a

	$n\text{-TMO}$	$\alpha - d_2$ TMO	$\beta - d_2$ TMO	$\alpha, \alpha' - d_4$ TMO	$d_6\text{-TMO}$
$A(\text{cm}^{-1})^b$	28.12	25.46	26.10	22.85	21.54
B^b	-1.465	-1.445	-1.465	-1.445	-1.445
(u)	95.7	110.4	107.3	129.8	141.8
$a(10^5\text{cm}^{-1} \text{ \AA}^{-4})^c$	7.16	7.07	7.19	7.07	7.07
$b(10^3\text{cm}^{-1} \text{ \AA}^{-2})$	-6.58	-6.13	-6.34	-5.81	-5.64
Barrier (cm^{-1})	15.1	13.3	14.0	11.9	11.2
H^d (cm^{-1})	12.2	11.3	11.3	10.2	9.6
Separation ^e ($\text{\AA}$)	0.135	0.132	0.133	0.128	0.126

^a Ref. 36.

^b Eq. [20].

^c Eq. [16].

^d H is the separation between the top of the barrier and the lowest energy level.

^e Separation between minima.

the quadratic term is more marked. If we consider interaction terms of the form $x^2 y_i^2$ and simply average over the $3N - 7$ small-amplitude modes, we obtain the effective potential function

$$V_{\text{eff}}(x) = ax^4 + (b + \sum_{i=1}^{3N-7} a_{ix} \langle v_i | y_i^2 | v_i \rangle) x^2 \quad [27]$$

In this degree of approximation (first-order perturbation theory), we would expect the quartic coefficient to be isotopically invariant and the quadratic term to change. That is, since the small-amplitude frequencies change on isotopic substitution, the averaging of terms like $\langle v_i | y_i^2 | v_i \rangle$ changes, and consequently differs for isotopic species. Equations [23a] and [23b] show the correction for a single mode carried out to second order.

No quantitative correction of the potential functions for trimethylene oxide is possible at this time for the effect of these type of interaction terms. It should be emphasized that the calculation of the dimensioned potential functions in Table 1 depends on the calculations of the reduced masses for the isotopic species of trimethylene oxide. These calculations are subject to the uncertainties pointed out in Appendix I.

It is comforting that the variation in the quadratic coefficients (Table 1) leads to a variation of only a few reciprocal centimeters in barrier heights among isotopic species. This indicates that one-dimensional treatment yields quite reliable barrier heights (within a few reciprocal centimeters) even when data for the normal isotopic species are available. In the few cases in which the individual a_{ix} interaction terms have been determined, both positive and negative interaction terms have been found. This means that both positive and negative terms may appear in the summation in eq. [27] and that they have a tendency to cancel each other. Consequently, the effect remains small.

The variation of the quartic terms in Table 1 cannot be attributed to second-order effects from $x^2 y_i^2$ interaction terms. The calculation of these potential constants depends on the value of the reduced masses used, and are subject to the errors and approximations discussed in Appendix I. However, the fact that the trend expected from eq. [27] is reflected in Table 1 is some indication of the effect of $x^2 y_i^2$ interaction terms. This also indicates the dangers in nitpicking over some of the finer details of the potential functions if some of these factors have not been considered.

6. 2,5-Dihydropyrrole

2,5-Dihydropyrrole is a pseudo-four-membered ring molecule with an asymmetric potential function having an extremely low

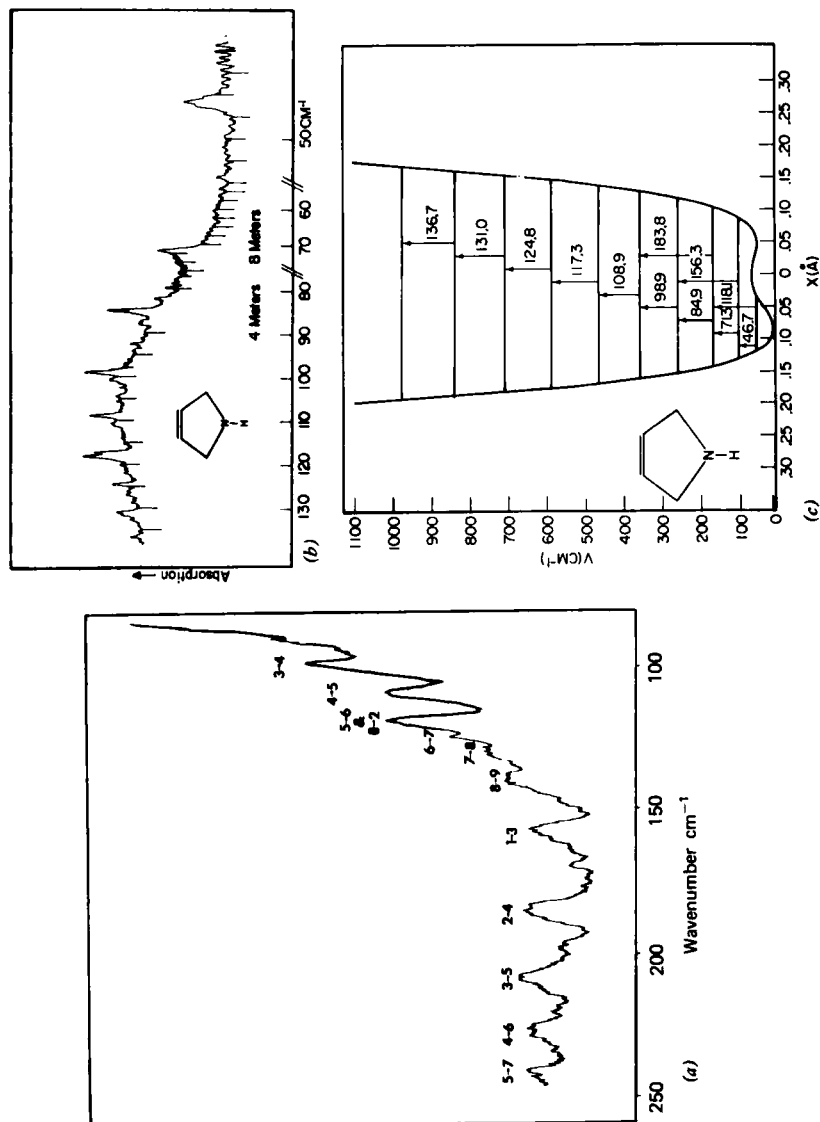


Fig. 26. Low-frequency Raman (a) and far-infrared (b) spectra and ring-puckering potential function for 2,5-dihydropyrrole. The Raman spectrum was recorded at the full vapor pressure at 25°C with a spectral slit width of 3 cm^{-1} , using a laser power of ca. 2 W at 514.5 nm. The far-IR spectra (ca. 0.5- cm^{-1} resolution) were obtained at 8 torrs, at path lengths of 4 m and 8 m, and indicated. (Reproduced with the permission of the American Institute of Physics, from ref. 23 and 67.)

barrier (23). The far-IR and Raman (67) spectra are shown in Fig. 26. Many of the frequencies of the observed Raman transitions are shown in Fig. 26. Many of the frequencies of the observed Raman transitions are the sum of two frequencies of transitions in the far-IR spectrum, thus verifying the assignment. Figure 26 indicates the potential function for the ring-puckering vibration in 2,5-dihydropyrrole. This potential function, though asymmetric, has only a very small barrier, and only one energy

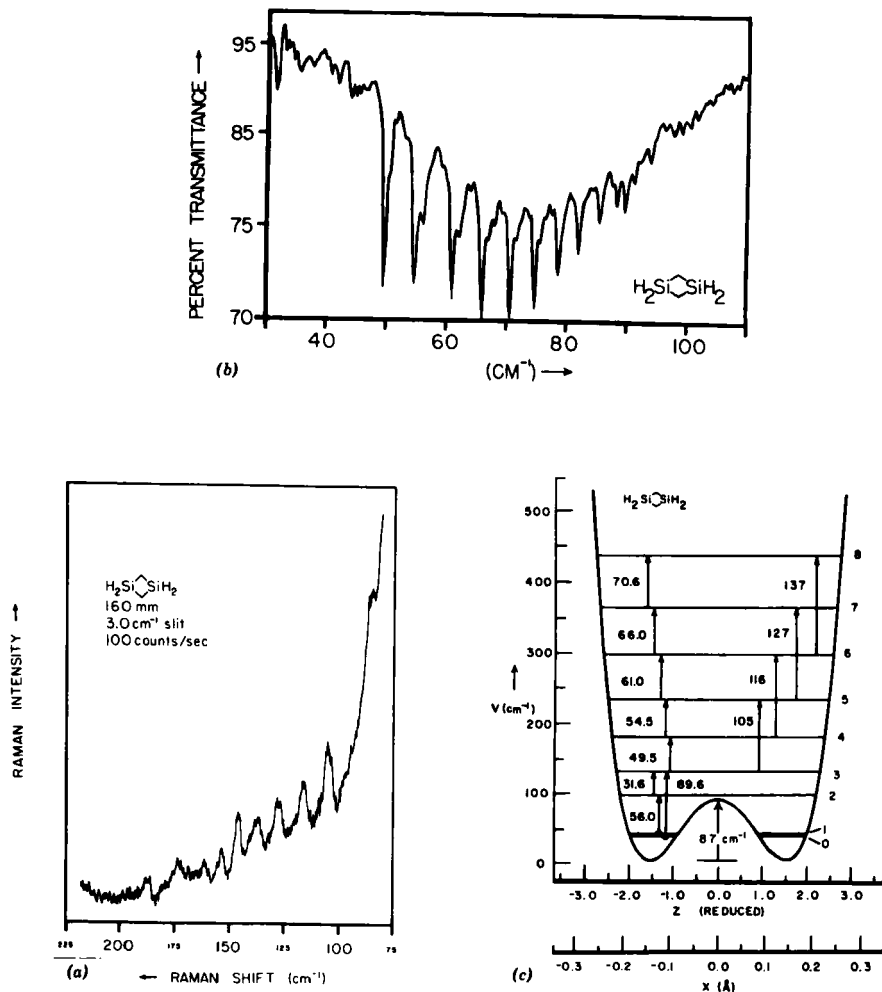


Fig. 27. Low-frequency Raman spectrum (a) and far-IR spectrum (b) and ring-puckering potential function (c) for 1,3-disilacyclobutane. The Raman spectrum was obtained at 3-cm⁻¹ resolution at a vapor pressure of 160 torrs. The far-IR spectrum at a resolution of 0.5-cm⁻¹ was obtained at a sample pressure of 140 torrs and a path length of 15 cm. (Reproduced with the permission of the American Chemical Society, from ref. 68.)

level occurs below this barrier. As for trimethylene oxide, the effect of the small barrier is hardly noticeable for transitions between higher energy levels.

7. 1,3-Disilacyclobutane

1,3-Disilacyclobutane is an example of a molecule having a barrier to planarity that is low, yet high enough to produce an inversion doublet below the barrier (68). Figure 27 shows the potential function and some of the far-IR ($\Delta v = 1$ or 3) and Raman ($\Delta v = 2$) transitions of 1,3-disilacyclobutane.

Reduced mass calculations and the potential function derived for 1,3-disilacyclobutane-1,1,3,3- d_4 from the far-IR spectrum indicate that the ring-puckering coordinate is a mixture of pure puckering and SiH_2 motion. The most likely candidate is the in-phase SiH_2 rocking mode, which is reasonably low in frequency and also of the same symmetry as the ring-puckering. Figure 28 shows the in-phase mixing of ring-puckering and SiH_2 rocking. It is necessary to mix the rocking vibration to account for isotopic shift of the ring-puckering frequencies from the normal compound to the 1,1,3,3- d_4 compound. This shift is underestimated by the reduced ratio calculated for a model in which the SiH_2 groups rigidly maintain a common bisector with the adjacent interior ring angle.

Extensive calculations have been carried out which include the reduced mass variation explicitly in the Schrödinger equation for a number of different models.

Satellite ring-puckering transitions were assigned in the spectrum of 1,3-disilacyclobutane, most likely originating from

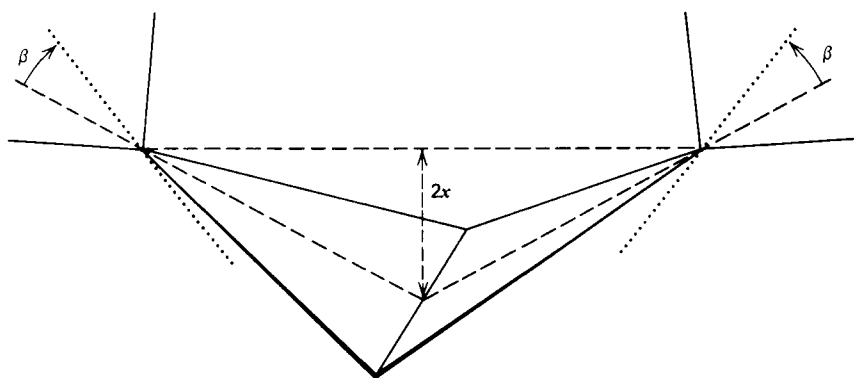


Fig. 28. Definition of ring-puckering (x) and rocking (β) coordinates for 1,3-disilacyclobutane; $\beta = Rx$. For 1,3-disilacyclobutane and its 1,1,3,3- d_4 analogue the isotopic shift is reproduced for $R = 0.4$. (Reproduced with the permission of the American Chemical Society, from ref. 68.)

the first excited state of the SiH_2 in-phase rocking. This is most likely the result of a potential energy cross term of the form $x^2\beta^2$ (Fig. 28). The cross term causing the mixing of coordinates (Fig. 28) is probably a harmonic term of the form $x\beta$. Extensive studies are in progress (69) on the mid-IR and mid-Raman spectra with a view of examining these and other interactions in 1,3-disilacyclobutane.

8. Cyclopentene

Cyclopentene is an example of a pseudo-four-membered-ring molecule with a double-minimum potential function and a moderate (ca. 232 cm^{-1} , 0.66 kcal/mol) barrier to planarity. The barrier height is such that the lowest pair of vibrational levels are quite closely spaced (see Fig. 15), the separation being of the order of typical rotational energy spacings. Consequently, it was necessary to treat the rather large vibration-rotation interaction to account for the transitions in the microwave region (70). The far-IR spectrum is shown in Fig. 29, as is the potential function derived from fitting the far-IR data (10).

There have been studies of ring-puckering progressions in the mid-IR (14,16) and mid-Raman (32) spectra of cyclopentene. In addition the low-frequency Raman spectrum was reported. This was one of the first examples of a gas-phase study of ring-puckering in the Raman spectrum (32,71). Although not as obvious as in the spectrum of 2,5-dihydrofuran, there is a satellite ring-puckering series originating from the first excited state of the ring-twisting mode. This series also was fitted with the one-dimensional constant effective mass Schrödinger equation (eq. [16]). The potential functions are given by Ground state of twisting:

$$V(\text{cm}^{-1}) = 24.3 (z^4 - 6.18 z^2) \quad [28a]$$

Excited state of twisting:

$$V(\text{cm}^{-1}) = 24.2 (z^4 - 6.22 z^2). \quad [28b]$$

As with 2,5-dihydrofuran, it was possible to fit the ring-puckering series and the ring-twisting frequency with the two-dimensional Hamiltonian given by eq. [20] (54).

Laane and co-workers have carried out extensive far-IR and low-frequency Raman studies on a number of deuterated analogues of cyclopentene (72,73). They have considered the effect of the reduced mass dependence on the coordinate and the effect of mixing CH_2 (CD_2) rocking with the ring-puckering coordinate. More recently, they have addressed the problem of fitting both ring-puckering and ring-twisting transitions two-dimensionally for the several deuterated species (74).

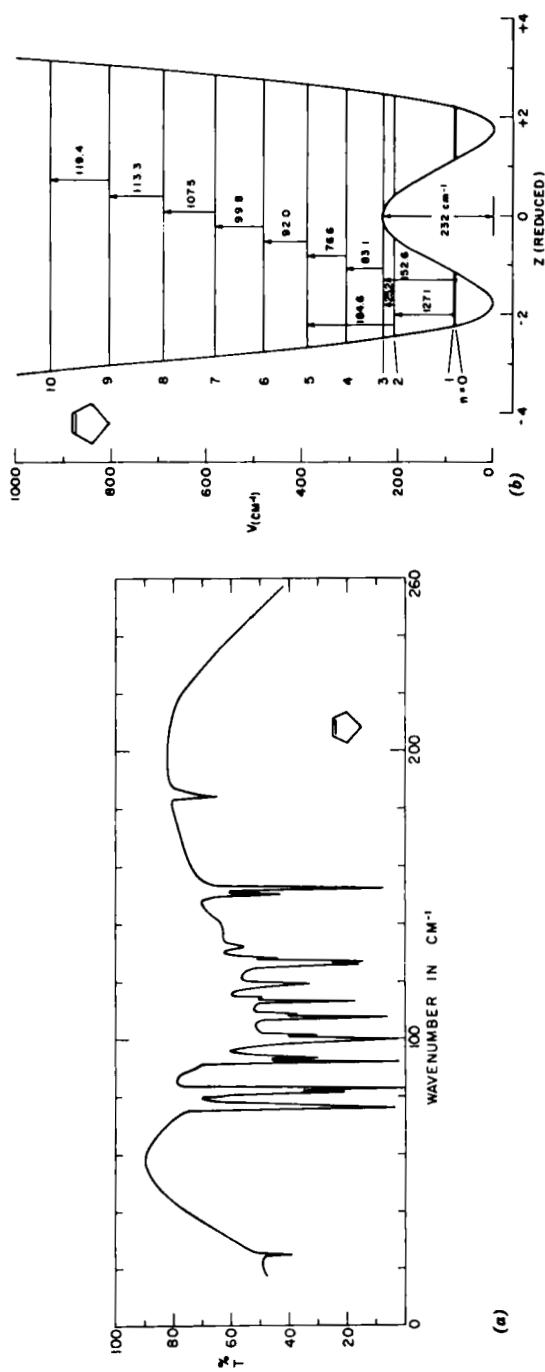


Fig. 29. Far-IR spectrum (a) and ring-puckering potential function (b) of cyclopentene. Pressure = 115 torr, path length = 4 m, resolution 0.2 to 0.5 cm^{-1} . (Reproduced with the permission of the American Institute of Physics, ref. 10.)

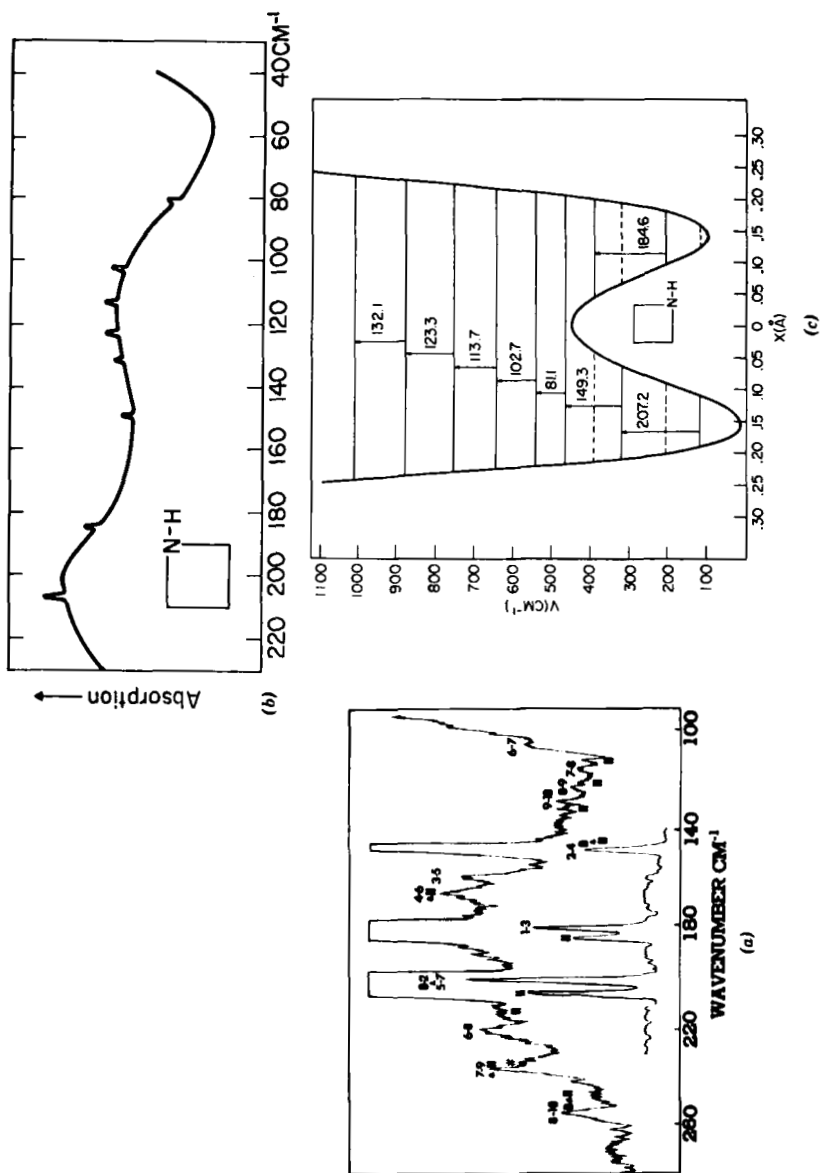


Fig. 30. Low-frequency Raman (a) and far-IR spectra (b) and ring-puckering potential function for tri-methylene imine. The Raman spectra were obtained at 3-cm^{-1} and 6-cm^{-1} resolution with ca. 2 W of laser power at 514.5 nm. The far-IR spectrum was obtained at 140 torr with a 30-cm path length. (Reproduced with the permission of the American Institute of Physics, from refs. 23 and 67.)

9. Trimethylene Imine

Trimethylene imine is an example of a four-membered-ring molecule with an asymmetric double-minimum potential function. Figure 30 indicates the far-IR spectrum (23) and the low-frequency Raman spectrum of the normal compound (67). Below the barrier the frequencies measured in the far-IR and Raman are the same, whereas above the barrier the strong Raman transition frequencies are the sum of two far-IR transition frequencies. This serves to unambiguously confirm the assignment.

The potential function determined from fitting the data is asymmetric. One puckered conformation has the imino proton axial, whereas the other has this proton equatorial. The levels below the barrier have a definite "left-well," "right-well" character, but this distinction becomes less clear for those levels above

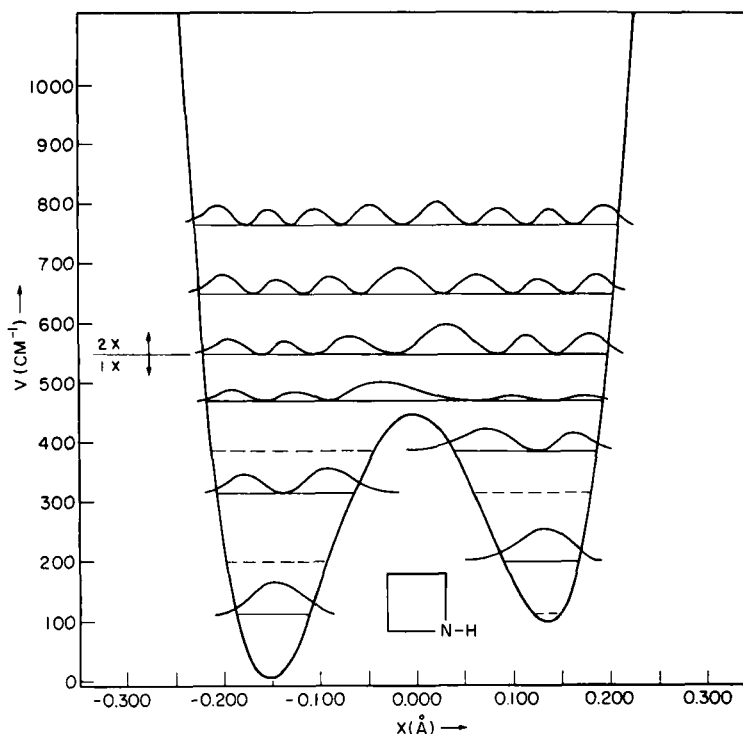


Fig. 31. Ring-puckering potential function and probability density (ψ^2) for trimethylene imine. As indicated, ψ^2 is multiplied by 2 for clarity for the higher levels. The levels below the barrier have a definite left well-right well identification. (Reproduced with the permission of the American Institute of Physics, from ref. 23.)

the barrier. This is shown in Fig. 31, which also indicates the probability density for the levels.

The availability of data for the two isotopic species and the fact that they are fitted with two slightly different potential functions allow us to estimate the reliability of the barrier heights and energy differences. Table 2 lists the barriers and determined ΔE values. Though not identical they are quite close and do not represent an unreasonable spread in values.

Table 2 Comparison of the Potential Functions for Trimethylene Imine and Trimethylene Imine N-d

	Barrier ^a (cm ⁻¹)	ΔE (cm ⁻¹)
Normal species	441	95
N-d species	442	91

^a Measured from the lowest minimum.

10. Cyclobutane

Cyclobutane is the parent hydrocarbon of all four-membered ring molecules, and considerable effort has been expended toward its study. Since it has no permanent dipole moment, no microwave data are available. The ring-puckering vibration is inactive in the IR region, and no direct observation of transitions in the far-IR spectrum has been made. The first estimate of the barrier to planarity from ring-puckering data was made by Ueda and Shimanouchi, based on observation of a difference-band progression in the CH stretching region (21). The only requirement for the observation of these bands is that the direct product of the symmetry species for the reference vibration (CH stretching) and the ring-puckering be a symmetry species that transforms as one of the dipole-moment component operators. Their estimate, 448 cm⁻¹, was slightly lower than the currently accepted value (500 to 515 cm⁻¹). Several years after the work of Ueda and Shimanouchi, two groups reported combination- and difference-band progressions in cyclobutane and cyclobutane-d₈ off CH₂(CD₂) scissoring modes (24,25). In addition, overtone ($\Delta v = 2$) transitions were observed in the low-frequency region of the Raman spectra. Minor differences in assignments and different methods of treating the data led to slight differences in the determined barrier heights. The two sets of data were later reconciled by Malloy and Lafferty (75). Table 3 summarizes the potential constants for the ground and excited states of the CH₂(CH₂) scissoring mode (75).

Table 3 Potential Constants, Band Centers, and Barriers Obtained for C_4H_8 and C_4D_8 ^a (Ref. 75)

	A (cm ⁻¹)	B	Barrier (cm ⁻¹)	ν_0	σ (cm ⁻¹)
C_4H_8					
Ground State	26.153 ± 0.074	-8.873 ± 0.034	514.8 ± 4.4	-	0.67
$\nu_{14} = 1$	26.117 ± 0.066	-8.763 ± 0.039	501.4 ± 5.5	1454.6 ± 2.3	0.53
		$\nu' - \nu'' = 13.4 \pm 7.1^b$			
C_4D_8					
Ground State	18.59 ± 0.043	-10.3768 ± 0.0027	500.6 ± 2.7	-	0.42
$\nu_{14} = 1$	18.561 ± 0.050	-10.223 ± 0.059	485.0 ± 6.8	1084.7 ± 2.5	0.43

^aErrors cited are three standard deviations. Errors cited for the upper state constants are relative to those determined for the ground state.

^bError calculated from $\sigma_{\Delta\nu} = (\sigma'^2 + \sigma''^2)^{1/2}$.

Several conclusions may be drawn. When treated one-dimensionally, slight differences (in this case 3%) may be obtained in the barrier heights determined for isotopic species. The primary reason is the difference in zero-point averaging over the small-amplitude vibrations for the isotopic species. On the other hand it was found that reduced mass calculations (Appendix I) underestimated the isotopic shift of the ring-puckering vibration for cyclobutane and cyclobutane- d_8 for a model in which the CH_2 (CD_2) groups maintained a common bisector with the adjacent C-C-C angle (24,25,75). Preliminary analysis of electron diffraction data indicates that the CH_2 groups in cyclobutane tilt (rock) forward as the ring puckers (76). These data are consistent with the vibrational data, which are not definitive on this point.

B. Two-Dimensional Potential Functions

Examples of two-dimensional potential functions have been mentioned earlier in connection with 2,5-dihydrofuran and cyclopentene. For these molecules the Schrödinger equation was approximately separable in cartesian coordinates, the cross term being treated by perturbation techniques. This is not always the case. Gwinn and co-workers have discussed various cases arising in the treatment of the two out-of-plane skeletal vibrations of five-membered-ring molecules (77). All the possible cases are not considered here, only those appropriate to the molecules used as examples in this section.

In 1947 Kilpatrick, Pitzer, and Spitzer introduced the notion of "pseudorotation" to explain the thermodynamic data on cyclopentane (78). Figure 32 indicates a potential energy contour diagram appropriate to pseudorotation in five-membered-ring molecules (77). Z_1 and Z_2 are dimensionless ring-puckering and ring-twisting coordinates (see Fig. 2), respectively. It is seen that the minimum energy track, $V = 0$, is surrounded by a steep wall on the outside, while there is an energy maximum at the origin, which corresponds to the planar conformation. Pure pseudorotation, as implied by Fig. 32, arises when bent and twisted conformations having the same vibrational amplitudes are equal in energy; interconversion occurs via intermediate bent-twisted forms having the same energy. Another way of stating this is to say that the potential energy function, expressed in polar coordinates, is independent of the angular coordinate.

In cartesian coordinates, for a constant mass model, the conditions on eq. [20] are that $a_1 = a_2 = a_{12}/2$, $b_1 = b_2$, and $\mu_1 = \mu_2$. In dimensionless coordinates the Schrödinger equation is given by

$$-\frac{\partial^2}{\partial Z_1^2} \psi + \frac{\partial^2}{\partial Z_2^2} \psi + (Z_1^2 + Z_2^2)^2 \psi + B(Z_1^2 + Z_2^2) \psi = \lambda \psi \quad [29]$$

where

$$z_1 = \left(\frac{\hbar^2}{2\mu a_2} \right)^{-1/6} x$$

$$z_2 = \left(\frac{\hbar^2}{2\mu a_2} \right)^{-1/6} y$$

and x and y are the ring-puckering and ring-twisting coordinates,

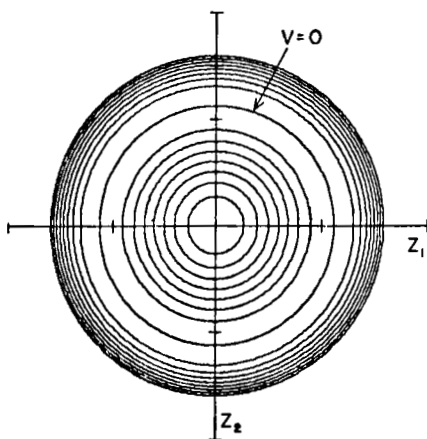


Fig. 32. Potential energy contour diagram appropriate to pseudorotation in five-membered-ring molecules. Here z_1 and z_2 are ring-puckering and ring-twisting coordinates. The minimum energy track, $V = 0$, is surrounded by steep walls on the outside and a high barrier at the origin. (Reproduced with the permission of the American Institute of Physics, from ref. 77.)

respectively; the energy levels are given by $E = A\lambda$, where A is the appropriate scale factor. In polar coordinates with

$$z_1 = \rho \cos \theta \quad [30a]$$

$$z_2 = \rho \sin \theta \quad [30b]$$

the Schrödinger equation is separable, the angular equation being

$$\frac{d^2\theta}{d\theta^2} = -\ell^2 \theta \quad [31]$$

with

$$\Theta = \frac{1}{\sqrt{2\pi}} e^{i\ell\Theta}, \ell = 0, \pm 1, \pm 2 \dots$$

and a series of radial equations for different $|\ell|$:

$$-\frac{1}{\rho} \frac{d}{d\rho} \rho \frac{d}{d\rho} + \frac{\ell^2}{\rho^2} R + (\rho^4 + B\rho^2)R = \lambda R \quad [32]$$

Figure 33 is a plot of the eigenvalues of eqs. [29] and [32] as a function of B (79). The limit on the left is an isotropic harmonic oscillator, in the center is an isotropic quartic oscillator, and pseudorotation is indicated on the right. When the barrier height is very high, the energy levels may be approximated by

$$E \approx \beta \ell^2$$

where β is the pseudorotational constant $A \langle v_\rho | 1/\rho^2 | v_\rho \rangle$. Frequencies of $\Delta\ell = +1$ transitions exhibit a linear dependence on quantum number:

$$v_\ell \rightarrow \ell+1 = \beta(2\ell + 1) \quad [34]$$

with a constant separation of 2β between transitions. The numerical solutions to eqs. [29] and [32] exhibit a negative curvature to the frequency vs. ℓ plots, being more pronounced for lower barriers (79). This has been observed experimentally.

Although very few, if any, molecules exhibit pure pseudorotation, it is a good starting point for the treatment of a number of other molecules. For molecules in which the barrier to planarity is much greater than the barriers between non-planar conformations, hindered pseudorotation may be appropriate. This case is described in some detail by Gwinn and co-workers (77). In this procedure the Schrödinger equation, eq. [20], is expressed in mass-weighted coordinates and then transformed to polar coordinates. The resulting equation may be averaged over the radial coordinate, and the following angular equation results:

$$-\beta \frac{d^2\Phi}{d\phi^2} + \sum_n \frac{V_n}{2} (1 - \cos n\phi) \bar{\Phi} = E\bar{\Phi} \quad [35]$$

The formalism from this point on is identical to that used in the treatment of internal rotation. The requirement for using this formalism is that the barrier to planarity be high compared to interconversion barriers and, consequently, the radial coordinate be approximately constant during the vibrational motion

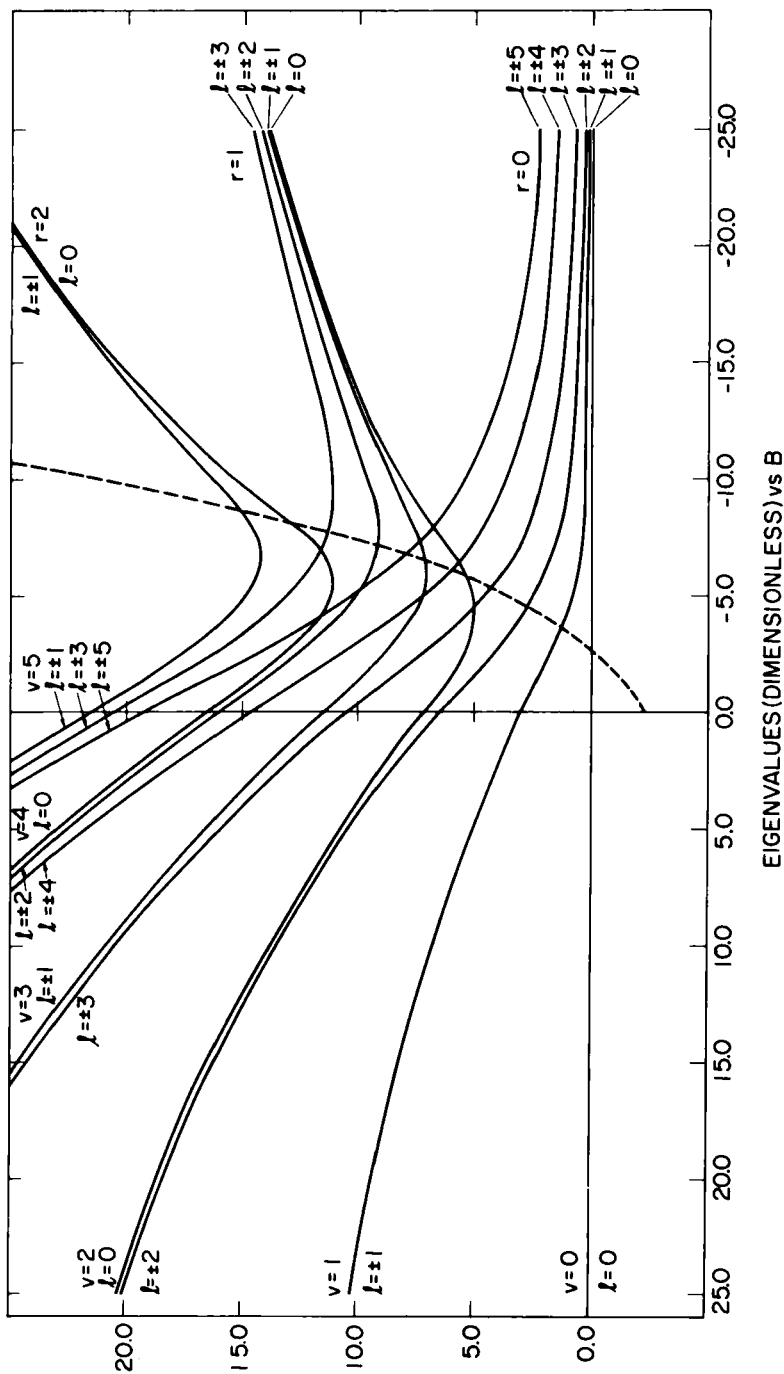


Fig. 33. Eigenvalues for the two-dimensional potential function $(Z_1^2 + Z_2^2)^2 + B(Z_1^2 + Z_2^2)$ vs. B . The dashed line gives the barrier height. The limit on the right is appropriate to pseudorotation. (Reproduced with the permission of the American Institute of Physics, from ref. 79.)

(77). The data for tetrahydrofuran and 1,3-dioxolane were treated in this fashion (80,82,83). In other cases polar coordinates are not a good choice for obtaining even approximately separable equations, and the two-dimensional Hamiltonians are treated directly.

1. *Cyclopentane*

As mentioned, in 1947 Kilpatrick, Pitzer, and Spitzer introduced the notion of pseudorotation to explain the thermodynamic data on cyclopentane (78). It was not until 1968 that direct spectroscopic evidence was obtained. As with cyclobutane, no direct observation of the transitions is possible in the far-IR. Durig and Wertz, however, observed combination- and difference-band progressions in the mid-IR in combination with a CH_2 scissoring mode (22). Later Carreira and co-workers reported the presence of hot bands involving the radial mode in the low-frequency Raman spectrum (84), and fitted the data two dimensionally, which allowed them to spectroscopically determine the barrier to planarity as $1824 \pm 50 \text{ cm}^{-1}$, quite close to that estimated by Pitzer and Donath from thermodynamic data (85). Extensive studies have been made on pseudorotation in various deuterated analogs of cyclopentane (86).

2. *Tetrahydrofuran*

Prior to the report of pseudorotational combination- and difference-bands in cyclopentane, spectroscopic evidence for pseudorotation had been obtained for tetrahydrofuran (87). Due to the presence of the oxygen atom, the pseudorotational transitions were allowed in the far-IR spectrum. Although tetrahydrofuran should be termed a hindered pseudorotator, for transitions originating from levels well above the pseudorotational barriers, the pattern of transitions follows those expected for a pure pseudorotator.

A microwave study of tetrahydrofuran indicated a complicated energy pattern for the lower levels (80). The rotational constants were determined in several vibrational states in addition to the small energy splittings between the 0-1 and 2-3 levels. These small energy splittings and rotational constant variations were used with the pseudorotational constant, $\beta = 3.25 \text{ cm}^{-1}$, from the previous far-IR study (87) to determine the potential function

$$V(\phi) = -15 \text{ cm}^{-1} (1 - \cos 2\phi) - 20 \text{ cm}^{-1} (1 - \cos 4\phi) \quad [36]$$

from eq. [35]. The potential function is shown in Fig. 34. The potential function represents the minimum energy path for inter-conversion on the potential surface in bending and twisting coordinates.

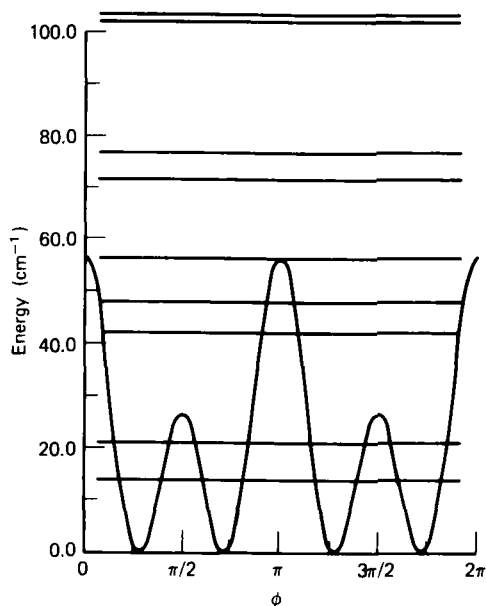


Fig. 34. Pseudorotational potential function for tetrahydrofuran. Tetrahydrofuran interconverts via bent and twisted conformations, the highest barrier being ca. 0.15 kcal/mol. The barrier to planarity, on the other hand, is several kilocalories per mole. (Reproduced with the permission of the American Institute of Physics, ref. 80.)

Concurrently with the microwave study, a high-resolution study of the far-IR spectrum showed it to be quite complex, with a number of pseudorotational bands being split by Coriolis interactions (81). Fitting the observed bands with the Schrödinger equation of eq. [35] led to the potential function

$$V(\phi) = -13.5 \text{ cm}^{-1} (1 - \cos 2\phi) - 20 \text{ cm}^{-1} (1 - \cos 4\phi) \quad [37]$$

with β , the pseudorotational constant, equal to 3.19 cm^{-1} . This is in quite reasonable agreement with the potential function derived from microwave data.

3. Cyclopentanone

One of the dangers of using one-dimensional approximations for some five-membered-ring molecules came to the fore in the study of cyclopentanone. Although it was possible to fit the far-IR data for cyclopentanone with a one-dimensional periodic potential function (eq [35]), the "barrier" derived has no meaning (6,88). For this approach to be valid, the barrier to

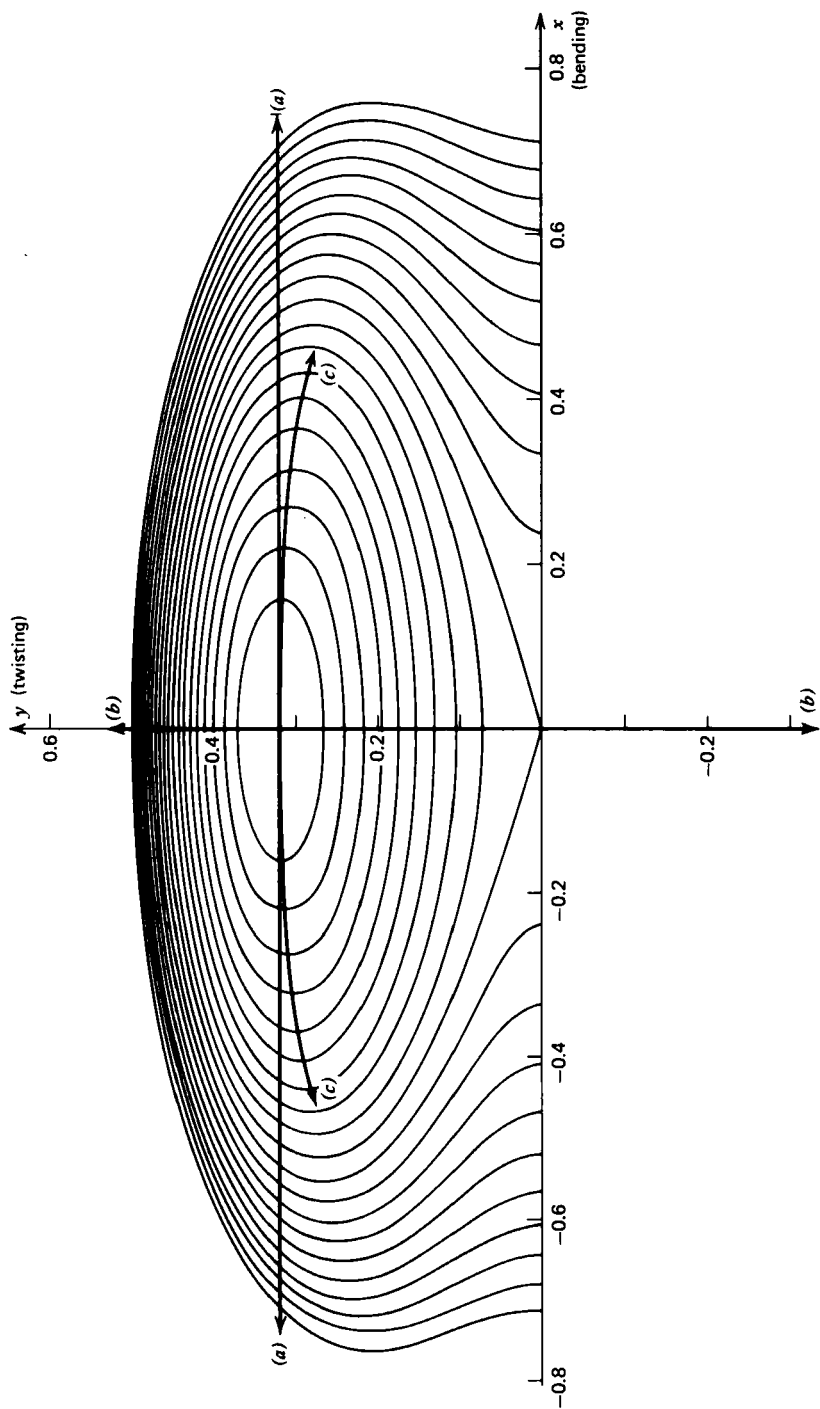


Fig. 35. Potential energy contour diagram for cyclopentanone. The third and fourth quadrants are mirror images of the first and second quadrants. The minima lie along the y (twisting) axis. Interconversion of the two equivalent C_2 conformers takes place via the planar ring conformation. The barrier to interconversion is ca. 750 cm^{-1} . (Reproduced with the permission of the American Institute of Physics, from ref. 89.)

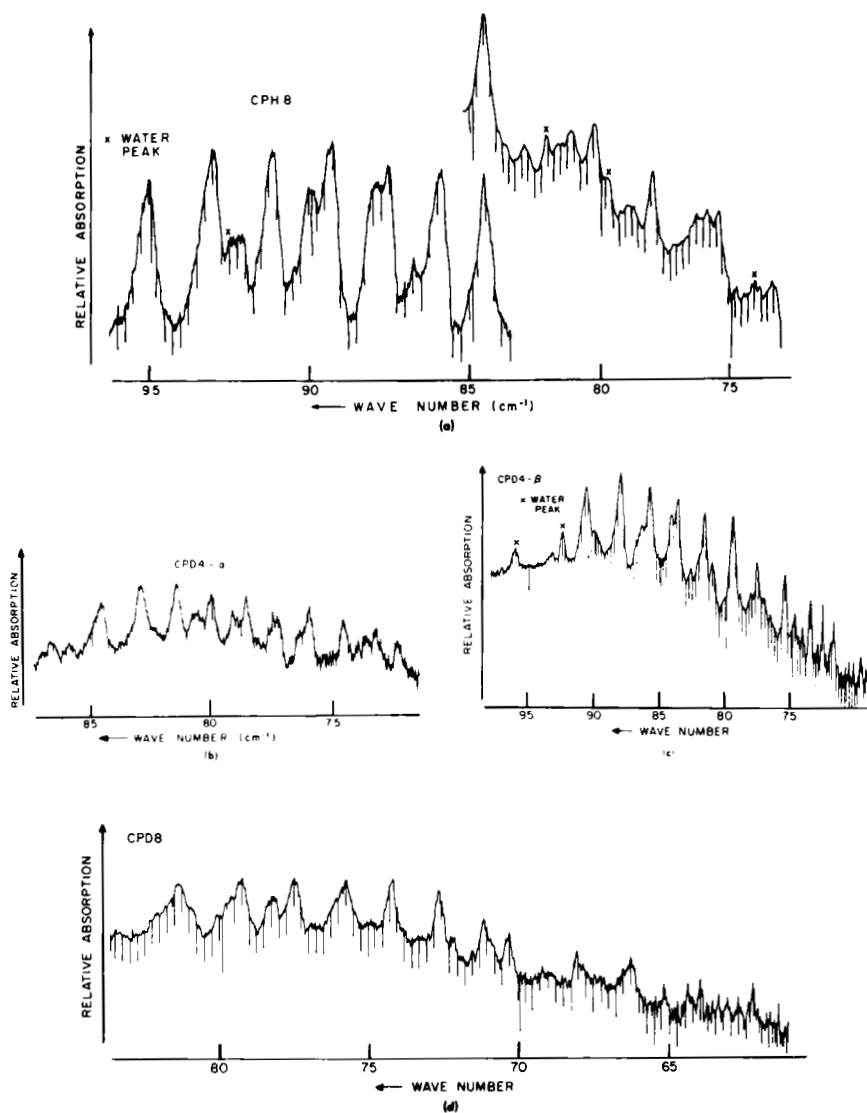


Fig. 36. Far-IR spectra of cyclopentanone, cyclopentanone- $\alpha,\alpha,\alpha',\alpha'=d_4$, cyclopentanone- $\beta,\beta,\beta',\beta'=d_4$, and cyclopentanone- d_8 . Spectral slit with 0.15 to 0.4 cm⁻¹. Pressure ca. 5 torrs, path lengths 4 to 12 m. (Reproduced with the permission of the American Institute of Physics, from ref. 89.)

planarity must be very high compared to the pseudorotational barriers. A rather thorough study of the far-IR spectra of cyclopentanone and its α - d_4 , β - d_4 , and d_8 analogs yielded the potential surface shown in Fig. 35 (89). The two equivalent, stable twisted-ring (C_2 symmetry) (90) conformers interconvert via the planar conformation, which is ca. 750 cm^{-1} less stable. There are no minima corresponding to the equivalent bent (C_s) conformers.

For cyclopentanone full treatment of a two-dimensional Hamiltonian is required. The observed spectra are shown in Fig. 36, the calculated spectra in Fig. 37. To reproduce the isotopic shift it was necessary to mix methylene rocking at the α position with the ring-twisting. However, the isotopic shift was accounted for without mixing rocking at the β positions (89).

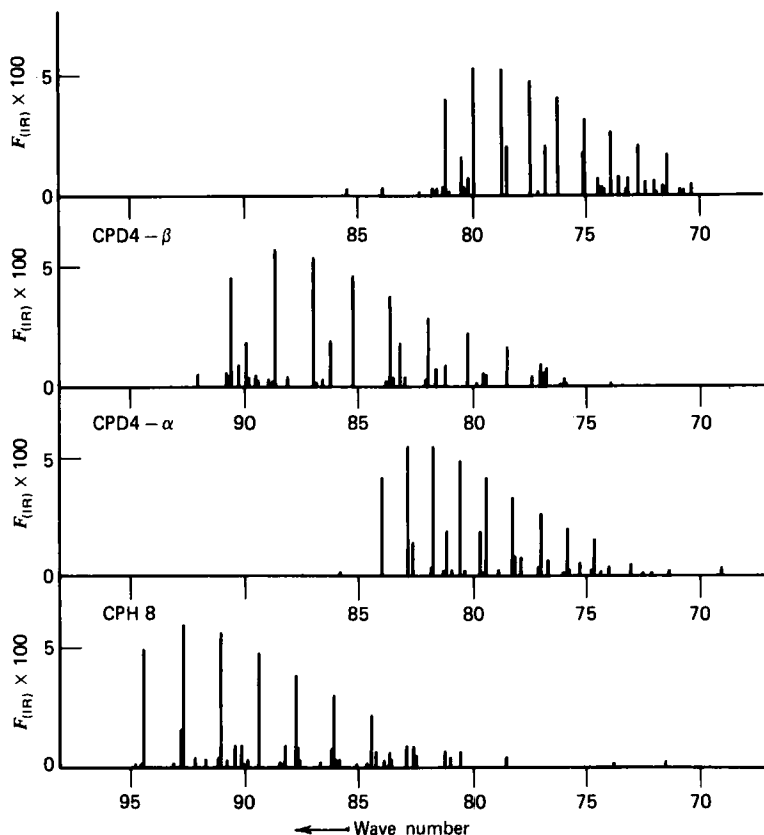


Fig. 37. Calculated far-IR transitions for cyclopentanone and its deuterated analogues. (Reproduced with the permission of the American Institute of Physics from ref. 88.)

4. 1,4-Dioxene

The preceding examples are molecules for which barrier heights may be derived to an accuracy of a few reciprocal centimeters or, at worst, a few tens of reciprocal centimeters. Gas-phase rotational and vibrational spectroscopy has also been applied to the determination of barriers to interconversion in cyclohexene analogs. In these cases the barrier heights involved are 6 to 10 kcal/mol, and their determination represents extrapolation above the point for which data are available. This results in barriers whose uncertainty may be several hundred reciprocal centimeters, or ca. 10 to 15%. On the other hand barriers in this range may be determined by NMR techniques, and this offers an opportunity to compare the results determined from two very different techniques.

1,4-Dioxene may be considered a pseudo-five-membered-ring molecule. The two low-frequency out-of-plane ring vibrations are shown in Fig. 38 (91). The third out-of-plane skeletal vibration

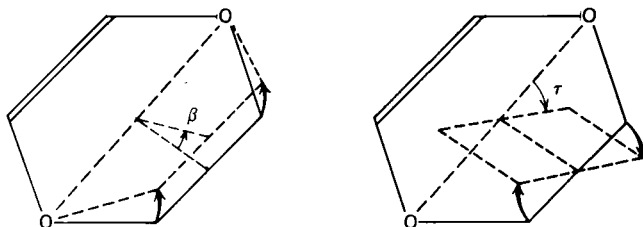


Fig. 38. Ring-twisting (τ) and ring-puckering (β) coordinates for 1,4-dioxene. The third out-of-plane ring mode is a twisting about the double bond. (Reproduced with the permission of the American Institute of Physics, from ref. 92.)

is a twisting about the C=C double bond which is somewhat higher in frequency and is treated as a small-amplitude harmonic vibration. The far-IR spectrum of 1,4-dioxene, which is rather rich in detail, is shown in Fig. 39. The prominent features between 150 and 200 cm^{-1} are Q -branch transitions of a - c hybrid bands involving primarily $\Delta v_b = +1$ selection rules, where v_b is a serial quantum number for the bending (β) mode. The weak series of Q -branch transitions from 90 to 125 cm^{-1} represent difference bands, where $\Delta v_b = -1$ and $\Delta v_t = +1$, with v_t a serial quantum number for the twisting mode. The weak, featureless adsorption near 300 cm^{-1} represents overlapped b -type-bands corresponding to $\Delta v_t = +1$ transitions. However, since the equilibrium conformation has C_2 symmetry (92), a twisted conformer, the twisting vibration is totally symmetric and the resulting hot-band structure is evident in the Raman spectrum (93) (Fig. 39).

The combination of far-IR and Raman data allow unambiguous assignment of the transitions. The sum of a bending Q branch and

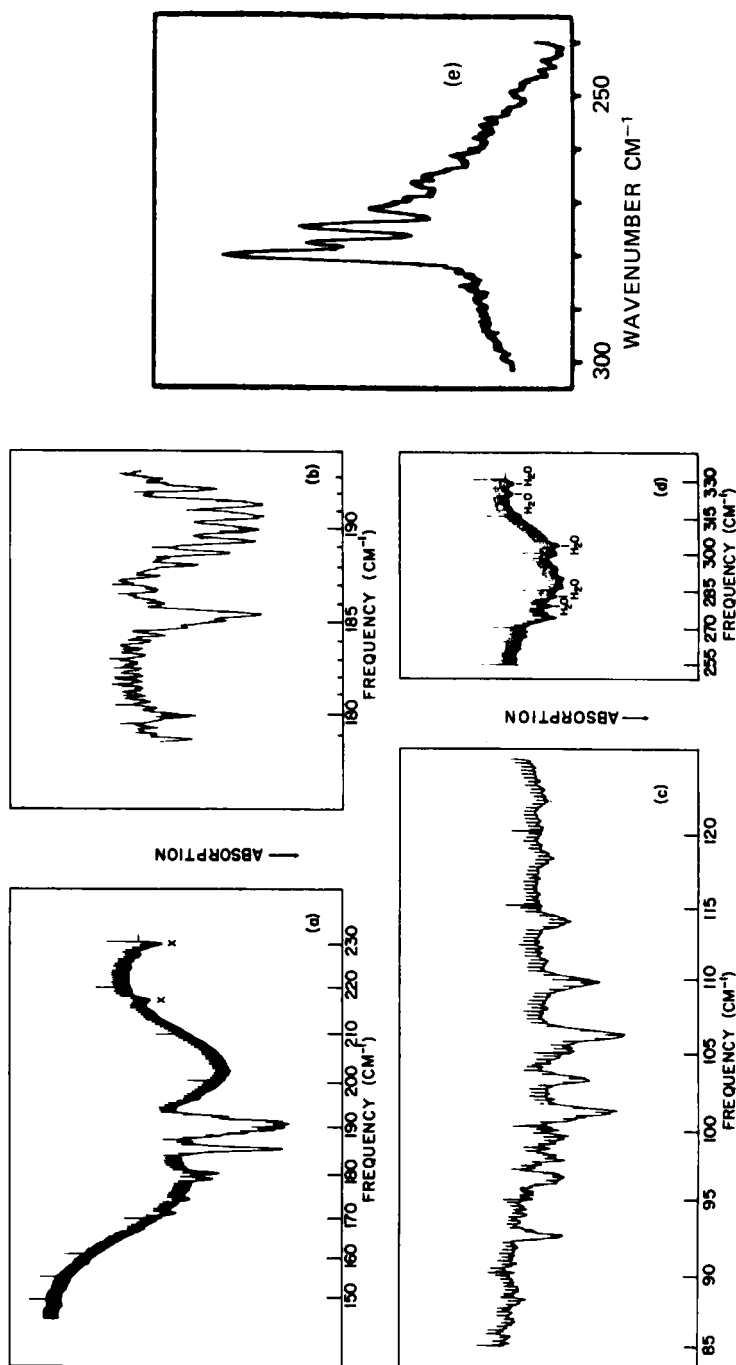


Fig. 39. Far-IR (a-d) and low frequency Raman (e) spectra of 1,4-dioxene. (a) Survey of the bending region ($230\text{--}150\text{ cm}^{-1}$) (c) difference band region ($130\text{--}80\text{ cm}^{-1}$ at 8 m and 10 torr (d) twisting band region ($315\text{--}250\text{ cm}^{-1}$) at 4 m and 10 torr (e) Raman spectrum of twisting band region showing hot band structure. (Reproduced with the permission of the American Institute of Physics) (References 91 and 93).

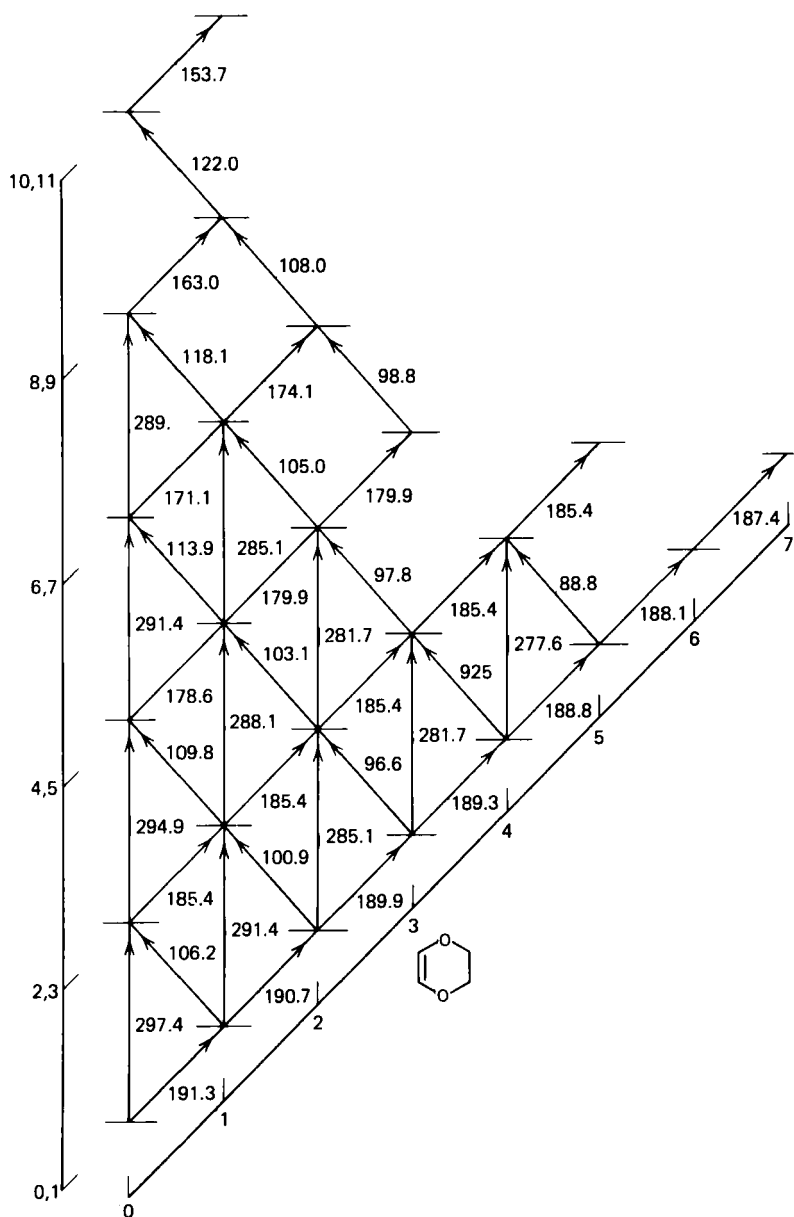


Fig. 40. Assignment of the far-IR and Raman transitions for 1,4-dioxene. There are numerous checks on the internal consistency of the assignment. (Reproduced with the permission of the American Institute of Physics, from ref. 93.)

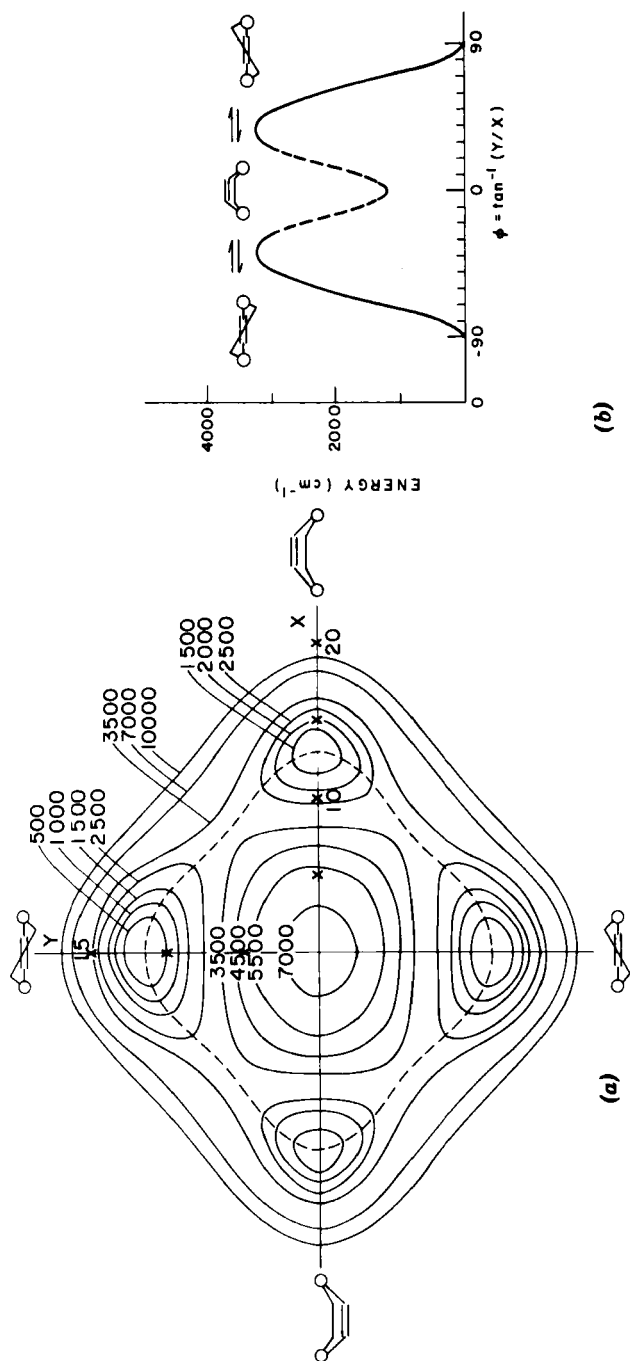


Fig. 41. (a) Potential energy surface for 1,4-dioxene and a cross section along the minimum energy path for interconversion. The dashed line of the surface indicates the minimum energy path to interconversion. (b) The energy (cm⁻¹) along this path.

difference band in the far-IR spectrum must equal one of the Raman Q branches (twisting transitions). The assignment of the transitions is shown in Fig. 40. The data were fitted by least squares variation of the five potential constants in eq [20]. Figure 41 indicates the determined potential energy surface. It is seen that the two equivalent twisted forms interconvert via a metastable bent (C_S) form rather than via the planar conformation. The minimum energy path is denoted by the dashed line. Figure 41 also shows a plot of the energy for the indicated minimum energy path. The shape of the potential in the second minimum corresponding to the bent (C_S) conformation is indicated by a dashed line. It should be emphasized that no direct data have been obtained in this well. The spectroscopic transitions were observed for the twisted (C_S) conformation. While extrapolation of the curve to estimate the barrier height is a reasonable approximation, in no way are the data definitive as to the energy of the second minimum. The value of ΔE , the energy difference between the two forms, when subjected to a statistical analysis of the least squares fitting procedure, is found to be uncertain by the amount of its own magnitude.

With all these cautions it is still possible to estimate the barrier to interconversion from the potential surface. Subsequent study of the temperature dependence of the NMR spectrum yielded a barrier within 1 kcal/mol of that determined from the vibrational data (94). Considering the different approximations involved and the fact the experimental data were obtained for the molecule in different phases, the agreement is satisfactory.

IV. SUMMARY OF INVESTIGATIONS OF SMALL-RING MOLECULES

This section is an attempt at summarizing the results on ring molecules studied in the gas phase by low-frequency vibrational and rotational spectroscopy. We have included only those molecules studied by these techniques and only those for which some data involving the low-frequency modes were obtained. We have not, for example, included determination of molecular symmetry based on selection rules in the mid-IR or mid-Raman spectra. When we refer to mid-IR or mid-Raman studies in Table 4, we include only those studies involving ring-puckering band progressions.

The following abbreviations have been used:

FIR far-IR
MIR mid-IR
R low-frequency Raman
MR mid-Raman
MW microwave

Where applicable, barriers have been given in reciprocal centimeters. The following conversion factors may prove useful:

$$1 \text{ kcal/mol} = 350 \text{ cm}^{-1} = 4.184 \text{ kJ/mol}$$

Table 4 Summary of Investigations of Small-Ring Molecules

Formula	Structure	Name	Techniques	Comments	References
$C_2H_3FO_3$	$\overline{OCH_2OCHO}$ F	fluoroethylene ozonide	MW	Half-chair ring, fluorine axial.	103
$C_2H_4O_3$	$\overline{OCH_2OCH_2O}$ F	ethylene ozonide	MW	Half-chair ring. Several isotopic species.	104-106
$C_2F_4S_2$	$\overline{CF_2SCF_2S}$	1,1,3,3-tetrafluorodithiethane	FIR	Planar, harmonic.	107
$C_2H_8Si_2$	$\overline{CH_2SiH_2CH_2SiH_2}$	1,3-disilacyclobutane	FIR, MIR, R, MR	One-dimensional, double-minimum potential function barrier 87 cm^{-1} , deuterated species (see text).	68,69
$C_3H_2O_3$	$\overline{CH-CHOCO}$ O	vinylene carbonate	MW	Planar, excited states assigned. Isotopic species.	108,109
$C_3H_4F_2O$	$\overline{OCH_2CF_2CH_2}$	3,3-difluoroioxetane	FIR, MW	One-dimensional potential function determined from both MW and FIR. Planar.	110,111
$C_3H_4O_2$	$\overline{CH_2CCH_2O}$ O	3-oxetanone	FIR, MW	One-dimensional potential function determined from both FIR and MW data. Planar. Isotopic species in MW.	6,112,113
$C_3H_4O_2$	$\overline{CH_2COCH_2}$ O	β -propiolactone (2-oxetanone)	MW	Planar. Spectrum assigned in excited states.	114
$C_3H_4O_3$	$\overline{CH_2OCOCH_2}$ O	ethylene carbonate	MW	Half-chair. Splitting characteristic of double-minimum potential function observed in MW spectrum	115

C_3H_4OS	$\overline{CH_2CCH_2S}$ $\parallel$ O	3-thietanone	FIR, MW	One-dimensional potential function determined from both FIR and MW data. Planar (see text).	41,51
C_3H_5NO	$\overline{CH_2CH=NOCH_2}$	2-oxazoline	MIR, MW	One-dimensional potential function from MIR band progressions and MW data. Planar.	116
$C_3H_6N_2$	$\overline{CH_2N=NCH_2CH_2}$	1-pyrazoline	FIR	One-dimensional potential function. Barrier 113 cm^{-1} .	117,118
C_3H_6O	$\overline{CH_2CH_2CH_2O}$	trimethylene oxide	FIR, MIR, MW, R, MR	One-dimensional potential function from FIR and MW data. Several isotopic species. Extensive vibration-rotation interaction studies. Barrier 15.3 cm^{-1} (smaller than zero-point energy) (see text).	14,16,27 29-31,34-39, 63-66
$C_3H_6O_2$	$\overline{CH_2OCH_2OCH_2}$	1,3-dioxolane	FIR, MW	Pseudorotational barrier 45 cm^{-1} C_5 ca. 10 cm^{-1} lower in energy than C_2 . Barrier to planarity is much higher. Half-chair, methyl equatorial. Isotopic species.	81-83,119
$C_3H_6O_3$	$\overline{OCH_2OCHO}$ $\mid$ CH ₃ $\overline{CH_2CH_2SCH_2}$ $\parallel$ O	propylene ozonide	MW		120
C_3H_6OS	$\overline{CH_2CH_2SCH_2}$ $\parallel$ O	trimethylene sulfoxide	MW	Puckered ring with 0 equatorial. Isotopic species.	121
C_3H_6S	$\overline{CH_2CH_2SCH_2}$	trimethylene sulfide	FIR, MIR, MW, R	One-dimensional potential function from vibrational and MW data. Barrier 274 cm^{-1} . Isotopic species.	28,40,42, 43,122-124

Table 4 Continued

Formula	Structure	Name	Techniques	Comments	References
C ₃ H ₆ Se	$\overline{\text{CH}_2\text{CH}_2\text{SeCH}_2}$	trimethylene selenide	FIR, MIR, MW	One-dimensional, double-minimum potential function from FIR and MW data. Barrier 373 cm ⁻¹ .	125,126
C ₃ H ₇ N	$\overline{\text{CH}_2\text{CH}_2\text{NHCH}_2}$	trimethylene imine	FIR, R	One-dimensional, asymmetric, double-minimum potential function. Barrier 441 cm ⁻¹ , ΔE=90 cm ⁻¹ . Assignment confirmed by Raman study. N - D species (see text).	23,67
C ₃ H ₈ Si	$\overline{\text{CH}_2\text{CH}_2\text{SiH}_2\text{CH}_2}$	silacyclobutane	FIR, MIR, R, MR, MW	One-dimensional, double-minimum potential function. Barrier 440 cm ⁻¹ . SiD ₂ species.	7,8,26,127
C ₄ H ₄ F ₄	$\overline{\text{CH}_2\text{CF}_2\text{CF}_2\text{CH}_2}$	1,1,2,2-tetrafluorocyclobutane	MW, FIR	Nonplanar based on MW data. No barrier determined.	128,129
C ₄ H ₄ O ₂	$\overline{\text{CH}=\text{CHOCH}=\text{CHO}}$	1,4-dioxadiene	FIR	One-dimensional potential function. Planar. Evidence for interaction with ring-twisting mode.	54,130
C ₄ H ₄ O ₂	$\overline{\text{OC}\begin{array}{c}\text{CH}_2\text{C} \\ \parallel \\ \text{CH}_2\end{array}\text{O}}$	diketene	FIR, MW	Planar, harmonic.	6,131
C ₄ H ₆ F ₂	$\overline{\text{CH}_2\text{CH}_2\text{CF}_2\text{CH}_2}$	1,1-difluorocyclobutane	MW	One-dimensional, double-minimum potential function from variation of rotational constants and inversion	132

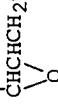
$C_4H_6F_2Si$	$\overline{CH=CHCH_2SiF_2CH_2}$	1,1-difluorosilacyclopent-3-ene	MW	splittings. Barrier 241 cm^{-1} . Planar.	133
C_4H_6O	$\overline{CH_2CH_2C\overset{\overset{O}{ }}{CH_2}}$	cyclobutanone	FIR, MW, MIR	One-dimensional potential function. Barrier 7.6 cm^{-1} (less than zero-point energy). Several isotopic species.	16,42-44, 134
C_4H_6O	$\overline{OCH_2C\overset{\overset{CH_2}{ }}{CH_2}}$	3-methyleneoxetane	MW, FIR	One-dimensional potential function. Planar.	135,136
C_4H_6O	$\overline{CH=CHCH_2OCH_2}$	2,5-dihydrofuran	FIR, MIR, R	One-dimensional potential function. Planar. Spectra show evidence for interaction between ring-puckering and ring-twisting modes (see text).	6,46,53,54, 71,118
C_4H_6O	$\overline{CH=CH-OCH_2CH_2}$	2,3-dihydrofuran	FIR, MIR MW, R	One-dimensional, double-minimum potential function. Barrier 83 cm^{-1} . Nonplanar.	14,118,137-139
$C_4H_6O_2$	$\overline{CH_2CH_2CO\overset{\overset{O}{ }}{CH_2}}$	γ -butyrolactone	MW		140
$C_4H_6O_2$	$\overline{CHCHCH_2OCH_2}$ 	3,6-dioxabicyclo[3.1.0]hexane	FIR, R, MW	One-dimensional, asymmetric single-minimum, potential function from FIR data confirmed by Raman study. Boat conformation determined from MW data (see text).	55-57
$C_4H_6O_2$	$\overline{CH=CHOCH_2CH_2O}$	1,4-dioxene	FIR, R, MW	Two-dimensional potential surface determined from FIR and Raman data. The two equivalent C_2 (from MW) con-	91-93

Table 4 Continued

Formula	Structure	Name	Techniques	Comments	References
$C_4H_6O_2$	$\begin{array}{c} \overline{CH_2COCH} \\ \quad \quad \quad \parallel \\ \quad \quad \quad O \quad CH_3 \end{array}$	β -butyrolactone	MW, FIR	formers interconvert via metastable C_s conformers (see text). Planar.	141,142
C_4H_6S	$\overline{CH=CHCH_2SCH_2}$	2,5-dihydrothiophene	FIR, MR	One-dimensional potential function. Planar.	14,118,143
C_4H_6S	$\overline{CH=CHSCH_2CH_2}$	2,3-dihydrothiophene	MIR, R	One-dimensional, double-minimum potential function from Raman. Barrier 325 cm^{-1} .	14,138
C_4H_7Br	$\begin{array}{c} \overline{CH_2CH_2CHCH_2} \\ \quad \quad \quad \\ \quad \quad \quad Br \end{array}$	bromocyclobutane	MW, FIR, R	One-dimensional, asymmetric, single-minimum potential function (FIR, R) corresponding to a puckered ring with the bromine equatorial (MW). Same as bromocyclobutane.	144-147 147-150
C_4H_7Cl	$\begin{array}{c} \overline{CH_2CH_2CHCH_2} \\ \quad \quad \quad \\ \quad \quad \quad Cl \end{array}$	chlorocyclobutane	FIR, R, MW	Same as bromocyclobutane.	147,148, 150
C_4H_7F	$\begin{array}{c} \overline{CH_2CH_2CHCH_2} \\ \quad \quad \quad \\ \quad \quad \quad F \end{array}$	fluorocyclobutane	R, MW	Same as bromocyclobutane.	147,148, 150
C_4H_7N	$\overline{CH=CHCH_2NHCH_2}$	2,5-dihydropyrrole	FIR, R, MW	One-dimensional, asymmetric, double-minimum potential function with a barrier of the order of the zero-point energy. N - D species studied,	23,67,151

C_4H_8	$\overline{CH_2CH_2CH_2CH_2}$	cyclobutane	MIR, R	and assignment confirmed by Raman study (see text). One-dimensional, double-minimum potential function. Barrier 515 cm^{-1} . C_{4D_8} species studied. Evidence for mixing of CH_2 motion (see text).	21,24,25, 75
C_4H_8O	$\overline{CH_2CH_2OCH_2CH_2}$	tetrahydrofuran	FIR, MW	Twisted and bent forms interconvert with a small pseudorotational barrier rather than via the planar conformation (see text). Half-chair, methyl equatorial. Isotopic species.	80,81,87, 119
$C_4H_8O_3$	$\overline{\begin{array}{c} O-CH-O-CH-O \\ \quad \quad \\ CH_3 \quad CH_3 \quad CH_3 \end{array}}$	butylene ozonide	MW		120
C_4H_8S	$\overline{CH_2CH_2SCH_2CH_2}$	tetrahydrothiophene	MW	Half-chair conformation.	152
C_4H_8Se	$\overline{CH_2CH_2SeCH_2CH_2}$	selenacyclopentane	MW	Half-chair conformation.	153
C_4H_8Si	$\overline{CH=CHCH_2SiH_2CH_2}$	silacyclopent-3-ene	FIR, MIR, R	One-dimensional potential function. Planar. SiD_2 species.	8,26,118, 154
C_4H_8Si	$\overline{CH=CHSiH_2CH_2CH_2}$	silacyclopent-2-ene	FIR, MIR	One-dimensional potential function. Planar.	26,155
C_4H_9N	$\overline{CH_2CH_2CHCH_2}$ $\quad \quad \quad $ $\quad \quad \quad NH_2$	cyclobutyl amine	FIR, R	One-dimensional, asymmetric, single-minimum potential function. ^a ND_2 species.	156
$C_4H_{10}Ge$	$\overline{CH_2CH_2GeH_2CH_2CH_2}$	germacyclopentane	FIR, MIR, R, MW	Two-dimensional surface determined from FIR and Raman data. The two equivalent half-chair forms (from MW) interconvert via the planar conformation ^b .	157-159

Table 4 Continued

Formula	Structure	Name	Techniques	Comments	References
C ₄ H ₁₀ Si	$\overline{\text{CH}_2\text{CH}_2\text{SiH}_2\text{CH}_2\text{CH}_2}$	silacyclopentane	FIR, R, MW	(see discussion of cyclopentanone in text). Barrier 1454 cm ⁻¹ .	18,160-162
C ₅ H ₆ O	$\overline{\text{CH}=\text{CHCH}_2\text{C}(=\text{O})\text{CH}_2}$	3-cyclopenten-1-one	FIR, MW	Same as germacyclopentane. ^b Barrier 1414 cm ⁻¹ .	163-167
C ₅ H ₆ O	$\overline{\text{CH}=\text{CHCCH}_2\text{CH}_2}$ $\parallel$ O	2-cyclopenten-1-one	FIR, MW	One-dimensional potential function. Planar. Isotopic species in MW.	167-169
C ₅ H ₇ N	$\overline{\text{CH}_2\text{CH}_2\text{CHCH}_2}$ $\parallel$ CN	cyanocyclobutane	MW, FIR	One-dimensional potential function from FIR. Puckered ring with CN equatorial (MW).	147,170, 171
C ₅ H ₈	$\overline{\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_2}$	cyclopentene	FIR, MIR, R, MR, MW	One-dimensional, double-minimum potential function. Barrier 232 cm ⁻¹ . Isotopic species. Evidence for interaction between ring-puckering and ring-twisting (see text).	10,14,16, 32,54,70-74,118,172
C ₅ H ₈	$\overline{\text{CH}_2\text{CH}_2\text{CCH}_2}$ $\parallel$ CH_2	methylenecyclobutane	MW, MIR, R	One-dimensional, double-minimum potential function. Barrier 140 cm ⁻¹ . Isotopic species (MIR).	17,45,124

C ₅ H ₈ O	$\overline{\text{CH}_2\text{CH}_2\text{CCH}_2\text{CH}_2}$ $\parallel$ O	cyclopentanone	FIR, MW	Two-dimensional potential energy surface determined from FIR data. The two equivalent half-chair conformers (from MW) interconvert via the planar conformation. Several deuterated species (see text).	6,89,90
C ₅ H ₈ O	$\overline{\text{CH}=\text{COCH}_2\text{CH}_2}$ $\mid$ CH ₃	2-methyl-4,5-dihydro-furan	FIR	One-dimensional, double-minimum potential function. Barrier 98 cm ⁻¹ .	6
C ₅ H ₈ O	$\overline{\text{CHCHCH}_2\text{CH}_2\text{CH}_2}$ $\mid$ O	6-oxabicyclo[3.1.0]hexane	FIR, R, MW	Same as 3,6-dioxabicyclo[3.1.0]hexane.	23,55,56 60
C ₅ H ₈ O	$\overline{\text{CHCHCH}_2\text{OCH}_2}$ $\mid$ CH ₂	3-oxabicyclo[3.1.0]hexane	FIR, MW, R	Same as 3,6-dioxabicyclo[3.1.0]hexane.	55,56,61
C ₅ H ₈ O	$\overline{\text{CH}=\text{CHCH}_2\text{OCH}_2\text{CH}_2}$	3,4-dihydropyran	MW	Half-chair conformation.	173
C ₅ H ₈ O	$\overline{\text{CH}=\text{CHOCH}_2\text{CH}_2\text{CH}_2}$	2,3-dihydropyran	FIR, R	Two-dimensional surface for interconversion of half-chair conformation (see 1,4-dioxene).	91,93
C ₅ H ₈ S	$\overline{\text{CHCHCH}_2\text{CH}_2\text{CH}_2}$ $\mid$ S	6-thiabicyclo[3.1.0]hexane	MW	Boat conformation.	174
C ₅ H ₉ N	$\overline{\text{CH}=\text{CHCH}_2\text{NHCH}_2\text{CH}_2}$	1,2,3,6-tetrahydropyridine	MW	55% half-chair NH equatorial to 45% half-chair NH axial at room temperature. N - D species.	175
C ₅ H ₁₀	$\overline{\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2}$	cyclopentane	MIR, R	Pure pseudorotation. Barrier to planarity 1824 cm ⁻¹ .	22,84,86, 176

Table 4 (Continued)

Formula	Structure	Name	Techniques	Comments	References
C ₅ H ₁₀ O		3,3-dimethyloxetane	FIR	Isotopic species. Two-dimensional treatment.	177
C ₆ H ₈		1,2-dimethylenecyclobutane	MW	One-dimensional, double-minimum potential function. Barrier 46 cm ⁻¹ . Planar (see text).	52
C ₆ H ₈		1,3-cyclohexadiene	R, MW	Half-chair conformation (MW). One-dimensional, double-minimum potential function (R). Barrier 1099 cm ⁻¹ . Planar.	178,179
C ₆ H ₈		1,4-cyclohexadiene	FIR, R		179,180
C ₆ H ₈ O		2-cyclohexen-1-one	MW, R	All ring atoms coplanar except for C ₅ (MW). Barrier to planarity 935 cm ⁻¹ (R).	181,182
C ₆ H ₈ O		7-oxabicyclo[4.1.0]hept-3-ene	FIR, MW	Slightly anharmonic potential function (FIR). Boat conformation (MW).	183,184
C ₆ H ₈ O		2-oxabicyclo[3.2.0]hept-6-ene	FIR, R	Single-minimum, asymmetric potential function.	185
C ₆ H ₁₀		cyclohexene	MW, R	Half-chair interconverts via half-boat (see 1,4-dioxene).	93,186, 187
C ₆ H ₁₀		bicyclo[3.1.0]hexane	FIR, R, MW	Same as 3,6-dioxabicyclo[3.1.0]hexane (see text).	55,56,67

V. CONCLUSIONS

We have reviewed applications of gas-phase, low-frequency vibrational spectroscopy and rotational spectroscopy to the determination of conformations, barriers, and interconversion pathways in small-ring molecules. We feel that these techniques have led to some of the most accurately determined barriers in the range of 0 to 3 kcal/mol. We are, quite obviously, proponents of these techniques, and feel quite strongly that, when applicable, these should be the methods of choice for barrier determinations in this range. We have, however, attempted to be honest about the shortcomings of some of these techniques, and have tried to give reasonable estimates of the uncertainties and sources of error. We feel that in most cases we have been quite conservative in the claims we have made.

In some cases, for example, in the determination of the puckering angle of a four-membered-ring molecule, extensive data may be required to reduce the uncertainty. It may be that other techniques, or a combination of gas-phase spectroscopic data and data from other techniques, might lead to a more certain determination of this quantity. As mentioned in our Introduction, we excluded consideration of other techniques, experimental and calculational, not through value judgment of their worth, but in order to concentrate on the case at hand. We have not given a complete review of gas-phase spectroscopy, nor of the stereochemistry of small-ring molecules, by any means. We have tried to critically examine the application of gas-phase spectroscopy to small-ring molecules.

Low-frequency spectroscopy is not limited to the study of ring molecules, and there have been many applications to large-amplitude vibrations in quasilinear molecules such as carbon suboxide, among others, and to studies of internal rotation. It was not possible to consider all of these topics here.

APPENDIX I

The experience of a number of chemists with reduced masses is limited to the reduced mass of a two-particle system:

$$\mu = \frac{m_1 m_2}{m_1 + m_2} \quad [A1-1]$$

The vibrational coordinate, a change in the distance between m_1 and m_2 , does not appear in the expression for μ . Most spectroscopists are aware that the G matrix elements corresponding to, for example, the angle-bending coordinate for a triatomic molecule depend on the value of the angle. However, in dealing with small changes from the equilibrium value of the angle, this G matrix element is taken to be constant and evaluated at the equilibrium value.

On the other hand, for a large-amplitude motion where the reduced mass depends on the vibrational coordinate, obtaining a suitable quantum mechanical kinetic energy operator presents a problem. The correspondence in most elementary quantum mechanics texts,

$$\frac{p^2}{2\mu} \rightarrow -\frac{\hbar^2}{2\mu} \frac{d^2}{dx^2} \quad [\text{Al-2}]$$

is no longer valid, since the resulting operator is not Hermitian. However, as pointed out by Harris and co-workers (40), one may use an operator of the form of [Al-2] with the following justification. If

$$\bar{\mu} = \mu(x) \quad [\text{Al-3}]$$

a new coordinate $\bar{x}$ may be defined by a nonlinear coordinate transformation

$$\bar{x} = \int \left[\frac{\mu(x)}{\mu(0)} \right]^{1/2} dx \quad [\text{Al-4}]$$

The coordinate $\bar{x}$ has an effective reduced mass that is constant and equal to the value of $\mu(x)$ at $x = 0$. The kinetic energy operator is then

$$\frac{p^2}{2\mu(0)} \rightarrow -\frac{\hbar^2}{2\mu(0)} \frac{d^2}{d\bar{x}^2} \quad [\text{Al-5}]$$

The coordinate $\bar{x}$ is the one referred to throughout the text. The "true" potential function is related to this by using a constant reduced mass Hamiltonian by the nonlinear transformation [Al-4]. In practice this is not a serious problem. Barrier height determinations are only very slightly affected (a few reciprocal centimeters). The geometry corresponding to the minimum energy is only slightly affected (ca. $\pm 1^\circ$).

Wilson, Decius, and Cross (3) refer to a procedure for obtaining a quantum mechanical kinetic energy operator, given in a text by Kemble (193). The result for a molecule with a single large-amplitude mode is

$$T = \frac{-\hbar^2}{2} \frac{d}{dx} g_p(x) \frac{d}{dx} + V'(x) \quad [\text{Al-6}]$$

where $g_p(x)$ ($=1/\mu(x)$) is the G matrix element corresponding to ring-puckering and $V'(x)$ is a "pseudopotential." The pseudopotential for ring-puckering is generally a slowly varying function of x , and may be neglected or absorbed into the effective potential function. In general the operator in [Al-5] is quite adequate, and [Al-6] should be used only if there is some

pressing need to take into account small differences in potential functions (118).

In practice the potential function in a dimensionless coordinate (see Appendix II) is that which is determined from the experimental data. Except for small changes arising from the nonlinearity of [A1-4], the determination of barrier heights is entirely independent of model calculations of a reduced mass. The barrier height is given by

$$\text{barrier} = \frac{AB^2}{4} \quad [\text{A1-7}]$$

in terms of the reduced coordinate Z (eq. [16]).

The puckering angle, however, does depend on the reduced mass. For the potential function of eq. [16]

$$V = A(Z^4 + BZ^2) \quad [\text{A1-8}]$$

with $B < 0$. The values of Z corresponding to the minima are

$$|Z_{\min}| = \sqrt{\frac{-B}{2}} \quad [\text{A1-9}]$$

To calculate a puckering angle, we require the distance $|x|$ corresponding to the minimum (actually $|\bar{x}|$),

$$|x_{\min}| = \left[\frac{\hbar^2}{2\mu(0)} (-AB) \right]^{1/2} \quad [\text{A1-10}]$$

which requires knowledge of μ at $x = 0$. This value of μ depends on the model used for the vibration. Particularly if ring-puckering involves mixing with methylene rocking modes, μ may change by ca. 20 to 30% or more (75). Consequently, unless data are available indicating the extent of mixing of CH_2 or other low-frequency modes, puckering angles derived in this fashion may be somewhat uncertain. However, to reiterate, this *does not* affect the determination of barrier heights.

APPENDIX II

The most widely used potential function for symmetric ring-puckering vibrations is the mixed quartic-quadratic, $V = ax^4 + bx^2$, where a and b are the dimensioned potential constants. The one-dimensional wave equation that must be solved for the energy levels is

$$-\frac{\hbar^2}{2\mu} \frac{d^2\psi}{dx^2} + (V - E)\psi = 0 \quad [\text{A2-2}]$$

where μ is the reduced mass for the vibration, which is assumed to be constant (see Appendix I). For many calculations μ is not known, and the dimensioned equation cannot be solved. This problem is circumvented by removing the dependence on the reduced mass by means of a linear transformation to a dimensionless coordinate Z . The dimensionless or reduced potential constants and energy levels can then be calculated without explicit knowledge of the reduced mass. Many different transformations have been used, resulting in a wide variety of potential constants, making it difficult to compare potential functions. The relationships between the various reduced potential constants and the dimensioned potential constants are given below. The transformations have been reviewed by Laane (49) and by Gibson and Harris (112). (Note: Gibson and Harris used the dimensioned potential $V = ax^2 + bx^4$.)

The first two transformations are of the type used by Ueda and Shimanouchi (46). The first is the most widely used transformation, where

$$Z = \left(\frac{2\mu}{\hbar^2} \right)^{1/6} a^{1/6} x \quad [\text{A2-3}]$$

The wave equation in reduced form is now

$$\frac{d^2\psi}{dZ^2} + (\lambda - Z^4 - BZ^2)\psi = 0 \quad [\text{A2-4}]$$

where

$$V = A(Z^4 + BZ^2) \quad [\text{A2-5a}]$$

$$A = \left(\frac{2\mu}{\hbar^2} \right)^{-2/3} a^{1/3} \quad [\text{A2-5b}]$$

$$B = \left(\frac{2\mu}{\hbar^2} \right)^{1/3} a^{-2/3} b \quad [\text{A2-5c}]$$

The wave equation is solved for the eigenvalues λ , and these are related to the energy levels by the scale factor A :

$$E = \lambda A \quad \text{so} \quad \lambda = \left(\frac{2\mu}{\hbar^2} \right)^{2/3} a^{-1/3} E \quad [\text{A2-6}]$$

The eigenvalues λ have been tabulated by Laane (49) for many values of B .

When the potential is nearly harmonic, it is more convenient to use the second transformation,

$$Z_\beta = \left(\frac{2\mu b}{\hbar^2} \right)^{1/4} x \quad [\text{A2-7}]$$

The dimensionless wave equation is

$$\frac{d^2\psi}{dz_\beta^2} + (\lambda_\beta - \beta z_\beta^4 - z_\beta^2) \psi = 0 \quad [\text{A2-8}]$$

where

$$V = A_\beta (\beta z_\beta^4 + z_\beta^2) \quad [\text{A2-9a}]$$

$$A_\beta = (2\mu/\hbar^2)^{-1/2} b^{1/2} \quad [\text{A2-9b}]$$

$$\beta = \left(\frac{2\mu}{\hbar^2}\right)^{-1/2} b^{-3/2} a \quad [\text{A2-9c}]$$

and

$$\lambda_\beta = \left(\frac{2\mu}{\hbar^2}\right)^{1/2} b^{-1/2} E \quad [\text{A2-9d}]$$

These reduced constants are related to A , B , and λ as follows:

$$A_\beta = B^{1/2} A \quad [\text{A2-10a}]$$

$$\beta = B^{-3/2} \quad [\text{A2-10b}]$$

$$\lambda_\beta = B^{-1/2} \lambda \quad [\text{A2-10c}]$$

Similar transformations, which differ by only a factor of 2 in the momentum transformation, have been used by Chan and co-workers, (47).

In the first of these transformations

$$z_\eta = \left(\frac{8\mu}{\hbar^2}\right)^{1/6} a^{1/6} x \quad [\text{A2-11}]$$

The wave equation becomes

$$4 \frac{d^2\psi}{dz_\eta^2} + (\lambda_\eta - z_\eta^4 - \eta z_\eta^2) \psi = 0 \quad [\text{A2-12}]$$

where

$$V = A_\eta (z_\eta^4 + \eta z_\eta^2) \quad [\text{A2-13a}]$$

$$A_\eta = \left(\frac{8\mu}{\hbar^2}\right)^{-2/3} a^{1/3} = 4^{-2/3} A \quad [\text{A2-13b}]$$

$$\eta = \left(\frac{8\mu}{\hbar^2}\right)^{1/3} a^{-2/3} b = 4^{1/3} B, \quad [\text{A2-13c}]$$

$$\lambda_{\eta} = \left(\frac{8\mu}{\hbar^2}\right)^{2/3} a^{-1/3} E = 4^{2/3} \lambda \quad [\text{A2-13d}]$$

In the second transformation

$$z_{\xi} = \left(\frac{8\mu b}{\hbar^2}\right)^{1/4} x \quad [\text{A2-14}]$$

The wave equation is now

$$4 \frac{d^2 \psi}{dz_{\xi}^2} + (\lambda_{\xi} - \xi z_{\xi}^4 - z_{\xi}^2) \psi = 0 \quad [\text{A2-15}]$$

where

$$V = A_{\xi} (\xi z_{\xi}^4 + z_{\xi}^2) \quad [\text{A2-16a}]$$

$$A_{\xi} = \left(\frac{8\mu}{\hbar^2}\right)^{1/2} b^{1/2} = 1/2 B^{1/2} A \quad [\text{A2-16b}]$$

$$\xi = \left(\frac{8\mu}{\hbar^2}\right)^{-1/2} b^{-3/2} a = 1/2 B^{-3/2} \quad [\text{A2-16c}]$$

$$\lambda_{\mu} = \left(\frac{8\mu}{\hbar^2}\right)^{1/2} b^{-1/2} E = 2B^{-1/2} \quad [\text{A2-16d}]$$

Chan and co-workers have also used a transformation in which α is a measure of the anharmonicity, varying from 0 for a harmonic oscillator to 1 for a quartic oscillator:

$$z_{\alpha} = \left[\frac{4\mu}{\hbar^2} (2b + \left(\frac{a^2 \hbar^2}{\mu}\right)^{1/3})\right]^{1/4} x \quad [\text{A2-17}]$$

The wave equation reduces to

$$4 \frac{d^2 \psi}{dz_{\alpha}^2} + [\lambda_{\alpha} - \alpha^{3/2} z_{\alpha}^4 - (1 - \alpha) z_{\alpha}^2] \psi = 0 \quad [\text{A2-18}]$$

where

$$\alpha = [1 + \left(\frac{8\mu}{\hbar^2}\right)^{1/3} a^{-2/3} b]^{-1} = (1 + 4^{1/3} B)^{-1} \quad [\text{A2-19a}]$$

$$V = A_{\alpha} [\alpha^{3/2} z_{\alpha}^4 + (1 - \alpha) z_{\alpha}^2] \quad [\text{A2-19b}]$$

$$A_{\alpha} = [b \left(\frac{\hbar^2}{8\mu}\right) + a^{2/3} \left(\frac{\hbar^2}{8\mu}\right)^{4/3}]^{1/2} = 4^{-2/3} (1 + 4^{1/3} B)^{1/2} A \quad [\text{A2-19c}]$$

$$\lambda_{\alpha} = a^{-1/3} \left(\frac{8\mu}{\hbar^2}\right)^{2/3} [1 + ba^{-2/3} \left(\frac{\hbar^2}{8\mu}\right)]^{-1/2} E = 4^{2/3} (1 + 4^{1/3} B)^{-1/2} \lambda \quad [\text{A2-19d}]$$

Eigenvalues have been tabulated for many values of α (47).

The dimensioned constants can be found from the reduced constants if μ is known. The relations are as follows:

$$\text{I. } a = \left(\frac{2\mu}{\hbar^2}\right)^2 A^3 \quad b' = \left(\frac{2\mu}{\hbar^2}\right) A^2 B \quad [\text{A2-20a}]$$

$$\text{II. } a = \left(\frac{2\mu}{\hbar^2}\right)^2 A_\beta^3 \beta \quad b = \left(\frac{2\mu}{\hbar^2}\right) A_\beta^2 \beta \quad [\text{A2-20b}]$$

$$\text{III. } a = \left(\frac{8\mu}{\hbar^2}\right)^2 A_\eta^3 \eta \quad b = \left(\frac{8\mu}{\hbar^2}\right) A_\eta^2 \eta \quad [\text{A2-20c}]$$

$$\text{IV. } a = \left(\frac{8\mu}{\hbar^2}\right)^2 A_\xi^3 \xi \quad b = \left(\frac{8\mu}{\hbar^2}\right) A_\xi^2 \xi \quad [\text{A2-20d}]$$

$$\text{V. } a = \left(\frac{8\mu}{\hbar^2}\right)^2 \alpha^{3/2} A_\alpha^3 \quad b = \left(\frac{8\mu}{\hbar^2}\right) A_\alpha^2 (1 - \alpha) \quad [\text{A2-20e}]$$

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Stereochemical Aspects of Phosphorus-Containing Cyclohexanes

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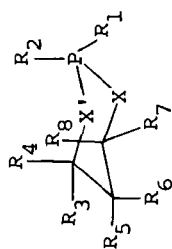
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I. INTRODUCTION

Although diverse phosphorus-containing heterocycles had been synthesized as early as the late nineteenth century, work was still sparse in this area as recently as 1950 (1,2). The realization, around 1950, of the importance of phosphorus substances in biological processes resulted in intense activity in preparative organophosphorus chemistry and in an upsurge of research on structural and mechanistic problems (3-6).

This post-1950 revolution in organophosphorus chemistry was followed by investigations of varied organophosphorus heterocycles, including probes into reaction mechanisms, stereochemistry, and spectroscopic properties. The accumulation of general organophosphorus stereochemical studies and spectral work, documented in some texts (5,6) and in numerous reviews (7-15), laid a foundation for conformational studies. A concern for the conformational analysis of organophosphorus compounds emerged in the late 1960s, succeeding the major surge in conformational research, which occurred between 1950 and 1965 (16-23). Emphasis centered on the six-membered-ring (phosphorinane) (24) system, interest in which was heightened because of its presence in biologically important substances: (1) the cyclic nucleotides

Table 1 List of Compounds^a



Compound	X = X'	R ₁	R ₂	R ₃	R ₅	R ₄	R ₆	R ₇	R ₈	Reference
1a	O	1p	OCH ₃	-(CH ₂) ₄ -		H	H	H	H	30
1b	O	OCH ₃	1p	-(CH ₂) ₄ -		H	H	H	H	30
2a	O	S	OCH ₃	-(CH ₂) ₄ -		H	H	H	H	30
2b	O	OCH ₃	S	-(CH ₂) ₄ -		H	H	H	H	30
3a	O	1p	OCH ₃	CH ₃	H	H	H	CH ₃	H	30
3b	O	OCH ₃	1p	CH ₃	H	H	H	CH ₃	H	30
4a	O	S	OCH ₃	CH ₃	H	H	H	CH ₃	H	30
4b	O	OCH ₃	S	CH ₃	H	H	H	CH ₃	H	30
5a	O	O	OCH ₃	CH ₃	H	H	H	CH ₃	H	30
5b	O	OCH ₃	O	CH ₃	H	H	H	CH ₃	H	29a
6a	O	O	N(CH ₃) ₂	CH ₃	H	H	H	CH ₃	H	29a
6b	O	N(CH ₃) ₂	O	CH ₃	H	H	H	CH ₃	H	29a
7a	O	O	CH ₃	CH ₃	H	H	H	CH ₃	H	29a
7b	O	CH ₃	O	CH ₃	H	H	H	CH ₃	H	29a
8a	O	O	H	CH ₃	H	H	H	CH ₃	H	29a
8b	O	H	O	CH ₃	H	H	H	CH ₃	H	29a
9a	O	S	Cl	-(CH ₂) ₃ O-		H	H	H	H	34
9b	O	Cl	S	-(CH ₂) ₃ O-		H	H	H	H	34
10a	O	S'	OCH ₃	-(CH ₂) ₃ O-		H	H	H	H	34
10b	O	OCH ₃	S	-(CH ₂) ₃ O-		H	H	H	H	34

11a	O	S	CH ₃	CH ₃	-(CH ₂) ₃ O-	H	H	H	34
11b	O	CH ₃	S	S	-(CH ₂) ₃ O-	H	H	H	34
12a	O	S	N(CH ₃) ₂	N(CH ₃) ₂	-(CH ₂) ₃ O-	H	H	H	34
12b	O	N(CH ₃) ₂	S	S	-(CH ₂) ₃ O-	H	H	H	34
13a	O	lp	OCH ₃	H	t-C ₄ H ₉	H	H	H	35
13b	O	OCH ₃	lp	H	t-C ₄ H ₉	H	H	H	35
14b	O	t-C ₄ H ₉	lp	H	t-C ₄ H ₉	H	H	H	35
15a	O	lp	NH(CH ₃)	H	t-C ₄ H ₉	H	H	H	35
15b	O	NH(CH ₃)	lp	H	t-C ₄ H ₉	H	H	H	35
16	O	O	OC ₆ H ₅	H	H	H	H	H	36
17	O	O	OC ₆ H ₅	H	CH ₃	H	H	H	36
18a	O	S	F	CH ₃	H	H	H	H	37
18b	O	F	S	CH ₃	H	H	H	H	37
19a	O	O	H	CH ₃	H	H	H	H	38
19b	O	H	O	CH ₃	H	H	H	H	38
20a	O	S	H	CH ₃	H	H	H	H	39
20b	O	H	S	CH ₃	H	H	H	H	39
21a	O	Se	H	CH ₃	H	H	H	H	39
21b	O	H	Se	CH ₃	H	H	H	H	39
22a	O	O	CH ₂ C ₆ H ₅	CH ₃	H	H	H	H	40
22b	O	CH ₂ C ₆ H ₅	O	CH ₃	H	H	H	H	40
23a	O	Se	CH ₂ C ₆ H ₅	CH ₃	H	H	H	H	40
23b	O	CH ₂ C ₆ H ₅	Se	CH ₃	H	H	H	H	40
24	O	lp	OCH ₃	H	H	H	H	H	42
25	O	lp	OCH ₃	H	CH ₃	H	H	H	42
26	CH ₂	lp, CH ₃	lp, CH ₃	H	H	H	H	H	43
27	CH ₂	lp, C ₂ H ₅	lp, C ₂ H ₅	H	H	H	H	H	43
28	CH ₂	lp, i-C ₃ H ₇	lp, i-C ₃ H ₇	H	H	H	H	H	43
29	CH ₂	lp, t-C ₄ H ₉	lp, t-C ₄ H ₉	H	H	H	H	H	43
30	CH ₂	lp, C ₆ H ₅	lp, C ₆ H ₅	H	H	H	H	H	43
31a	CH ₂	S	CH ₃	H	CH ₃	OH	H	H	43
31b	CH ₂	CH ₃	S	H	CH ₃	OH	H	H	43

Table 1 Continued

Compound	X = X'	R ₁	R ₂	R ₃	R ₅	R ₄	R ₆	R ₇	R ₈	Reference
32a	CH ₂	S	CH ₃	H	t-C ₄ H ₉	H	OH	H	H	43
32b	CH ₂	CH ₃	S	H	t-C ₄ H ₉	H	OH	H	H	43
33a	CH ₂	lp	CH ₃	H	t-C ₄ H ₉	H	OH	H	H	43b
33b	CH ₂	CH ₃	lp	H	t-C ₄ H ₉	H	OH	H	H	43b
34	NCH ₃	lp, OCH ₃		H	H	H	H	H	H	45
35	NCH ₃	lp, OCH ₃		H	CH ₃	H	CH ₃	H	H	45
36	NCH ₃	lp, C ₆ H ₅		H	H	H	H	H	H	45
37	NCH ₃	lp, C ₆ H ₅		H	CH ₃	H	CH ₃	H	H	45
38	NCH ₃	lp, C ₆ H ₅		H	CH ₃	H	H	H	H	45
39	See text									45
40	See text									45
41a	S	O	OC ₆ H ₅	D	C ₆ H ₅	D	H	H	H	46
41b	S	OC ₆ H ₅	O	D	C ₆ H ₅	D	H	H	H	46
42	S	t-C ₄ H ₉	lp	H	CH ₃	H	CH ₃	H	H	47
43	S	lp	C ₆ H ₅	H	CH ₃	H	CH ₃	H	H	47
44	S	lp	C ₆ H ₅	H	t-C ₄ H ₉	H	H	H	H	47
45	S	lp	C ₆ H ₅	H	H	H	H	H	H	48
46	S	t-C ₄ H ₉	lp	H	H	H	H	H	H	48
47	S	N ⁱ -C ₃ H ₇	lp	H	H	H	H	H	H	48
48a	S	O	C ₆ H ₅	H	t-C ₄ H ₉	H	H	H	H	49
48b	S	C ₆ H ₅	O	H	t-C ₄ H ₉	H	H	H	H	49
49a	S	lp	C ₆ H ₅	CH ₃	H	H	H	CH ₃	H	51
49b	S	C ₆ H ₅	lp	CH ₃	H	H	H	CH ₃	H	51
50a	S	lp	OC ₂ H ₅	CH ₃	H	H	H	H	H	50
50b	S	OC ₂ H ₅	lp	CH ₃	H	H	H	H	H	50
51a	S	lp	Cl	CH ₃	H	H	H	H	H	50

51b	S	Cl	lp	CH ₃	H	H	H	H	H	50
	$X \neq X'$									
52	O, NCH ₃	O	OC ₆ H ₅	H	H	H	H	H	H	53
53	O, NCH ₃	S	OC ₆ H ₅	H	H	H	H	H	H	53
54	O, NC ₆ H ₅	O	OC ₆ H ₅	H	H	H	H	H	H	54
55a	O, NH	O	N(CH ₂ CH ₂ Cl) ₂	CH ₃	H	H	H	H	H	55
55b	O, NH	N(CH ₂ CH ₂ Cl) ₂	O	CH ₃	H	H	H	H	H	55

^alp = lone pair of electrons

adenosine 3',5'-monophosphate (cyclic AMP) and guanosine 3',5'-monophosphate (cyclic GMP), mediators of cell metabolism and proposed ubiquitous intracellular "second" messenger substances; (2) the antimetabolic, antitumor agent cyclophosphamide and its congeners; and (3) other pharmacologic agents (25). Certain biological aspects relating to phosphorinanes are discussed in Section III-D.

Over the past 15 to 20 years a voluminous, widely dispersed body of information has accrued on the stereochemical aspects of phosphorus-containing cyclohexane derivatives. This review attempts to draw these widespread data together, with a main concern for critical and historical assessment of relevant studies, rather than, necessarily, and exhaustive survey of the literature (covered up to mid-1977). We are particularly attentive to exposing key, general themes, and to indicating significant conclusions that develop from them.

This chapter is divided into major segments treating (1) tricoordinate, (2) tetracoordinate, and (3) pentacoordinate compounds, with further subdivisions along structural and mechanistic lines, as required. A section on the application of nuclear magnetic resonance (NMR) spectroscopy to the study of organophosphorus stereochemistry precedes this, since a background in this subject is essential for dealing with stereochemical and conformational questions.

Some stereochemical information on phosphorinanes has been collected in other reviews (5-8,15,26,27). To keep this chapter to an acceptable length, we avoid discussion of areas such as nonsix-membered rings, chiefly inorganic heterocycles, and benzo-fused or otherwise unsaturated molecules. Since X-ray structural data have already been organized and presented (15), we only refer to X-ray work briefly, in support of structural discussions.

II. APPLICATIONS OF NMR SPECTROSCOPY

Developments in NMR spectroscopy and conformational analysis have paralleled each other, and NMR probably provides more information about the shape of complicated molecules in solution than any other physical method (28). Both NMR chemical shifts and spin-spin coupling constants are very sensitive to the spatial arrangement of atoms in a molecule, and both may be used effectively to elucidate molecular structure and conformation (28). This section discusses the use of NMR data in the analysis of various phosphorinane systems (see Table 1). Since several recent publications (7b,27,29) have also addressed this subject, this section mainly deals with overviews of empirical trends and generalizations along systemic lines, since each general system type has its own norms.

A. 1,3,2,-Dioxaphosphorinanes

The identification of isomeric cyclic phosphorus compounds can be assisted by proton, carbon-13, and phosphorus-31 chemical shift data. For example, conformationally rigid molecules such as the highly biased chair systems 1-12 (Table 1) may be considered. In the isomers with an axial methoxy group on phosphorus (1a, 3a), the C₄ carbons are shifted upfield relative to those of the isomers with an equatorial methoxy group (1b, 3b) (cmpd, $\delta^{13}\text{C}$): (1a, 63.8), (1b, 67.0), (3a, 65.7), (3b, 69.7). The same trend is followed by ^{31}P chemical shifts also (see Table 2). Additionally, by comparing the ^{31}P chemical shifts for two highly biased model compounds epimeric at phosphorus with the values for conformationally nonbiased analogs, the fraction of each conformer in the nonbiased system can be estimated (27).

The ^{31}P chemical shift trend is not without exception, even in relatively rigid systems: for example, $\delta^{31}\text{P}$ 8a, 2.9; 8b, -1.3; 12a, 75.1; 12b, 74.4. The notion that the chemical shifts of axial protons on the carbons β to phosphorus are shifted downfield relative to the corresponding equatorial protons, when the (nonchalcogen*) group on phosphorus (phenyl excluded) is axial, is not general: for example, 1a: R₇, 3.49; R₈, 3.94; 2a: R₇, 3.91; R₈, 3.59.

Proton-proton, proton-phosphorus, and carbon-phosphorus coupling constants are more reliable for the study of molecular conformations than are chemical shift data. The angular dependence of J_{HH} , J_{PC} , and J_{PH} has been extensively studied (7b,13, 27,29), and this section is devoted to empirical interpretations of the available data.

Table 2 Chemical Shift Data

A. ^1H Chemical Shifts (δ , ppm downfield from TMS)

Compound	Solvent	R ₁	R ₂	R ₃	R ₄	R ₇	R ₈	Reference
1a	CCl ₄					3.49	3.94	30
1b	CCl ₄					3.91	3.59	30
2a	CDCl ₃					4.10	4.05	30
2b	CDCl ₃					4.14	4.13	30
3a	neat						4.49	30
3b	neat						4.18	30
8a	CDCl ₃		6.90	1.41	4.60			33
8b	CDCl ₃	6.95		1.39	4.60			33
13a	CDCl ₃		3.45	3.87	4.24			35
13b	CDCl ₃	3.46		4.39	3.92			35

*Chalcogen refers to group VI of the Periodic Table just as halogen refers to group VII.

Table 2 Continued

B. ^{13}C Chemical Shifts (δ , ppm downfield from TMS)

Compound	Solvent	OCH_3	C_4	C_5	C_6	Reference
1a	CDCl_3	49.4	63.8	43.0		32
1b	CDCl_3	48.7	67.0	40.9		32
3a	CDCl_3	49.4	65.7	42.7	65.7	32
3b	CDCl_3	48.0	69.7	40.7	69.7	32
19a	unknown		74.4	33.7	65.7	38
19b	unknown		74.8	32.7	64.6	38
22a	C_6H_6		75.5	33.4	66.4	40
22b	C_6H_6		73.5	33.1	65.2	40
23a	C_6H_6		75.6	32.8	64.8	40
23b	C_6H_6		71.8	34.8	63.8	40
50a	C_6D_6	33.9	35.7	26.7	25.3	50
50b	C_6D_6	37.1	33.0	22.2	24.7	50
51a	C_6D_6	35.9	35.4	28.7	25.8	50
51b	C_6D_6	39.3	31.7	22.8	25.1	50

Compound	Solvent	$\text{C}_{2,6}$	$\text{C}_{3,5}$	C_4	$\text{P}-\underline{\text{C}}$	$\text{P}-\text{C}-\underline{\text{C}}$	Reference
26	CHCl_3	27.0	23.7	28.6	11.2		43
27	CHCl_3	25.2	24.0	28.7	20.4	10.0	43
28	CHCl_3	24.4	24.2	28.6	26.7	19.3	43
29	CHCl_3	21.7	25.3	28.7	23.7	27.0	43
30	CHCl_3	24.9	23.7	28.2			43

C. ^{31}P Chemical Shifts (δ , ppm downfield from 85% H_3PO_4)

Compound	Solvent	^{31}P	Ref	Compound	Solvent	^{31}P	Reference
1a	neat	129.3	32	8a	CDCl_3	3.1	33
1b	neat	132.0	32	8b	CDCl_3	-1.2	33
3a	neat	127.2	32	9a	unknown	55.5	34
3b	neat	131.5	32	9b	unknown	59.0	34
5a	C_6H_6	-7.06	29a	10a	unknown	63.6	34
5b	C_6H_6	-4.98	29a	10b	unknown	67.8	34
6a	C_6H_6	3.49	29a	11a	unknown	86.5	34
6b	C_6H_6	6.58	29a	11b	unknown	94.6	34
7a	C_6H_6	19.4	29a	12a	unknown	75.1	34
7b	C_6H_6	28.0	29a	12b	unknown	74.4	34

Table 2 Continued

Compound	Solvent	^{31}P	Ref	Compound	Solvent	^{31}P	Reference
15a	C_6D_6	129.3	35	34	C_6H_6	131.6	45
15b	C_6D_6	137.8	35	35	C_6H_6	122.6	45
16	CDCl_3	126.0	36	36	C_6H_6	91.9	45
17	CDCl_3	126.5	36	37	C_6H_6	81.3	45
18a	C_6H_6	57.2	37	38	C_6H_6	85.8	45
18b	C_6H_6	57.6	37	39	C_6H_6	94.3	45
19a	C_6H_6	4.5	39	40	C_6H_6	108.8	45
19b	C_6H_6	-1.0	39	44	C_6D_6	28.9	47
20a	C_6H_6	64.2	39	45	C_6D_6	40.0	48
20b	C_6H_6	61.2	39	46	CDCl_3	97.3	48
21a	C_6H_6	67.7	39	47	C_6D_6	125.0	48
21b	C_6H_6	66.0	39	48a	C_6H_6	55.1	49
22a	C_6H_6	19.0	40	48b	C_6H_6	47.3	49
22b	C_6H_6	24.5	40	49a	C_6H_6	37.0	51
23a	C_6H_6	92.0	40	49b	C_6H_6	63.5	51
23b	C_6H_6	96.9	40	50a	C_6D_6	145.2	50
24	C_6H_6	131	42	50b	C_6D_6	154.2	50
25	C_6H_6	123	42	51a	C_6D_6	139.5	50
31a	CDCl_3	28.8	43	51b	C_6D_6	146.5	50
31b	CDCl_3	31.1	43	55a	unknown	11.0	55
32a	CDCl_3	29.4	43	55b	unknown	13.4	55
32b	CDCl_3	31.9	43				
33a	CDCl_3	64.6	43b				
33b	CDCl_3	57.7	43b				

Coupling constants characteristic of chair conformations can be gleaned by examination of systems 1-3, which are anancomeric due to either an annelated ring or 4,6-dimethyl substitution. Typical three-bond coupling constants include $^3J_{\text{HaHa}}$, which ranges from 11.2 to 11.8 Hz, $^3J_{\text{HaHe}}$, which varies from 2.2 to 5.5 Hz, and $^3J_{\text{POCHa}}$, which is typically 1.7 to 4.6 Hz, whereas $^3J_{\text{POCHe}}$ is larger, ranging from 8.3 to 25.0 Hz. Note that J_{POCHe} is often larger (22 to 25 Hz) for the tetracoordinate phosphorus compounds than for the tricoordinate ones (8 to 10 Hz). For tricoordinate compounds, when the group on phosphorus is equatorial, $^3J_{\text{POCC}_5}$ is routinely greater (^3J ca. 14 Hz) than when the group is axial (^3J ca. 4.5 to 5.0 Hz). Therefore analysis of the coupling pattern can lead to the determination of ring conformation, and give some indication of the stereochemistry at phosphorus (see Table 3).

The magnitude of certain stereospecific three-bond couplings furnishes knowledge of the conformation of the ring only. The ^3J 's of compounds 14b and 16 are comparable and indicate a bias to a chair conformation: $^3J_{\text{HaHa}}$ ca. 11, $^3J_{\text{HaHe}}$ ca. 3 to 4,

Table 3 Coupling Constant Data

A. J_{HH} and J_{PH}

Compound	Solvent	$^3J_{\text{H}_a\text{H}_a}$	$^3J_{\text{H}_a\text{H}_e}$	$^3J_{\text{PH}_a}$	$^3J_{\text{PH}_e}$	$^1J_{\text{PX}}$	$^4J_{\text{PXCOCH}_3}$	Reference
1a	CCl ₄	11.4	4.2	2.5	10.8			30
1b	CCl ₄	11.2	5.5	4.6	8.3			30
2a	CDCl ₃	11.8	4.4	1.7	25.0			30
2b	CDCl ₃	11.2	4.5	4.2	24.3			30
8a	CDCl ₃					664	1.7	33
8b	CDCl ₃					719	1.8	33
13a	CDCl ₃	11.9	3.71	2.89	11.0			35
13b	CDCl ₃	4.9	4.65	8.40	5.03			35
14a	C ₆ D ₆	11.18	3.84	2.50	19.75			35
14b	oDCB	10.81	3.75	2.39	21.56			35
15b	C ₆ D ₆	10.24	4.58	2.32	20.24			35
16	CDCl ₃	11.4	2.7	2.9	21.9			36
17	CDCl ₃			1.7	22.5			36
18a	C ₆ H ₆					1130		37
18b	C ₆ H ₆					1140		37
20a	C ₆ H ₆					591		39
20b	C ₆ H ₆					639		39
21a	C ₆ H ₆					566		39
21b	C ₆ H ₆					618		39
19a	C ₆ H ₆					667		39
19b	C ₆ H ₆					714		39
22a	CDCl ₃						1.9	40
22b	CDCl ₃						1.9	40
23a	CDCl ₃					909	1.0	40
23b	CDCl ₃					883	1.6	40

34	CDCl ₃	11.8	3.15	4.2	8.7	45
35	C ₆ D ₆	-	-	4.9	9.1	45
36	C ₆ D ₆	12.4	2.8	0	5.3	45
37	C ₆ D ₆	-	-	0	5.5	45
41a	CDCl ₃	10.8	2.9	8.9	28.0	46
41b	CDCl ₃	8.0	4.6	17.7	24.5	46
42	C ₆ D ₆			1.5	14.5	47
43	C ₆ D ₆			2.5	0	47
44	C ₆ D ₆	10.5	1.7-2.0	1.5-1.8	0	47
45	C ₆ D ₆	12.3	2.1	3.1	0.1	48
46	C ₆ D ₆	11.5	2.0	1.6	16.5	48
47	CDCl ₃	12.4	2.2	4.0	26.0	48
48a	C ₆ D ₆	7.2	6.0	14.5	22.5	49
48b	C ₆ D ₆	9.6	3.5	11.6	19.6	49
49a	C ₆ H ₆					51
49b	C ₆ H ₆					51
52	C ₆ D ₆				0.4	53
					0.4	
53	C ₆ D ₆			2.5 ^a	23.0	55
				1.7 ^b	24.5	
				5.4 ^a	22.6	
54	C ₆ D ₆			5.2 ^b	21.8	54
				3.0 ^a	21.8	
				2.4 ^b	20.2	
55a	unknown			12.4 ^a	2.1	55
				12.1 ^b	2.4	

^aPOCH coupling constant.

^bPNCH coupling constant.

Table 3 Continued

B. J_{P-C}

Compound	Solvent	$^2J_{C_4P}$	$^2J_{C_6P}$	$^3J_{C_5P}$	$^3J_{PXCCH_3}$	$^1J_{P-C}$	Reference
1a	CCl ₄	1.8	2.1	4.7			31
1b	CCl ₄	1.7	2.2	14.0			31
3a	neat	2.7	2.7	4.2			31
3b	neat	1.8	1.8	13.5			31
19a	unknown	5.9	5.3	6.1	8.9		38
19b	unknown	7.2	6.8	9.9	4.8		38
22a	CDCl ₃	5.9	5.9	7.4	6.5		40
22b	CDCl ₃	7.4	7.4	4.4	7.4		40
23a	CDCl ₃	10.3	8.8	8.8	5.9		40
23b	CDCl ₃	5.9	5.9	5.9	10.3		40
31a	CDCl ₃					50	43b
31b	CDCl ₃					54	43b
32a	CDCl ₃					52	43b
32b	CDCl ₃					55	43b
33a	CDCl ₃					16	43b
33b	CDCl ₃					12	43b
45	C ₆ D ₆			0			48
46	CDCl ₃			8.4			48
47	C ₆ D ₆			12.1			48
50a	C ₆ D ₆	14.0	13.8	1.5	3.6		50
50b	C ₆ D ₆	11.3	12.1	1.3	0.5		50
51a	C ₆ D ₆	13.6	13.6	1.7	3.8		50
51b	C ₆ D ₆	13.0	12.8	1.2	1.2		50

Compound	Solvent	$^3J_{PC4}$	$^2J_{PC3,5}$	$^1J_{PC2,6}$	$^1J_{P-Cexo}$	$^1J_{P-C}$	Reference
26	CHCl ₃	2	3	13	19		43
27	CHCl ₃	3	4	14	14		43
28	CHCl ₃	2	6	12	12		43
29	CHCl ₃	3	7	18	28		43
30	CHCl ₃	2	4	14			43

$^3J_{\text{HaP}}$ ca. 3, $^3J_{\text{HeP}}$ ca. 22 Hz. Note that in *14b* the *t*-butyl substituent on phosphorus is equatorial, whereas in *16* the phenoxy group is axial. Thus in 1,3,2-dioxaphosphorinanes $^3J_{\text{HH}}$ and $^3J_{\text{HP}}$ reveal little about the disposition of substituents on phosphorus. Consideration of the ^3J values for the isomers of *13* leads to the conclusion that *13a* is predominantly a chair, and that *13b*, given the middling values of $^3J_{\text{HaHa}}$ and $^3J_{\text{HaHe}}$, is a mixture of several conformers. Indeed, thorough analysis of these coupling constants can afford an estimate of conformer distribution (see ref. 35).

For dioxaphosphorinanes that have 4- and/or 6-methyl substituents, a $^4J_{\text{POCCH}_3}$ of 2 to 3 Hz generally indicates an equatorial methyl group, while a lower value (0.5 to 1.5 Hz) indicates a conformational mixture of axial and equatorial methyl groups: compare the values for *22a*, *22b*, *23b* with *23a*. The coupling of phosphorus to a 4- and/or 6-equatorial methyl carbon is often larger when the substituent on phosphorus is axial: $^3J_{\text{POCCH}_3}$ for *3a*, *19a*, *22a*, and *23a* are 3.2, 8.9, 6.5, and 5.9 Hz, respectively, while those for *3b*, *19b*, *22b*, and *23b* are 1.6, 4.8, 7.4, and 10.3 Hz. Note that at least one isomer of the variant system (*23a*) has been judged a mixture of conformers on the basis of $^4J_{\text{POCCH}_3}$ data.

Several systems in which NMR-active nuclei are directly bonded to the phosphorus atom exhibit stereospecific (43) one-bond coupling constants (see systems *18*, *19*, *20*, *23*, Table 3). Typically $^1J_{\text{PX}}$ for $X = ^1\text{H}$, ^{13}C , ^{19}F , and ^{77}Se is larger when the predominant conformer is a chair with an equatorial PX arrangement. Although systems *19-21* do not follow the $\delta^{31}\text{P}$ trend, they do follow the $^1J_{\text{PX}}$ (and for *19* the $^3J_{\text{POCC}_5}$) trend.

Systems *22* and *23* point out the complexity of making isomer assignments: $^1J_{\text{PC}}$ is greater for *22b* and *23b* and $^1J_{\text{PSe}}$ is greater for *23a* than that value for their respective isomers; also *22a* and *23a* each have a ^{31}P chemical shift that is upfield from the corresponding *b* isomers. All information supports the assignments as made. However, the ^{13}C resonances of C_4 and C_6 show no γ effect, and $^3J_{\text{PC}_5}$ is less for the *b* isomers with equatorial benzyl groups. An axial methyl group is indicated in isomer *23a* by a $^4J_{\text{POCCH}_3}$ value of 1.0 Hz; all data combined suggest a conformational mixture. X-Ray crystallographic data and chemical reactivity patterns could be used to determine configuration unambiguously.

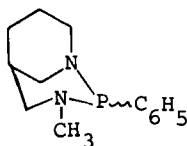
B. Phosphorinanes

Most of the information regarding the conformation of phosphacyclohexanes has been gathered through the use of ^{13}C NMR data. Systems *26-30* (Table 1) are conformationally unbiased, but several useful trends in ^{13}C chemical shifts and coupling constants are evident. A γ effect is operative on carbon atoms C_2 , C_6 , C_3 , and C_5 . As methyl groups replace hydrogens on the exocyclic P-C substituent (thus increasing the number of α carbons there), the chemical shifts of C_2 and C_6

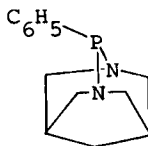
move to higher field (Table 2). As the substituent increases in bulk, the chemical shifts of C_3 and C_5 move to lower field; this is probably caused by a decrease in the normal axial preference of the phosphorus substituent as the steric size of the substituent increases. The two-bond coupling constant $^2J_{PC_{3,5}}$ gives an indication of conformational preference, varying in line with the chemical shifts of C_3 and C_5 (as discussed above): that is, for *33a* with an axial methyl group on phosphorus, $^2J_{PC_{3,5}} = 0$ to 1 Hz, whereas for *33b* with an equatorial methyl group on phosphorus $^2J_{PC_{3,5}} = 7$ Hz. Compound *29* must have a high population of the equatorial conformer, as the $^2J_{PC_{3,5}}$ value is the same as for the locked system *33b*. For the exocyclic substituent $^1J_{PC}$ increases with an increasing amount of equatorial conformer. Even $^2J_{PH}$ seems stereoselective; for example, $^2J_{PH}$ for *33a* is 2.1 Hz contrasted with $^2J_{PH}$ of 4.0 Hz for *33b*. The ^{31}P chemical shifts of the 4-phosphorinanol sulfides *31* and *32* show an upfield shift for the isomers with axial P groups; the opposite is true for *33*. Also for *31* and *32* $^1J_{PC}$ for the isomer with the axial methyl group is less than that for the isomer with the equatorial methyl group; again, the opposite is true for system *33*. The nature of this effect is certainly not well understood (44).

C. 1,3,2-Diazaphosphorinanes

A limited amount of NMR analysis has been performed on diazaphosphorinanes, which have an added dimension of complexity because of the other tricoordinate heteroatoms in the system (two additional stereocenters). One series of N,N'-dimethyl systems (*34-37*) has been found to have predominantly a single chair conformation (45). The three-bond coupling constants are reminiscent of those in the dioxo systems: values for *34* and *36*, respectively, are $^3J_{HaHa}$, 11.8, 12.4 Hz; $^3J_{HaHe}$, 3.15, 2.8 Hz. For system *39*, with the N-methyl group constrained in an equatorial position, $^3J_{PNCH_3}$ is 12 Hz (51); in these systems $^3J_{PNCH_3}$ are all in the range of 15-18 Hz (ca. 15 Hz for *P*-phenyl compounds). The three-bond proton-phosphorus coupling shows a large variance with the nature of the substituent on phosphorus; $^3J_{HaP}$ and $^3J_{HeP}$ vary from 4.5 and 9 Hz in *34* and *35* to 0 and 5 Hz in *36* and *37*. For compounds with 5,5-dimethyl substituents (such as *35* and *37*), the methyl signals in the ^1H spectrum are of unequal height; the $\omega_{1/2}$ of the methyl resonance at lower field is broader, implying an axial methyl group which couples to the axial protons on carbons C_4 and C_6 through a W pathway. The 5,5-gem-dimethyl groups seem to cause a 10-ppm upfield shift in the ^{31}P resonance with respect to the corresponding 5,5-unsubstituted compound (compare the ^{31}P chemical shift of *34* and *35*, *36*, and *37*). This same effect is noticed in dioxo systems *24* and *25* but not in dioxo systems *16* and *17*. A study (45) of the ^{31}P chemical shifts of 1,3,2-diazaphosphorinanes has shown that the ^{31}P atom is most shielded when the N atoms are oriented with the lone pairs of electrons axial; thus



39



40

38, with presumably two axial nitrogen lone pairs, resonates at 85.8, while 39, with one axial lone pair, resonates at 94.3, and 40, with no axial nitrogen lone pairs, resonates at 108.8 ppm. The observed shielding appears to be stepwise in nature.

Further study (such as ^{13}C NMR) is needed to elucidate the configurations at phosphorus and at nitrogen in these systems.

D. 1,3,2-Dithiaphosphorinanes

Like the diazaphosphorinanes the dithiaphosphorinanes have not been studied extensively, and thus the observed trends may be reversed when additional data are obtained. Whereas isomers with tetracoordinate phosphorus have been separated and each isomer analyzed by NMR techniques (46,49), complete analyses of both isomers of tricoordinate phosphorus systems have not yet been reported. Experimentally the isomers are not easily separated (51), and the NMR spectral patterns are complex.

Analysis of the three-bond coupling constants for the specifically deuterated, tetracoordinate compound 41 showed that both isomers have a chair conformation. The magnitudes of the coupling constants compare well with the diaza and dioxo systems; that is, $^3J_{\text{H}_a\text{H}_a}$ 10, $^3J_{\text{H}_a\text{H}_e}$ 3 to 5, $^3J_{\text{PH}_e}$ 25, and $^3J_{\text{PH}_a}$ 10 to 17 Hz. However, a different picture emerges upon examination of the tricoordinate systems 42-47. In 42, 46, and 47 the predominant conformer was assigned an equatorial phosphorus substituent; $^3J_{\text{PSCC}_5}$ [shown (48) to give an indication of the configuration at tricoordinate phosphorus] is equal to a characteristic 8 to 12 Hz, indicative of an equatorial substituent. Compounds 43-45 have been assigned an axial group on phosphorus in the predominant conformer; a $^3J_{\text{PSCC}_5}$ of zero for 45 and shielded ^{31}P chemical shifts (40 for 45 and 28.9 for 44 vs. 97, 125, and 64 for 46, 47, and 49b, respectively) support the assignment. The conformations of 42-47 are confirmed by $^3J_{\text{PH}}$ values: $^3J_{\text{PH}_e}$ for 42, 46, and 47 (equatorial substitution on P) are 14.5, 16.5, and 26.0 Hz, respectively, while $^3J_{\text{PH}_a}$ for 43-45 (axial substitution on P) are all nearly zero! This trend is not found in the dioxo- and diazaphosphorinanes, and is indicative of the stereochemistry at phosphorus in the dithiaphosphorinanes. An interesting discussion of the possible reasons for the strange P-S-C-H coupling constants is presented in ref. 51.

For the tetracoordinate phosphorus systems 48a the averaged values for $^3J_{\text{HH}}$ and $^3J_{\text{PH}}$ are evidence for a twist-boat/chair conformational equilibrium. Both isomers (52) have a small value (1.5-2 Hz) for $^3J_{\text{PSCC}_5}$; as in the dioxo systems, $^3J_{\text{PSCC}_5}$

is not indicative of the stereochemistry of a tetracoordinate phosphorus center.

The small values of $^3J_{\text{PSCC}5}$ for 50 and 51, together with the absence of a γ effect for the ^{13}C chemical shifts of C_4 , lead to the conclusion that both systems are biased toward conformers having an axial phosphorus substituent.

E. 1,3,2-Oxazaphosphorinanes

Several of the oxazaphosphorinanes studied (53-55) were found to have predominantly chair conformations. The typical three-bond coupling constants indicative of the chair conformation for systems 52 and 53 are, respectively; $^3J_{\text{POCH}_a}$ 2.5, 5.4 Hz; $^3J_{\text{POCH}_e}$ 23.0, 22.6 Hz; $^3J_{\text{PNCH}_a}$ 1.7, 5.2 Hz; $^3J_{\text{PNCH}_e}$ 24.5, 21.8 Hz. Both systems have been assigned equatorial *N*-methyl groups and axial *P*-phenoxy groups, but the assignment seems arbitrary. A $^3J_{\text{PNCH}_3}$ of 11.0 and 14.0 Hz, respectively, for 52 and 53 may imply an equatorial *N*-methyl group. Similarly, analysis of the coupling constants for 55, indicates a chair conformation. For system 55, where both isomers were studied, 55a was assigned an equatorial phosphoryl bond, since the ^{31}P chemical shift is upfield (11.0) relative to that for 55b (13.5), and the phosphoryl IR stretching frequency is higher (56); $^4J_{\text{PNCH}_3}$ is lower for 55a (2.9 Hz) than for 55b (1.9 Hz). For 55a a $^3J_{\text{PNCH}_3}$ of 7.6 Hz results from a conformational mixture, while a value of 12.1 Hz for 55b implies a bias toward one conformation. Work on this type of system is also novel and more data must be compiled before the stereochemistry at nitrogen or phosphorus can be assigned with confidence.

F. Lanthanide-Induced-Shift (LIS) Method

The lanthanide-shift technique is useful for determination of the stereochemistry of phosphorus-containing cyclohexanes, and it has been discussed at some length elsewhere (7b,27,29,49, 51). If the original coupling constants remain the same throughout the LIS experiment, the results usually lead to accurate conclusions. However, if the coupling constants vary, the conformational population is changing as a result of complexation of the substrate with the shift reagent, making stereochemical interpretations more complex. Further discussion of the LIS method is contained in Sect. III-B-1-a (also see ref. 142c).

G. Conclusion

Throughout this section we have organized NMR information which allows one to characterize chair conformations for phosphorinane rings, to determine whether the conformational equilibrium is biased, and to suggest the disposition of substituents on phosphorus. The power of such analyses has recently been pointed out in the determination of the conformation and configuration of cyclic nucleotides (57-59).

Critical discussions of NMR and other methods for structural determination of phosphorinanes have been published (13, 27-29). We hope that this section will contribute to an understanding of the scope and limitations of NMR methods for the determination of phosphorinane structure, configuration, and conformation.

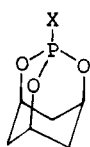
III. STRUCTURE, CONFORMATION, AND STEREOCHEMISTRY OF CYCLOHEXANE RINGS CONTAINING TETRACOORDINATE PHOSPHORUS

A. Polycyclic Phosphites

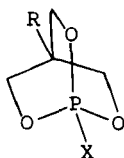
In the early 1960s the chemistry of polycyclic phosphites 57a (60) and 58a (61,62) began to arouse some interest. As is evident in the succeeding discussion, reactions of these compounds served to introduce the problem of stereochemistry in six-membered phosphorus-containing rings.

1. 1-Phospha-2,6,7-trioxabicyclo[2.2.2]octane

The bicyclo[2.2.2]octane system first attracted the attention of Wadsworth and Emmons (63). Bicyclic phosphite 58a was observed to undergo the Arbuzov reaction (eq. [1]) when heated

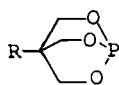


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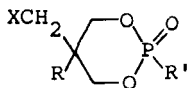
58 (R = H, CH₃, C₂H₅)

X = a) lone pair
b) O
c) S

with an alkyl halide (64), generating a six-membered-ring phosphonate by severance of a bridge. The product with benzyl chlo-



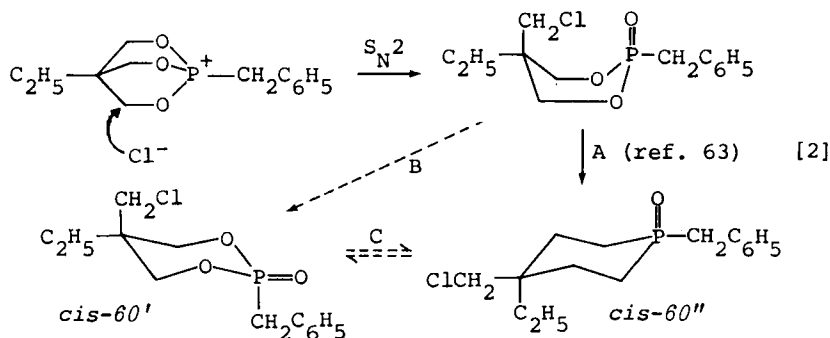
58a



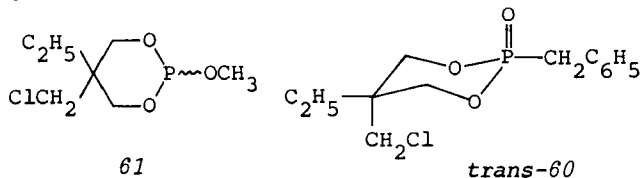
59

[1]

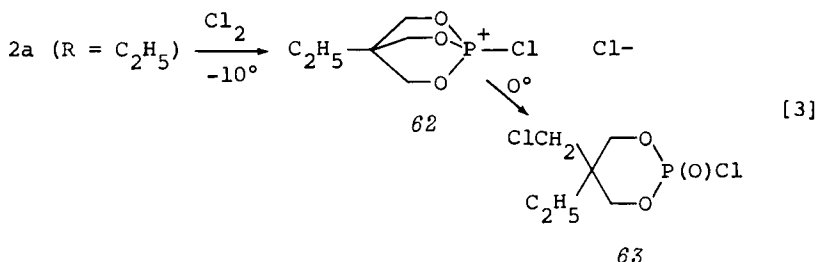
ride (59, R = C₂H₅, R' = C₆H₅CH₂) appeared to be a single isomer, and was presumed to be *cis* on mechanistic grounds (eq. [2]) (64,65). The initially formed boat conformation converted to the chair form *cis*-60" (path A), since this conformer is presumed (63) to be more stable by analogy to cyclohexane systems. Although pathways B and C (eq. [2]) were not considered (63), they must occur as well. Comparison of infrared (IR) spectral data for *cis*- and *trans*-60, the latter derived from 61 (*cis*/*trans* mixture) and C₆H₅CH₂Cl, led to a proposal that the isomeric phosphonates (60) differed by the orientation of the groups at the 5-position. Thus the *trans* isomer was assigned the config-



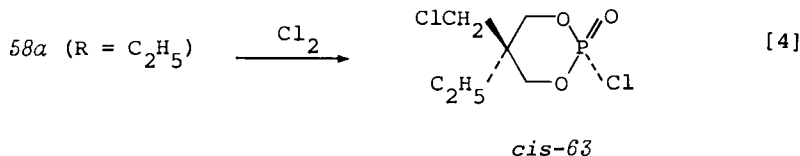
uration and conformation (actually predominant conformation) shown here; this conformational analysis is discussed more fully later on.



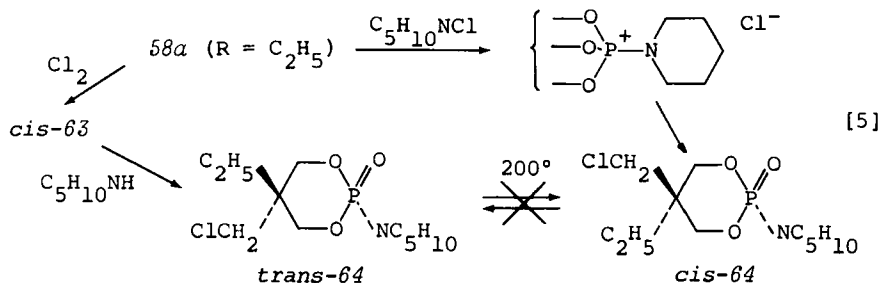
Wadsworth and Emmons also observed that *58a* ($\text{R} = \text{C}_2\text{H}_5$) reacted with chlorine (63) to give a stable crystalline intermediate, assumed to be *62* (66), which rearranged to phosphorochloridate *63* (eq. [3]). Since *63* was also formed from treatment of a monocyclic phosphite, such as *61*, with chlorine, these authors concluded (incorrectly) that the synthesis of phosphorohalidates (e.g., *63*) from bicyclic precursors (*58a*) is not stereospecific. The reaction of *58a* with halogen has since been



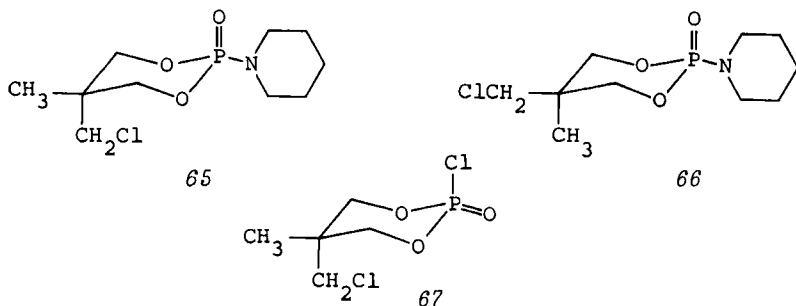
established to proceed stereospecifically, with retention (eq. [4]) (69,70).



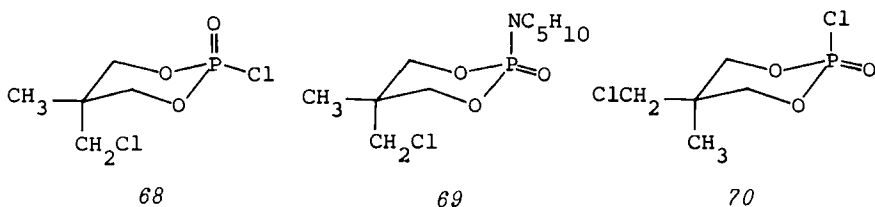
Wadsworth explored the reaction of *58a* ($R = C_2H_5$) with *N*-chloropiperidine ($C_5H_{10}NCl$) (70). A single product, presumably *cis-64*, was obtained (eq. [5]).



A single isomeric solid, *trans-64*, was also obtained from *cis-63* and piperidine. The configurational relation in *trans-64* was later verified by X-ray analysis of *65*, prepared in the same manner from *58a* ($R = CH_3$) (71). Edmunson and Mitchell reported similar results with *58a* ($R = CH_3$) a year later (72a), and suggested that their phosphoramidates (and phosphorochloridate intermediate) possessed chair structures on the basis of ^1H NMR spectral data. Values of $\Delta\delta$ for CH_3 and CH_2Cl were employed (72) to tentatively propose that their homologues of *64* differed in conformation at C_5 ; that is, that their *trans* and *cis* isomers were mostly *65* and *66*, respectively, in solution (72a); the phosphorochloridate was suggested to be mostly conformer *67*. The

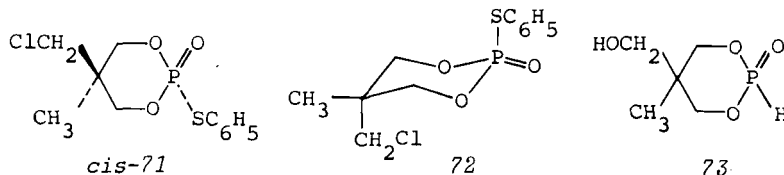


conformational preferences derived from the qualitative $\Delta\delta = \delta(CDCl_3) - \delta(C_6H_6)$ method (72) are parallel to conformations manifested in the solid state in 2-*R*-2-oxo-1,3,2-dioxaphosphorinanes rather unbiased by substitution at positions 4, 5, and 6: axial Cl (69), Br (73); equatorial piperidine (71).



The action of Cl_2 and of SO_2Cl_2 on *58a* ($\text{R} = \text{CH}_3$) was initially thought (74) to produce different isomers (67 and 68, respectively), which on further reaction with piperidine supposedly led to different isomers of the corresponding phosphoramidates (65 and 69). Since three isomeric phosphoramidates (65, 66, 69) were thought to have been synthesized and isolated, Wadsworth asserted (74) that 65 and 69, not interconvertable even at 250° , defined conformational isomers that were separated by an exceptionally high barrier to chair-chair interchange. This proposal was similar to a previous, erroneous suggestion (72a) that the two chair forms of 5,5-dimethyl-2-piperidino-2-oxo-1,3,2-dioxaphosphorinane are detectable at ambient temperature. Later work (71b,76) established that the phosphorochloridate (67, 68) and phosphoramidate (65, 69) pairs are actually the same: the phosphoramidate from the Cl_2 /piperidine route is an impure specimen of that obtained in a pure state from the SO_2Cl_2 /piperidine sequence.

The conformational equilibria for the 5-methyl analogs of *cis*-64 and *cis*-63 were realized to be strongly dominated by one-chair species (based on ^1H NMR $^3\text{J}_{\text{POCH}}$ data): structures 66 and 70, respectively (79). On the contrary, the 5-methyl analogs of

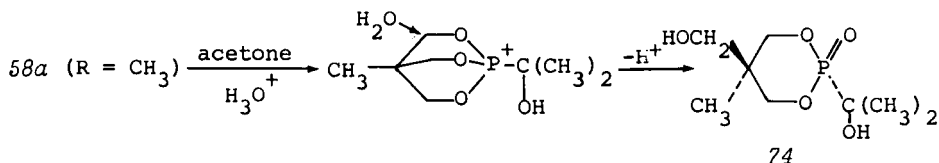


trans-64 and *trans*-63 appeared to be conformationally heterogeneous, possibly being ca. 80% 65 and ca. 50% 67, respectively (79). Although twist forms were proposed to be the major conformers for the 5-methyl analogues of *trans*-64 and *trans*-63, these forms probably are not important in their conformational equilibria. The topic of twist conformations in 1,3,2-dioxaphosphorinanes is discussed in Sect. III-B-1-a.

Another ring-opening reaction of *58a* ($\text{R} = \text{CH}_3$) occurred with $\text{C}_6\text{H}_5\text{SCl}$, affording a single isomer, *cis*-71, which exists mainly in conformation 72 (71b). Reaction of *cis*-63 ($\text{R} = \text{CH}_3$) with $\text{C}_6\text{H}_5\text{SNa}$, lacking the clean stereospecificity observed with the amine nucleophiles (74,76), produced a mixture of *trans*- and *cis*-71 in a 90:10 ratio. It was proposed that *trans*-71 exists mainly in the conformation with axial CH_3 and axial $\text{C}_6\text{H}_5\text{S}$ groups (71b). Additional discussion on the stereochemistry of nucleophilic substitution at phosphorus in phosphorinanes is reserved for Sect. III-B-2-a.

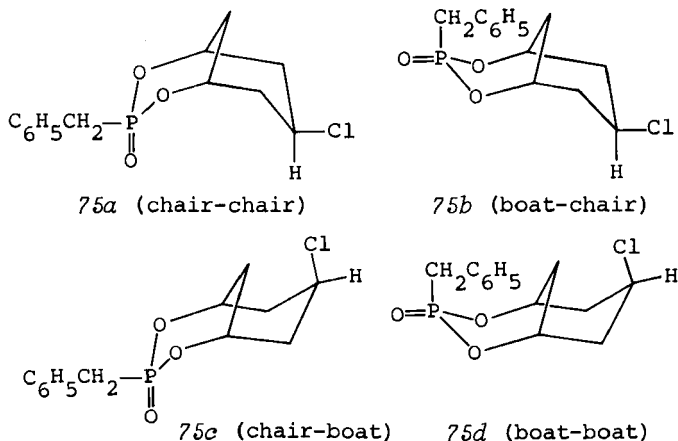
Acid-catalyzed hydrolysis of *58a* ($\text{R} = \text{CH}_3$) occurs non-stereospecifically to give *cis*- and *trans*-73, whose dominant conformations in solution are chair forms with axial P-H bonds (80). The phosphoryl oxygen was shown to arise from the water, rather than a bridging oxygen, by ^{18}O -labeling experiments.

Reaction of *58a* ($R = \text{CH}_3$) with acetone in the presence of acid gave a single crystalline product, whose stereochemistry is uncertain since the mechanism of this process is unknown (78,81); however, a *trans* structure (74) was postulated.



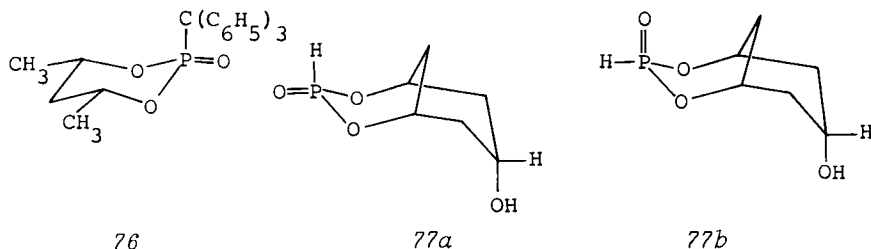
2. 1-Phospha-2,8,9-trioxadamantane

Berlin and co-workers (82) investigated the Michaelis-Arbuzov reaction of *57a*, which underwent a ring-cleavage process with benzyl chloride to afford a single isomer (75). This molecule (75) may be considered as an equilibrium mixture of four conformations: *75a-75d*. The authors felt that chair-boat conformations were favored and, of the two possibilities, they preferred *75b* (82b). IR spectral data, dipole moment measurements, and ^1H NMR arguments supported *75b* as the predominant conformation (82). The solid-state structure was established as *75b* by



X-ray diffraction (83). The O-P-O region of the boat ring is flattened into a "half-chair" conformation, which presumably alleviates serious 1,4 steric interaction between the 3-benzyl and 9-hydrogen groups. A similar half-chair structure for a 1,3,2-dioxaphosphorinane ring was observed in the X-ray analysis of *76*. The interested reader is directed to other structural investigations of bicyclo[3.3.1]nonanes (85).

Reactions of *57a* with other benzylic halides (82b), methyl halides (80), bromine (80), and aqueous acid (80,86) have also been reported. Hydrolysis (80,86) of *57a* was not stereospecific (cf. the acidic hydrolysis of *58a*), thus two isomeric products

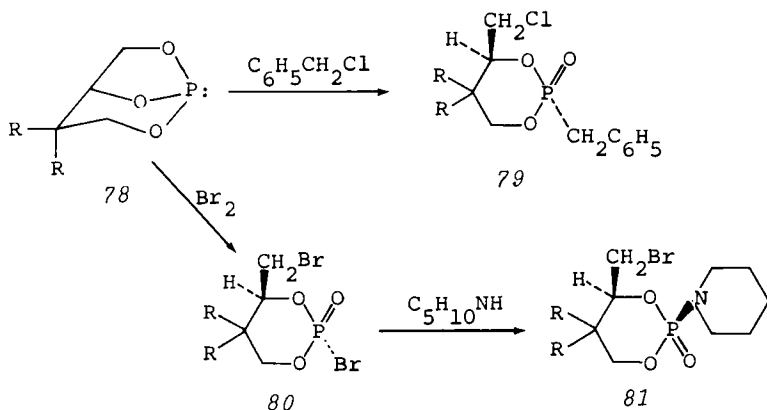


77a and 77b, were obtained; structural assignments were based on IR and ^1H NMR spectroscopic data (86). The structure of 77a was subsequently confirmed by an X-ray structural analysis (87), which shows an unflattened boat ring. The favored conformation for the 1,3,2-dioxaphosphorinane ring of 77b is less definite and may be a flattened boat (or a chair), since the phosphoryl oxygen normally prefers an equatorial position vs. a hydrogen substituent (see Sect. III-B-1-a. and ref. 21).

Both isomers of 77 dehydrated back to 57a at 120° in vacuo, or to derivatives of 57a under the influence of Cu^{2+} or trityl cation (87). Hydrated divalent metal ions such as Zn^{2+} and Fe^{2+} acted on 57a to form complexes of general formula $[\text{M}(57a \cdot \text{H}_2\text{O})_4](\text{X})_2$ (X = monovalent anion), wherein $57a \cdot \text{H}_2\text{O}$ was suggested to be an "enol" form of 77a (i.e., a hydroxyphosphine), bound to the metal via phosphorus. Although 77a also formed identical complexes, attempts to produce complexes from 77b were unsuccessful. The mode of coordination of the phosphorus ligand with transition metals is uncertain since X-ray data are not available.

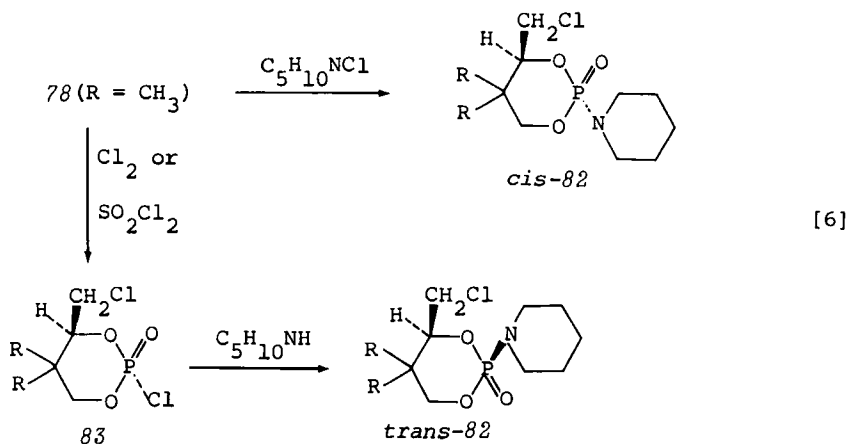
3. 1-Phospha-2,7,8-trioxabicyclo[3.2.1]octane

The Arbuzov reaction of 78 ($\text{R} = \text{H}$) (88) with benzyl chloride yielded only benzyl phosphonate 79 ($\text{R} = \text{H}$); no alternative opening of the six-membered ring took place. The reaction of 78 ($\text{R} = \text{H}$) with Br_2 was also stereospecific, occurring by opening of the



five-membered ring to give **80** ($R = H$), characterized by its conversion with piperidine to **81** ($R = H$), presumably with inversion of configuration at phosphorus. Conformational questions regarding **79-81** had been unanswered at that time. More recent work (90) concerning electrophilic cleavage of **78** ($R = H$ or CH_3) revealed that the reactions involving alkyl chlorides, alkyl tosylates, and *N*-chloramines are stereospecific, furnishing single products, formulated as 1,3,2-dioxaphosphorinanes.

Edmunson (79) focused on the reaction of **78** ($R = CH_3$) with *N*-chloropiperidine, and the chlorination of **78** ($R = CH_3$) followed by treatment with piperidine (eq. [6]). Compounds **83** and *trans*-**82** are chiefly one chair form, whereas *cis*-**82**, displaying

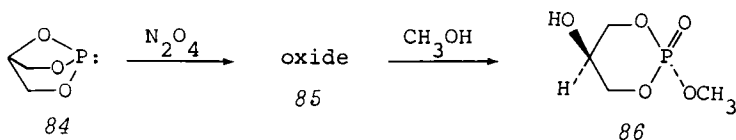


nearly equivalent $^3J_{POCH}$ values, is conformationally heterogeneous. As discussed in Sect. III-B-1-a, this conformational outcome derives from favorable axial chloro/equatorial $P=O$ and equatorial dialkylamino/axial $P=O$ arrangements in **83** and *trans*-**82**, and an unfavorable axial amino/equatorial $P=O$ arrangement in *cis*-**82** (in a chair form). Edmunson (79) suggested that *cis*-**82** may possess a skew (twist-boat) conformation, which is compatible with reports of low-energy (1 to 2 kcal/mol) twist conformations for certain 2-oxo-1,3,2-dioxaphosphorinanes (35,91). However, since the twist form is still at least 1 kcal/mol higher in energy than the chair form, the chair forms of *cis*-**82** probably account for the major portion of the conformer distribution. Little temperature dependence in the ^1H NMR spectra was observed for **82** or **83**.

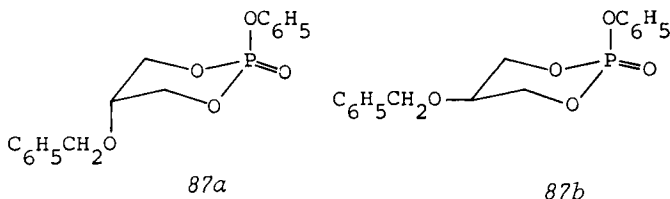
4. 1-Phospha-2,5,7-trioxabicyclo[2.2.1]heptane

Although attempts by Edmunson and Mitchell to synthesize strained phosphite **84** were abortive (88), this compound was prepared from glycerine and $(CH_3O)_3P$ by Denney and Varga (92,93).

The oxide of **84** (i.e., **85**), generated using N_2O_4 , was very sensitive to hydrolysis, as was **84** itself (93). Reaction of **85**

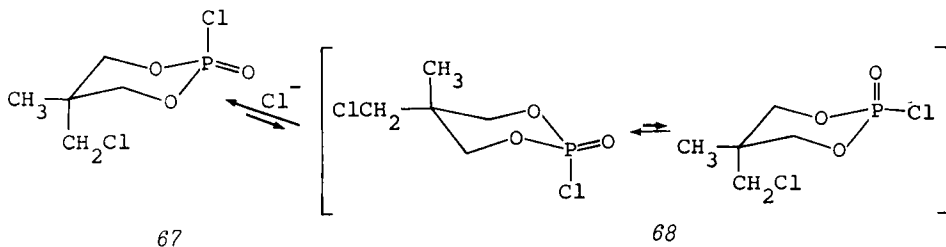


with methanol occurred readily with formation of a single product, phosphorinane **86**, by preferential fission of the five-membered ring (**94**). Although no conformational study has been reported for **86**, two diastereomers related to **86** have been described (**95**) as highly biased chair conformations with equatorial P=O groups (viz., **87a** and **87b**).



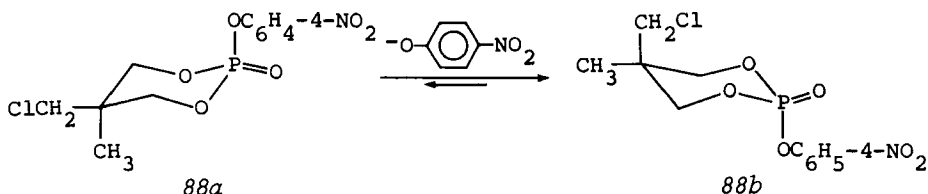
5. General Comments

In Sect. III-B-1-a we fully discuss the conformational properties of 1,3,2-dioxaphosphorinanes; at that point the preferences for substituents on phosphorus are addressed. In an otherwise unbiased 1,3,2-dioxaphosphorinane ring these preferences control the conformational equilibrium, but in rings (unequally) substituted at positions 4, 5, or 6, substituent competition becomes important in describing the conformational distribution. As a case in hand, in 5-halomethyl/5-alkyl derivatives the question of bias, induced by the inequivalent substitution, arises.

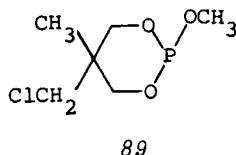


Wadsworth and co-workers (**71b**) obtained equilibrium mixtures of **67** and **68** in a solvent-independent ratio of ca. 2.5:1. Since the axial P-Cl/equatorial P=O arrangement is strongly preferred by at least 3 kcal/mol (see Sect. III-B-1-a), the compromise of conformational preferences, favoring **67**, apparently indicates a strong axial preference for the 5-chloromethyl group over the methyl group. Of course, this bias has to be accounted

for in any measurement of the free-energy difference between substituents on phosphorus. Likewise, Edmunson (79), using $^3J_{\text{POCH}}$ values, noted some 5-chloromethyl/5-methyl compounds that were virtually one chair conformer (65 and 67), and some that were more or less heterogeneous (66, 69, and 68). These results are in accord with the axial favoring of the chloromethyl substituent (ΔG° for CH_2Cl vs. CH_3 is ca. 1 kcal/mol). The preference of a chloromethyl group over methyl has also been reported for 88 (88b/88a = 2.5) (96) and 89 (42).



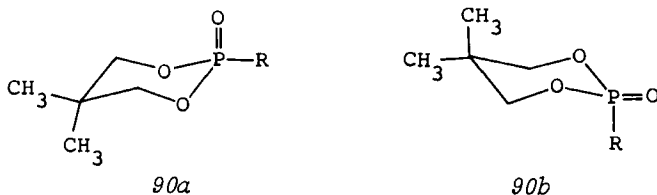
A similar axial preference of 5-halo- (97), 5-hydroxy- (98), and 5-methoxymethyl (98) groups, and other 5-polar substituents (98), has been observed in 1,3-dioxanes and attributed to dipole-charge attractions (97,98). The magnitude of axial preference for a 5-halomethyl group relative to a 5-methyl group in 1,3-dioxanes was estimated to be ca. 1 kcal/mol (97).

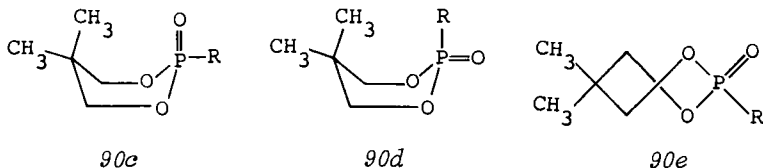


B. 1,3,2-Dioxaphosphorinanes

1. Structure and Conformation

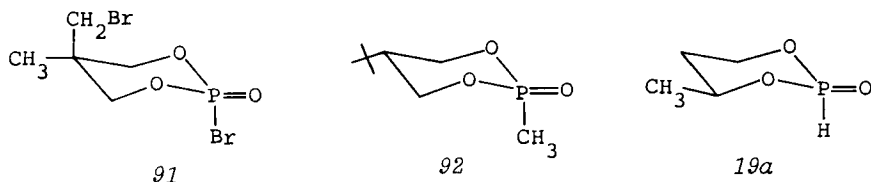
2-Oxo Compounds. Early on, Edmunson (99) briefly considered the conformational aspects of 2-oxo-1,3,2-dioxaphosphorinanes. For 90 [e.g., $\text{R} = \text{OCH}_3$, SC_2H_5 , $\text{NHCH}(\text{CH}_3)_2$] chair forms (90a and 90b) were suggested instead of boat forms (90c and 90d) on the basis of molecular models (a twist-boat conformation 90e was ignored).





The first X-ray crystallographic structure determination of a six-membered tetracoordinate phosphorus ring, *91*, was reported by Beineke (69a). The conformation of *91* is a distorted chair, somewhat flattened at the phosphorus end of the ring (C-O-P angles ca. 118.5°), with the bromo and bromomethyl groups in axial positions. The ring flattening results in partial loss of distinction between axial and equatorial sites on phosphorus. Similar solid-state structural results were found for *17* [*90* (R = OC₆H₅)] (100). X-Ray structures for two other 2-aryloxy derivatives also show axial ArO substituents (101).

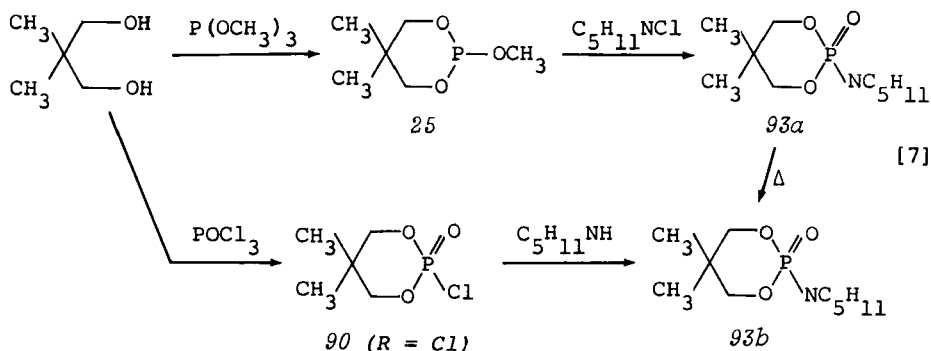
Eventually, X-ray crystallographic data became available on a number of 2-*R*-2-oxo-1,3,2-dioxaphosphorinanes in which R = CH₃ (102a), OH (103), C₆H₅ (104), H (105), Cl (73), 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane-2-yl (106b), piperidino (71), 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane-2-yl-oxy (106a), anilino (106c), 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane-2-yl-thio (106d), formamido (106e), OCH₃ (102b), and trityl (84). The ring shapes are consistent for the related structures except in the case of the trityl derivative *76*, which is forced to adopt a distorted "half-chair" conformation to accommodate the bulky axial group (84). In the other compounds the OH, C₆H₅, 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane-2-yl, 2-yl-oxy, and 2-yl-thio; anilino; and Cl groups are oriented axially in otherwise unbiased molecules. In compound *92* (102a) the methyl group is axial (107), in *65* the piperidino group is equatorial (71), and



in *19a* the hydrogen is axial (105). The X-ray data for six-membered-ring compounds may be compared with those for five-membered-ring cognates in which considerable flattening of the O-P-O region is also observed (108).

In an early ¹H NMR investigation of some 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanes (*90*, R = CH₃, H, *t*-C₄H₉, trityl, CH₂C₆H₅, CCl₃, OC₂H₅, OCH₃, OC₆H₅, O-*i*-C₃H₇, NH-*t*-C₄H₉, NH-*i*-C₃H₇, Cl), Edmunson and co-workers concluded that most of the compounds studied are biased toward one chair conformation

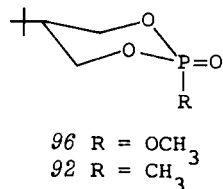
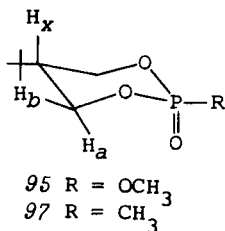
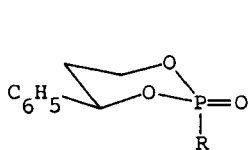
(109), and suggested (72) that the axial P=O form is favored. In addition they claimed that stable conformational isomers (93a and 93b) were isolated, but this seems unlikely (eq. [7]) (72).



Dipole moment measurements on 90 [R = NH-*n*-C₃H₇, NH-*t*-C₄H₉, N(C₂H₅)₂, O-*n*-C₃H₇, OC₆H₅] evoked the suggestion that the conformation with an equatorial P=O bond predominates in solution (110). However, later work showed that a dialkylamino group is actually favored in an equatorial orientation relative to P=O (*vide infra*).

The application of vicinal P-O-C-H coupling constants (³J_{POCH}) to the stereochemical study of the 2-oxo-1,3,2-dioxaphosphorinanes rapidly advanced understanding of their conformational behavior, spin-spin coupling data being more reliable for structural description than chemical shift data. Certainly, the marked stereospecificity of ³J_{POCH} (Sect. II-A), along with its Karplus-type variation of magnitude with dihedral angle, has been particularly useful. Kainosho and co-workers (111) reported that 90 (R = Cl, Br, and OH) and 94 (R = Cl and O⁻K⁺), conformationally biased by the 4-phenyl group, assume virtually single chair forms in solution, by consideration of vicinal H-H and P-H coupling constants. Hall and Malcolm (36,112) supplied ³J_{POCH} data which indicated that 94 (R = OC₆H₅) is also virtually one chair conformation.

Bentrude and Hargis (113) utilized ¹H NMR vicinal H-H coupling constants for cis/trans pairs of 2-oxo-5-*t*-butyl-1,3,2-dioxaphosphorinanes of known geometry (92, 95-97) to show that the rings are largely single chair conformers, with the 5-*t*-butyl group equatorial (see Table 4). Whereas 96 and 97 are anan-



comeric (19), *92* and *95* have a contribution from another conformer, either the alternative chair form with an axial *t*-butyl group or a twist-boat form. It was later learned that the chair-

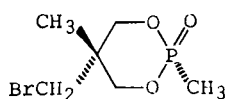
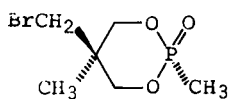
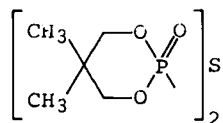
Table 4 ^1H NMR Vicinal Coupling Constants (113)

Compound	$^3J_{AX}$	$^3J_{BX}$	$^3J_{AP}$	$^3J_{BP}$
<i>95</i>	sum	= 11.8 Hz	sum	= 23.4 Hz
<i>96</i>	11.6	4.4	10.1	22.8
<i>97</i>	10.5	4.5	4.1	20.2
<i>92</i>	10.1	4.7	6.8	16.9

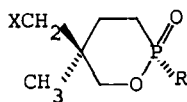
boat energy difference for the 2-oxo-1,3,2-dioxaphosphorinane system may be as low as ca. 1.0 kcal/mol (35,91), which contrasts with a ΔG° (chair $\rightarrow$ boat) for 1,3-dioxane of 8.3 ± 0.5 kcal/mol (114). If it is assumed that the conformational preference for the 5-*t*-butyl group is about 1.4 kcal/mol, as seen in 1,3-dioxanes (115), then competition between a chair form with an axial 5-*t*-butyl group and a twist form would be fairly balanced.

The X-ray structure of *92* displayed the six-membered ring as a distorted chair, with the 5-*t*-butyl group equatorial and the methyl group axial (102a). That *92* is not as strongly biased toward one conformation, as is *96*, could be a consequence of unfavorable steric interactions in *92*, arising from an axial 2-methyl group, and/or stabilization of the axial 2-methoxy conformation by electrostatic interactions (the generalized anomeric effect). X-Ray analysis of *95*, the epimer of *96*, showed a flattened chair conformation with axial 2-methoxy and 5-*t*-butyl groups (102b).

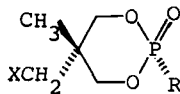
The temperature dependence observed for *92* pointed to displacement of a conformational equilibrium. Evidence for "conformational mobility" in 2-oxo-1,3,2-dioxaphosphorinanes had also been presented by others (78,116,117) [such as for *98a*, *98b*, *cis*-60, *90* ($R = \text{CH}_3$) and *90* ($R = \text{C}_6\text{H}_5$)].

*98a**98b**99*

Estimates of conformational preferences for 2-oxo-1,3,2-dioxaphosphorinanes can be deduced from POCH coupling constants (see Sect. II-A). Katritzky and co-workers (117) and Edmunson and Mitchell (116b) arrived at estimates for systems without strong biasing substituents on ring positions 4, 5, or 6. Some



100a: X = OTs
b: X = Br



101a: X = OTs
b: X = Br

Table 5 P-H Coupling Values and Conformer Distribution (109,117)

Compound	$^3J_{\text{POCH}}(1)$	$^3J_{\text{POCH}}(2)$	% Major Conformer ^{a,b}
99	26.7	1.0	100
90 (R = CH ₃)	14.0	9.9	60
90 (R = CH ₂ C ₆ H ₅)	14.9	7.8	65
90 (R = <i>sec</i> -C ₄ H ₉)	15.9	6.0	75
90 (R = <i>t</i> -C ₄ H ₉)	19	2	100
90 (R = NH- <i>t</i> -C ₄ H ₉)	16.3	7.8	ca. 75 ^c
90 [R = C(C ₆ H ₅) ₃]	15.7	6.6	75
<i>cis</i> -60	11	11	50
100a (R = CH ₂ C ₆ H ₅)	13.0	10.4	55
100a (R = CH ₃)	14.4	9.0	65
101a (R = CH ₂ C ₆ H ₅)	12.1	11.5	50
101a (R = CH ₃)	11.7	8.9	65
100b (R = CH ₂ C ₆ H ₅)	11.6	10.0	55
100b (R = CH ₃)	18.9	4.6	90
101b (R = CH ₂ C ₆ H ₅)	19.4	3.2	85
101b (R = CH ₃)	14.5	8.7	70

^aMeasured in chloroform or benzene.

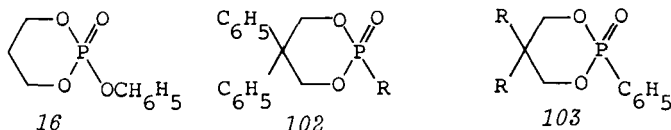
^bUsing $^3J_{\text{POCH}}(1) = nJ_t + (1 - n)J_g$; $^3J_{\text{POCH}}(2) = nJ_g + (1 - n)J_t$; $J_g = 3 \cdot ^3J_{\text{POCH}}(\text{acyclic}) - [^3J_{\text{POCH}}(1) + ^3J_{\text{POCH}}(2)]$; $J_t = 2[^3J_{\text{POCH}}(1) + ^3J_{\text{POCH}}(2)] - 3 \cdot ^3J_{\text{POCH}}(\text{acyclic})$.

^cNot reported; estimated from given coupling constants.

$^3J_{\text{POCH}}$ values and (approximate) % major conformer are given in Table 5. Although the conformational quantitation had offered no conclusive evidence for the identities of the favored conformers, this work suggested that secondary and tertiary alkyl groups on phosphorus reside mainly in an equatorial orientation, whereas primary alkyl groups populate axial and equatorial positions about equally in the absence of other biasing ring substituents. Compound 99 was believed to have the sulfur group equatorial, which is probably unlikely (see pp. 209, 222-223). Verkade and co-workers (78) gathered ¹H NMR data which were consistent with the prevalence of one chair conformer with an equatorial P=O bond, when the P substituents were alkoxy, bromo, chloro, and hydrogen; and with a rather heterogeneous equilibrium when the P substituents were primary alkyl, benzyl, phenyl, and trityl.

Extensive studies by Navech and co-workers on 2-oxo-1,3,2-dioxaphosphorinanes (118-126), employing IR ($\nu_{\max}$ P=O) and ^1H NMR data, provided conformational preferences (118-120) and approximate equilibrium free-energy values (119,121,124,125).

The ^1H NMR spectrum for 16 (AA'BB'KLX) was solved as an A_2B_2KLX approximation to give H-H coupling data. The values obtained were similar to those found for anancomeric 1,3-dioxanes (127), and indicative of a chairlike structure for the $-\text{OCH}_2\text{CH}_2\text{O}-$ portion of the ring, which is strongly biased toward one conformation ($\Delta H^\circ \geq 2$ kcal/mol). The conformational picture for 90 and 102 [$\text{R} = \text{OC}_6\text{H}_5$, Cl, $\text{N}(\text{CH}_3)_2$] is a strongly



biased equilibrium with 80 to 90% of one chair conformer; an axial position is preferred by phenoxy and chloro, whereas an equatorial position is preferred by dimethylamino. An equatorial preference for the phenyl group was suggested for 90 ($\text{R} = \text{C}_6\text{H}_5$) from a correlation of phosphoryl stretching frequencies (118).

Conformational free energies were estimated (120,121a) for 90 ($\text{R} = \text{C}_6\text{H}_5$) and related compounds by $^3\text{J}_{\text{POCH}}$ values (and IR data). In carbon disulfide the more stable conformer of 103 ($\text{R} = \text{H}$, CH_3 , C_2H_5 , C_6H_5) is that with an axial phosphoryl bond: $\Delta G_{298^\circ\text{K}}$ is ca. -600 cal/mol for $\text{R} = \text{H}$ (IR), ca. -600 to -650 cal/mol for $\text{R} = \text{CH}_3$ (IR, ^1H NMR), ca. -1050 to -1200 cal/mol for $\text{R} = \text{C}_6\text{H}_5$ (IR, ^1H NMR), and ca. -350 to -600 cal/mol for $\text{R} = \text{C}_2\text{H}_5$ (IR, ^1H NMR). In pyridine the equatorial P=O conformation is slightly favored for 103 ($\text{R} = \text{CH}_3$), and ($\text{R} = \text{C}_2\text{H}_5$): $\Delta G_{298^\circ\text{K}}$ is ca. 100 to 200 cal/mol; whereas 103 ($\text{R} = \text{C}_6\text{H}_5$) still had a preference for an axial P=O conformation; ΔG° ca. -400 cal/mol (all by ^1H NMR). A more thorough solvent-effect study on 103 ($\text{R} = \text{CH}_3$, C_2H_5 , C_6H_5), 16 and 90 ($\text{R} = \text{OC}_6\text{H}_5$, OC_2H_5 , Cl) indicated that polar solvents stabilize the equatorial P=O conformation, probably by solvation of the P=O bond (121b). Conformational free-energy values have been given for compounds with a variety of P substituents (121b,122-125), and some are given in Table 6. The trends of conformational preference reported by Navech and co-workers, and others (*vide supra*), were reflected in dipole moment and Kerr constant measurements by Arbuzov and co-workers (128) [P substituent = CH_3 , $\text{C}(\text{C}_6\text{H}_5)_3$, Cl, H]. Narech's group (124) computed group ΔG° values for various P substituents, given the ΔG° value for hydrogen vs. P=O in 90 ($\text{R} = \text{H}$), and found similarities and differences when they compared the values with those for 1,3-dioxanes.

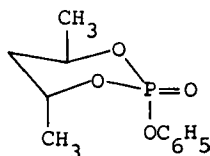
Complexation of 90 [$\text{R} = \text{OC}_6\text{H}_5$, OC_2H_5 , C_6H_5 , $\text{N}(\text{CH}_3)_2$] with BF_3 , affording 1:1 adducts, altered the conformational distri-

Table 6 Conformational Free Energies

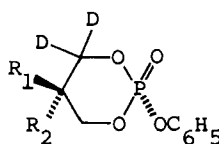
Compound	$\Delta G_{298^\circ K}^\circ$ (kcal/mol)				
	CS ₂	C ₆ D ₆	C ₅ D ₅ N	CH ₃ CN	CHCl ₃
90 (R = OC ₆ H ₅)	-	1.6	4.3	>5	2.0
90 (R = OC ₂ H ₅)	1.4 (1.5)	-	2.4-3.0	-	-
90 (R = C ₆ H ₅)	-0.6	-	0.1	0.2	-0.1
90 [R = N(CH ₃) ₂]	-	-1.1	-1.0	-0.8	-
90 (R = H)	-	1.2	1.1	0.8	-

bution (126). Thus 90 (R = OC₆H₅, OC₂H₅), with an axial P substituent strongly preferred in the uncomplexed form, showed increased conformational heterogeneity when complexed. On the other hand 90 (R = C₆H₅), which normally is mixture of conformers, showed a strong preference for a single form when complexed. The dimethylamino derivative, normally having a strong predilection for an equatorial amino conformation, showed little change in conformational distribution in the complex. It appears that the P=O bond is predisposed to an axial position in the BF₃ adducts. Changes in conformational proportions have also been noted in the complexation of certain 2-oxo-1,3,2-dioxaphosphorinanes with europium(III) chelates (*vide infra*; see Sect. II-F) (91b, 129-131). The shift of conformational equilibria for a number of unbiased derivatives of 90, on complexation with Eu(fod)₃, was toward the axial P=O bond conformer (131), in analogy to the BF₃ complexation.

Hall and Malcolm also studied 16 and 90 (R = OC₆H₅, Cl, OH, C₆H₅) as well as 104 and 105. Their analysis of the ²H-decoupled ¹H NMR spectrum of 105a showed a marked bias (ca. 100%) toward a chair conformer with equatorial 5-phenyl and P=O groups (46).



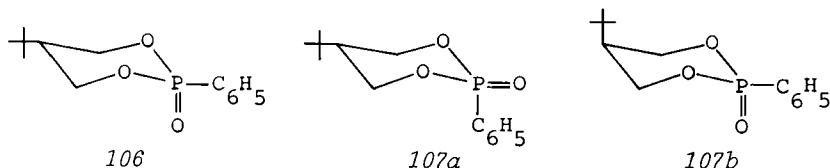
104

105a: R₁/R₂ = H/C₆H₅b: R₁/R₂ = C₆H₅/H

However, because of the strong predilection of the 2-phenoxy group for an axial orientation (vs. P=O), 105b favors (80 to 90%) a conformation with the 5-phenyl group in the less stable axial arrangement (46).

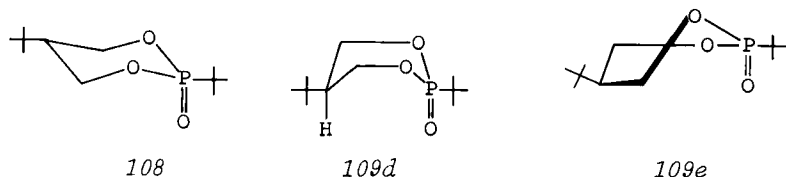
The use of europium(III) shift reagents to facilitate assignment of configuration and conformation of 2-oxo-1,3,2-dioxaphosphorinanes

phosphorinanes was first reported by Bentrude and co-workers (129,132,133). ^1H NMR parameters for 97 and 106 were consistent

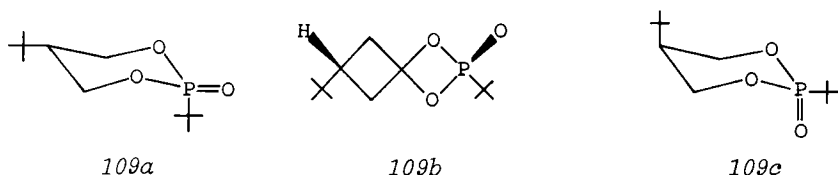


with chair conformations having equatorial 5-*t*-butyl and phenyl or methyl groups. In contradistinction the *cis* isomers 92 and 107 were found to be conformationally heterogeneous. Addition of Eu chelate displaced the conformational equilibria of 92 and 107, but did not do so with 97 and 106. For 107 the ratio of 107a to 107b was ca. 85:15 with 0.0 mol Eu/mol of compound, ca. 60:40 at 0.51 mol Eu/mol of compound, and ca. 47:53 at 0.95 mol Eu/mol of compound. Thus, the formation of the Eu·107 (or 92) complex shifts to the equilibrium in the direction of the axial P=O bond conformer.

Di-*t*-butyl compound 108 was found to exist completely in the diequatorial conformation (shown) (91a), and $^3J_{\text{POCH}}$ values for 108 were almost identical to those for 90 ($\text{R} = t\text{-C}_4\text{H}_9$), the latter lacking the biasing 5-substituent (109,117). In comparison the identical $^3J_{\text{POCH}}$ values (10 Hz) for 109 indicated either boat conformations (109b-109e) or a mixture of boat forms and chair conformers (109a and 109c), with 109c present to a minor extent (from ^1H - ^1H vicinal coupling constants) (91a). Evidently severe syn-axial nonbonded interactions in 109a and 109c cause an escape to the boat structures. The nonaveraged ^1H - ^1H vicinal

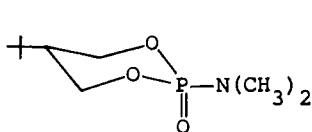


coupling constants observed are more in accord with a rigid boat form (109d) as the predominant conformation, since more average values should be seen with flexible, pseudorotating forms (109b and 109c) (91b).

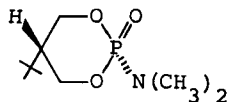


The ΔG° for chair-boat interconversion in 109 was estimated to be ca. 1 kcal/mol, which is low compared to ca. 8.3 ± 0.5

kcal/mol in 1,3-dioxane (114). Likewise, for the 2-dimethylamino derivatives 110 and 111, trans isomer 110 showed essentially one chair conformation, while the cis isomer (111) is a conformational mixture (91b). Furthermore, whereas 110 was conformationally stable to added $\text{Eu}(\text{dpm})_3$, 111 experienced alteration of its



110



111

conformational equilibrium (the effect was less dramatic than that observed for 107) (91b,130). The conformational equilibrium for 111 was composed of ca. 90% chair conformers, which had the axial 5-*t*-butyl form favored over the equatorial 5-*t*-butyl form by 2:1. An analogous situation was observed for the 2-isopropyl congener (91b).

Given the tendency for participation of a nonchair conformation in the conformational profile for cis isomers 109 and 111, [ΔG° (chair-boat) = 0.7 to 1.0 kcal/mol], caution should be exercised in considering conformational equilibria for other (especially closely related) 2-oxo-1,3,2-dioxaphosphorinanes. It is possible that 92 and 107 also have a twist form that is significantly involved in their conformational equilibria, a point which was not brought out in the preceding discussion.

A number of reports dealing with biased, diastereomeric systems have furnished data on the preferred disposition of groups on phosphorus in the 2-oxo-1,3,2-dioxaphosphorinane system. A strong axial preference has been observed for hydrogen (33,105,134-136) [$\Delta G^\circ_{40^\circ\text{C}} = -1.6 \pm 1$ kcal/mol (33)], alkoxy (136b), chloro (71b,136b,137,138), isothiocyanato (139), cyano (140), aryloxy (71b,138b), and fluoro (138b,141) vs. the phosphoryl bond. To summarize, in the 2-oxo-1,3,2-dioxaphosphorinanes P substituents such as fluoro, chloro, bromo, alkoxy, aryloxy, cyano, isothiocyanato, methylthio (131), and hydrogen strongly favor an axial orientation in nonpolar media. Conversely, the *t*-butyl and dialkylamino moieties are strongly favored in an equatorial orientation. Other substituents such as primary and secondary alkyl, benzyl, trityl, aryl, and primary amino tend to exist in an equatorial orientation to an extent between 50 and 85%, in nonpolar media. It should always be kept in mind that the conformational distribution of 2-oxo-1,3,2-dioxaphosphorinanes may be highly sensitive to solvent, as shown especially in the work of Navech and co-workers. Estimates of conformational preferences for various groups on phosphorus vs. P=O in nonpolar media are displayed in Table 7.

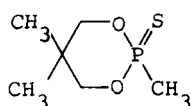
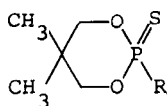
General explanations of the conformational preference in 2-oxo-1,3,2-dioxaphosphorinanes, based on the interactions of the lone pairs on the 1,3 oxygen atoms with the adjacent groups on phosphorus, have been advanced (142). A theoretical discus-

Table 7 Conformational Preferences of Groups on Phosphorus vs. P=O

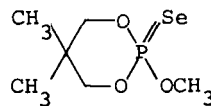
Substituent	Approximate % Equatorial
methyl	50-60
benzyl	55-65
trityl	65-75
phenyl	60-70
t-butyl	95-100
amino	75-85
dimethylamino	85-95
phenoxy	5-15
methoxy	5-10
hydrogen	10-20
chloro	0-5
fluoro	0-5
methylthio	0-10

sion of factors involved in conformational selection appears in Sect. IV.

2-Thiono and 2-Seleno Compounds. X-Ray structure determinations on 2-thiono- and 2-seleno-1,3,2-dioxaphosphorinanes *112*, *113a*, *113b*, and *114* revealed chair conformations in each case (143). The P=S and P=Se bonds in *113a* and *114* are equatorial, while the P=S bond in *112* and *113b* is axial. The cis diastereomers *115* (144a) and *116a* (102b) assumed chair conformations,

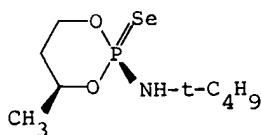
*112*

113a: R = OC₆H₅
b: R = N(CH₃)₂

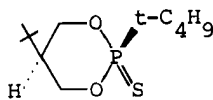
*114*

the former having the 4-methyl group equatorial and P=Se bond axial, and the latter having the 5-*t*-butyl group and P=S bond axial. Ring-puckering at the phosphorus end was unusually large for *116a*, which in addition was flattened at the other end of the ring (102b). Interestingly, *116a* has an axial 5-*t*-butyl moiety rather than a twist-boat structure, which occurs in the solid-state structures of related 1,3,2-dithiaphosphorinanes (Sect. III-C-4). Conversely, the related cis compound *116b* has a chair structure with equatorial 5-*t*-butyl and axial 2-phenyl groups in the solid state (102b).

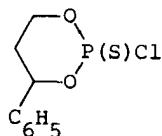
Early ¹H NMR investigations of some 5,5-dimethyl-2-thiono derivatives (72b,109) suggested strongly biased chair conformations in solution for *113* [R = N(CH₃)₂, NH-*i*-C₃H₇, OCH₃, Cl]. Kainosho and co-workers (111) reported that *113* (R = Cl), by comparison with *117*, exists virtually in one chair conformation.



115

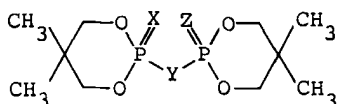


116

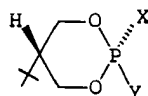


117

Katritzky's group (117) estimated the amount of major conformer for 118a, 118b, and 118c to be 95%, 95%, and 80%, respectively, using $^3J_{\text{POCH}}$ values. Majoral and Navech reported ^1H NMR data for 113 (R = Cl, OC_6H_5) and the 5,5-diphenyl analogs (119a). The $^3J_{\text{POCH}}$ values for 113 (R = C_6H_5) were employed to estimate a conformational free energy in carbon disulfide of 650 cal/mol; the direction of preference was ambiguous (121a). It is possible that the conformational tendency for 113 (R = C_6H_5) was opposite in CS_2 and pyridine. Free-energy differences of 300 to 900 cal/mol have also been estimated for 113 (R = OH) in various solvents (124).

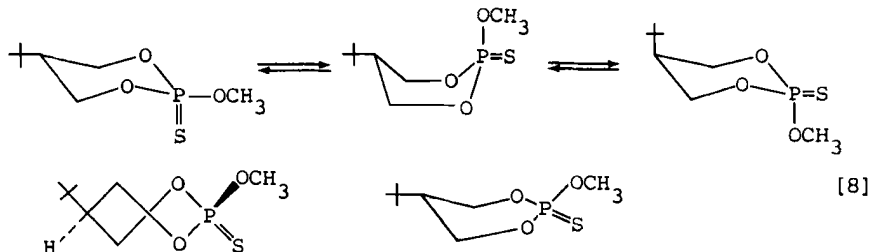


118a: X = Y = O; Z = S
 b: X = Z = S; Y = SeSe
 c: X = Z = Se; Y = SS



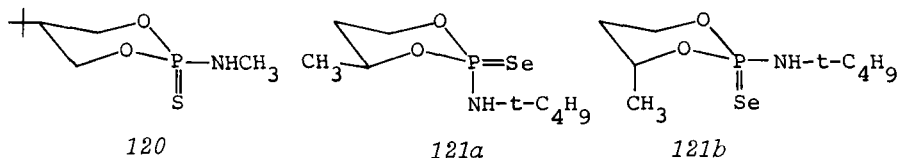
119a: X/Y = OCH_3/S
 b: X/Y = S/OCH_3

Investigation (^1H NMR) of 119 indicated a chair structure with equatorial *t*-butyl and P=S groups for the trans isomer (119a), but a heterogeneous conformational equilibrium for 119b (113). Since the vicinal proton-proton coupling constants for 119b did not vary nearly as much as the $^3J_{\text{POCH}}$ values, the *t*-butyl end of the ring is substantially fixed, leading to a proposal that the other conformer present in 119b is a boat (or "chaise-longue") structure (eq. [8]). Thus competition between P=S and P-OCH₃ favors the axial P-OCH₃ conformer.

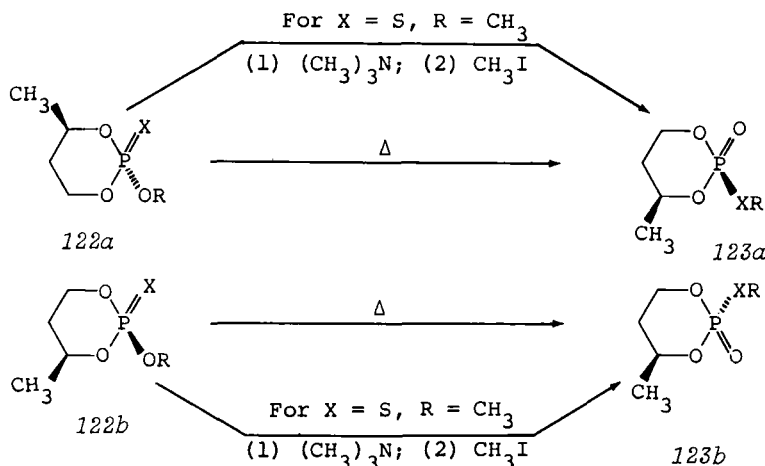


^1H NMR data for 120 were supportive of virtually a single chair conformation with equatorial *t*-butyl and methylamino groups (91b), reflecting the stable arrangement of substituents

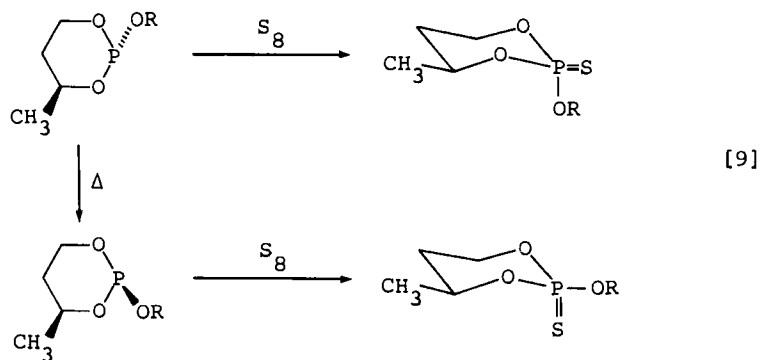
at phosphorus. The preference of the alkylamino group for an equatorial position is similar to observations for the 2-oxo- and trivalent ring analogs. The trans isomer of 115 (i.e., 121), based on NMR data and comparison with the cis isomer 115, is a mixture of considerable amounts of both chair conformers (ca. 60% 121a and 40% 121b) (144b). X-Ray analysis of 121 showed a chair conformer with the methyl and seleno substituents equatorial (144c).



Diastereomers of 122 [X = S, R = CH₃ (146,147), C₂H₅ (145)] were obtained through stereospecific reaction of the corresponding phosphites with sulfur; the methyl derivatives were converted to salts of the same thioacids, which were produced by the stereospecific reaction of diastereomeric hydrogen phosphites 19 with sulfur and a secondary amine (see Sect. III-B-2-a) (146,147). Comparable work was published for the analogous selenium compounds (146,147), and selenoesters 122 (R = CH₃, X = Se) were discovered to thermally rearrange to isomeric selenoesters 123 (R = CH₃, X = Se) with complete retention of configuration at phosphorus. Acid-catalyzed rearrangements of this kind for sulfur and selenium compounds have been discussed (148).



Dipole moment measurements were used to assign axial alkoxy orientations for a series of thiophosphates 122 (R = CH₃, C₂H₅, i-C₃H₇; X = S) derived from the more stable phosphites; equatorial alkoxy positions were assigned for sulfides from the less stable phosphites (eq. [9]) (149). Russian workers later re-



ported similar results for 122 ($R = \text{CH}_3$, $X = \text{S}$) (150a) on the basis of dipole moment data and molecular Kerr constants. The preferred conformations of 124 ($R = \text{Cl}$, CH_3) were suggested to be those with chloro axial and methyl equatorial (151a); conclusions of an earlier paper of these workers are of uncertain validity (151b). Raevskii and co-workers (152) applied IR data to a conformational study of thiono compounds, but conclusions from this type of work are probably ambiguous. Robert's group (153) has used $^3\text{J}_{\text{POCH}}$ values to estimate conformational preferences for nonanacomeric 2-thiono-1,3,2-dioxaphosphorinanes (113) in a polar and a nonpolar medium (Table 8).

Table 8 Percentage of Axial P=S

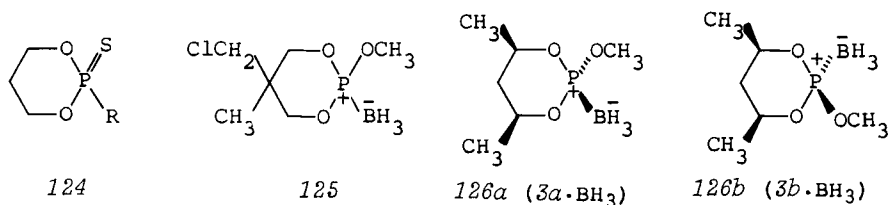
113	CCl_4	CD_3CN
$R = \text{CH}_3$	95	70
$R = \text{C}_6\text{H}_5$	100	70
$R = \text{OC}_6\text{H}_5$	10	15
$R = \text{Cl}$	0	0

Miscellaneous P-X Compounds. Little work on 2-imino-1,3,2-dioxaphosphorinanes has appeared in print, though a few isolated papers concerned with chemical aspects exist (39,167,183).

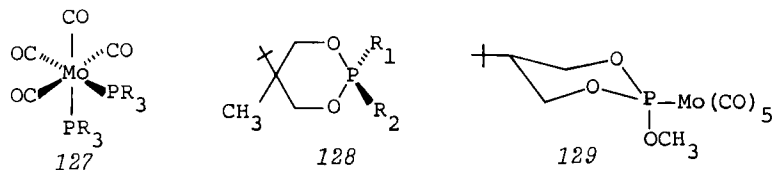
Borane adducts of 1,3,2-dioxaphosphorinanes have been studied (154a,155). The methoxy groups in both isomers of 125 are axially disposed, based on dipole moment data (154a). X-Ray analysis of adduct 126a (155) showed a chair conformation with equatorial 4,6-dimethyl and BH_3 substituents (154b). The equatorial positioning of the BH_3 group is thermodynamically more stable (vs. that of the methoxy group). B-H stretching frequencies for the isomers of 126 suggest that an equatorial lone pair is less basic than an axial lone pair (155). Molybdenum

carbonyl complexes elicited a similar conclusion regarding phosphite basicity (156), as did low-temperature ^1H NMR $^1\text{J}_{\text{PH}}$ values on protonated derivatives of **3** (157). Denney (187) has mentioned this same trend (axial lone pair more nucleophilic than equatorial lone pair) with phosphites analogous to **3**.

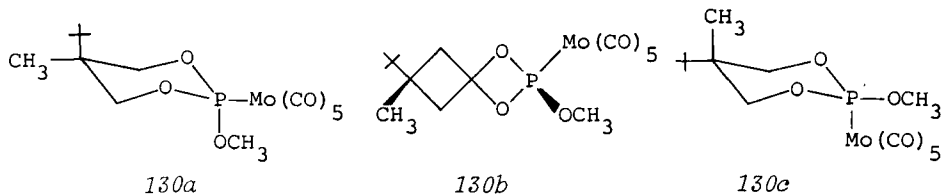
Transition metal-phosphine coordination complexes are common, and complexes of 1,3,2-dioxaphosphorinanes can be readily prepared. Arbuzov and co-workers (150a) reported isomeric 1:1 adducts of phosphites with CuCl . Cis complexes, **127**, of **3a** and **3b** with $\text{Mo}(\text{CO})_5$ have been obtained with retention of configuration at phosphorus (156). One-to-one molybdenum complexes of stereoisomeric phosphites closely related to **13a**



and **13b** have also been reported [128; $\text{R}_1, \text{R}_2 = \text{OCH}_3, \text{Mo}(\text{CO})_5$]; the complexes were formed with retention of stereochemistry (158). It was proposed that the $\text{Mo}(\text{CO})_5$ group in **128** would prefer an equatorial orientation, based on earlier studies (159). ^1H NMR spectral data for the isomeric complexes (**128**) supported different arrangements of the 5-*t*-butyl and 5-methyl groups. The cis complex was mainly chair conformation **129**. The trans complex was obviously conformationally heterogeneous, with a predomi-



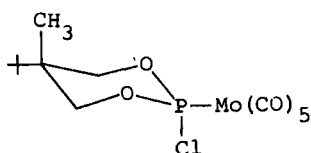
nance of **130a** and **130b**, and a minimal contribution from **130c**. Twist form **130b** was excluded from consideration (158), but a



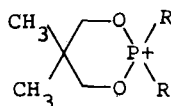
good structural analogy exists between this cis compound and *cis*-2-5-di-*t*-butyl-2-oxo derivative **109** (**9la**), which is populated by a substantial amount of twist-boat form in solution. Equilibration studies indicated that the cis complex is more stable than the trans: the equilibrium ratio was cis/trans =

88:12. Complexes with a chloro substituent in place of the methoxy were prepared [128; $R_1, R_2 = \text{Cl}$, $\text{Mo}(\text{CO})_5$] and equilibrated to a 95:5 cis/trans mixture. Displacement of chloride from 131 by methoxide occurred with predominant inversion but, since the less stable (trans) isomer was formed, the stereochemical results are confused by competitive epimerization of product 130 to 129.

Ethylation of 90 ($R = \text{OC}_2\text{H}_5$) with $(\text{C}_2\text{H}_5)_3\text{O}^+\text{BF}_4^-$ gave phosphonium salt 132a, whose ^1H NMR spectrum indicated no conformational bias (160). Related salt 132b showed similar behavior (161). Interconversion between conformers of 132b seemed to be rapid on the NMR time scale, even at -81° .



131



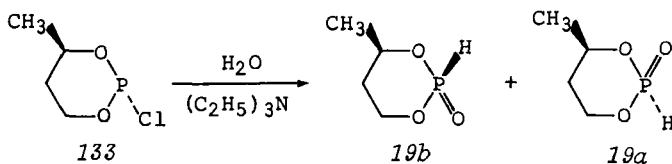
132a: $R = \text{OC}_2\text{H}_5$
 b: $R = \text{CH}_3$

2. Stereochemistry of Electrophilic and Nucleophilic Substitution Reactions at Phosphorus

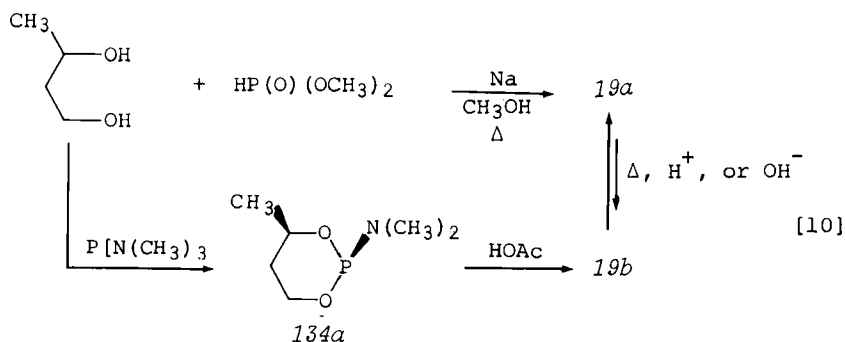
2-Oxo Compounds. In this section we turn to a discussion of diastereomeric and anancomeric (19) 1,3,2-dioxaphosphorinanes, such as 4-methyl, 4,6-dimethyl, and 5-*t*-butyl derivatives, touched on briefly in Sect. III-B-1. These systems, especially the 4-methyl series, have been useful in the study of reaction stereochemistry at the phosphorus center.

Chlorophosphite 133, prepared from 1,3-butanediol and PCl_3 (145,162), was hydrolyzed to a mixture of diastereomeric hydrogen phosphites, 19b and 19a (146,164), the latter of which predominated. Similar nonstereospecificity in phosphite hydrolysis was presented in Sect. III-A-1 and III-A-2 with regard to 58a ($R = \text{CH}_3$) (80) and 57a (80,86).

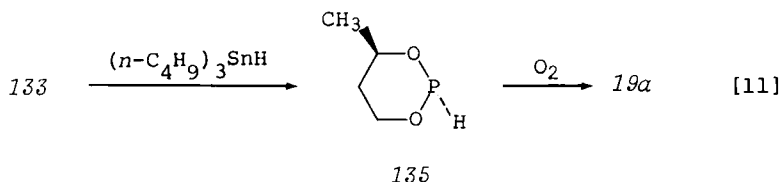
Nifant'ev and co-workers (134) discovered stereoselective syntheses of 19b and 19a, one involving ester exchange between dimethylphosphite and 1,3-butanediol, and the other involving



acidic hydrolysis of the more stable isomeric phosphoramidite 134a (eq. [10]). The liquid isomer 19b was found to transform to crystalline isomer 19a, especially well in the presence



of additives such as acids and bases (134,135). Stec's group also reported a stereoselective synthesis of 19a from 135 and dry air (eq. [11]) (39).



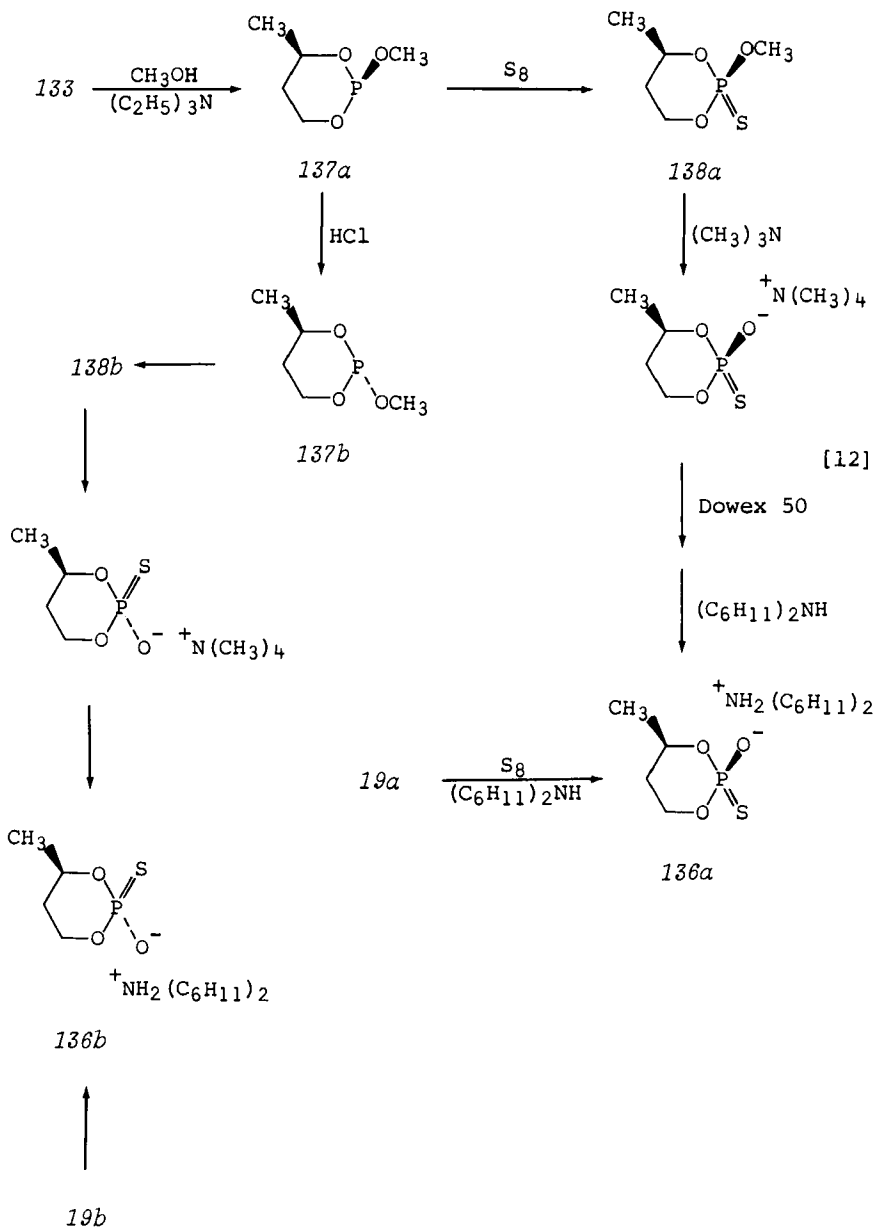
Structural and conformational assignments were formulated for 19a and 19b via ^1H NMR and dipole moment data (134); the conformational preferences are chair structures with equatorial 4-methyl groups. Although the configurational assignments (134) for 19a and 19b conflicted with a prior assignment (146), the work of Nifant'ev (134) was later fully corroborated (33, 105).

^1H NMR data for 19b and 19a (19b: $^4J_{\text{PCH}_3} = 2.0$ Hz, $^3J_{\text{HH}} = 9.7, 3.5$ Hz, 19a: $^4J_{\text{PCH}_3} = 1.2$ Hz, $^3J_{\text{HH}} = 8.0, 4.2$ Hz), in comparison with data for an anancomeric pair of isomers 8a and 8b (33), permit an estimation of the conformer population for 19: 19a has 95 to 100% and 19b has 55 to 60% of equatorial 4-methyl conformer.

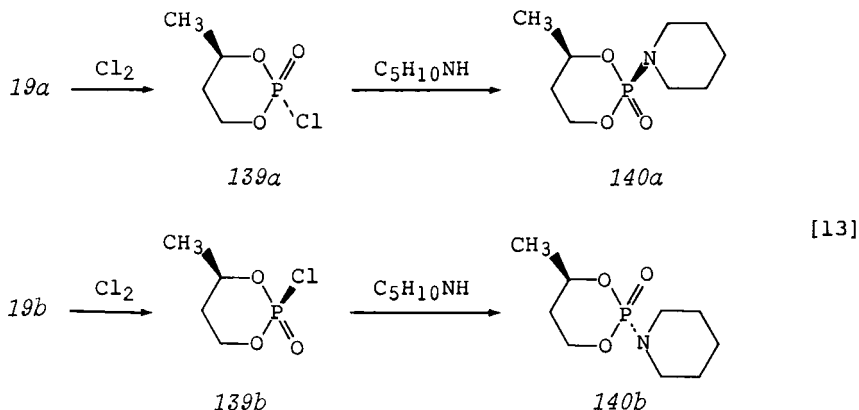
Mikolajczyk (146) found that the more stable phosphite 19a combines with sulfur to give (retention of configuration) a salt of 2-hydroxy-4-methyl-2-thio-1,3,2-dioxaphosphorinane, obtained earlier by an independent route (eq. [12]) (147). Since the initial assignments of configuration for 19 were reversed (146), the early structural correlation involving 136a is incorrect but, in a subsequent full paper (164), correct structures were presented for 19 along with the chemistry delineated in eq. [12].

Replacement of hydrogen in 19a and 19b by chlorine [SO_2Cl_2 (165a), Cl_2 (136b), *N*-chlorosuccinimide (136b)] occurs stereospecifically with retention of configuration (eq. [13]). Dis-

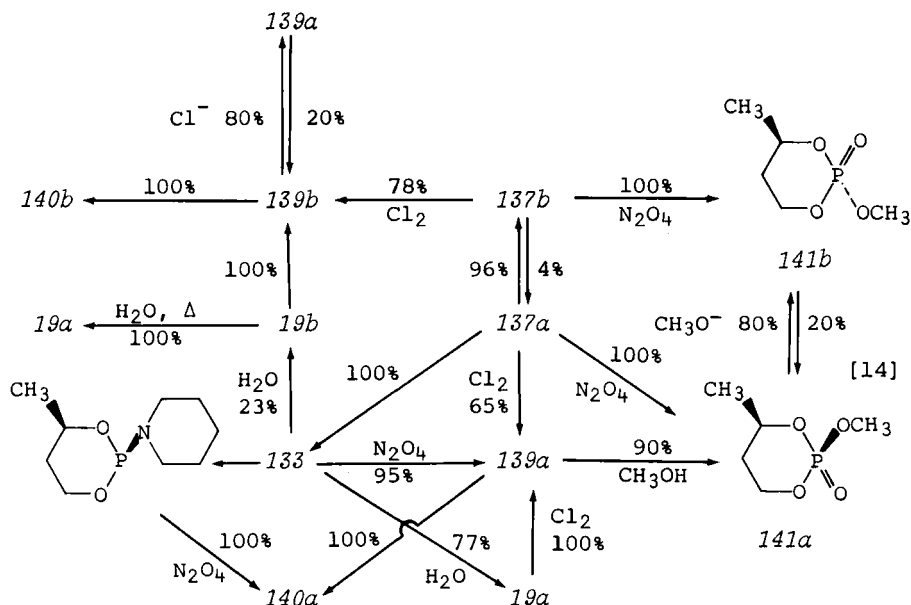
placement of chloride from 139 with piperidine gave 140 with inversion (136b), whereas displacement with methanol occurred with loss of stereochemical integrity (136b,137). Stereochemical



correlations are shown in eq. [14], along with the percentage of stereospecificity. The reaction of 1,3-butanediol with POCl_3 , subject to thermodynamic control, gave a mixture of **139a** and **139b** in a ratio of ca. 80:20, the same ratio observed for equilibration of phosphates **141** with NaOCH_3 (**136b**). A 76:24 ratio of

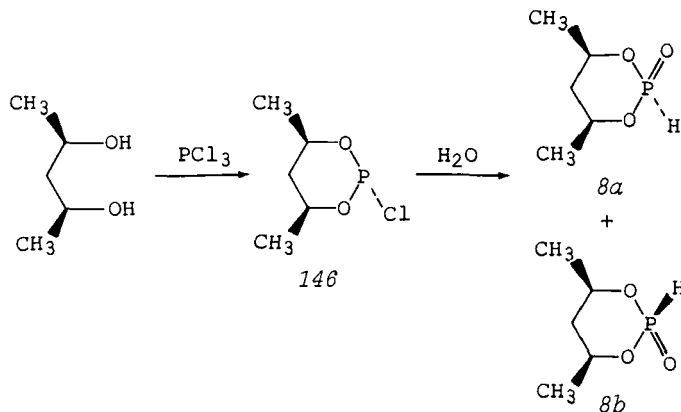


139a to **139b** was reported for a similar preparation by Stec and Mikolajczyk (137). The chlorination of **19** was also studied by Stec and Mikolajczyk (137), who were able to effect stereospecific chlorinolyses of trialkyl phosphites **137a** and **137b** with Cl_2 at -50° . Bromination of **137** with *N*-bromosuccinimide (NBS) or of **19** with Br_2 at -50° gave phosphorobromidates in a parallel



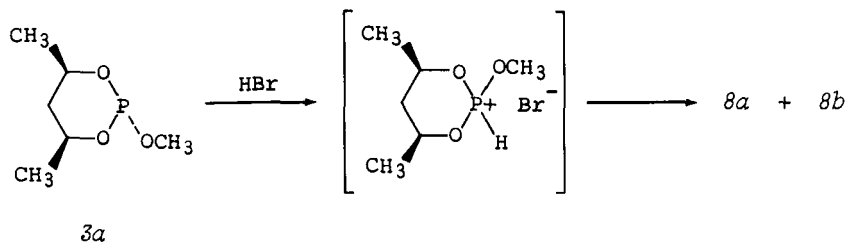
^1H NMR data for *139a* ($^4J_{\text{PCH}_3} = 3.0$ Hz) and *139b* ($^4J_{\text{PCH}_3} = 1.4$ Hz), and their bromine analogues, indicated that *139a* exists almost entirely in a chair conformation with an equatorial 4-methyl group, while *139b* is a conformational mixture composed of ca. 40-50% of a chair conformer with a equatorial 4-methyl group. The greater thermodynamic stability of *139a* compared to *139b* is a consequence of the disposition of substituents on phosphorus. Navech recorded similar observations with 2-phenoxy analogs of *139*: the one corresponding to *139a* is ca. 100% chair conformer with an equatorial 4-methyl group, whereas the one corresponding to *139b* is ca. 70% of the conformer with axial 4-methyl and *P*-phenoxy groups (119a). ^1H NMR and IR data indicated that *143a* and *143b* are predominantly chair conformations with an equatorial 4-methyl group (166).

Mosbo and Verkade studied both the 4-methyl and *cis*-4,6-dimethyl-2-oxo-1,3,2-dioxaphosphorinane series (33,136a,142b). Hydrolysis of *146* (presumably the more stable isomer) in acidic or basic media afforded a mixture of phosphite diastereomers, *8b* and *8a*, in a ratio of 70:30 (33). The *cis*-4,6-dimethyl substitution sterically constrains the phosphites to chair conformations with diequatorial methyl groups (167). Equilibrium experiments demonstrated that *8a* was more stable than *8b*, $\Delta G^\circ_{40^\circ} =$

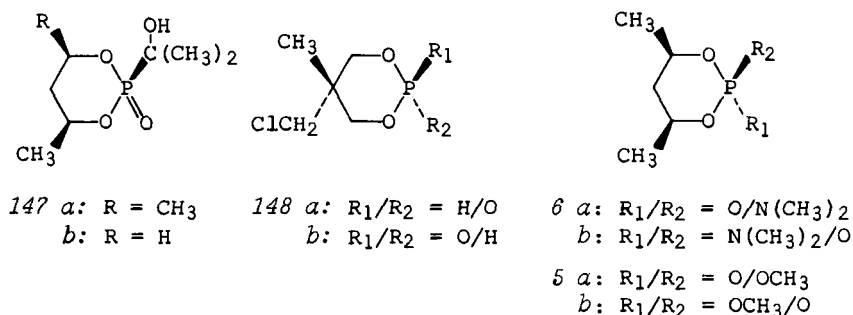


-1.6 ± 1 kcal/mol (compare ref. 135). Speculation on the mechanism of phosphite hydrolysis has been presented (80,87,135,136b), but no definitive mechanism has yet been determined.

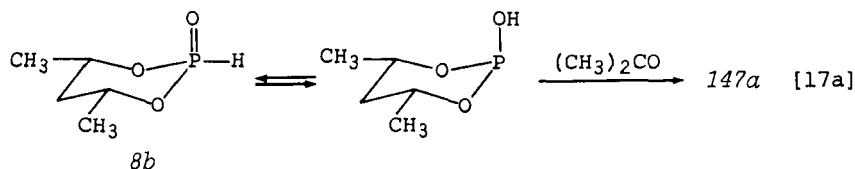
Phosphite *3*, first synthesized by Denney and Denney (163) and assigned its configuration via X-ray analysis of the borane adduct (154b), was protonolyzed with anhydrous HBr to a 50:50 mixture of *8a* and *8b*, rather than just *8a*, as expected through an Arbuzov-type mechanism (33). The reaction of *8b* and *19b* with acetone in the presence of acid gave adducts *147a* and *147b*, whereas the epimeric phosphites (*8a* and *19a*) were unreactive (33). Thus a distinct stereospecific dependence on the phosphorus configuration exists in the attack by acetone, which may be



connected with hydroxy tautomer formation in the reactive diastereomers *8b* and *19b* (see eq. [17a]). The high reactivity of



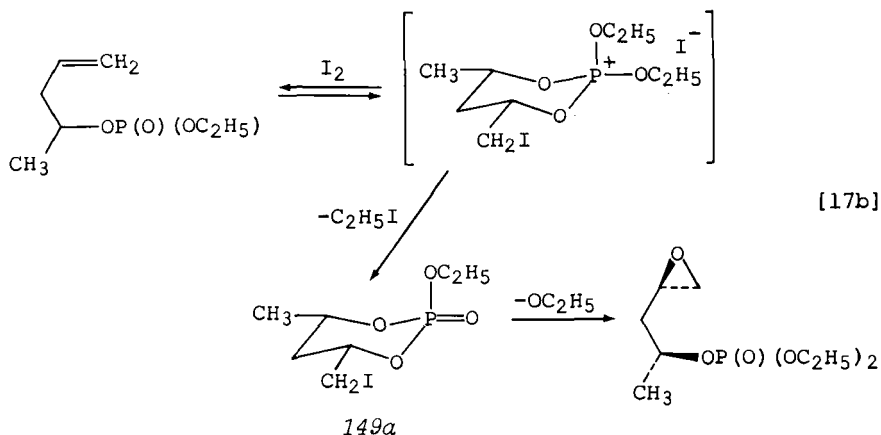
8b and *19b* could originate from a strong axial preference for the 2-hydroxy group in trivalent 1,3,2-dioxaphosphorinanes, as seen for the alkoxy group (see Sect. IV). Hydroxypropylation of *148a* and *148b* is also stereospecific (33).



Correct configurational assignments were proposed for the isomeric pairs *141*, *142*, *6*, and *5* (*136a*, *142b*) on the basis of ^1H NMR LIS data. Dipole moment and NMR data for both isomers of *6* and *5* indicated a strong preference for chair conformers with equatorial 4,6-methyl groups.

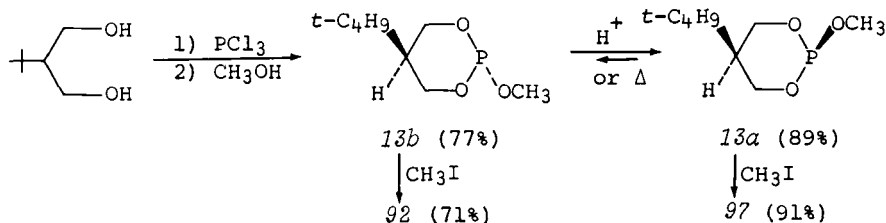
Bartlett and Jernstedt arrived at phosphates related to *5* as intermediates in a stereoselective functionalization of homoallylic alcohols (eq. [17b]) (168). One diastereomer (*149a*) was formed predominantly (>90%), either by selective dealkylation of the intervening diethoxyphosphonium salt or by equilibration of an initially produced epimeric mixture (*149*).

The Michaelis-Arbuzov reaction entails condensation of a trivalent phosphorus ester with an alkylating species to give an intermediate phosphonium salt, which decomposes to a phosphoryl compound (169). Hence this process could provide a variety of

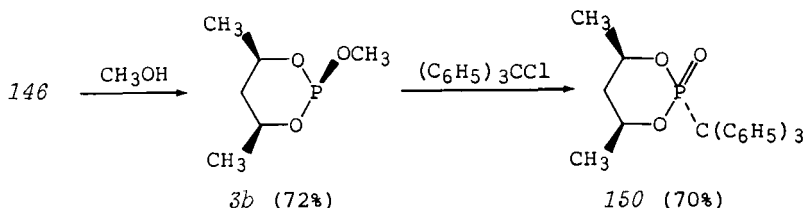


2-R-2-oxo-1,3,2-dioxaphosphorinanes from single 2-alkoxy-1,3,2-dioxaphosphorinanes.

Bentrude and Hargis (170) employed this reaction to prepare 92 [for X-ray crystallography (102)] from thermodynamically less stable phosphite 13b, and 97 from 13a (isomeric purity in parentheses). Reaction of a mixture (3) enriched in less stable

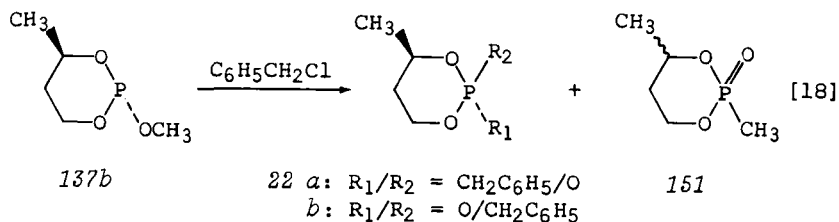


phosphite 3b with trityl chloride yielded, stereospecifically, a mixture enriched in 150 (78), which was isolated for an X-ray diffraction study (84).

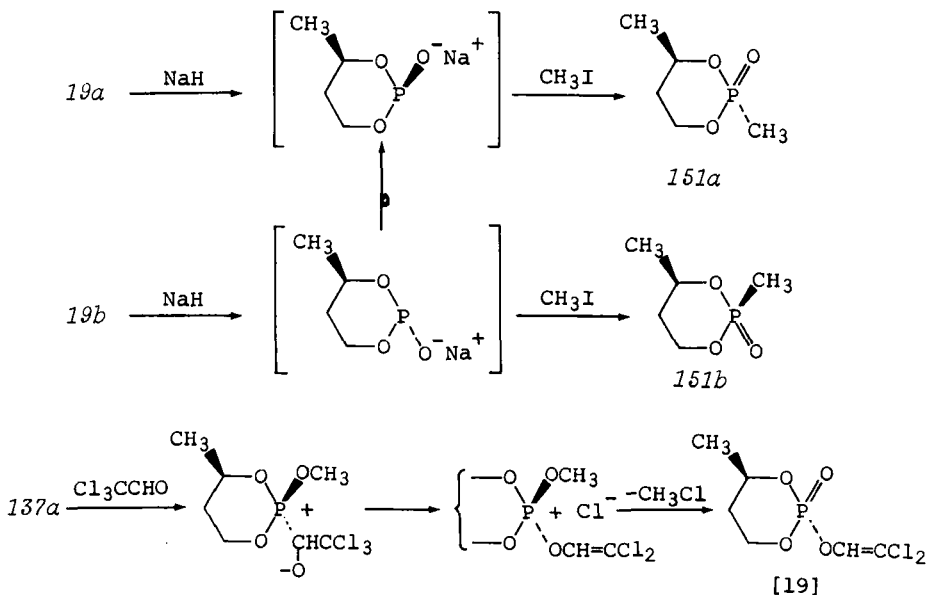


Bodkin and Simpson (171) reported that the reactions of certain 4-methyl-2-OR-1,3,2-dioxaphosphorinanes ($R = \text{C}_2\text{H}_5$, $i\text{-C}_3\text{H}_7$) with alkyl iodides occur nonstereospecifically; however, the same phosphites did react stereospecifically with trityl fluoborate. To explain these results, pentacoordinate intermediates, which could undergo pseudorotation, were invoked (171). Interestingly, recovered phosphites from incomplete reactions showed stereomutation in that some the less stable

cis phosphite had been converted to the trans isomer. This was rationalized by collapse of the pseudorotated, pentacoordinate intermediate to starting materials. Denney and co-workers (172), however, attributed the stereomutation to catalysis by traces of acid and/or iodine. Arbuzov and co-workers (150) also found that the stereospecificity of the Arbuzov rearrangement of 137 with methyl iodide depends on the reaction conditions, and could be made completely stereospecific. The reaction of 137*b* with benzyl chloride was not stereospecific, but harsh reaction conditions had to be employed (eq. [18]; 22*b* predominated) (40).

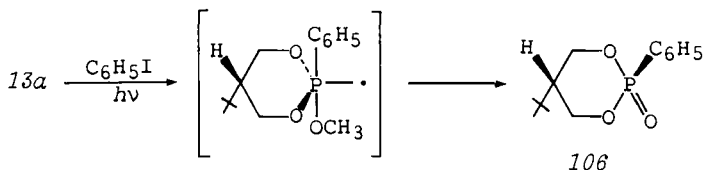


The (Michaelis-Becker) reaction of both 19*a* and 19*b* with benzyl iodide and sodium hydride afforded benzylphosphonates 22 with high, but not complete, stereospecificity (retention). The more stable phosphite 19*a* gave a 90:10 ratio of 22*a* and 22*b*, whereas the less stable phosphite 19*b* gave a 20:80 ratio. Stec's group (173) explored the related Michaelis-Becker reaction of 19 with methyl iodide. Reaction of the sodium salts with methyl iodide took place with complete retention but, when the addition of CH₃I was delayed, a 92:8 mixture of 151*a* and

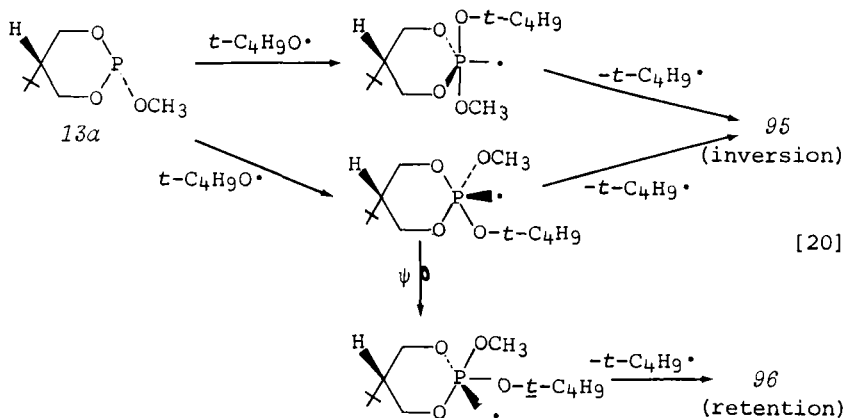


151b was obtained, independent of the starting phosphite. Since 19b and 19a did not epimerize under the reaction conditions with CH_3I , the formation of the sodium salt and its epimerization are slow compared to the rate of alkylation. Since the salt from 19b isomerizes to the salt from 19a, the favored orientation for the sodio-oxy group in 1,3,2-dioxaphosphorinanes is *equatorial*. Similar stereomutation has been observed with salts of acyclic hydrogenphosphites (174).

It should be noted that the stereospecific reactions of acetone and chloral with cyclic hydrogen phosphites are related to the Michaelis-Arbuzov process for P-C bond formation (33,165). The reaction of trialkyl phosphites 137 with chloral (Perkow reaction), leading to vinyl phosphate products, is also stereospecific (eq. [19]) (175).

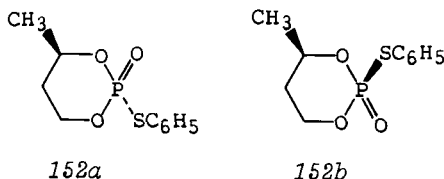


Bentrude and Yee (176) observed a stereospecific (retention) photoinduced Michaelis-Arbuzov reaction of 13a (90% *cis*) with iodobenzene to obtain 106, a reaction presumably involving a phenyl radical, which adds to 13a to generate an intermediate phosphoranyl radical. The stereochemistry of free-radical oxidation at trivalent phosphorus was also studied (177). Transfer of oxygen from *t*-butoxy radical ($t\text{-C}_4\text{H}_9\text{O}\cdot$) and sulfur from *n*-butylthiyl radical ($n\text{-C}_4\text{H}_9\text{SS}\cdot$) to 13b and 13a furnished the corresponding oxides and sulfides, respectively, stereospecifically with retention (177a). Neither stereospecificity nor retention of stereochemistry is demanded by this type of reaction, suggested to involve a tetraalkoxyphosphoranyl radical, since the presumably trigonal-bipyramidal radical could



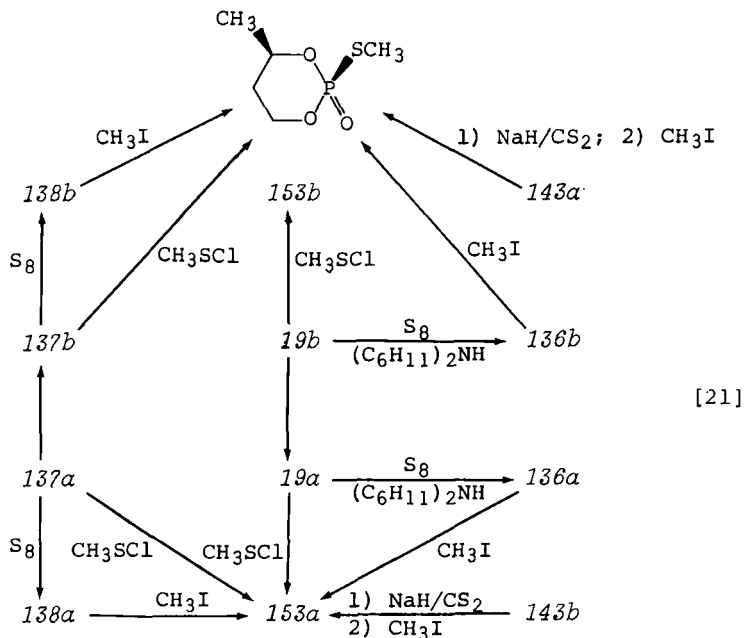
suffer permutational isomerism (pseudorotation). If competitive pathways do exist (eq. [20]), loss of $t\text{-C}_4\text{H}_9\cdot$ must be much faster than pseudorotation. Similar behavior was recorded for cyclic five-membered-ring phosphites (177b) and an optically active phosphine (177a). Free-radical Arbuzov reaction stereochemistries, involving $\text{C}_6\text{H}_5\cdot$, $(\text{CH}_3)_2\text{N}\cdot$, and cyclic phosphites, have been discussed with respect to permutational isomerization of the intermediate phosphoranyl radicals (179); the reactions were nearly stereospecific with retention. The compound with an axial lone pair (13b) was 6 to 8 times more reactive to $(\text{CH}_3)_2\text{N}\cdot$ than was 13a, in analogy to observations (125) for 137a and 137b (Sect. III-B-1-C).

Denney and Moskal (180) reported that phosphites 137a and 137b react with benzenesulfonyl chloride, under mild conditions, stereospecifically with retention to give phosphorothioates 152a and 152b, respectively. Their results were consistent with an ionic mechanism analogous to that of the Michaelis-Arbuzov reaction. Both 152a and 152b were suggested to assume preponderantly a chair conformation with the 4-methyl group equatorial.

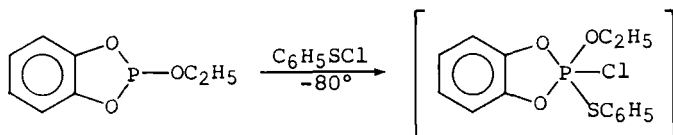


Reactions of 137 and 19 with alkylsulfonyl chlorides proceed stereospecifically, as shown in eq. [21], (stereochemical interrelationships provided). ^1H NMR data (300 MHz) indicated that 153a is virtually one chair conformer with equatorial 4-methyl and phosphoryl groups. The other isomer (153b) is also strongly favored in one chair form, with the ring methyl and methylthio groups equatorial. A disparity between the $^3\text{J}_{\text{POCH}}(4a)$ (4.5 Hz) and $^3\text{J}_{\text{POCH}}(6a)$ (8.0 Hz) values for 153b may be caused by some flattening or distortion of the ring and/or a small contribution from other possible conformers. A stereochemical correlation between the previously discussed anilides 143a and 143b and 153b and 153a, respectively, was accomplished through a novel, stereospecific P-N bond cleavage reaction, involving formation of the amide anion, treatment with CS_2 to yield a thioacid salt, and methylation (eq. [21]) (182). Stec and co-workers also related 153a and 153b to the trivalent heterocycles by stereospecific oxidation (N_2O_4) (183).

Although the reaction of cyclic phosphites 137a and 137b with sulfonyl chlorides had been rationalized in terms of an ionic mechanism (180, 182), a generalization for all trivalent phosphorus esters cannot be proffered. Catechol phosphite 154 combines at low temperature with $\text{C}_6\text{H}_5\text{SCl}$ to give a pentacoordinate intermediate (^{31}P NMR) (184). A phosphorane can still arise through a series of ionic steps, but a direct, biphilic insertion process is also possible (185). Evidence for a phosphorane



intermediate in the reaction of 154 with Cl_2 was also reported (184), and this result should be noted in considering the chlorinolysis of phosphites such as 137a and 137b. Furthermore, the reactions of 137a and 137b with neopentylhypochlorite have been interpreted in terms of ephemeral pentacoordinate intermediates, which are subject to permutational isomerization that is competitive with ionization (186). Interestingly, the less stable isomer 137a reacted with *neo*- $\text{C}_5\text{H}_{11}\text{OCl}$ much more stereospecifically than did 137b.

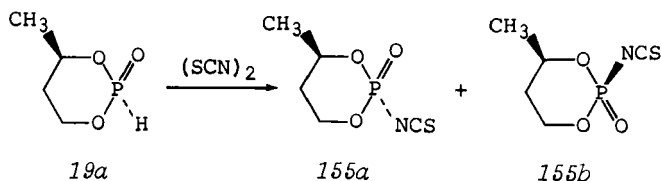


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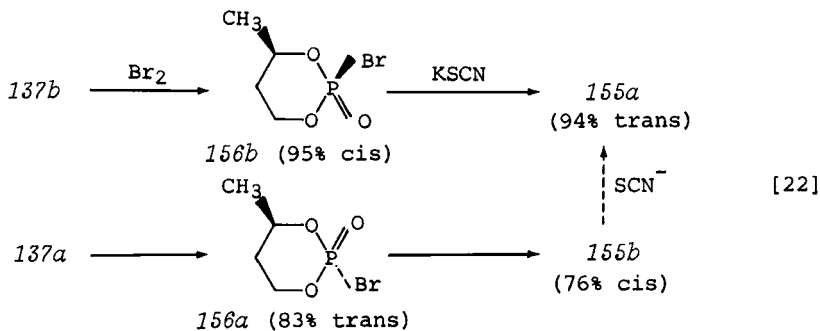
Reaction of cyclic phosphites with haloamines [examples of which have already mentioned (70,71b,72a,137)] fall into the same category as the reactions of phosphites with alkyl and sulfonyl halides. At -20° (then 10°) 137b reacts with $(\text{CH}_3)_2\text{NCl}$ to give a 9:1 mixture of 142a and 142b (90% retention), and at 0° 137a reacts to give a 2:3 mixture of 142a and 142b (60% retention). Treatment of 78b with $(\text{CH}_3)_2\text{NCl}$ in refluxing benzene gave a 2:1 mixture of 142a and 142b (67% retention) (phosphoramides 142a and

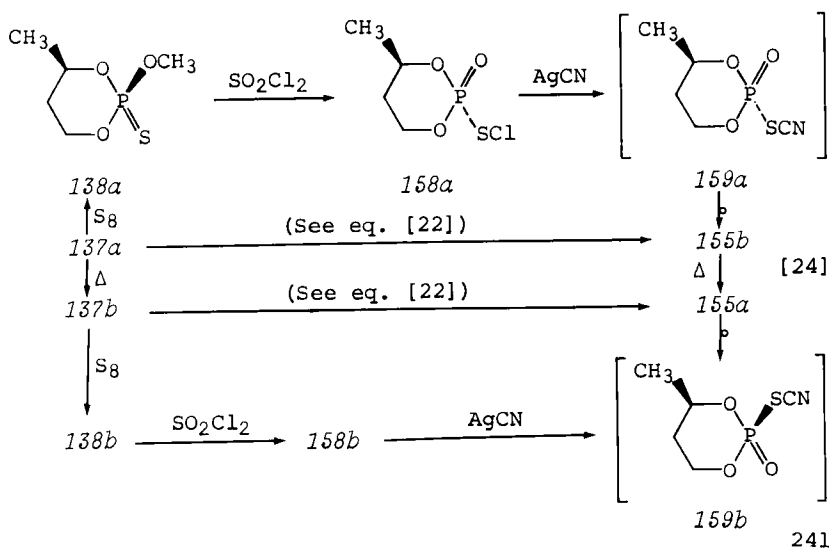
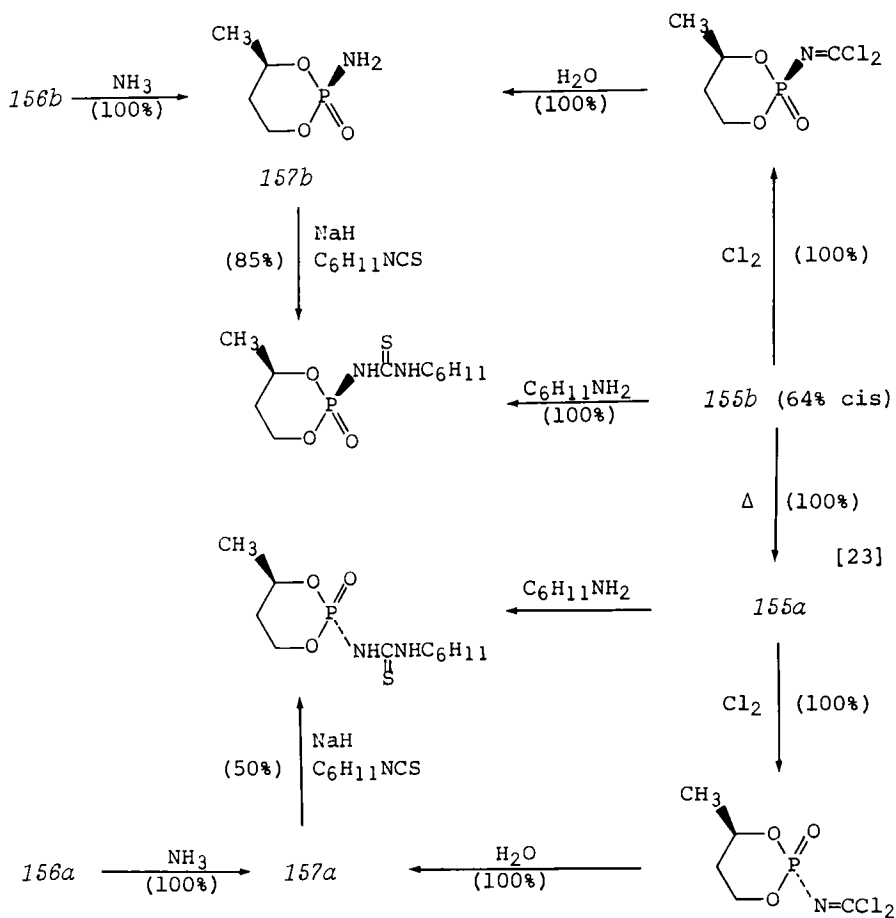
142b did not isomerize thermally) (136a). Treatment of phosphite 3a with $(\text{CH}_3)_2\text{NCl}$ afforded an epimeric mixture of 6 (60% retention) (142b). In the reaction of 137a and 137b with various chloramines [$(\text{CH}_3)_2\text{NCl}$, $(\text{C}_2\text{H}_5)_2\text{NCl}$, $\text{C}_5\text{H}_{10}\text{NCl}$], under a variety of conditions, loss of stereochemical integrity was consistently observed (187), in contrast to the results of other workers (137). Stereospecificity varied with solvent, temperature, and choice of chloramine (187). Stereomutation here (187) could be associated with a reaction with a phosphorane intermediate. The rates of reaction of trivalent phosphorus compounds having different nucleophilicities with $(\text{C}_2\text{H}_5)_2\text{NCl}$ did not follow their expected order, suggesting the prevalence of a direct insertion mechanism as opposed to an ionic one (which may still be competing) (187).

Thiocyanogen combines with 19a (94%) in a nonstereospecific fashion, giving 155a and 155b in a ratio of 79:21, but 19b (97%) reacted stereospecifically, giving a 2:98 ratio (139a). Bromo derivatives 105a and 105b were converted to 155a and 155b, re-



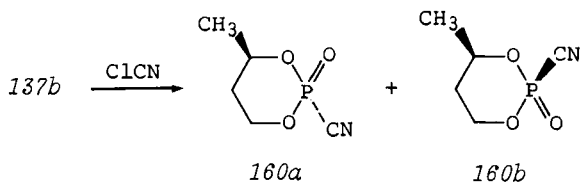
spectively, with nearly complete inversion (eq. [22]). The SCN^- ion and other nucleophiles catalyze the formation of 155a from thermodynamically less stable 155b; 155a probably prefers a chair conformation with equatorial 4-methyl and phosphoryl groups. Lopusinski and co-workers assembled a group of diverse reactions into an intriguing stereochemical correlation sequence (eq. [23]) (139a,188). On the basis of hard-soft acid-base (HSAB) concepts, the thiocyanate displacement probably takes place by direct formation of the phosphoroisothiocyanatidates (155), without the intervention of phosphorothiocyanatidates (159); the hard phosphoryl center is matched with the hard nitrogen site of the ambident thiocyanate ion. However, the thiocyanogen re-



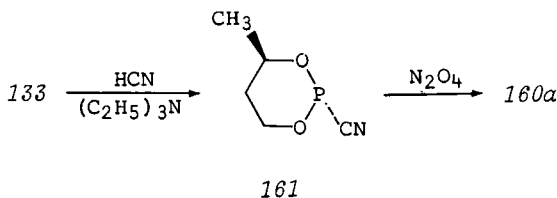


actions probably involved phosphorothiocyanatides (159), arising by nucleophilic attack of the soft phosphinyl anion on the soft sulfur site of $(-\text{SCN})_2$, with a subsequent thiocyno-isothiocyano rearrangement (189). Stereochemical evidence that this rearrangement proceeds by an $\text{S}_{\text{N}}2(\text{P})$ mechanism has been presented (139b). Diastereomeric phosphorothiocyanatides (159) were synthesized by the reaction of silver cyanide with phosphoryl-sulfenyl chlorides of known geometry, developing the stereochemical reaction cycle shown in eq. [24]. Condensation of 158a with AgCN at -15° gave only one phosphorothiocyanatide, 159a (^{31}P NMR), which rapidly isomerized at ambient temperature to a 74:26 mixture of 155b and 155a. The other sulfenyl chloride, 158b, gave a 67:33 mixture of 159b and 159a, which rearranged to mainly 155a. The lack of complete stereospecificity (inversion) in the $\text{RSCN} \rightarrow \text{RNCS}$ process derives from the competing conversion of 155b to 155a. A full disclosure of this work has recently appeared (139c).

Electrophilic substitution of cyanogen chloride on 137b was not stereospecific, producing a mixture of phosphorocyanidates (137b/137a of 94:6 gave 160/160b of 73:27; 137b/137a of 18:82 gave 160/160b of 78:22) (140). Apparently, 160a is thermodynamically more stable than 160b, 160a probably adopting chiefly a chair conformation with equatorial 4-methyl and phosphoryl groups. Oxidation of 161 with N_2O_4 led exclusively to 160a.

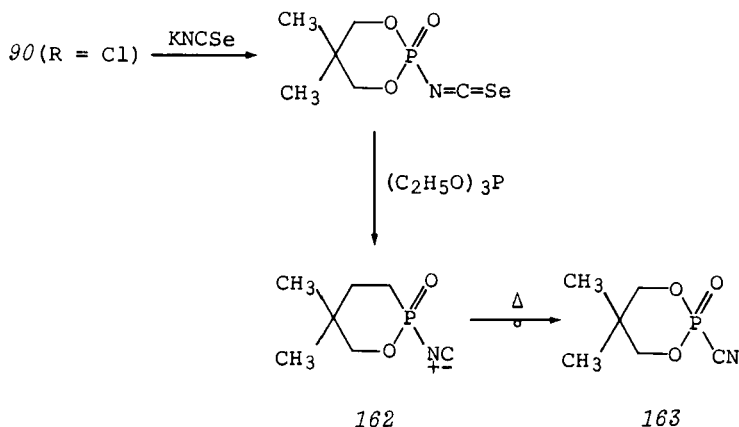


Phosphoroisocyanidate 162 thermally rearranges to the corresponding phosphorocyanidate 163; the stereochemical character of this



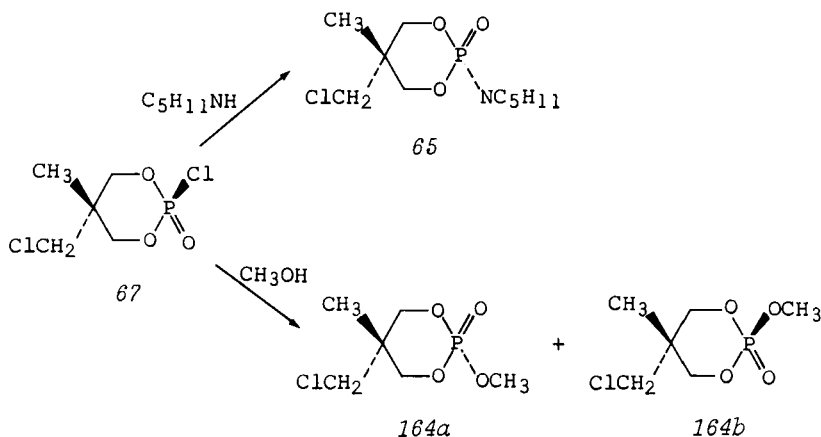
isomerization is still open to question (190).

Attention is now directed to the stereochemistry of nucleophilic substitution reactions at tetracoordinate phosphorus, examples of which have been mentioned in isolated circumstances [e.g., displacement of (1) halide by thiophenoxide, amines,



alkoxide, thiocyanate; (2) thiocyanate and isothiocyanate by thiocyanate ion].

Wadsworth and Horton (74) reported that the displacement of chloride from 67 with piperidine is virtually stereospecific with inversion [first assumed (74) and later established (71b)];



Edmunson made a similar observation (72a). On the contrary, solvolysis of 67 in methanol formed a pair of diastereomeric phosphates, 164a and 164b, in a ratio of 2:1. Methanolysis in the presence of silver nitrate was claimed to produce only one isomer, corresponding to 164a; this result was attributed to an $S_N1(P)$ mechanism involving stereoselective attack of methanol on an intermediate phosphorylium ion. The result without Ag^+ could be interpreted in terms of an $S_N2(P)$ process involving a pentacoordinate species, thus accounting for the lack of stereospecificity. Methanolysis (using $NaHCO_3$) gave essentially pure 164a (inver-

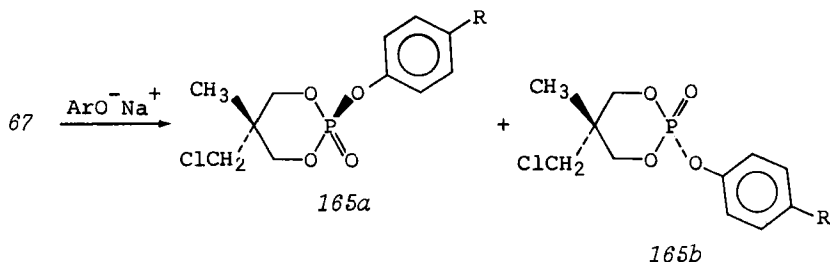
sion). Loss of stereochemical integrity in the methanolysis of *139a* was mentioned in eq. [14] (136b).

Displacement on *67* with different amines yielded only one of the two possible isomers, with inversion of configuration at phosphorus (71b). A sample of vigorously purified *67* was isomerized by LiCl, giving a 2.5:1 mixture (room temperature) of *67* and *70*, respectively. However, other salts (LiClO₄ and LiOTs) were ineffective under the same conditions. Vacuum distillation of pure *67* also caused epimerization to a 2.5:1 mixture, which gave *65* and *66* in a 2.5:1 ratio on treatment with piperidine (71b).

The stereochemical outcome of the reaction of *67* with phenoxide ions is dependent on the basicity of the nucleophile (Table 9) (71b). None of the phenoxy derivatives isomerized alone

Table 9 Stereochemistry of the Reaction of *67* with *para*-Substituted Phenoxide Ions

R	% <i>165a</i>	% <i>165b</i>
OCH ₃	57	43
CH ₃	50	50
H	48	52
Br	36	64
NO ₂	6	94

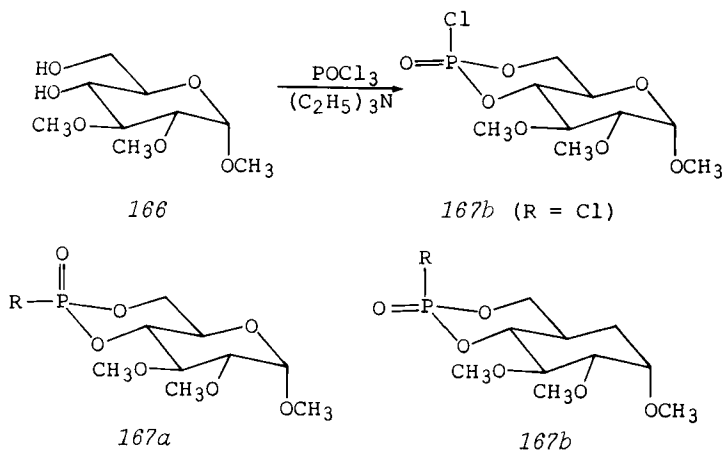


in solution, but *165b* (R = NO₂) was susceptible to epimerization in the presence of sodium *p*-nitrophenoxide, ultimately affording a 2.5:1 mixture of *165a* and *165b* (R = NO₂). Under heterogeneous displacement conditions the proportion of *165a* (retention product) was increased for R = H, NO₂, OCH₃. Treatment of *165b* (R = NO₂) with NaOC₆H₅ gave *165a* and *165b* (R = H) in a 1:3 ratio (predominant retention). Phosphorochloridate *67* underwent substitution with NaSC₆H₅ to give a 10:90 mixture of *cis*- and *trans*-*71*, and treatment of *cis*-*71* with NaOC₆H₅ gave *165b* (almost complete retention) (71b).

Wadsworth and co-workers ultimately downplayed the significance of a dissociative, S_N1(P), mechanism for the displacement

reactions at a phosphoryl center (71b,96), except, perhaps, for the cases of benzoyl, phosphoryl, and 2,4-dinitrophenyl phosphate esters (191). Data on the stereochemical influence of solvent and salt additives have been published (96). Evidently, the stereochemistry of nucleophilic substitution at a phosphoryl center may be complex and thus difficult to interpret satisfactorily. Further study (192) revealed that substitution reactions were dependent on the cation employed, with Li^+ ion causing dramatic stereochemical reversals in the reaction of 67 with $p\text{-CH}_3\text{OC}_6\text{H}_4\text{O}^-$.

Inch and co-workers have investigated the stereochemistry of displacement reactions on novel bicyclic phosphorinanes derived from $\alpha\text{-D-glucopyranoside}$ (138,193,194). On treatment with SbF_3 , 167b (R = Cl) produced a single phosphorofluoridate which



was assigned structure 167b (R = F) (138b), identical to the product from 166 and $\text{Me}_2\text{NP(O)F}_2$ (138b). Treatment of 167b (R = Cl) with ethanol gave a 9:1 mixture of 167a and 167b (R = OC_2H_5), and with dimethylamine gave a 10:1 mixture of 167a and 167b [R = $\text{N}(\text{CH}_3)_2$] (largely inversion) (138). However, 167b (R = Cl) combined with CH_3MgI to give a preponderance of retention at phosphorus, yielding a 1:5 mixture of 167a and 167b (R = CH_3), possibly because of complexation of magnesium with the P=O bond (138). Stereochemical data on some displacement reactions with the phosphoroglycosides are collected in Table 10 (138b). These observations may be compared with those of Wadsworth and co-workers (70,71b,191), Bodkin and Simpson (136b), Stec and co-workers (137,167), and Duff and Trippett (76); again, stereochemical complexity is apparent, being dependent on the particular leaving groups and nucleophiles.

Reaction of 166 with $\text{CH}_3\text{P(O)F}_2$ afforded 167 (R = CH_3) and, with $\text{C}_2\text{H}_5\text{OP(O)Cl}_2$, afforded 167 (R = OC_2H_5) (193). In the reaction with $\text{CH}_3\text{P(O)F}_2$ the ratio of products was time-dependent, starting out at a 1:5 mixture of 167a and 167b (R = CH_3)

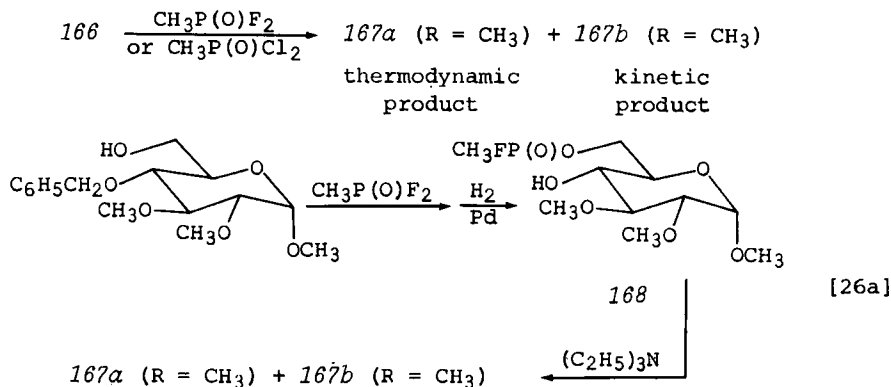
Table 10 Stereochemistry of
Phosphoroglycoside Displacements (138b)

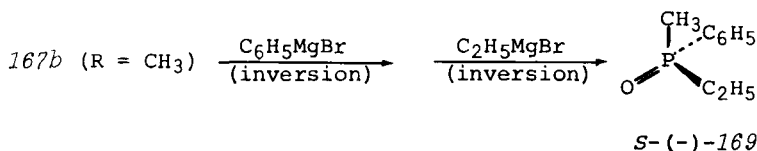
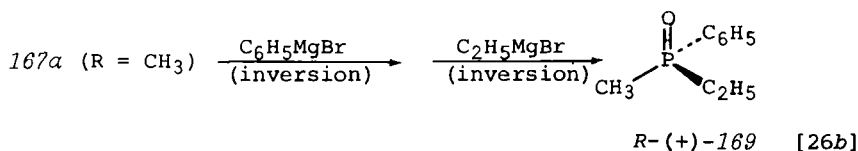
Compound	Reagent	Ratio of Inversion to Retention
167b (R = Cl)	C ₂ H ₅ OH	23
"	C ₂ H ₅ OH/(C ₂ H ₅) ₃ N	>85
"	C ₂ H ₅ OH/C ₂ H ₅ ONa	0.77
"	(CH ₃) ₂ NH	10
"	n-C ₃ H ₇ SNa	11
"	p-NO ₂ C ₆ H ₄ ONa ^a	>60
"	p-NO ₂ C ₆ H ₄ ONa ^b	ca. 0
"	CH ₃ MgI	0.2
167b (R = F)	C ₂ H ₅ OH/C ₂ H ₅ ONa	0.35
"	(CH ₃) ₂ NH	1.77
"	CH ₃ MgI	0.25
167b (R = n-C ₃ H ₇ S)	C ₂ H ₅ OH/C ₂ H ₅ ONa	ca. 0
167b (R = p-NO ₂ C ₆ H ₄ O)	C ₂ H ₅ OH/C ₂ H ₅ ONa	ca. 0
167b [R = N(CH ₃) ₂]	C ₂ H ₅ OH/H ⁺	>100
167a (R = n-C ₃ H ₇ S)	C ₂ H ₅ OH/C ₂ H ₅ ONa	ca. 0
167a (R = p-NO ₂ C ₆ H ₄ O)	C ₂ H ₅ OH/C ₂ H ₅ ONa	0.2
167a [R = N(CH ₃) ₂]	C ₂ H ₅ OH/H ⁺	>100

^aOne equivalent.

^bThree equivalents.

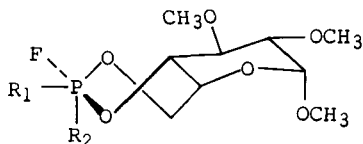
and finally giving an ca. 1:1 mixture. Cyclization experiments with 168 confirmed that 167b (R = CH₃) was a kinetic product (eq. [26a]). At equilibrium the ratio of 167a to 167b (R = CH₃) was 4:3, which provides an estimate of the positional preference of CH₃ vs. P=O in 2-oxo-1,3,2-dioxaphosphorinanes. Since the diastereomers of 168 disappeared at the same rate, the rate of epimerization (at phosphorus) had to be greater than the rate of ring closure to 167 (R = CH₃). In the reaction of 166 with





$\text{C}_2\text{H}_5\text{OP(O)Cl}_2$, 167*a* (R = OC_2H_5) predominated initially, but it eventually rearranged to form mostly 167*b* (R = OC_2H_5). Since there is a commanding axial preference for OC_2H_5 over P=O in 2-oxo-1,3,2-dioxaphosphorinanes, the more rapid generation of 167*a* (R = OC_2H_5) must reflect the disposition of an intervening species, possibly having a nonchair conformation.

Inch and co-workers rationalized their results on intermediate phosphoranes possessing mainly twist-boat conformations (*viz.*, 170). Thus the postulated intermediate leading to less

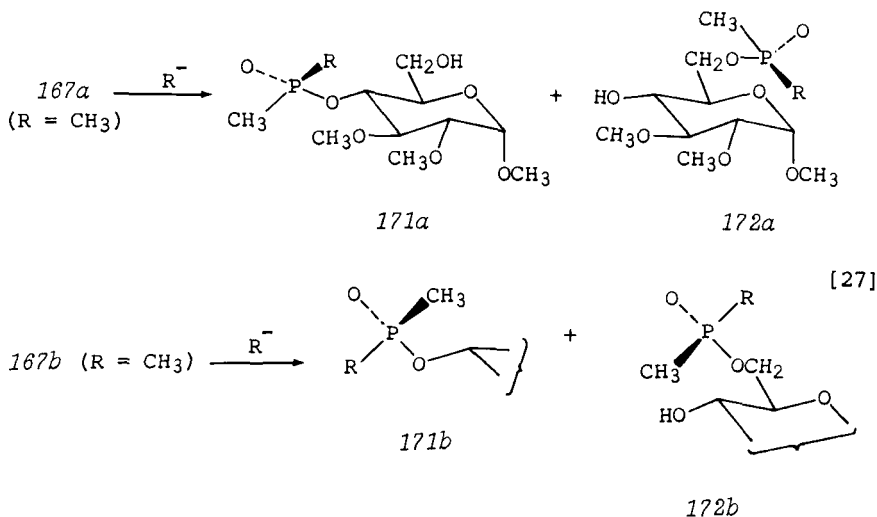


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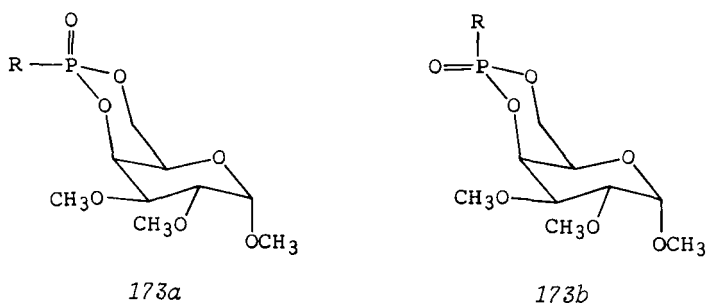
stable 167*b* (R = CH_3) has $\text{R}_1 = \text{CH}_3$ and $\text{R}_2 = \text{O}$ (in 170), with the methyl group in a sterically unhindered pseudoequatorial position. On the other hand the postulated intermediate leading to 167*a* (R = CH_3) would have the *P*-methyl group in a more sterically taxing arrangement. The same argument may be applied to the *P*-ethoxy case.

The phosphorus configurational assignments for 167 (R = CH_3) were verified by transformation of 167*a* and 167*b* (R = CH_3) into highly enantiomerically enriched phosphine oxides, *R*-(+)-169*a* and *S*-(-)-169*a*, respectively (eq. [26*b*]) (194). This constitutes a novel procedure for the synthesis of optically active phosphine oxides, analogous to the menthylphosphinate routes of Mislow and co-workers (195).

Phenylmagnesium bromide causes the cleavage of only the P-O_6 linkage of 167 (R = CH_3) with inversion to give exclusively the 171 pair (R = C_6H_5) (eq. [27]). With methanolic sodium methoxide, ring-opening of 167 (R = CH_3) first occurred by cleavage of the P-O_6 bond with inversion, giving the 171 series (R = OCH_3), followed by eventual transphosphorylation to generate the 172 series (R = OCH_3) (194).

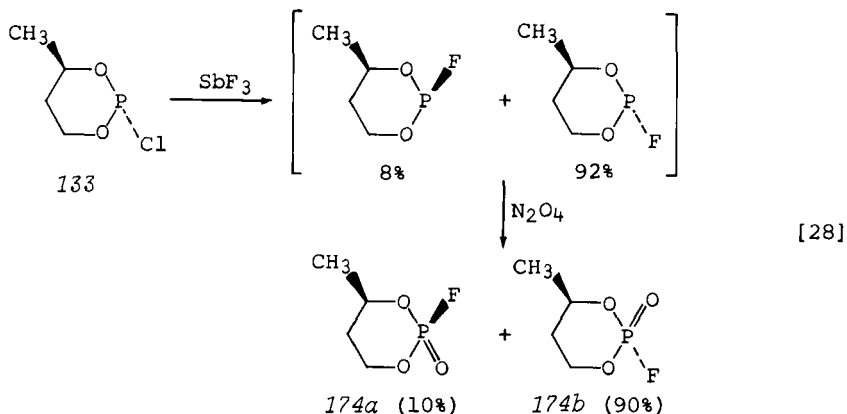


Derivatives of α -D-galactopyranoside (173) were briefly studied by Inch and co-workers (193b). When R is CH₃, 173b is more stable, but 173a is more stable with R = OC₂H₅. In the

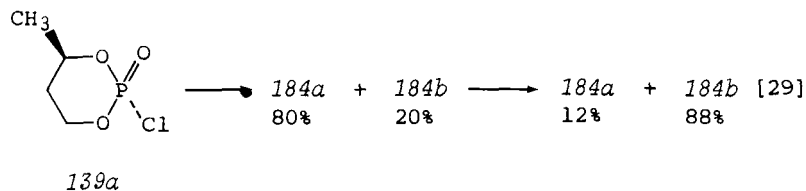


synthesis of the galactopyranoside series (R = CH₃ and OC₂H₅) the less stable diastereomers were kinetically favored. Comparison of the galacto- and glucopyranose series indicates that the stereochemical requirements for the rate of formation and stability of the 1,3,2-dioxaphosphorinane ring are independent of the ring fusion (cis or trans). In a further comparison, while the trans-fused glucose series underwent opening of the 1,3,2-dioxaphosphorinane ring readily with Grignard reagents, the cis-fused galactose series was inert to attack, even under strenuous conditions.

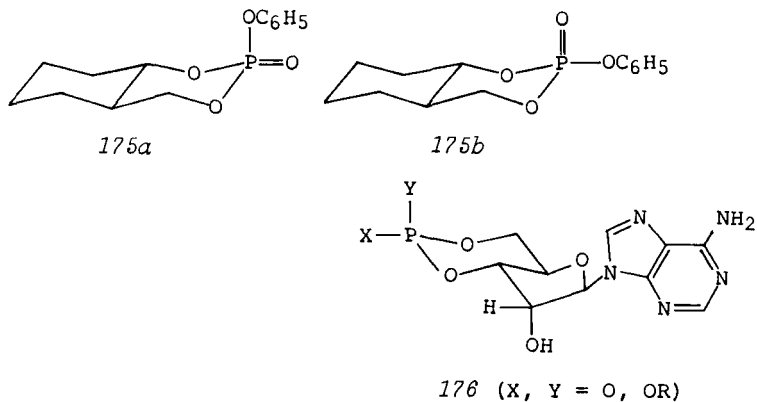
Okruszek and Stec obtained phosphorofluoridates 174a and 174b according to the reaction shown in eq. [28] (141, 196). Nucleophilic substitution on 139a by 1 equiv of NH₄F furnished a mixture enriched in 174a (predominant inversion), but use of



excess NH_4F equilibrated the system (eq. [29]). ^1H NMR data indicated *174b* to be virtually one chair conformation, with an equatorial 4-methyl group, whereas *174a* was conformationally heterogeneous with a large proportion of axial 4-methyl conformer, reflecting the strong preference of fluoro for an axial position vs. a $\text{P}=\text{O}$ bond (141,196).

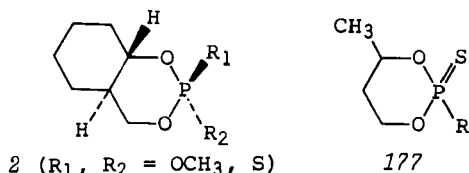


The kinetics of hydroxide-catalyzed hydrolysis of epimeric phosphates *175* supported a stereoelectronic theory for the phosphate ester hydrolysis mechanism (197). The equatorial phenoxy derivative *175b* "hydrolyzes considerably faster" than its axial epimer *175a*. A more extensive rate study, performed by

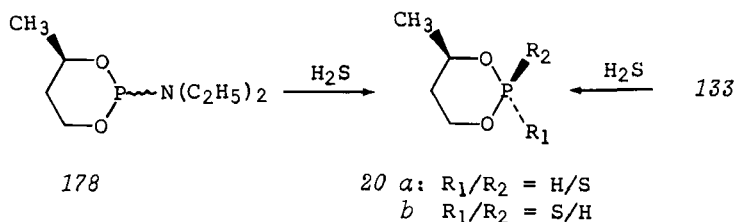


Engels and Schlaeger on epimeric adenosine 3',5'-cyclic phosphates 176, showed stereochemical rate differences in the same direction as seen with 175 (198); further discussion of this work appears in Sect. III-D-1.

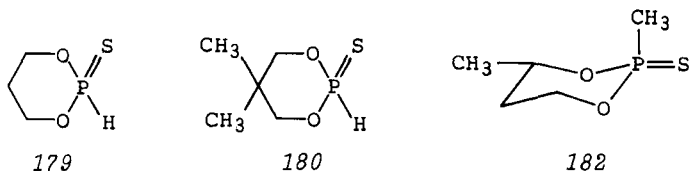
2-Thiono and 2-Seleno Compounds. ^1H NMR data and assignments for the anancomeric derivatives 2 have been published (30). Other anancomeric 2-thiono compounds (177, $\text{R} = \text{C}_6\text{H}_5$, Cl , OC_6H_5) have been described, but no assignment of configuration was offered (119a).



Hydrothiolysis of stereoisomeric mixture 178 gave a single phosphorothioite 20a, whereas the reaction of the corresponding phosphorochloridite gave both isomers of 20 (199). Dipole moment measurements indicated a major chair conformation with the $\text{P}=\text{S}$ group equatorial for 20a and 179 (199).

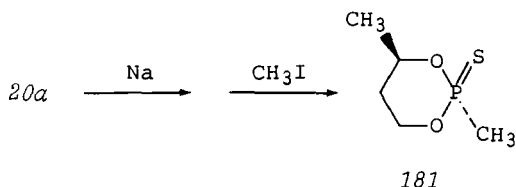


$^1\text{J}_{\text{PH}}$ coupling constants can be a useful criterion for establishing the orientation at phosphorus in compounds having a $\text{P}-\text{H}$ group (200). The $^1\text{J}_{\text{PH}}$ value for 20a is ca. 595 Hz, compared to ca. 635 Hz for 20b, and the former is known to have equatorial $\text{P}=\text{S}$ and axial hydrogen groups. Bartle and co-workers (109) reported $^1\text{J}_{\text{PH}} = 600$ Hz for 180, which implies a preference for an equatorial $\text{P}=\text{S}$ bond.

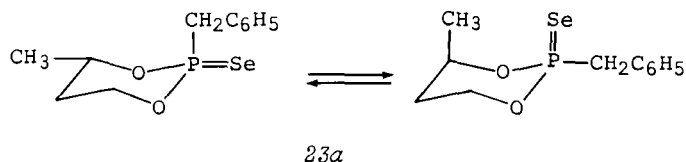


Aminomethylation of 20a occurs stereospecifically (201). The Michaelis-Becker reaction of 20a with CH_3I produced a single compound (181) (201), with the same dipole moment as the material supplied from the condensation of 1,3-butanediol and

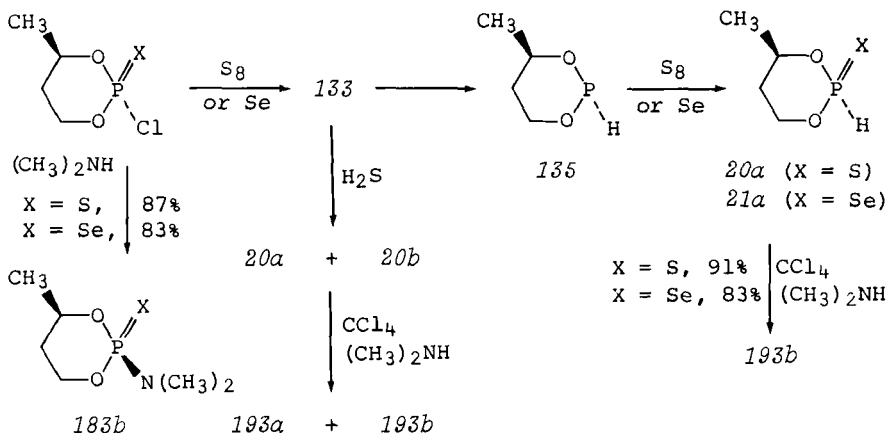
$\text{CH}_3\text{P}(\text{S})\text{Cl}_2$ (151a); thus the Michaelis-Becker reaction is allegedly stereospecific with retention. The conformational distribution for 181 was estimated to be ca. 80% 182, which has the less stable disposition of substituents about phosphorus (see Sect.



III-B-1-b) (151). A considerable population of the conformer with axial 4-methyl and seleno groups was indicated for 23a by the $^4\text{J}_{\text{POCCH}_3}$ value of only 1.0 Hz (in CDCl_3) (40); the other isomer, 23b, was virtually one chair conformer with equatorial 4-methyl and benzyl groups.

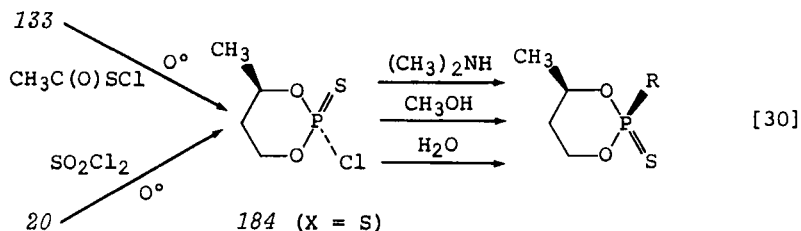


Stec and co-workers (202) prepared 20a and its seleno analog 21a from 135. Reaction of phosphorochloridite 133 with H_2S afforded a mixture of isomers of 20, which in turn supplied a mixture of 183 (X = S) on treatment with CCl_4 and $(\text{CH}_3)_2\text{NH}$ net inversion) (202). Reaction of isomerically pure 20a with CCl_4 and $(\text{CH}_3)_2\text{NH}$ proceeds with 91% inversion, giving 183b. A similar chemical correlation was performed on the 2-seleno ana-



logues. The CCl_4 -amine reaction was also described by a Russian group (203), who extended the process concept into a stereospecific synthesis of aryl thiophosphate derivatives (the direction of the steric course was not mentioned) (203).

Diastereomerically pure *184* ($X = S$), prepared by two methods (eq. [30]), was shown by ^1H NMR to have a chair conformation with equatorial 4-methyl and $\text{P}=\text{S}$ groups (204). Alkaline hydrolysis, aminolysis, and methanolysis of *184* ($X = S$) occurred predominantly with inversion (92 to 100%).



Wadsworth and Tsay suggested that *185a* and *185b* ($R = \text{Cl}$) favor a chair conformation with equatorial $\text{P}=\text{S}$ bonds (205). Nucleophilic substitution on *185b* ($R = \text{Cl}$) by phenoxides varied in steric direction: inversion decreased with the basicity of the nucleophile (Table 11). In contrast, treatment of various *cis*-arylthiophosphates *185a* ($R = \text{OAr}$) with sodium 4-methylphenoxide resulted in nearly complete retention (>95%, $\text{OAr} = \text{OC}_6\text{H}_5$,

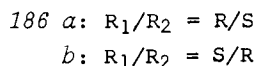
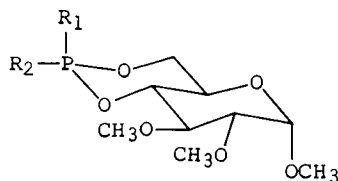
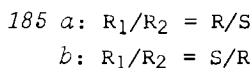
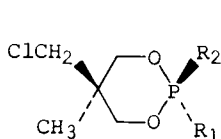
Table 11 Stereochemistry of Displacement Reactions of *185b*

Phenoxide	% Trans (retention)	% Cis (inversion)
4-OCH ₃	50	50
4-CH ₃	40	60
4-Br	24	76
4-NO ₂	5	95

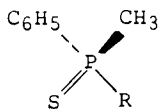
4-BrC₆H₄O, 4-NO₂C₆H₄O). In the displacement reactions of *185b* ($R = \text{Cl}$) and *185a* ($R = 4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$) added salts had a dramatic effect on the stereochemical outcome. The results on the 2-thiono system generally paralleled those for the 2-oxo system; however, equilibration of isomeric pairs *185* ($R = \text{Cl}$, 4-NO₂C₆H₄O) was much less facile. Nevertheless, the 4-NO₂ compound was equilibrated to a 6:1 ratio (*185a* and *185b*); equilibrium composition in the corresponding 2-oxo system was ca. 2.5:1 (*185a* and *185b*), within the same net stereochemical bias.

Substitution reactions with fused 2-thiono-1,3,2-dioxaphos-

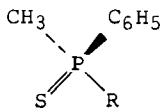
phorinanes *186* have been reported (138b,194,206). Configurational assignments of thiones *186* ($R = \text{CH}_3, \text{C}_6\text{H}_5, \text{OC}_2\text{H}_5$) were obtained through correlation with the 2-oxo series via oxidation (207) with *m*-chloroperbenzoic acid (206). Ethanolysis of *186a* ($R = \text{Cl}$) took place with predominant inversion but, when sodium ethoxide was added, mostly retention was observed (138b).



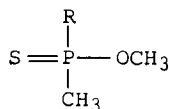
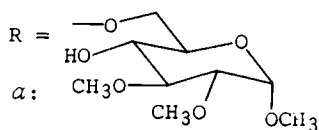
Reaction of *186a* ($R = \text{CH}_3$) with $\text{C}_6\text{H}_5\text{MgBr}$ resulted in two ring-opened products, *187a* and *188b* (both with inversion at phosphorus), in a ratio of ca. 4:3. Diastereomer *186b* ($R = \text{CH}_3$) gave only one product with retention, *188b* (194). Reaction of *186a* ($R = \text{C}_6\text{H}_5$) with CH_3MgI afforded one ring-opened derivative (*187b*) with inversion; whereas *186b* ($R = \text{C}_6\text{H}_5$) gave two products with retention, *187b* and *188a*, in a ratio of ca. 7:1 (194). Methanolysis of *186* ($R = \text{CH}_3, \text{C}_6\text{H}_5$) first resulted largely in formation of the ring-opened compounds *189b* and *190b*, followed by migration of the phosphoryl moiety from O_4 to O_6 , giving *189a* and *190a*. In the methanolyses the *186b* series reacted more slowly,



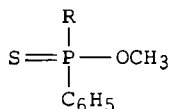
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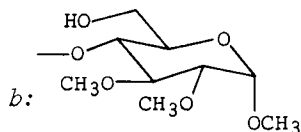
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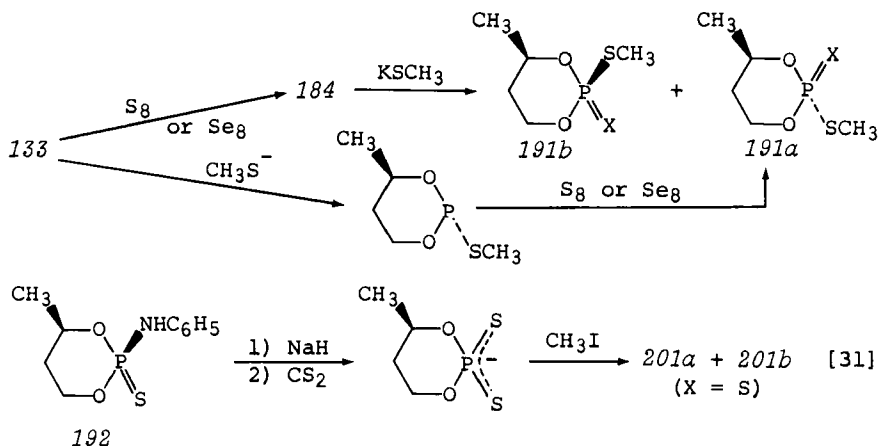


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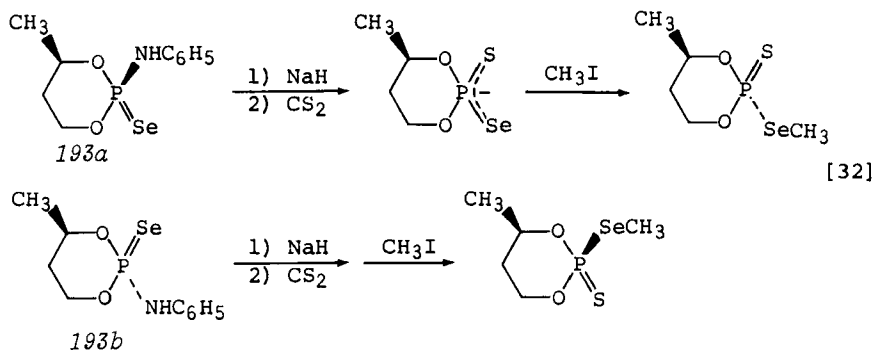


ly, and underwent transphosphorylation more rapidly, than did the *186a* series. Methanolyses and transphosphorylation tentatively occur chiefly by inversion of configuration at phosphorus (194).

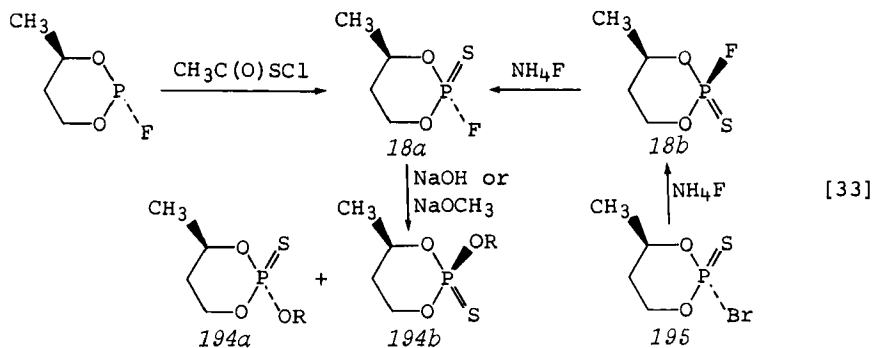
Displacement on *184* ($X = \text{S}, \text{Se}$) with methylmercaptide occurred with net inversion, giving a *191a*/*191b* ratio of ca. 65:35 (183). A 69:31 mixture of *191a* and *191b* ($X = \text{S}$) was obtained from *192* via a novel amide cleavage procedure, followed by



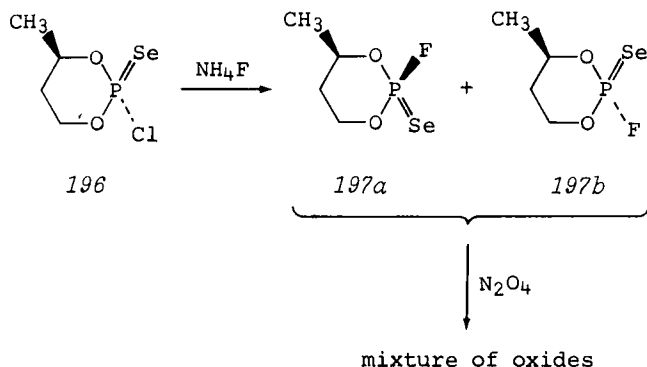
methylation (eq. [31]) (182). Performance of the same sequence on *193a* and *193b* resulted in alkylation *only on selenium* in a stereospecific conversion (retention) (eq. [32]).



Although *184* ($X = S$) and its bromo analogue *195* experience nucleophilic displacement (e.g., with methoxide) with complete inversion of configuration at phosphorus, the corresponding fluoro compound *18a* mainly reacts with retention when subjected to hydroxide or methoxide (eq. [33]) (37). With hydroxide the ratio of *194a* and *194b* ($R = H$) was 35:65, and with methoxide the



ratio of *194a* and *194b* ($R = \text{CH}_3$) was 16:84. The poorer leaving group, fluoride, may have conferred a longer lifetime to a pentacoordinate intermediate, allowing time for permutational isomerization to compete effectively. Equilibration of *171b* with NH_4F afforded a final *18a/18b* ratio of 83:17. Reaction of *195*

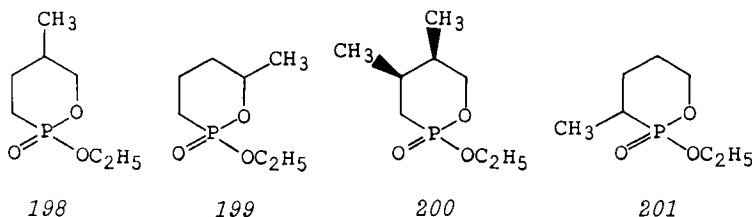


(37) and *196* (141) with NH_4F occurred with ca. 80 to 85% inversion (possibly greater because of fluoride-induced epimerization). Equilibration of an 80:20 mixture of *197a* and *197b* with NH_4F gave a 15:85 final mixture, comparable to the result obtained for the 2-thiono system. Thus the 2-fluoro group has a strong axial predilection against $\text{P}=\text{S}$ and $\text{P}=\text{Se}$, as well as against $\text{P}=\text{O}$ (Sect. III-B-1-a).

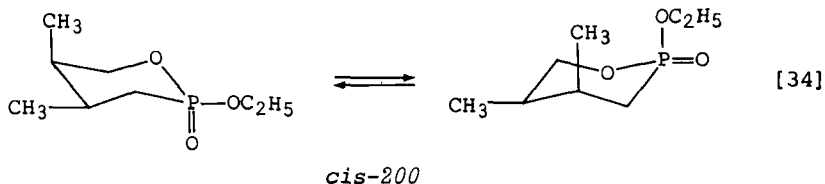
C. Other Phosphorinane Systems

1. 1,2-Oxaphosphorinanes

The *cis* and *trans* isomers of *198* and *199* were initially assigned (208) structures based on the modified Auwers-Skita rule (209). The presence of two phosphoryl IR maxima for *trans-198* and *cis-199* suggested conformational mixtures, whereas *cis-198* and *trans-199* were ostensibly a preponderance of one chair form, probably with axial ethoxy groups. ^1H NMR data implied that *cis-* and *trans-199* differ mainly by a change in orientation about the phosphorus atom, the 6-methyl group constantly occupying an equatorial position (210). Equilibration of the isomers

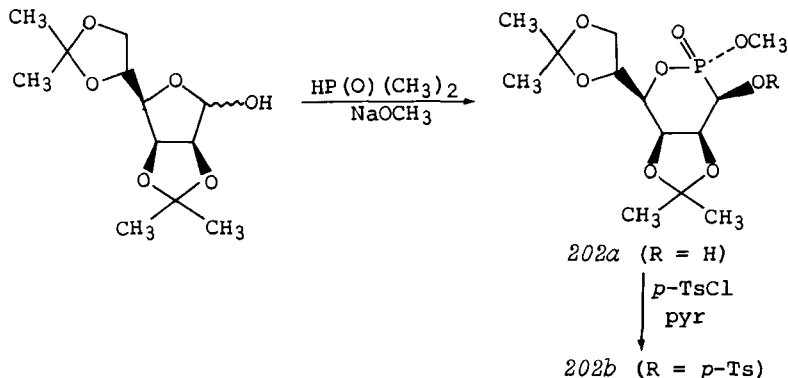


of *199*, with CF_3COOH , demonstrated *trans-199* to be more stable ($-\Delta H^\circ = 1.50 \pm 0.15$ kcal/mol, $-\Delta G_{180^\circ}^\circ = \text{ca. } 0.5$ kcal/mol) (210a). Additional data supported this description for the isomers of *198* (211). Although *cis-198* was suggested to be a mixture of conformers, no change in its ^1H NMR spectrum was recorded from -60° to $+120^\circ$. Equilibration of *cis-* and *trans-198* showed that the *cis* isomer is more stable by 0.3 kcal/mol. The *cis* isomer of *200* appeared to be a mixture of two chair conformers (eq. [34]), while the *trans* isomer is mostly one chair form, but the evidence presented is not conclusive (212a). Equilibration of *cis-* and *trans-200* indicated that the *trans* isomer is more stable ($-\Delta H^\circ = 0.9 \pm 0.1$ kcal/mol, $\Delta G_{180^\circ}^\circ = \text{ca. } 0.5$ kcal/mol).



The *cis* and *trans* isomers of *201* were suggested to have the same arrangement of substituents on phosphorus, thus differing in their methyl orientation. Equilibration gave a 1:1 mixture, signifying equal stability ($\Delta H = 0$) for the isomers. The lack of change in the ^1H NMR spectra for the *201* isomers showed that one conformation was strongly favored, presumably the one having an axial ethoxy group (212b).

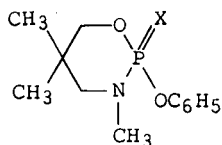
X-Ray analysis of *202b* revealed two types of structures for the 1,2-oxaphosphorinane ring in the unit cell: a nearly ideal boat conformation and a skew-boat conformation. The phosphoryl oxygen was found in a pseudoaxial position (213). The conformation in solution for *202b* and *202a* was claimed to be a slightly distorted boat structure (270-MHz ^1H NMR) (213). A twist-boat conformation was observed for *48a* and *48b* in the solid state, and for *48a* in solution (see Sect. III-C-4).



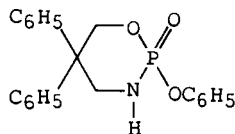
2. 1,3,2-Oxazaphosphorinanes

The 1,3,2-oxazaphosphorinane ring system is found in the anticancer agent cyclophosphamide, which is discussed in Sect. III-D-2.

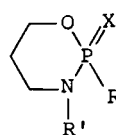
Navech and co-workers have studied this ring system spectroscopically (53,54,118,214). Analysis of ^1H NMR spectral data revealed a strong conformational preference for one chair form for 203a ($\text{X} = \text{O}, \text{S}$) (53). IR data ($\nu_{\text{max}} \text{P}=\text{O}$) for 203a ($\text{X} = \text{O}$), 203b ($\text{X} = \text{O}$), and 204 ($\text{R}' = \text{CH}_2\text{C}_6\text{H}_5$, $\text{R} = \text{C}_6\text{H}_5$, $\text{X} = \text{O}$; $\text{R}' = \text{H}$, $\text{R} = \text{C}_6\text{H}_5\text{O}$, $\text{X} = \text{O}$) were interpreted in terms of chair conformers with a preferential axial phenoxy group for 3° nitrogen compounds and equatorial phenoxy group 2° nitrogen compounds (214a). In other, unbiased derivatives having a 3° nitrogen, phenoxy and ethoxy were assigned axial, while dialkylamino was assigned an equatorial orientational preference vs. the $\text{P}=\text{O}$ bond.



203a

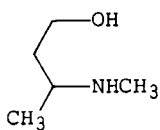


203b

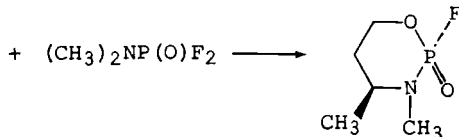


204

Condensation of 205 with $(\text{CH}_3)_2\text{NP}(\text{O})\text{F}_2$ supplied one cyclic product, 206, assigned a trans structure, chiefly a chair conformation with equatorial 4-methyl and phosphoryl groups (196). The orientation of the *N*-methyl group was not addressed.

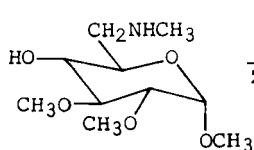


205

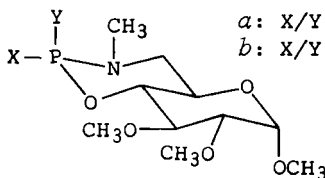
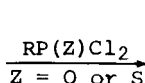


206

Aminoglycoside 207 was converted into a series of fused 1,3,2-oxazaphosphorinanes, 208 ($\text{R} = \text{CH}_3$, C_6H_5 , Cl , OR' ; $\text{Z} = \text{O}$ or S) (215). In the $\text{CH}_3\text{P}(\text{O})\text{Cl}_2$ reaction mainly 208b ($\text{R} = \text{CH}_3$, $\text{Z} = \text{O}$) was initially produced, but on prolonged heating it was con-



207



208

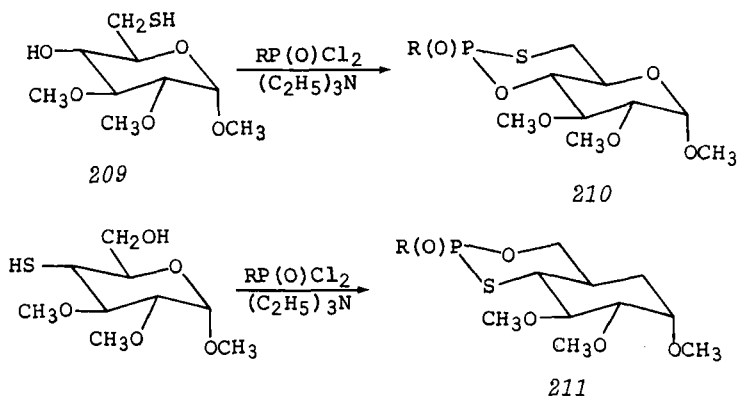
a: $\text{X/Y} = \text{R/O}$ or S
b: $\text{X/Y} = \text{O}$ or S/R

verted to a mixture having of a 1.3:1 ratio of *208b* and *208a* ($R = \text{CH}_3$, $Z = \text{O}$), respectively. This result is comparable to that seen with the related 1,3,2-dioxaphosphorinane analog (138b). A 4:3 ratio of *208b* to *208a* ($R = \text{C}_6\text{H}_5$, $Z = \text{O}$) was produced using $\text{C}_6\text{H}_5\text{P}(\text{O})\text{Cl}_2$ and *207*; $\text{CH}_3\text{P}(\text{S})\text{Cl}_2$ gave a 5:1 mixture of *208a* ($R = \text{CH}_3$, $Z = \text{S}$). Only one isomer was detected with POCl_3 and PSCl_3 , *208b* ($R = \text{Cl}$, $Z = \text{O}$ or S).

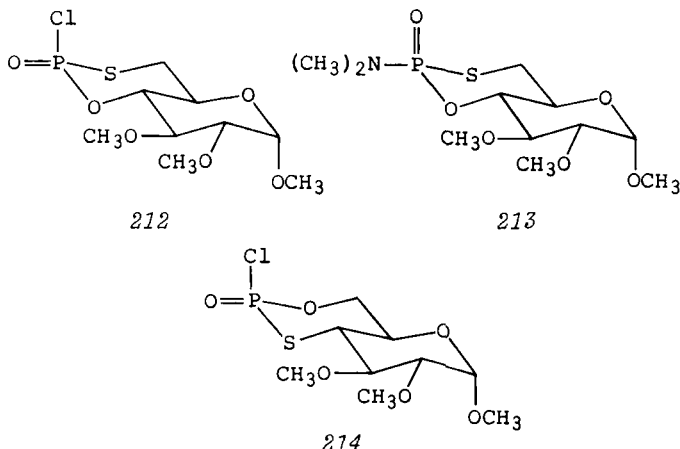
Treatment of *208b* ($R = \text{Cl}$, $Z = \text{O}$) with NaOCH_3 in CH_3OH , NaOC_2H_5 in $\text{C}_2\text{H}_5\text{OH}$, and $\text{NaO-}n\text{-C}_3\text{H}_7$ in $n\text{-C}_3\text{H}_7\text{OH}$ formed solely the isomers of inversion at phosphorus, that is, *208a* ($R = \text{OR}'$, $Z = \text{O}$); *208b* ($R = \text{Cl}$, $Z = \text{S}$) behaved similarly. The action of sodium 4-nitrophenoxide, at room temperature, on *208b* ($R = \text{Cl}$, $Z = \text{O}$) gave rise to one product, *208a* ($R = 4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$, $Z = \text{O}$), but heating of the product with excess reagent generated the epimeric phosphoramidate, *208b* ($R = 4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$, $Z = \text{O}$). Although *208b* ($R = 4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$, $Z = \text{O}$) and NaOCH_3 reacted with complete inversion, *208a* ($R = 4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$, $Z = \text{O}$) gave only ca. 85% inversion. It should be noted that Harrison and co-workers (215) relied on two assumptions for stereochemical assignments: (1) the chloro and more stable $4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$ derivatives had equatorial $\text{P}=\text{O}$ bonds, and (2) the displacement of chloride by $\text{NaOC}_6\text{H}_4\text{-4-NO}_2$ proceeded with inversion. Ring-opening reactions were studied but these will not be described herein (215,216).

3. 1,3,2-Oxathiaphosphorinanes

Stereochemical studies on 1,3,2-oxathiaphosphorinanes have been limited (138b,193,206). Pairs of diastereomers of *210* and *211* ($R = \text{CH}_3$, OC_2H_5) were tentatively assigned structures based on comparisons of IR phosphoryl stretching frequencies and ^{31}P NMR chemical shifts, in analogy with the corresponding 1,3,2-dioxaphosphorinanes (206). ^1H NMR data indicated that the 1,3,2-oxathiaphosphorinane rings assume a chair conformation. Other derivatives of *210* and *211* [$R = \text{Cl}$, $(\text{CH}_3)_2\text{N}$, and $4\text{-NO}_2\text{C}_6\text{H}_4\text{O}$]



have been reported (138b). In the condensation of 209 with POCl_3 only one phosphorochloridate, assigned structure 212, was found. Treatment of 212 with $(\text{CH}_3)_2\text{NH}$ yielded only one phosphoramidate, 213, the product of inversion. Simple ethanolysis of 212 and 213 gave only inversion products; but in the ethanolysis of 213 catalyzed by $(\text{C}_2\text{H}_5)_3\text{N}$ or NaOC_2H_5 only retention was observed, presumably because of thermodynamic control in this latter process.



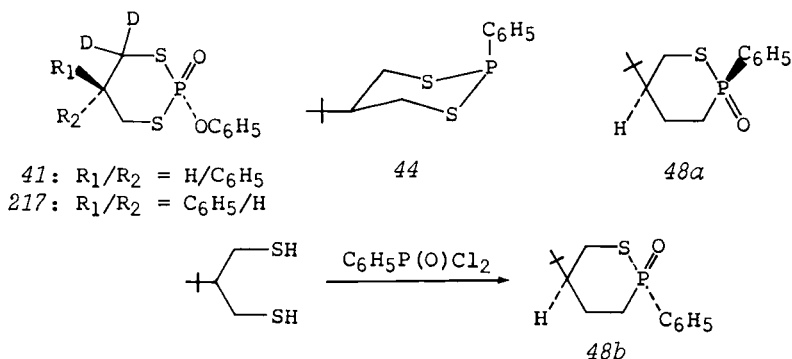
In the reaction of 212 with $\text{NaOC}_6\text{H}_4\text{-4-NO}_2$, one equivalent of reagent gave clean inversion, whereas excess reagent led to retention, the latter conversion affording the allegedly more stable axial phenoxy derivative. In a similar fashion phosphorochloridate 214 (138b) reacted with ethanol, giving inversion at phosphorus.

Ring-opening 215b with $\text{C}_6\text{H}_5\text{MgBr}$ occurred with both P-O and P-S bond cleavage (195). The phosphorus stereochemistry in the products from P-O fission could not be assigned, but the P-S fission was determined to occur with retention, as seen in an acyclic analogy (217). The ring-opening reactions of 215 with oxygen nucleophiles (methoxide and phenoxide) took place first by P-O bond cleavage. The methoxide reactions eventually gave rise to phosphoryl transfer from sulfur to the neighboring oxygen, as well as hydrolysis to 209 and $(\text{CH}_3\text{O})_2\text{P}(\text{O})\text{CH}_3$; the phenoxide reaction did not result in transphosphorylation. The phosphoryl exchange was not stereospecific, but proceeded chiefly with inversion. Ring-opening of the diastereomers of 210 ($\text{R} = \text{OC}_2\text{H}_5$) with NaOCH_3 and NaOC_6H_5 occurred only with P-S bond fission. The equatorial OC_2H_5 diastereomer produced only 216a (complete inversion); the axial OC_2H_5 diastereomer cleaved with net inversion at phosphorus, giving 216b.

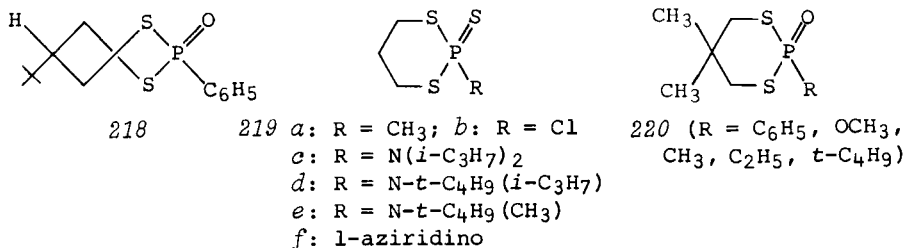
An interesting transformation of 2-thio-1,3,2-dioxophosphorinanes into 2-oxo-1,3,2-oxathiaphosphorinanes (eq. [35]) has been reported (218), but stereochemical aspects of this reaction were not explored.

intervention of a twist form in the conformational equilibrium for 217, a view fortified by the following discussion concerning 48a and 48b.

Stereospecific oxidation of 44 with 3% H₂O₂ furnished 48a (49), verifying the original assignment of configuration for 44 (47). The configuration of 48a was established by ¹H NMR data (49) and, more recently, by X-ray analysis (220). The configuration of diastereomer 48b, obtained as the major product from direct condensation (49), was also determined from ¹H NMR (49) and X-ray (220) data. Although 48b adopts essentially one chair conformation (>90%) with equatorial 5-*t*-butyl and 2-phenyl substituents, 48a is substantially conformationally heterogeneous. The conformational equilibrium for 48a was interpreted as a mixture of a chair conformer with equatorial *t*-butyl and axial phenyl groups, and a twist form (218); the NMR data suggested very little contribution of the chair form with an axial *t*-butyl



group. Complexation of 48a with Eu(fod)₃ had no significant influence on the conformational distribution (49), in contrast to observations made by Bentrude and co-workers for the related 2-oxo-1,3,2-dioxaphosphorinane system (91b,129,130). A parallelism may be drawn between the isomers of 48 and the isomeric pair 41 and 217, mentioned above.



Evidently, the introduction of proximate sulfur and phosphorus atoms into a cyclohexane ring significantly lowers the chair-boat free-energy difference, such that twist forms may substantially populate the conformational equilibria. A comparison of chair-boat energy differences (ΔG°) for cyclohexane (ca. 5.3 kcal/mol) (221), 1,3-dioxane (ca. 8.3 kcal/mol) (114), and 1,3-dithiane (ca. 1.7 kcal/mol) (222) clearly reflects this

behavior. Furthermore, the chair-boat energy difference for 109, which corresponds to insertion of a phosphorus atom into a 1,3-dioxane ring, may be as low as 1.0 kcal/mol (91); that for tricoordinate derivative 13b is ca. 1.5 to 2.0 kcal/mol (35). Extrapolation of this information to 2-oxo-1,3,2-dithiaphosphorinanes (e.g., 48) points to a further reduction in ΔG° (chair-boat) in this system. Indeed, X-ray determinations for 48a and 48b revealed that both molecules adopt twist conformations in the solid state (220), an unprecedented observation which suggests that such rings have ready access to the twist arrangement. On the other hand tricoordinate compound 44 adopts a chair conformation (as shown) in the solid state, as do the 2-thiones 219a and 219b (P=S bond equatorial) (223), 219c (P=S bond axial) (224), and 219f (P=S bond equatorial) (224b). Derivatives 219c, 219d, and 219e apparently prefer a single chair conformation in solution (224a). 1,3,2-Dioxaphosphorinane 116a, related to 48a, adopts a chair conformation with axial 5-t-butyl and equatorial 2-t-butyl groups in the solid state, whereas 116b adopts a chair conformation with equatorial 5-t-butyl and axial 2-phenyl groups (102b).

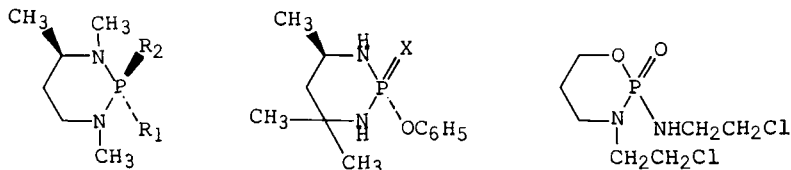
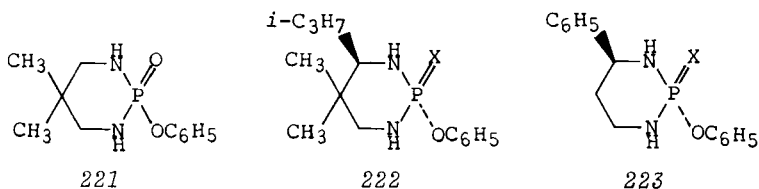
^1H NMR spectral data for a series of 2-oxo-1,3,2-dithiaphosphorinanes (220) displayed nonequivalent 5,5-dimethyl groups, indicative of a bias toward one chair form (51). Displacement of conformational equilibrium with solvent (as indicated by solvent-dependent $^3J_{\text{PSC H}}$ values) was noted, but no clear conclusions could be drawn regarding the intervention of twist forms. However, the near equivalency of the two $^3J_{\text{PSC H}}$ values for 220 ($\text{R} = \text{C}_6\text{H}_5$, alkyl) suggested an averaging in the conformational equilibria (i.e., a mixture of chair and/or twist forms) (225). ^1H NMR data for a series of 2-thiono-1,3,2-dithiaphosphorinanes have been reported (226b).

Examples of unconstrained, saturated six-membered-ring compounds (lacking trigonal atoms) that adopt flexible twist conformations in preference to the chair forms are rare; however, a few exceptions to the chair preference have been noted (227-229).

5. 1,3,2-Diazaphosphorinanes

On the basis of IR spectral evidence Navech and co-workers (118,230) suggested that the preferred conformation of 221 ($\text{R} = \text{H}$, CH_3) and some of its congeners (222-224, $\text{X} = \text{O}$) (presumed to be chair structures) was that with an axial P=O bond. The $^3J_{\text{PNCH}}$ values seemed to support the chair assignments but permitted no conclusion regarding the orientation of groups on phosphorus. The 2-thiono compounds were analogized to the 2-oxo series.

Isomeric mixtures of 225a and 225b [$\text{R} = \text{OCH}_3$, $\text{N}(\text{CH}_3)_2$] were analyzed by $\delta^{31}\text{P}$ and IR data (231). Assuming equatorial 4-methyl groups, 225a and 225b were claimed to differ in the disposition of substituents on phosphorus. Conformational aspects involving



225 a: $R_1/R_2 = R/O$

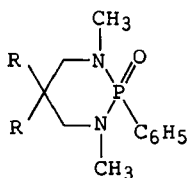
b: $R_1/R_2 = O/R$

the nitrogen stereocenters were not considered (231), although the possibility exists that the nitrogen atoms are planar, as seen for the ring nitrogen in the X-ray crystal structure of isophosphamide (226) (232).

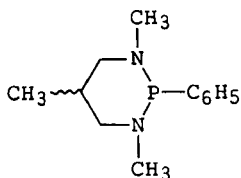
Fluoro derivatives 225a and 225b ($R = F$) were prepared by Amos and co-workers (196). The isomer ratio of the mixture produced from the 1,3-diamine and $(CH_3)_2NP(O)F_2$ was unaltered after equilibration with fluoride, suggesting that the condensation is probably thermodynamically controlled. In comparison, a mixture of isomers was not obtained in the preparation of oxaza analog 206. An axial fluoro orientation for both isomers of 186 ($R = F$) was proposed ($^2J_{PF}$ and IR data), which, if valid, implies that a 4-methyl group is not an effective biasing substituent. Interestingly, the N,N' -dimethyl groups in each isomer were assigned different orientations (one axial, one equatorial) on the basis of different $^4J_{FPNCH_3}$ values for the anisochronous N,N' -methyl resonances.

The ^1H NMR spectrum for 227 ($R = CH_3$) showed isochronous *gem*-dimethyl groups and an average ring methylene region; the ^1H NMR spectrum for 227 ($R = H$) was similar (233). Oxidation of isomeric mixture 38 (ca. 1:1) with H_2O_2 gave 228 as a mixture of isomers, but the ^1H NMR spectrum for 228 showed only one 5-methyl doublet and a deceptively simple ring methylene region. Tentatively, 227 ($R = H$ and CH_3) and 228 appear to be NMR averaged, implying that they are an unbiased mixture of chair forms, a twist or boat-type structure, or a combination of these two possibilities. It is noteworthy that similar ^1H NMR observations have been recorded with the analogous 2-phenyl-1,3,2-diazaboracyclohexanes, which probably have nearly planar nitrogen atoms (234).

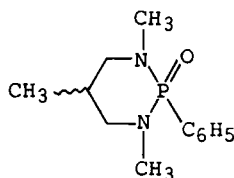
The structural information available thus far on the 2-oxo-1,3,2-diazaphosphorinanes should be regarded as highly tentative until additional careful and systematic studies appear in print.



227



38

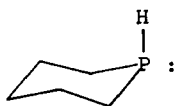


228

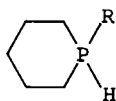
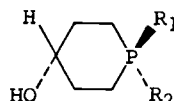
6. Phosphorinanes (235)

The conformational preference of the *N*-proton in piperidine has been the object of intense interest and controversy for many years (26). Although an axial *N*-H group was claimed to be the more stable conformation (26,236), Anet and Yavari (237) recently have proved that the equatorial *N*-H conformation predominates (at least at ca. -150°).

Extension of work (236) to phosphorinane (229), the phosphorus analog of piperidine, revealed that the proton in 229 was strongly favored in the axial position of a chair structure (as shown). More information on the tricoordinate system is present-

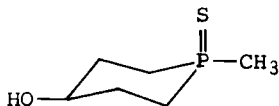


229

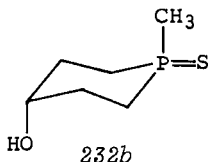
230 a: R = S
b: R = CH₃231 a: R₁/R₂ = CH₃/S
b: R₁/R₂ = S/CH₃

ed in Sect. IV. Sulfide 230 was also assigned a chair conformation with axial P-H; however, no conclusions could be offered on methiodide 230b (236).

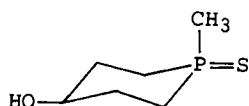
A large group of phosphorinane-1-sulfides has been studied by Quin and co-workers (43a,43d,238a,b). X-Ray analysis of 231a revealed that both possible chair conformations 232a and 232b exist in the crystal, in a ratio of 2:1--an unusual observation



232a

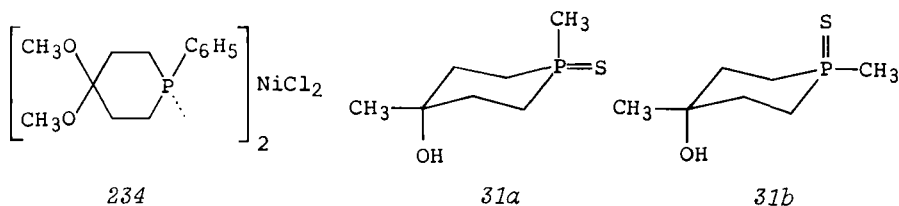


232b



233

in conformational studies of simple saturated ring systems (43d, 238a). The other sulfide, 231b, had conformation 233 in the solid state (43d,238a). X-Ray analyses of the 4-methyl analogues, 31a and 31b, showed single chair conformations with axial 4-hydroxy groups and a different arrangement of groups on phosphorus (43d,238a). An X-ray analysis of the trans square-planar complex 234 showed both phosphorinane rings in a chair conforma-

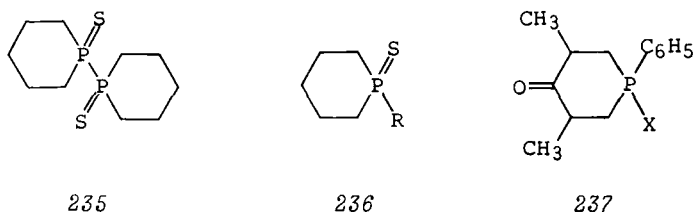


tion; however, the phenyl groups were oriented differently in each ligand: axial in one and equatorial in the other (239). The co-occurrence of two different chair conformations in the solid state points to a relatively small energy difference between the two forms in question (≤ 1 kcal/mol). Both phosphorinane rings of 235 have a chair conformation with the P=S bond oriented axially, in the solid state (239b).

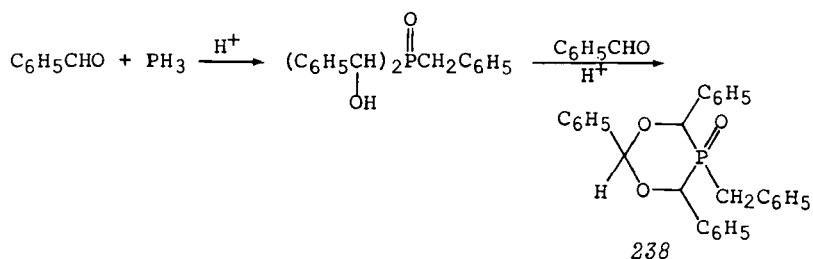
^{13}C NMR chemical shift data for 238 [R = CH₃, C₂H₅, (CH₃)₃C, C₆H₅] support a preponderance of a chair conformer with an equatorial R group (43a, 238a); X-ray analysis of 236 (R = CH₃) shows a chair structure with the methyl group equatorial (238b, 238c).

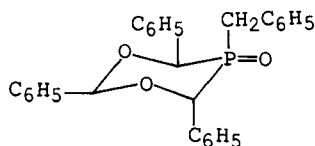
Although some phosphorinane-1-oxides were prepared (238a), the conformational properties of these compounds remain largely unreported. However, some conformationally biased 1-oxide derivatives have been discussed (238b).

Equilibration studies on 237 (X = lone pair, O, S, Se) have appeared, along with a discussion of the relative stability of the three isolable diastereomers (240a).

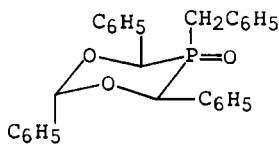


Two of the eight possible diastereomers of 238 were isolated by Pepperman and Siddall (240b), and assigned structures 239a and 239b based on ^1H NMR data.



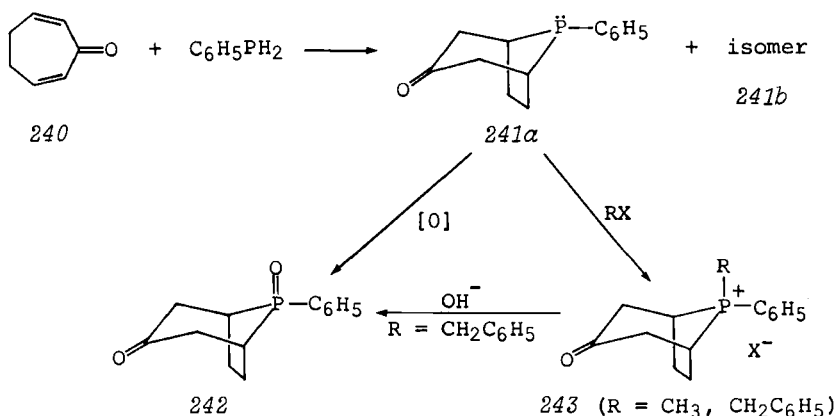


239a

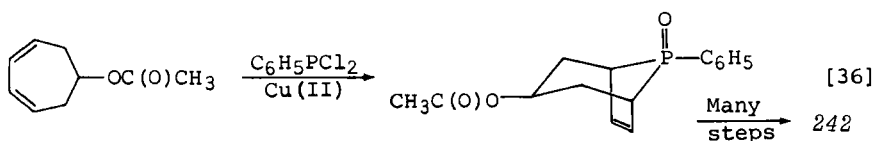


239b

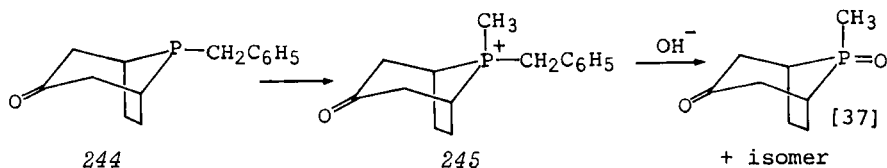
Condensation of 240 with $\text{C}_6\text{H}_5\text{PH}_2$ afforded two epimeric, bridged phosphorinanes (241), of which 241a greatly predominated (244). Oxidation of 241a with H_2O_2 gave 242, which was also obtained by benzylation of 241 and subsequent alkaline fragmenta-



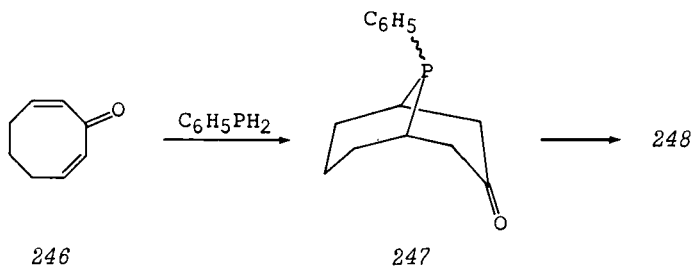
tion of 243 (with 90% retention). An independent synthesis of 242 involved the process outlined in eq. [36]. Benzyl phosphine 244 was quaternized, and basic hydrolysis of 245 gave 70% retention of configuration at phosphorus (eq. [37]). X-Ray data (242) corroborated the stereochemistry reported by Kashman and



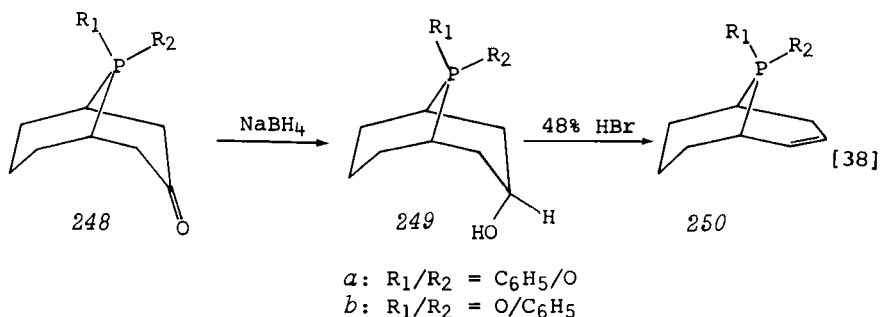
Awerbouch, which was first ascertained through ^1H NMR arguments (241).



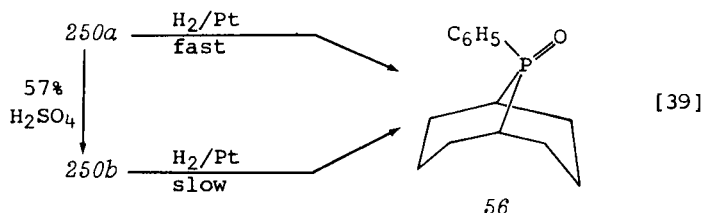
A stereochemical study of 9-phenyl-9-phosphabicyclo[3.3.1]-nonane derivatives has been reported (243). Addition of $\text{C}_6\text{H}_5\text{PH}_2$ to 246 gave a mixture of phosphines 247 (243,244). The oxides from 247 were separated, and their stereochemistry was assigned (243). Each isomeric oxide (248) was reduced stereoselectively



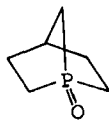
with NaBH_4 to give the corresponding alcohols (249), which were dehydrated to 250 (eq. [38]). With strong acid 250a was converted to 250b, by either a trans-annular hydride-shift process or



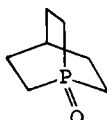
an acid-catalyzed oxygen-exchange reaction at phosphorus (eq. [39]). ^{13}C NMR spectral data provided evidence for a preference of chair-chair conformations in 248, 250, and 56, but for chair-boat conformations in 249 (243). The X-ray structure of a square-planar nickel(II) complex of 56, $[\text{trans}-(56)]_2 \cdot \text{NiCl}_2$, showed a double chair conformation in the solid state (245).



Bicyclic phosphorinane oxides 251 and 252, constrained into boat ring conformations, were studied by Wetzel and Kenyon (246).



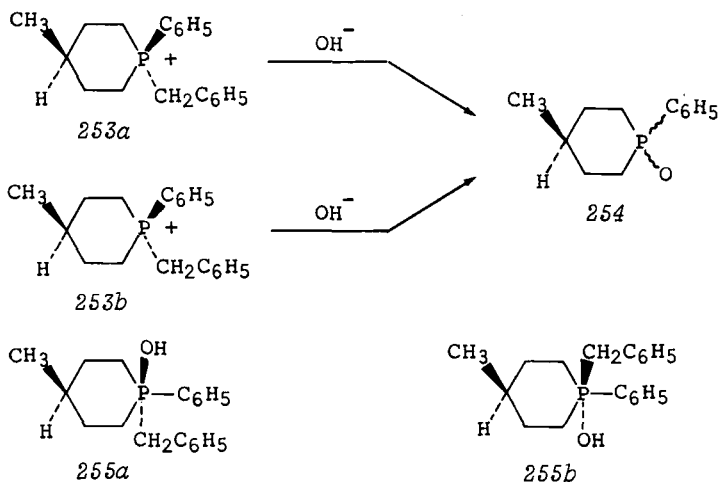
251



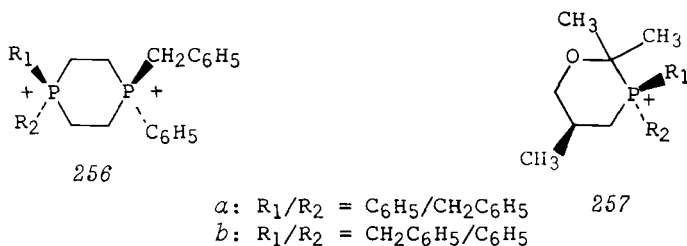
252

The alkaline cleavage reaction of benzyl phosphonium salts, briefly mentioned above, is stereochemically interesting (247). Fragmentation of acyclic salts by aqueous hydroxide normally occurs with inversion of configuration at phosphorus (248). Benzyl phosphetanium salts hydrolyze with mixed stereochemistry (249); benzyl phospholanium salts are transferred to phosphine oxides with complete retention (250); and phosphhepanium salts undergo hydrolysis with complete inversion (251).

Hydrolysis of *cis*-phosphorinanium salt 253*a* gave a mixture of 48% *cis*-oxide (retention) and 52% *trans*-oxide (inversion), whereas the *trans* salt 253*b* gave 22% *cis*-254 (inversion) and 78% *trans*-254 (retention) (252). The alkaline cleavages proceed via two diastereomeric intermediates 255*a* and 255*b*. Unfavorable steric interactions between the methyl and benzyl groups in 255*b* were proposed as a possible source of the diminished inversion for the *trans* salt. Although hydrolysis of benzyl phosphetanium salts gave a loss of stereospecificity, the *cis* and *trans* pairs each gave mixtures of phosphine oxides with identical diastereomeric composition. In this case epimerization occurred faster than hydrolysis, giving an equilibrium mixture of oxides, whereas in the phosphorinanium fragmentation kinetic control was evident. Thus there are two competing reaction pathways: the "McEwen mechanism," affording inversion, and a "phospholanium mechanism," affording retention (248,250-252). A comparison of the base cleavage of 253*a* and 253*b* with the corresponding 4-*t*-butyl derivatives has been published (43f), together with a



mechanistic discussion (not considered here because of space limitations). Nonstereospecificity has been observed in the alkaline hydrolysis of 1,4-diphosphorinane diastereomers, *256a* and *256b* (253a). On the other hand hydroxide cleavage of *257a*

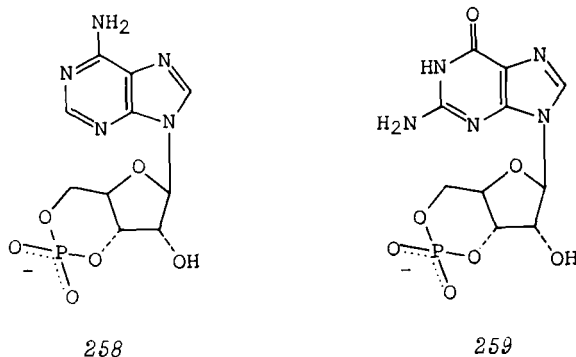


and *257b* occurred with complete retention of configuration at phosphorus (253b).

D. Biological Aspects

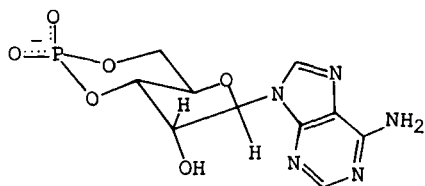
1. Cyclic Nucleotides

The cyclic nucleotide adenosine 3',5'-phosphate (c-AMP), *258*, is a ubiquitous hormonal messenger, involved in the regulation of many cellular processes (e.g., lipolysis, protein synthesis, and active transport) (254). The biological importance

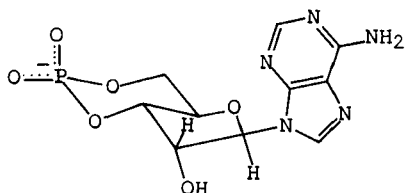


of other endogenous cyclic nucleotides, such as guanosine 3',5'-phosphate (c-GMP), *259*, has also been recognized (255). A general chemical review on cyclic nucleotide derivatives is available (256).

The crystal and molecular structure of c-AMP has been determined by X-ray diffraction (257), which shows two molecules per asymmetric unit, having different conformations about the glycosidic bond (see *260a* and *260b*) (other details being rather constant); the 1,3,2-dioxaphosphorinane ring adopts a chair conformation and the ribose ring is puckered in both cases. The

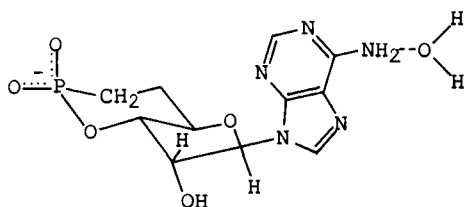


260a (anti conformer)

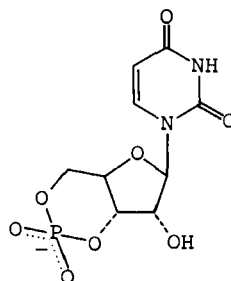


260b (syn conformer)

molecular structure of an isosteric phosphonate analog, 261, possessing biological activity, was similar to that of the syn form of c-AMP (260b) (258). The axial ethyl ester of c-AMP (176, X = O, Y = OC₂H₅) has an anti base-ring conformation and a flattened chair 1,3,2-dioxaphosphorinane ring (X-ray data) (259).



261



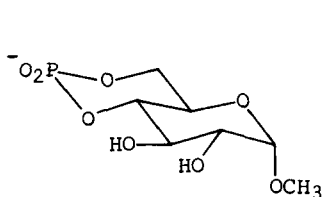
262

The crystal and molecular structure (260) of the (C₂H₅)₃NH⁺ salt of uridine 3',5'-phosphate (c-UMP), 262, demonstrated the (anti) geometry shown (two molecules per asymmetric unit), in accord with other cyclic nucleotides. In c-GMP, 259 (sodium, tetrahydrate), the phosphate ring assumes a chair conformation, flattened at the phosphorus end, with a syn arrangement about the glycosyl bond (261a). Methyl α-D-glucopyranoside 4,6-phosphate (263, cyclohexylammonium salt) also exhibits a chair form for the 1,3,2-dioxaphosphorinane ring (261b). In the 2-deoxyribose thymidine 3',5'-N,N-dimethylphosphoramidate, prepared by oxidation of the product from thymidine and tris-(dimethylamino)phosphine (262a), the dimethylamino group is equatorially oriented and the phosphorus end of the molecule is highly puckered (X-ray data) (262b), compared to, for example, phosphate triester 176 (X = O, Y = OC₂H₅) (259). X-Ray data are also available for some five- (108b, 263) and seven- (264a) membered-ring nucleotides, and a highly simplified derivative of a 5-membered-ring nucleotide (264b).

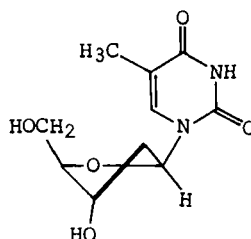
Of greater interest is the conformation of the cyclic nucleotides in solution, since this more accurately represents

a biological situation. The preferred conformation of c-AMP in an aqueous milieu was determined by ^1H NMR lanthanide-shift studies (265), which indicated that the ribose and phosphorinane ring conformations are consistent with the solid-state structures. A syn conformation of the glycosyl bond predominated (see 260b). ^1H relaxation measurements (T_1 and T_2) from lanthanide-shifted spectra of c-AMP, and the changes thereon induced by Gd^{+3} , supported the same preferred conformations (265b). Other NMR studies of 3',5'-nucleotides also revealed a similarity between the solution and solid-state conformations for the rings (57,58,266). Spin-spin coupling constants for conformationally biased (anionic) phosphate six-membered rings were established in numerous studies (57a,58,266a,267). Blackburn and co-workers (57a) determined (^1H NMR data) that the furanose and cyclic phosphate rings are "rigid" in c-AMP, c-TMP (2'-deoxy-c-UMP), and dibutyryl c-AMP. The phosphate ring assumes a chair conformation, the furanose rings of c-AMP and dibutyryl c-AMP are in a 3'-endo-4'-exo conformation, and the furanose ring of c-TMP is in a 4'-exo conformation. ^{13}C NMR data support the conclusions derived from the ^1H NMR investigation (57b). Cyclic UMP, GMP, and CMP have phosphate ring conformations akin to those of c-AMP and c-TMP. Lee and Sarma (58), in studying 18 different nucleoside derivatives by NMR spectroscopy, concluded that the phosphate rings in c-AMP, c-GMP, c-UMP, c-CMP, 2'-deoxy-c-AMP, and c-TMP adopt a slightly flattened, "rigid" chair conformation. Kainosho and Ajisaka (266b) suggested a 3'-endo conformation for the sugar moieties of c-AMP, c-UMP, c-GMP, c-CMP, and c-IMP, and a chair conformation for the phosphorinane ring (independent of the heterocyclic substituent), based on lanthanide ion-assisted ^1H NMR analyses. The conformation of the 2'-deoxy derivative c-TMP was found to be 4'-exo in the lanthanide ion-assisted work, as well (266b).

The conformation of nucleosides can be described largely by the torsional angles at the $\text{C}_1'-\text{N}_1$ glycosidic linkage, the furanose ring C-C bonds, and the $\text{C}_4'-\text{C}_5'$ bond. X-Ray data reveal that these angles fall into narrow ranges (268a). Although the glycosidic bond has been found in either syn or anti orientations in the crystal (268a), pyrimidine nucleosides and nucleotides show a strong preference for the anti disposition in an aqueous environment (e.g., see predominant conformation for thymidine, 264; c-UMP, 262, is anti in the solid state) (260). With the furanose and phosphate rings in cyclic 3',5'-nucleotides largely restricted to the $^4\text{T}^3$ (3'-endo, 4'-exo) and chair conformations, respectively, the only conformational variable remaining is rotation about the glycosyl bond. Analysis of this torsion by potential energy calculations indicated that pyrimidine bases U, T, and C prefer the anti range of conformations (268b). The calculations predicted that c-GMP and c-IMP favor the syn conformation over the anti by 95:5 and 70:30, respectively, while c-AMP prefers the anti conformation over the syn by 70:30 (268b). A recent NMR study (268c) indicated a syn/anti ratio



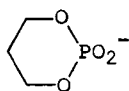
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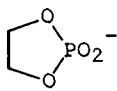
264

of 1:1 for C-AMP in aqueous solution (at pH 2.0). The relatively large degree of rotational freedom of noncyclic nucleotides, compared to their cyclic counterparts, may have some bearing on comparative biological properties.

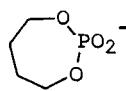
One outstanding facet of cyclic nucleotides is their hydrolysis to noncyclic nucleotides, with or without enzymic assistance, a process that has received considerable attention (269). Generally, cyclic nucleoside phosphates have high heats of hydrolysis. Cyclic AMP has a free energy and enthalpy of hydrolysis 2 kcal/mol higher than that for the conversion of ATP to ADP and inorganic phosphate (269a) and, interestingly, the heat of hydrolysis of simple six-ring cyclic phosphate 265 is 8 kcal/mol less than that for c-AMP. The latter comparison affords some indication of the strain (270) contained in the ribofurano-



265



266



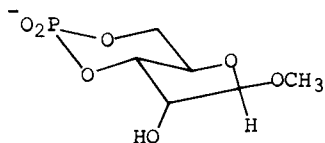
267

side 3,5-phosphate system (see Table 12). Representative enthalpies of hydrolysis are presented in Table 12.

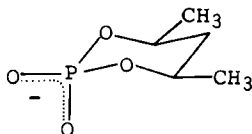
Table 12 Enthalpies of Hydrolysis (263a)

Phosphodiester	$-\Delta H$ (kcal/mol)
$(C_2H_5O)_2PO_2^-$	2.5
266	6.9
265	3.8
267	2.5
c-AMP (258)	11.5 (5'-bond; 12.1 for 3'-bond)
2',3'-AMP	9.4 (2'-bond)
263	6.9
268	11.7

Phosphate basicity is dependent on angle strain and axial/equatorial orientation in six-membered rings (27,271). This stereochemical aspect (271b) has obvious relevance to cyclic 3',5'-nucleotides, wherein the two exocyclic P-O bonds could be differentiated by electrophiles or cations. Hong and co-workers



268

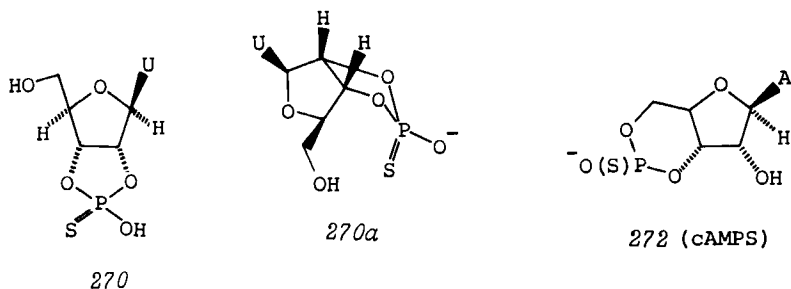


269

(271b) reported that diazomethane reacts preferentially with the axial oxygen of 269, in the presence of relatively noncoordinating cations [e.g., Na^+ , Cs^+ , $(\text{CH}_3)_4\text{N}^+$], but with the equatorial oxygen in the presence of Li^+ and NH_4^+ , the difference being ascribed to the strong affinity of the latter ions for the more basic, axial coordination site. A theoretical argument for the much greater basicity of the axial P-O group has been expounded by Verkade (27,271a). The association of the basicity properties with biological activity remains to be demonstrated. In the reaction of c-AMP with diazoalkanes axial esters were formed as readily as or in preference to equatorial esters (198a); c-UMP and some derivatives gave similar results (198b).

In Sects. III-B-2-a and III-B-2-b the stereochemistry relating to pyranoside cyclic phosphorus compounds was discussed. Since interest in furanoside derivatives is closely allied with nucleotide chemistry, the topic is dealt with in this section.

Reports on diastereomeric, nonbiologic furanoside cyclic phosphorus derivatives have been sparse (272). A number of papers have appeared concerning the preparation of diastereomeric derivatives of synthetic cyclic nucleoside phosphates (epimeric at phosphorus) (198,259,262,273). In many cases no attempt was made to identify diastereomers, but some reports exist in which epimers have been separated and/or characterized. Eckstein (273b) separated the two isomers of uridine 2',3'-cyclophosphorothioate (270) by crystallization of triethylammonium salts. X-Ray analysis of the crystalline diastereomer of 270 showed the P=S bond in an endo position (i.e., anti to the ribose-ring 2', 3' hydrogen atoms) (see 270a) (263b). Both isomers of 270 were substrates for pancreatic ribonuclease (273b). The kinetics of the RNase A catalyzed hydrolysis showed marked differences for the compounds (Table 13). Epimer 270a had the same affinity (K_m) as its cyclic phosphate congener 271, but a fivefold lower rate constant (k_{+2}) (274), whereas epimer 270b bound much more weakly to the enzyme (eightfold lower) with the same k_{+2} value as that for 270a. This implies that the sulfur atom in 270a is



not primarily involved in binding to the enzyme, but in *270b* the the sulfur atom interferes with the binding process; alternatively, the results may be explained in terms of differential availability of the anionic oxygen for complexation with a site on

Table 13 Binding and Hydrolysis Rate Constants (273b)

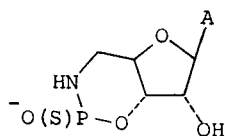
Compound	K_m (M)	k_{+2} (sec^{-1})
uridine-2',3'-cyclic phosphate (271)	6.3×10^{-3}	2.5
270a (endo sulfur)	6.2×10^{-3}	0.5
270b (exo sulfur)	50×10^{-3}	0.5

the enzyme. The guanosine analogue of *270* was obtained as a mixture of diastereomers that could not be separated (273i). In the reaction of the mixture of guanosine epimers with RNase T1, in water-methanol, only the alleged endo P=S isomer underwent reaction.

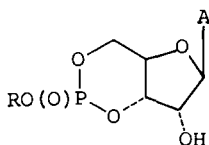
After an initial failure (273d), the phosphorothioate analogue of c-AMP (272) was prepared as a mixture of diastereomers, which was very slowly hydrolyzed by phosphodiesterase (beef heart and rabbit brain cortex) (273e). With the former enzyme 272 bound about the same as c-AMP, and the two epimers were hydrolyzed at the same rate. Interpretation of the results is complicated by the simultaneous presence of both diastereomers, which may have different affinities for the enzyme. Mixture 272 was about one-half as active as c-AMP in stimulating protein kinase; the apparent binding of 272 was 10 to 20 times greater than that of c-AMP. Nothing is known about the biological activities of the individual epimers of 272, since they have yet to be separated. One may speculate that since the exo P=S disposition in *270* (viz., *270b*) is less acceptable to the ribonuclease enzyme system, the equatorial (or exo) P=S bond epimer of 272 may also be less biologically acceptable than the axial (endo) P=S compound. Further work here is eagerly awaited, as it also has relevance to the P=O basicity concepts

advanced by Verkade (271). A recent stereospecific synthesis of thymidine 3',5'-phosphorothioate diastereomers should be applicable to the stereo-controlled synthesis of the diastereomers of 272 (273m).

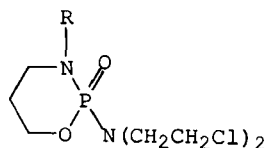
The two diastereomers of 273 (of unknown relative configuration) show different behavior in stimulation of c-AMP-dependent protein kinase (bovine skeletal muscle) (273k). The (ca. twofold) more active isomer had a K_m similar to its phosphate congener,



273



274



275 a: R = H

b: R = CH₂CH₂Cl

and was hydrolyzed by phosphodiesterase (beef heart); the other epimer of 273 was not attacked by the phosphodiesterase enzyme, even on incubation for several days, although it did appear to bind to the enzyme (acting as an inhibitor). Both diastereomers were resistant to hydrolysis by rabbit-brain phosphodiesterase.

Significantly, the work of Eckstein and co-workers with nucleoside phosphorothioates has provided information on enzyme mechanisms (275). In particular, the diastereomeric derivatives of 270 served to probe the stereochemistry of enzymatic transformations by virtue of the extra molecular information intrinsic to the chirality at phosphorus.

In Sect. III-B-2-a we mentioned the unequal (exocyclic) hydrolysis of diastereomeric phosphates. A series of c-AMP triesters (274) was synthesized from the free acid and diazoalkanes, and the diastereomeric mixtures were separated (198a). In hydrolysis of the triesters, which occurs by benzylic C-O bond cleavage (273o), the equatorial isomer was found to react ca. four times faster than the axial isomer (see Table 14); the triesters show-

Table 14 Half-Life (Hr) at 50° in H₂O (198a)

R in triester	Axial isomer	Equatorial isomer
CH ₂ C ₆ H ₅ -p-CH ₃	0.1	too unstable
CH ₂ C ₆ H ₅	2.2 (9.5 ^a)	0.5 (3.0 ^a)
CH ₂ C ₆ H ₅ -o-NO ₂	300	83
CH ₂ C ₆ H ₅ -p-NO ₂	240	73

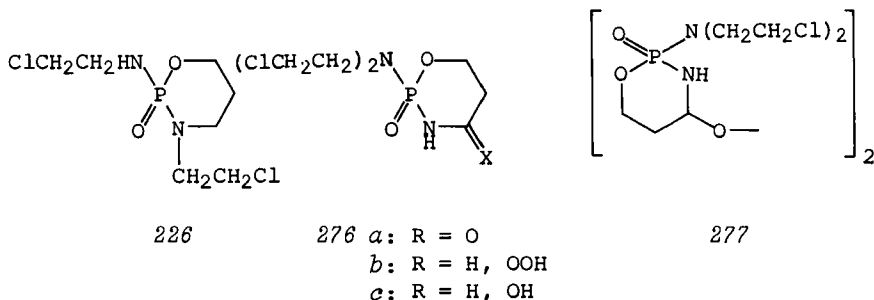
^aIn Mops buffer (pH 6.5) at 30°.

ed little (*in vitro*) activation of c-AMP-dependent protein kinase, and were not suitable as substrates for c-AMP phosphodiesterase (*in vitro*) (198a).

2. Cyclophosphamide and Related Compounds

Cyclophosphamide (276), 275a, is a clinically useful anti-tumor drug, which has little cytotoxic activity until activated by the mixed-function oxidase system of liver microsomes (277). Thus active metabolites of 275a are also of interest. Pharmacologically, 275a may also be useful as an immunolytic and anti-inflammatory agent.

X-Ray structural data are available for 275a and some of its relatives. The monohydrate of 275a shows a chair conformation for the 1,3,2-oxazaphosphorinane ring with an equatorial amino group (278). The crystal structure of isophosphamide (226) also shows a chair structure with the less bulky $\text{NHCH}_2\text{CH}_2\text{Cl}_2$ group in an equatorial position; the ring nitrogen atom possesses a virtually planar geometry (angle sum = 353°) (232). The general structure of triphosphamide (275b) is close to that of 226 and 275a (279a). Ketophosphamide 276a exhibits a nonchair structure, presumably due to the presence of an endocyclic carbonyl moiety (279b). The 4-hydroperoxy (276b) (280a,280b) and 4-peroxy (277) (280c) derivatives, synthetically obtained by

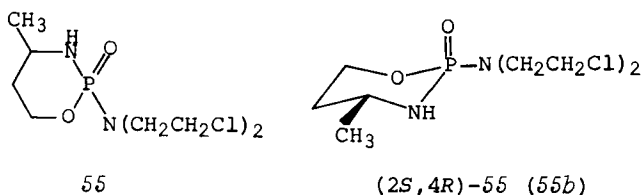


Fenton oxidation of 275a, have chair rings with equatorial amino groups and axially connected 4-hydroperoxy and 4-peroxy groups, respectively; no equatorial oxygenation was observed (280). Camerman and co-workers (280a) suggested that the *in vivo* metabolite 276c may have the same relative configuration. X-Ray analyses of both isomers of 4-hydroperoxyisophosphamide showed axial 4-peroxy groups and a change in orientation at phosphorus; the major (*cis*) isomer (assumed to be the thermodynamically more stable one) has an equatorial amino group (280b). Recently, 4-hydroperoxyisophosphamide and related derivatives were studied by Takanizawa and co-workers (281). Acid-catalyzed equilibration afforded a 1:1 mixture of 4-hydroperoxy diastereomers, both of which favor axial 4-peroxy conformations in solution; both diastereomers exhibited antitumor activity (281).

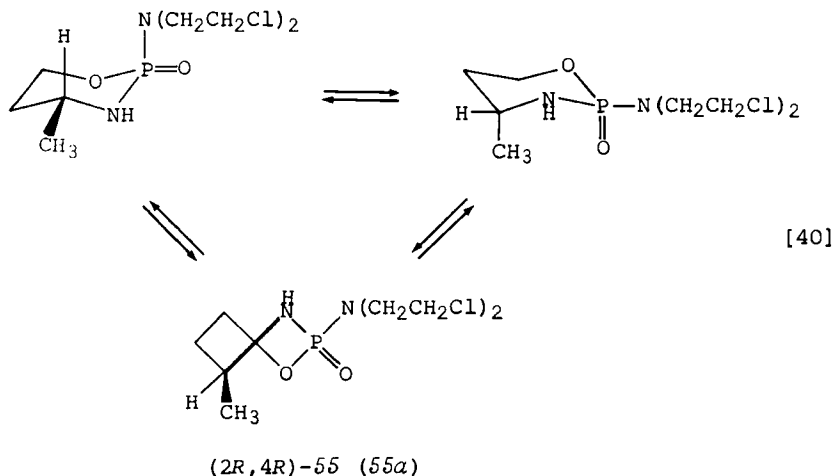
^1H and ^{13}C NMR work on *275a* attested to a relatively low barrier to ring inversion (282), as expected from the earlier suggestions relating to this ring system (see Sect. III-C-2).

The synthesis of enantiomeric cyclophosphamides was achieved independently by Stec and co-workers (283a), and by Zon (283b). Since the (-)-enantiomer was isolated from the urine of patients dosed with racemic *275a*, a stereospecific metabolism must take place *in vivo* (284). In a test against mouse plasma tumor cells (ADJ/PC6), the (-)-form was twice as effective (ID_{90}) as the (+)-form (284). The absolute configurations of (-)-*275a* and (+)-*275a* were determined to be *S* and *R*, respectively, by anomalous dispersion X-ray crystallography (285).

Stec and co-workers (55) reported the synthesis and configurational assignments of the four optically active forms of *55*, correcting earlier *cis/trans* assignments (286). ^1H NMR coupling constant data established that (2*S*,4*R*)-*55* is virtually



one chair conformer, whereas ^{13}C NMR coupling constants indicated that (2*R*,4*R*)-*55* is conformationally heterogeneous (eq. [40]). No appreciable difference in activity of the *cis* and *trans* isomers of *55* against L1210 leukemia *in vivo* was observed (286); both isomers were less active than cyclophosphamide (*275a*), probably because of less efficient microsomal oxidation at C_4 (286,287).



IV. STRUCTURE, CONFORMATION, AND STEREOCHEMISTRY OF CYCLOHEXANE RINGS CONTAINING TRICOORDINATE PHOSPHORUS

A. Introduction

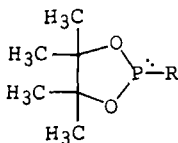
The relatively high barriers to pyramidal inversion for most tricoordinate phosphorus derivatives (288,289) confers isolability at convenient temperatures to diastereomers of appropriately substituted phosphorus heterocycles, facilitating study of their stereochemical and conformational properties. The pyramidal inversion process furnishes a means for thermally equilibrating diastereomeric pairs to obtain thermodynamic parameters. Thus in anancomeric (19) derivatives the conformational preferences of substituents on phosphorus may be ascertained.

B. 1,3,2-Dioxaphosphorinanes

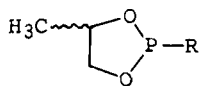
The 1,3,2-dioxaphospholanes and, especially, the 1,3,2-dioxaphosphorinanes have occupied a central position in stereochemical investigations of tricoordinate, saturated phosphorus heterocycles, primarily because of their similarity to widely studied carbocyclic five- and six-membered-ring analogs.

In the early 1960s Goldwhite (290) recognized the accumulation of evidence (291,292) that pointed to the conformational stability of trivalent phosphorus, and suggested configurational stability in dioxaphospholanes 278 ($R = Cl$) and 279 ($R = Cl, OCH_3$), based on ^1H NMR data. Thus 279a and 279b were shown to be a mixture of noninterconverting geometric isomers at ambient temperature, but separation or assignment of isomers was not essayed. Further exploration demonstrated (293) that derivatives of 279 (b-e) are configurationally stable up to 150° ; 279a underwent concentration-dependent ligand reorganization, resulting in stereomutation at phosphorus (294). Similar observations of pyramidal stability were made with derivatives 280; also no inversion of 281 was observed by ^1H NMR up to 200° (295).

As evidence mounted for the configurational stability of trivalent phosphorus (296), considerable interest was aroused. Denney and Denney (163) reported that the less stable isomers of the diastereomeric pairs 3, 137, and 281 rapidly isomerize to the more stable forms on treatment with methanol. Only partial

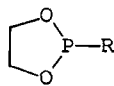


278



279

- a: $R = Cl$
 b: $R = OCH_3$
 c: $R = OC_6H_5$
 d: $R = N(CH_3)_2$
 e: $R = C_6H_5$

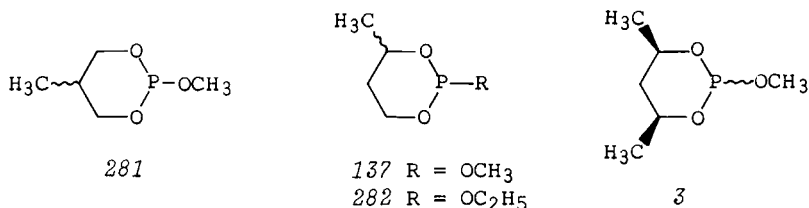


280

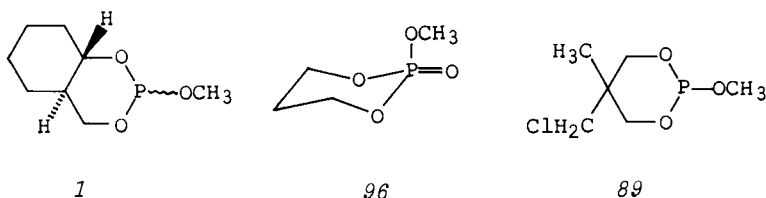
- $R = Cl, OCH_3, F,$
 $OAc, OC_6H_5,$
 $OC(O)C_6H_5$

separation of the geometric isomers was achieved, however, because isomerization is very sensitive to acid catalysis (145). With the firm realization of the pyramidal stability of tri-coordinate phosphorus, several studies employing NMR spectroscopy (30-32,35,39,42,91,130,136a,140,141,142b,149,166b,170,176,183,297-301), dipole moment measurements (149,151b,154a,302), electron diffraction (303), and correlations involving assumed stereochemical paths in displacement reactions at phosphorus (84,102,141,145,154b,183) were conducted with an aim at delineating the geometry and conformations of six-membered-ring (and to a lesser extent five-membered-ring) compounds.

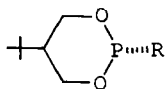
Several groups have established that alkoxy or aryloxy (30, 42,149,170,300b,302c) and chloro (30,42,149,170,300,302b,303) substituents on trivalent phosphorus prefer an axial disposition in the chair conformation. Thus Bentrude and Hargis (170) reported that the cis isomers of 2-R-5-*t*-butyl-1,3,2-dioxaphosphorin-



anes, *284a* and *284b*, are more stable than the trans isomers. ^1H NMR analysis supported an equatorial orientation for the *t*-butyl group in both cases. The configuration about phosphorus was correlated with *96* by stereospecific oxidation on *284b* [*t*- $\text{C}_4\text{H}_9\text{OOH}$ (304)], and the structure of *284b* was confirmed by X-ray analysis of *92* (derived from *284b*) (102). On the strength of dipole moment measurements (on borane adducts) and ^1H NMR data, Verkade and co-workers (42) demonstrated the axial preference for the methoxy group in several 2-alkoxy-1,3,2-dioxaphosphorinanes, *3* and *89*. Likewise, Bodkin and Simpson (149), employing ^1H NMR spectroscopy and dipole moment measurements, established that the more stable stereoisomer of *282* possesses the trans configuration, with axial ethoxy and equatorial methyl groups. The less stable cis isomer (derived from phosphorochloridite *133*) was postulated to consist of a mixture of rapidly interconverting chair conformers, the form with equatorial methyl and ethoxy groups being principally populated; thereby a predominantly axial chloro group was suggested for *133* (149).

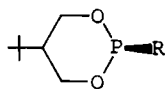


Direct NMR evidence for the axial preference of chloro and alkoxy substituents on phosphorus was provided by Haemers and co-workers (30). They obtained characteristic ^1H NMR data for the *cis* and *trans* isomers of 1 and 3, whose rings are immobilized by the nature of the alkyl substitution. Their work indicated that the disposition of the phosphorus lone pair may have hardly any effect on the relative magnitudes of $^3J_{\text{POCH}}$ in the 1,3,2-dioxaphosphorinanes, but this independence is frequently not observed in phosphine derivatives (35,295,297,301).

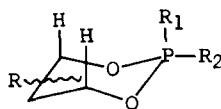


283

- a*: R = Cl
b: R = OCH₃ (13)
c: R = C₆H₅
d: R = *i*-C₃H₇
e: R = CH₃
f: R = *t*-C₄H₉ (14)
g: R = (CH₃)₂N
h: R = CH₃NH (15)



284



285

- a*: R₁ = O
b: R₂ = O

More recently, axial preferences have been found for other polar substituents including fluoro (141), cyano (140), thioalkoxy (183), anilino (166b), 1-aziridino (301), and possibly dialkylphosphino (305), primarily by NMR techniques. A 2-hydrogen substituent also prefers to occupy an axial position (39).

The axial preference for electronegative groups is not surprising, since it could be ascribed, at least in part, to the generalized anomeric effect (306) (*vide infra*), which, for example, produces axial preferences in analogous 1,3-dioxanes (306,307). However, Bentrude and co-workers (35,176) found that 284*c*, having equatorial 5-*t*-butyl and axial phenyl groups, is more stable than 283*c*; similar conclusions for 283*d* and 284*d* (35,229) and for 283*e* and 284*e* (35) followed. On the other hand *t*-butyl (35), dimethylamino (35,91b,130,136a,142b), 1-piperidino (301), and methylamino (35,91b,130) groups were found to prefer equatorial orientations in 1,3,2-dioxaphosphorinanes.

Isomer assignments have been accomplished in general through NMR data and/or dipole moment measurements (for R = methylamino, piperidino, and dimethylamino) (91b,130,136a,142b), and stereospecific oxidation at phosphorus (308) to the corresponding oxides. Structures of oxides of 283*c,e,f* were determined by X-ray analysis (102). It is noteworthy that lanthanide-shift reagents (309) offer a useful tool for identifying *cis-trans* isomers, such as the 2-oxides of 283 and 284 (see 285) (91b,129,130,132,136a,142b). Complexation with the phosphoryl oxygen distinguishes the *trans*-2-oxides 285*a* by a substantial downfield shift of the proximate 4,6-axial protons.

Estimations of conformational populations for *cis* and *trans* diastereomers **283** and **284** were made via proton coupling and chemical shift data. For the *cis* forms the conformations with equatorial 5-*t*-butyl and axial *P*-R substituents greatly predominate for R = Cl (**170**), alkoxy (**170**), methyl (**35**), *i*-propyl (**35**), and phenyl (**35**). However, when R was *t*-butyl (**35**), methylamino (**91b**), or dimethylamino (**91b**), the *cis* isomers were observed to be conformationally heterogeneous, composed of equilibrium mixtures of chair and twist forms (**91b**).

In the preceding cases the isomeric *cis*-*trans* pairs were thermally equilibrated, and the equilibrium populations were measured. The free-energy differences (ΔG values) between isomers are presented in Table 15, along with the estimated distribution of the isomers **283** and **284** A,B,C (**35**). From these data (Table 15) the approximate conformational free-energy (ΔG) values could be estimated, providing rough estimates for the corresponding ΔG values of the groups attached to the 2-position in 1,3,2-dioxaphosphorinanes; the conformational free-energy values are presented in Table 16 (**35**).

Table 15 Equilibrium Data for
1,3,2-Dioxaphosphorinanes (**284**→**283**) (**35**)

R	<i>cis</i> -(284)		<i>trans</i> -(283)		$\Delta G^\circ_{298^\circ\text{K}}$
	284A	284B/284C	283A/283B	283C	
Cl	93		1.5	5.5	1.5 kcal/mol
CH ₃ O	92		0.4	3.6	1.45
CH ₃	84		10.5-12.0	-	0.98
<i>i</i> -C ₃ H ₇	74		18-21	-	0.62
<i>t</i> -C ₄ H ₉		7	93	-	-1.5
C ₆ H ₅	90		4.7		1.3
(CH ₃) ₂ N	11	6	83	-	-0.94
CH ₃ NH	42	3	55	-	-0.12

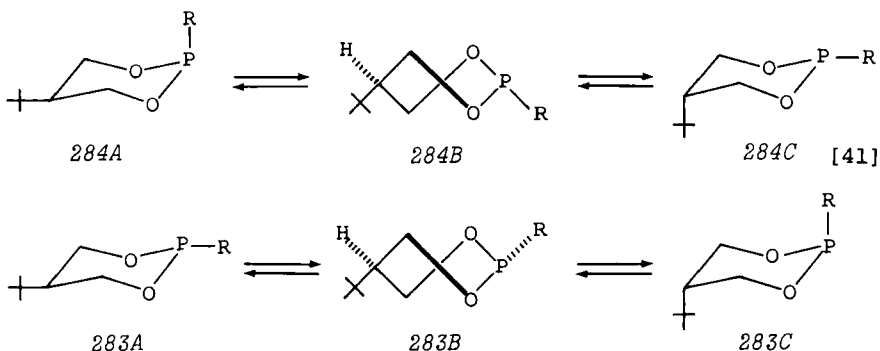


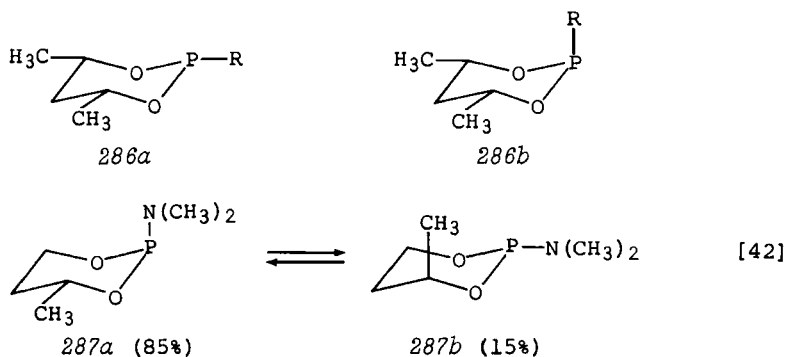
Table 16 Conformational Free-Energy ($\Delta G_{298^\circ\text{K}}^\circ$) Values for 2-Substituents in 1,3,2-Dioxaphosphorinanes (284A→283A) and 1,3-Dioxanes

R	K_{eq}	ca. $\Delta G_{298^\circ\text{K}}^\circ(\text{ax} \rightarrow \text{eq})$ (284A→283A) ^a	$\Delta G_{298^\circ\text{K}}^\circ$ 1,3-Dioxanes ^b
Cl	> 62	>2.4 kcal/mol	0.36 kcal/mol
CH ₃ O	≥230	≥3.2	0.62
C ₆ H ₅	≥ 19	≥1.7	-3.12
CH ₃	7-8	1.1-1.2	-3.98
<i>i</i> -C ₃ H ₇	3.5-4.1	0.7-0.8	-4.17
CH ₃ NH	0.76	-0.15	
(CH ₃) ₂ N	0.13	-1.2	
<i>t</i> -C ₄ H ₉	<0.004	<-3.2	

^aEstimated as the conversion of 284A to 283A from the values given for them in Table 15.

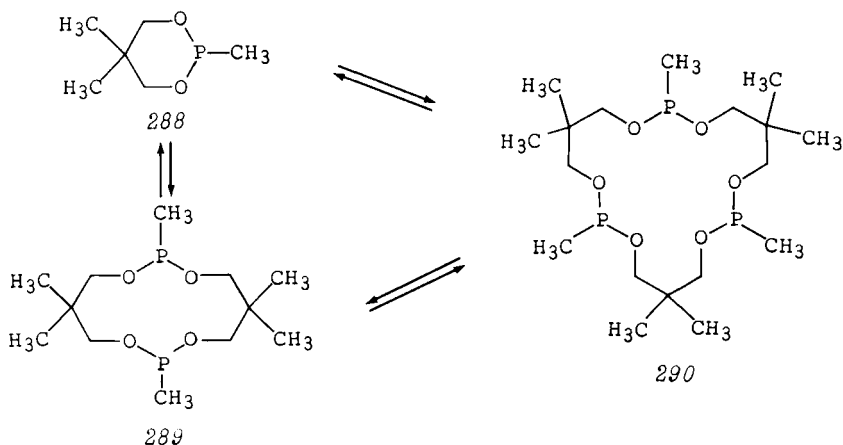
^bReferences 115 and 307b.

In the 4,6-dimethyl compounds, 286a and 286b, similar conclusions were reached (142b) when R was methoxy or dimethylamino, via dipole moment and NMR data, except that the less stable isomers retained a chair conformation with diequatorial 4,6-methyl groups because of the severe interactions that result from diaxial placement of 1,3 methyl groups in cyclohexane systems. The less stable 4-methyl compound 287 was suggested to be an 85:15 mixture of 287a and 287b, respectively [eq. (42)] (301).



Phosphonite 288 equilibrates with dimeric (12-membered-ring) and trimeric (18-membered-ring) forms, 289 and 290, each of which exists as two different diastereomers (310). The two diastereomers of 289 formed in a statistical (1:1) ratio. At a given temperature the relative amounts of 288, 289, and 290 in the equilibrium mixture are governed by the starting concentration of monomer 288. The tendency for 1,3,2-dioxaphos-

phorinanes to oligomerize depends on the phosphorus substituents, with an order of facility $t\text{-C}_4\text{H}_9 > i\text{-C}_3\text{H}_7 > \text{C}_2\text{H}_5 > \text{CH}_3 > \text{C}_6\text{H}_5$ (311). Dimerization of 1,3,2-dioxaphospholanes and 1,3,2-dioxaphosphanes to 10- (312) and 14-membered-ring (311) molecules has also been reported. These novel macrocycles may serve as effective ligands for metal cations and ammonium ions.

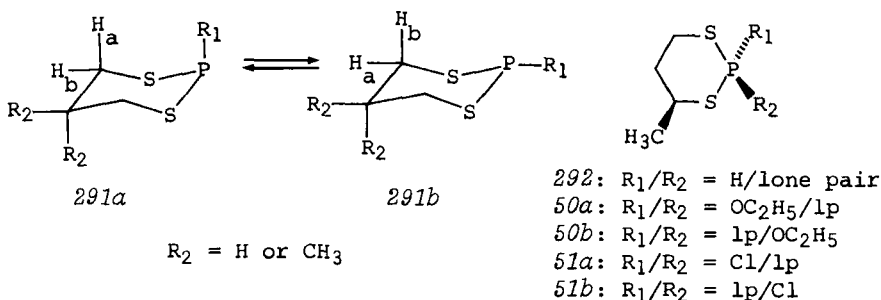


The isosteric 2-chloro-1,3,2-dioxaarsenane system adopts a chair conformation with an axial preference for the 2-chloro group (dipole moment and Kerr constant data) (313a). Aksnes (313b) suggested that 2-chloro-, 2-bromo-, 2-methoxy-, and 2-phenoxy-1,3,2-dioxaarsenanes have a strongly biased chair conformation with axial 2-substituents.

A recent discussion of 1,3,2-dioxaphospholane stereochemistry has been given by Bentrude and Tan (314a). An electron diffraction study of 2-chloro-1,3,2-dioxaphospholane has been reported (314b).

C. 1,3,2-Dithiaphosphorinanes

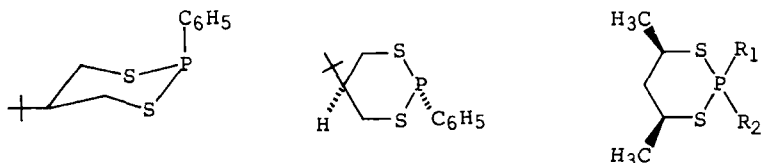
Although very few investigations of trivalent 1,3,2-dithiaphosphorinanes have been disclosed (47,48,50,51,226a), the limited data support conclusions on the overall geometry and orientational preferences of phosphorus substituents as observed for the 1,3,2-dioxa analogs. Hutchins and Maryanoff (47) and Robert and co-workers (48,226a) concluded from NMR data that the 1,3,2-dithiaphosphorinane ring adopts a chair conformation (perhaps slightly flattened), and that the axial orientation for phosphorus substituents greatly predominates in 291 ($\text{R}_2 = \text{H}, \text{CH}_3$) with $\text{R}_1 = \text{C}_6\text{H}_5, \text{OCH}_3, \text{Cl}, \text{CH}_3, \text{C}_2\text{H}_5$, and 1-aziridinyl, while the equatorial position is highly favored for $\text{R}_1 = \text{N}(i\text{-C}_3\text{H}_7)(t\text{-C}_4\text{H}_9)$, $\text{N}(i\text{-C}_3\text{H}_7)_2$, and $t\text{-butyl}$. A mixture of conformations is present for $\text{R}_1 = \text{NH-}t\text{-C}_4\text{H}_9$ ($K_{\text{eq}} = 1$ to 1.5 and $\text{R}_1 = 1\text{-piperidino}$ ($K_{\text{eq}} = 1.5$ to 3.0)).



Nifant'ev and co-workers (50) concluded from NMR studies of 50 and 51 that the more stable isomers have the trans configuration (50a and 51a). The preferred orientation at phosphorus in 292, 50a, 50b, 51a, and 51b is axial. Thus ^1H and/or ^{13}C NMR data indicated that 51a assumes a chair conformation with an equatorial 4-methyl group, whereas 50b and 51b are chiefly chair conformers with an axial 4-methyl group.

Notably, the three-bond coupling, $^3J_{\text{PH}_a}$, between the ^{31}P nucleus and the 4,6-equatorial protons in the compounds with an axial P substituent (viz., 291a) is very weak (0 to 1.4 Hz); the four-bond coupling between phosphorus and the equatorial 5-proton ($^4J_{\text{PH}_5}$) is uniquely large (7.5 to 10 Hz). On the other hand, in the group of compounds with an equatorial P substituent (viz., 291b) the corresponding equatorial three-bond coupling, $^3J_{\text{PH}_a}$, is large (16.5 to 26.0 Hz) and $^4J_{\text{PH}_5}$ is small (ca. 1 Hz). Both the ^{31}P - ^1H coupling constants and the $^3J_{\text{PC}_5}$ values are dramatically dependent on the orientation at phosphorus: for axial P-R $^3J_{\text{PC}_5} \approx 0.5$ Hz and for equatorial P-R $^3J_{\text{PC}_5} \approx 11.5$ Hz. The unusual $^3J_{\text{PSCH}}$ data obtained for the trivalent 1,3,2-dithiaphosphorinane compounds indicate that a Karplus relation does not apply to vicinal PSCH coupling constants (51).

A nuclear Overhauser experiment on 291a ($R_1 = \text{CH}_3$, $R_2 = \text{CH}_3$) confirmed the proximity of the P- CH_3 group and the axial 4,6-protons (47,51). Further verification of the assignments came from an X-ray analysis (220) of 44 (the more stable of two diastereomers (47,51), which showed a chair conformation, slightly flattened at the phosphorus end of the ring, and an axial 2-phenyl group. Minor isomer 293 has not yet been isolated, although it has been detected by NMR (47,51).



49 a: $R_1/R_2 = \text{lp/C}_6\text{H}_5$
 b: $R_1/R_2 = \text{C}_6\text{H}_5/\text{lp}$

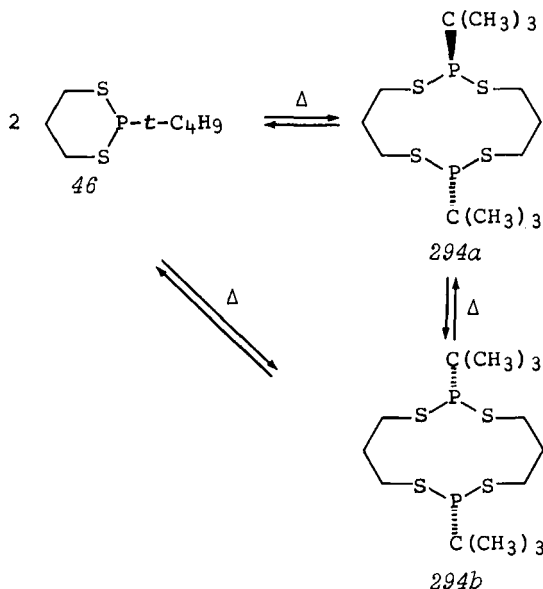
The only quantitative study, in this area, of conformational preferences for phosphorus substituents involved measurements of the thermal equilibration of 44 and 293. From the K_{eq} and the measured kinetics of interconversion, $\Delta G_{298^\circ K}^\ddagger$ and $\Delta G_{298^\circ K}$ were determined to be 1.91 ± 0.2 kcal/mol and 31.4 kcal/mol, respectively (47,51). A comparison of $\Delta G_{298^\circ K}^\ddagger$ of 1.9 kcal/mol with that of 1.8 kcal/mol for the corresponding 1,3,2-dioxaphosphorinanes (283c and 284c) suggests similar conformational preferences for P-substituents in the two ring systems. Thermal equilibration of 49a and 49b (initially obtained as a 3:2 mixture) gave a 9:1 final ratio (GLC, ^1H NMR), corresponding to $\Delta G_{443^\circ K}^\ddagger = 2.05$ kcal/mol (51). For 44 and 293 K_{eq} was ca. 6.5 at $175^\circ C$, giving $\Delta G_{448^\circ K}^\ddagger = 1.65$ kcal/mol. Some estimates of conformational preferences can be gleaned from the data on 291 ($R_2 = H$) reported by Martin and co-workers (48). Such estimates from $^3J_{HH}$ are compiled in Table 17. ^{31}P - ^1H and ^{31}P - ^{13}C couplings, not used here for fear that they may vary with the P substituent independently of conformational factors (45), are consistent with the estimates in Table 17 (48).

Table 17 Estimated Conformational Preferences for 2-Substituents in 1,3,2-Dithiaphosphorinanes (291, $R_2 = H$)

R_1	% axial P- R_1
CH_3	85-95
C_6H_5	90-100
OCH_3	90-100
Cl	95-100
C_2H_4N -	90-100
$NH-t-C_4H_9$	40-50
$C_5H_{10}N$ -	25-30
$t-C_4H_9$	10-15
$N(i-C_3H_7)(t-C_4H_9)$	0-10

The P-chloro derivative 291 ($R_1 = Cl$, $R_2 = CH_3$) was observed (^1H NMR) (51) to be much less labile with respect to chlorine exchange than the corresponding dioxo or diaza analogues. In fact, both moisture and acid were ineffective in initiating the exchange reaction; however, when chloride ion was added, exchange was rapid. This suggests that the mechanism of exchange in the dioxo and diaza system may involve a similar chloride-induced process, since facile hydrolysis of these latter systems would provide the needed chloride anions. In this regard chloride anion does greatly accelerate exchange in the dioxo ring system (42,315).

Interestingly, 1,3,2-dithiaphosphorinanes oligomerize in a manner similar to 1,3,2-dioxaphosphorinanes. Thus an equilibrium between 46 and 12-membered-ring dimers 294a and 294b can be achieved at 160° (relative ratio, 46/294a/294b = 6:3:1) (316).

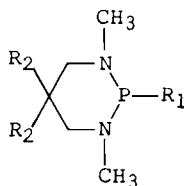


Isosteric 2-chloro-1,3,2-dithiaarsenane is strongly biased into one chair conformation, probably with an axial 2-chloro group (317). The conformational equilibrium for the analogous 2-phenyl compound is also one-sided, but the disposition of the phosphorus substituent is ambiguous (313b).

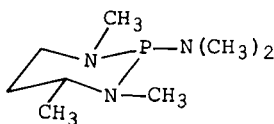
Robert and co-workers (318a) have reported ^1H NMR data on the homologous 1,3,2-dithiaphospholane system. Unusually small $^3\text{J}_{\text{PSC}}\text{H}$ values were also seen in this series for a variety of derivatives. An X-ray structural determination for a trivalent 1,3,2-dithiaphospholane has been published (318b).

D. 1,3,2-Diazaphosphorinanes

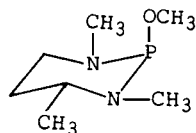
The very limited information available for 1,3,2-diazaphosphorinanes (45,50,51,231) indicates that a normal chair conformation is adopted with a strong bias toward one form, for 295 ($\text{R}_1 = \text{Cl}, \text{OCH}_3, \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5$; $\text{R}_2 = \text{H}, \text{CH}_3$). No definitive description of the disposition of substituents on phosphorus has yet been offered. The absence of a nuclear Overhauser enhancement in 295 ($\text{R}_1, \text{R}_2 = \text{CH}_3$) upon irradiation of the *P*-methyl group (45), and the apparent predominance of *cis* isomer 296 and *trans* isomer 297 tentatively indicate the conformational properties of this ring system: methyl and dimethylamino favor equatorial, methoxy favors axial, orientations. Nifant'ev and



295



296

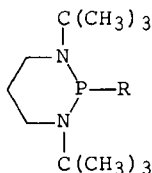


297

co-workers (50) studied the 298 series, in which the *N,N'*-*t*-butyl substituents should strongly populate equatorial positions. ^1H NMR data showed that 298a and 298c are biased toward one chair form. Based on ^{13}C NMR γ effects, 298a-298c were claimed to have an axial preference for the substituents on phosphorus. Other work (51) implied that Cl and OCH_3 favor an axial orientation and that CH_3 , C_2H_5 , and C_6H_5 favor an equatorial orientation.

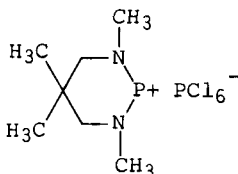
For the 2-chloro-1,3,2-diazaphosphorinanes, like the 1,3,2-dioxa and 1,3,2-dithia derivatives, halogen exchange readily takes place; the apparent stereochemical rigidity is lost under exchange conditions. Treatment of 295 ($\text{R}_1 = \text{Cl}$, $\text{R}_2 = \text{CH}_3$) with PCl_5 generated diaminophosphenium ion 299 with attendant loss of stereochemical "rigidity" of the ring (319).

The question of orientation of the *N*-methyl groups in 295 was approached by using ^1H and ^{31}P NMR, which pointed to equatorial positioning of the 1,3-methyl groups. An angular dependence of N-P $p\pi-d\pi$ bonding was suggested from comparison of ^{31}P chemical shifts for 295 ($\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{H}$), in which both nitrogen lone pairs may be axial, and the rigid bicyclic structures 39, 40, and 300, in which one (39) or two (40, 300) lone pairs are constrained to equatorial arrangements. A stepwise deshielding was observed in going from 295 ($\text{R}_1 = \text{C}_6\text{H}_5$, $\text{R}_2 = \text{H}$) to 39, to 40, and 300, as expected from the more efficient overlap provided by an axial lone pair (45).

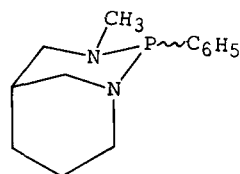


298 a: R = H

b: R = Cl

c: R = OC_2H_5 

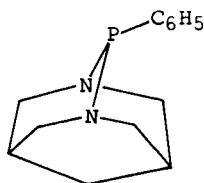
299



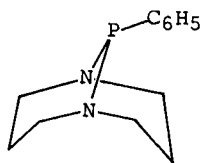
39

Ring $^3J_{\text{PNCH}}$ values for the 295 series vary drastically with the P-substituent, from ca. 10 Hz for 4,6-axial and equatorial protons with $\text{R}_1 = \text{Cl}$ to $^3J_{\text{PNCH}_a} = 0$ Hz and $^3J_{\text{PNCH}_e} = 5$ Hz with

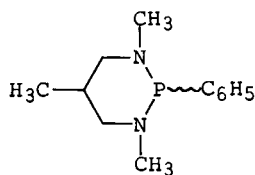
$R_1 = C_6H_5$. The $^3J_{PNCH_3}$ values for 295 ($R_2 = C_6H_5$; $R_2 = CH_3$, H) and (at least the major isomer of) 38 are 14 to 15 Hz, but $^3J_{PNCH_3}$ for 39 is only 12 Hz; the $\underline{N}-CH_3$ in the latter (39) is also shifted upfield by 0.1 ppm. Further study of the two possible isomers of 38 and 39 would help to unveil stereochemical uncertainties surrounding 1,3,2-diazaphosphorinane stereochemistry.



40



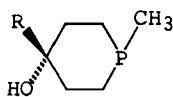
300



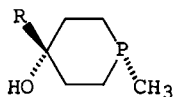
38

E. Phosphorinanes

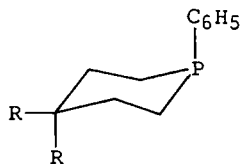
Geometrical isomerism in substituted phosphorinanes was demonstrated in 1965 by Quin and co-workers (43b,320), who prepared a series of isomeric phosphorinanol 301 [$R = H$, C_2H_5 ,



301a

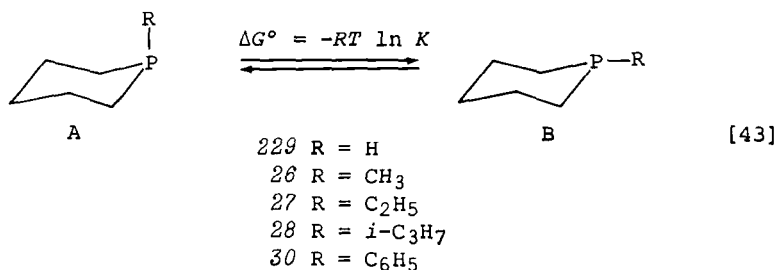


301b

302 $R, R = O$ 303 $R, R = OCH_3$

$CH_2CO_2C_2H_5$, CH_2CH_2OH , C_6H_5 , $t-C_4H_9$ (33)] and successfully separated the C_2H_5 , C_6H_5 , and $t-C_4H_9$ derivatives. The assignment of cis and trans isomers was tentatively accomplished by IR and NMR properties (43b,320), which led to the (then) unprecedented suggestion that a methyl group on phosphorus could readily occupy either axial or equatorial positions. The assignments were corroborated through X-ray analysis of the *t*-butyl derivative 33a (301a, $R = t-C_4H_9$) (321), which adopts a chair conformation with axial methyl and hydroxy groups. X-Ray analyses of rings unbiased by carbon substitution, 302 and 303, likewise showed chair conformations, with the *P*-phenyl group axial in both cases (322). In the same vein Lambert and co-workers (236,323) deduced from ^1H NMR data that the parent compound, phosphacyclohexane 229, exists almost entirely in the axial P-H conformation. Thus a body of evidence denoted a situation in which substituents on phosphorus in phosphorinanes prefer (or at least are unhindered in) the axial orientation.

To place these observations on a quantitative basis, Quin and Featherman (324) investigated the conformational equilibria between simple 1-substituted phosphorinanes (26-28, 30) (eq. [43]) by low-temperature ^{31}P and ^1H NMR spectroscopy. From the



variable temperature behavior of the equilibria, thermodynamic parameters were determined (Table 18). A surprising result is revealed by the data: while the relatively small enthalpy difference (ΔH°) between the isomers favors the equatorial conformation (B) at low temperatures, the entropy difference (ΔS°) cancels

Table 18 Thermodynamic Parameters for Phosphorinane Derivatives (324), and Comparison with Data for Cyclohexane (325)

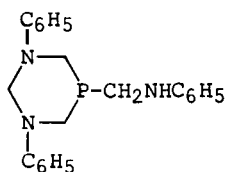
No.	R	ΔH° (kcal/mol)	ΔS° (e.g.)	ΔG° , kcal/mol		ΔG° for cyclohexyl-R	
				163°K	300°K ΔG°		
26	methyl	-0.7	-3.4	-0.1	0.35	8.7	-1.70
27	ethyl	-0.7	-3.2	-0.2	0.25	8.4	-1.75
30	phenyl	-0.6	-2.6	-0.15	0.2	9.3	-3.0
28	i-propyl			-0.5		8.6	-2.15

this preference as the temperature is increased, so the axial conformation (A) predominates over the equatorial one. At room temperature the axial form (A) predominates. The preference (ΔG°) for the equatorial conformer at low temperature, resulting mostly from the ΔH° term, still was quite small compared to that in cyclohexane (325) systems (Table 18). The equatorial preference for 26 at -130°C of only 2:1 is remarkably low when compared to that of methylcyclohexane (99:1 at -110°C) (326) or *N*-methylpiperidine (95:1 at -150°C) (327a). 1-Methylarsenane, which assumes a chair conformation, has an equal population (1:1, $\Delta G^\circ = 0$) of axial and equatorial conformers at -144°C (327b).

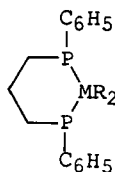
Barriers to ring inversion ($\Delta G^\ddagger$) for **26-28** and **30**, determined by DNMR (324b), were in the range 8.4 to 9.3 kcal/mol (Table 18), slightly lower than the barrier for cyclohexane and methylcyclohexane of 10 to 11 kcal/mol (328). The value of $\Delta G^\ddagger$ for **26** (8.7 kcal/mol) compares with a $\Delta G^\ddagger$ of 11.8 kcal/mol for *N*-methylpiperidine (**26**) and 6.8 kcal/mol for 1-methylarsenane (327a), the relative order roughly corresponding to the atomic radius of the heteroatom.

Quin and Lee (238b) have reported on the stereochemical consequences of mono-*C*-methylation of positions 3 or 4 of 1-methylphosphorinane. The energetics were found to be dominated by the added methyl group.

Quin and collaborators have reported reliable ^{13}C NMR procedures for the assignment of diastereomeric phosphorinanes (43a,43c,238b). Lambert and co-workers (43e) have discussed the application of ^{13}C NMR to the determination of conformational preferences of 1-substituents in phosphorinanes, and in penta-methylene heterocycles in general. The effect of steric environment on ^{31}P chemical shifts has also been explored (238b,329).



304



305

Diazaphosphorinane **304** was tentatively assigned a chair conformation with an axially favored $-\text{CH}_2\text{NHC}_6\text{H}_5$ group (330). The barriers to pyramidal inversion at phosphorus of 1,3-diphosphorinanes **305** [$\text{MR}_2 = \text{C}(\text{CH}_3)_2$, $\text{Ge}(\text{C}_2\text{H}_5)_2$, $\text{Si}(\text{CH}_3)_2$] were studied by Hauser and co-workers (331).

F. Origin of the Axial Preference for Substituents on Phosphorus

The most noteworthy aspect of conformational studies of phosphorus heterocycles is the observation that substituents on phosphorus are relatively unstrained in an axial orientation. This axial preference contrasts with the situation in cyclohexane, where relatively strong equatorial preferences for, *inter alia*, alkyl groups is reflected in large, negative conformational energies ($-\Delta G^\circ$ axial $\ddagger$ equatorial), ranging from 1.7 kcal/mol for methyl to >4.4 kcal/mol for *t*-butyl (325).

Early in the development of conformational theory methyl- and other alkyl-substituted cyclohexanes were examined intensively, and the concept of equatorial preferences as the norm was embedded in traditional thinking (326,332). This generality has

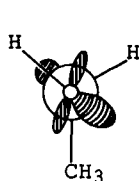
been augmented by the discovery of equatorial preferences for alkyl groups in various six-membered heterocyclic systems such as 1,3-dioxanes (20,115,305b,307b), 1,3-dithianes (222), and 1,3-oxathianes (although the degree of preference varies with the ring system and position of substitution). A strong equatorial preference has also been demonstrated for the methyl group in *N*-methylpiperidine at ambient temperature ($\Delta G^\circ = -3.0$ kcal/mol) (333). However, investigations of other heterocyclic systems have shown that an equatorial orientation for substituents on heteroatoms is not universally preferred. *S*-Alkylthianium salts display greatly diminished equatorial preferences ($-\Delta G^\circ = 0.0$ to 0.3 kcal/mol) (335), and the previously discussed 1-alkylphosphorinanes have a predominance of axial 1-alkyl groups at ambient temperatures ($\Delta G^\circ = 0.19$ to 0.35 kcal/mol) (324). Calculations for 1-methylsilacyclohexane predict essentially no conformational favoring for the methyl group ($\Delta G^\circ = 0.0$ to 0.2) (334). Other examples (26) of axial preferences have been noted for protonated thiane, thiane-1-oxide, and thiane-1-(*N*-tosyl)imide (336); selenane derivatives (336g,337); arsinane derivatives (43e,313, 327b); and 2-oxo-1,3,2-dioxathianes (338).

Suggested explanations for the tendency of substituents on certain heteroatoms (of cyclohexane rings) to assume an axial orientation include: (1) replacement of the normal 1,3 *syn*-axial repulsions found in cyclohexyl rings with attractive 1,3 *syn*-axial interactions (336g,337), and (2) relief of 1,3 *syn*-axial repulsions by a substantial flattening of the ring at the heteroatom end (324b). The latter interpretation is physically represented in X-ray crystallographic studies, which show flattened rings for *S*-methylthianium salts (335) and for phosphorinanes 302a and 302b (322). Allinger and Wertz proposed (332d) that the equatorial preference displayed by methylcyclohexane is caused by four unfavorable vicinal gauche hydrogen-hydrogen interactions when the methyl group is axial, as opposed to only two unfavorable interactions when the methyl is equatorial (and not to the usually assumed repulsive *syn*-axial methyl-hydrogen interactions). The Allinger-Wertz interpretation implies that removal of such gauche interactions by replacement of a carbon with a heteroatom bearing lone electron pairs should depress the equatorial preference. However, the hypothesis regarding methylcyclohexane has been challenged (332e), and it does not account for the similar conformational energies of groups at the 2-position in 1,3-dithianes or the elevated ΔG° values (compared to cyclohexane) observed for 2-substituents in 1,3-dioxanes. The alleviation of gauche interactions may partly account for the apparent increased flexibility of heterocycles, that is, the flattening of the heteroatom portion of the ring, which reduces repulsive interactions at the *syn*-axial positions.

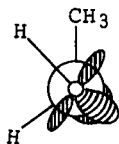
The placement of additional heteroatoms adjacent to phosphorus, as in 1,3,2-dioxo-, 1,3,2-dithia-, and 1,3,2-diazaphosphorinanes, introduces additional considerations into the determination of conformational preferences. This is readily apparent

from a comparison of group conformational energies for 1-alkyl-phosphorinanes (Table 18) with the corresponding values for 1,3,2-dioxaphosphorinanes (Table 15). Thus, for example, both 1-methyl and 1-phenyl groups show substantially enhanced axial preferences in 1,3,2-dioxaphosphorinanes ($\Delta G_{\text{CH}_3} = 1.1$ to 1.2 kcal/mol; $\Delta G_{\text{C}_6\text{H}_5} \geq 1.8$ kcal/mol) (35), than in the parent phosphorinane system ($\Delta G_{\text{CH}_3} = 0.25$ kcal/mol; $\Delta G_{\text{C}_6\text{H}_5} = 0.19$ kcal/mol) (324). In addition, the strong axial preferences displayed by small, polar substituents in 1,3,2-dioxaphosphorinanes ($\Delta G_{\text{CH}_3\text{O}} \geq 3.2$ kcal/mol; $\Delta G_{\text{Cl}} > 1.5$ kcal/mol) (35) and in 1,3,2-dithiaphosphorinanes points to an exaggeration of axial preferences due to adjacent ring oxygen or sulfur atoms. Although this favoring is predicted by the "generalized anomeric effect," in which polar groups (e.g., CH_3O , Cl) at the 2-position in 1,3-dioxanes show a marked axial favoring, the preference is considerably greater in 1,3,2-dioxaphosphorinanes, indicating an interaction between the ring oxygens (or sulfurs) and the phosphorus. An explanation and evaluation of this interaction may be provided by the "gauche effect" (339), a theoretical rule that can predict the relative stabilities of rotational isomers containing adjacent electron pairs and/or polar bonds. Thus the gauche effect attributes maximum stabilization to the conformation with the maximum number of gauche arrangements of electron pairs (barring repulsive steric interactions) and polar bonds with the stipulation that the favoring of adjacent polar bonds outweighs the favoring of a polar bond adjacent to two lone pairs.

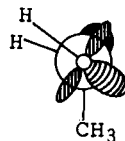
Perhaps the clearest description of the relevant interactions involves a comparison of the internal rotational potential function provided by Radom, Mehre, and Pople (340) for CH_3NHOH compared to 2-substituted 1,3,2-dioxaphosphorinanes. Calculations predict that structures 306A and 306B are the two stable conformations for CH_3NHOH , and this was confirmed by experiment (341). Rotamer 306C represents a potential energy



306A



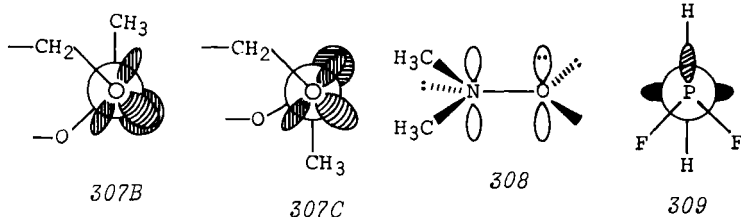
306B



306C

maximum, calculated to be ca. 4.0 kcal/mol higher in energy than 306B. By analogy (35) the corresponding forms 307B and 307C for 2-R-1,3,2-dioxaphosphorinanes represent the R-axial and R-equatorial forms, respectively. Thus 307B with axial alkyl corresponds to the more stable conformation.

The theoretical rationale for the preferred rotational conformers stems from a bonding stabilization shown for CH_3NHOH

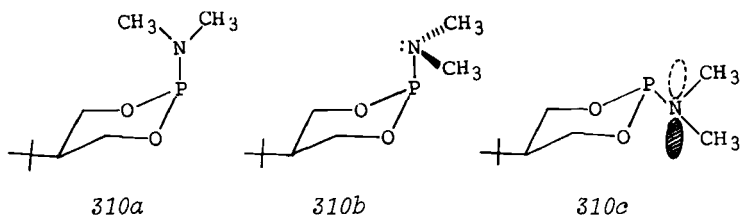


(308), in which donation from the highest energy lone pair on oxygen to the partially vacant $2p$ orbital on nitrogen (a type of back-bonding) is maximized by conformation 306A (or 306B). This stabilization is apparently enhanced by replacement of R-alkyl by a more electronegative group and thus presents a theoretical argument for the anomeric effect found in systems having electronegative groups adjacent to lone pairs of electrons. A related treatment (342) of such interactions pictures the stabilization of pertinent conformations as a result of donation of an adjacent lone pair into a neighboring σ^* orbital, and such donation has the same orientational requirement as shown in 306A and 306B. Likewise, the stabilization is increased when the σ^* antibonding orbital energy is lowered by augmentation of the polarity of the bond (i.e., with Cl and CH_3O). Similar interactions are also relevant to the 1,3,2-dithiaphosphorinane system.

Superimposed on the electronic interactions depicted here are the steric interactions suffered by an axial substituent on phosphorus with the 1,3-axial hydrogens. This is reflected in the decrease of ΔG (ax $\rightarrow$ eq): $\text{CH}_3 > i\text{-C}_3\text{H}_7 > t\text{-C}_4\text{H}_9$ (Table 15); apparently with the very bulky $t\text{-C}_4\text{H}_9$ group, this steric interaction dominates such that an equatorial orientation is preferred in both 1,3,2-dioxaphosphorinanes (35) and 1,3,2-dithiaphosphorinanes (47,48,51).

The preferred equatorial orientation demonstrated for the $(\text{CH}_3)_2\text{N}$ and CH_3NH groups (35,130) apparently arises from a $p\pi\text{-}d\pi$ interaction which is maximized when the nitrogen is equatorial. As demonstrated by microwave studies, the preferred conformation for F_2PNH_2 is that shown in 309 (343), which may reflect p -orbital back-donation from nitrogen into the available phosphorus d orbitals. The corresponding, favored conformation for the axial $\text{N}(\text{CH}_3)_2$ group in a 1,3,2-dioxaphosphorinane, 310a, would experience severe *syn*-axial interactions with the 4,6-axial hydrogens. Electronically unfavored conformation 310b, in which the offending *N*-methyls are directed away from the ring, would be a likely, but poor, alternative. On the other hand the equatorial $(\text{CH}_3)_2\text{N}$ can adopt conformation 310c, in which maximal $p\pi\text{-}d\pi$ stabilization is allowed and steric problems are absent.

Diverse discussions on the origin of the axial preference of substituents on phosphorus in tricoordinate and tetracoordinate compounds have been presented elsewhere (27,35,142b,324b).

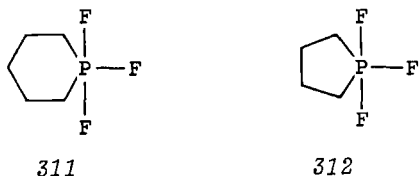


V. Stereochemistry of Compounds with Cyclohexane Rings Containing Pentacoordinate Phosphorus

A fascinating property of pentacoordinate phosphorus compounds is the occurrence of intramolecular exchange of ligands about the central phosphorus atom, a process commonly referred to as pseudorotation. The permutation of ligands about the (groundstate) trigonal bipyramidal (local D_{3h}) phosphorus can be effected by different mechanisms, two of which, the Berry and turnstile mechanisms, have been proposed to take place in real systems. The more prevalent Berry mechanism involves the pairwise positional exchange of two apical and two equatorial groups (with one stationary equatorial group acting as a pivot ligand); the transition state for this mechanism has local C_{4v} symmetry. A large body of work has been published on this subject, including many reviews (94,344).

Pentacoordinate species, which have the option of intramolecular ligand reorganization, are produced as intermediates in a variety of reactions at phosphorus. Some stereochemical aspects of this have already been presented in preceding segments of this review. In this section the discussion is limited to relatively stable, observable phosphoranes.

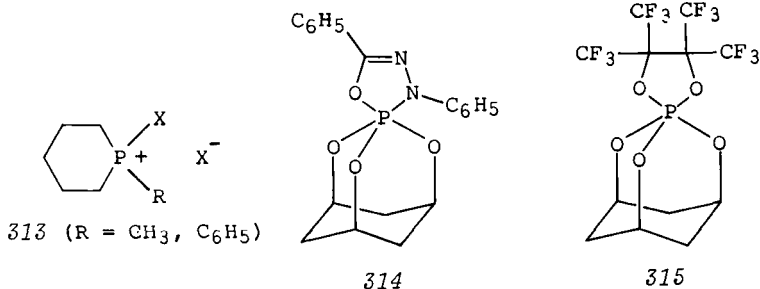
Muetterties and co-workers (345) obtained **311**, which shows no pseudorotation at 100° ; **311** may be strongly conformationally biased to the structure with apical fluorines and a diequatorial bridging six-membered ring. Compound **312** does pseudorotate at room temperature, and on cooling adopts a structure in which the



ring is diequatorial. In general, because of the apicophilicity of electronegative substituents, R_3PF_2 compounds do not show pseudorotation at room temperature, unlike RPF_4 and R_2PF_3 compounds. Superimposition of ring-bridging constraints further affects pseudorotation: three-atom bridging is restricted to an apical-equatorial connectivity. Calculations have predicted a

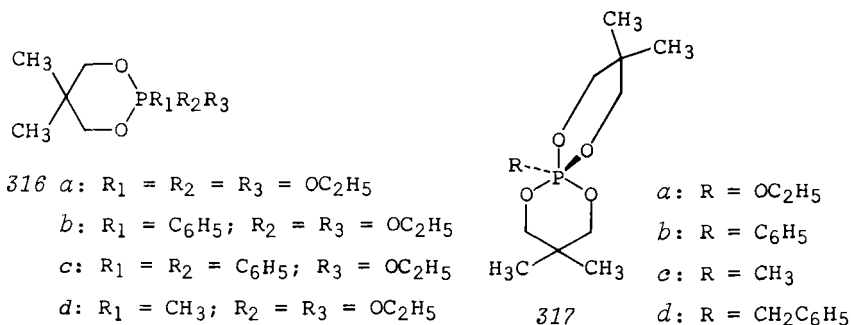
preference of the phosphorinane ring for a diequatorial orientation in a trigonal bipyramidal phosphorane (346).

The 1:1 adducts of I_2 , Br_2 , and Cl_2 with 1-methyl- and 1-phenylphosphorinane are markedly ionic molecular complexes (see 313) rather than phosphoranes (347). Complexes of the corresponding (1:1) arsenic compounds with chlorine and bromine are conversely trigonal bipyramidal, covalent adducts.



Oxyphosphoranes have received considerable attention. An X-ray structural analysis of 314 reveals a distorted trigonal bipyramid with the five-membered ring spanning apical-equatorial positions (ring oxygen apical, nitrogen equatorial). Other caged, polycyclic phosphoranes with phosphorus-containing cyclohexane rings have been studied from a structural and mechanistic viewpoint (348,349). Compounds such as 315 have been suggested to undergo permutational isomerization by a turnstile mechanism (344b,348).

Denney and co-workers (350) prepared compounds with one or two 1,3,2-dioxaphosphorinane rings incorporated in a penta-coordinate structure. The ^1H NMR spectra of all of these compounds were best explained by rapid intramolecular ligand reorganization. In 317 one ring must be equatorial-equatorial, thus



the single substituent is apical. Variable-temperature NMR spectra of 316a, 316b, 316d, and 317a were unchanged to ca. -60°. Compound 316c showed two doublets for the methylene protons of one ring at -65°, attributed to the prevalence of 318. The

formational properties of the six-membered ring. These considerations are pertinent to mechanisms of nucleophilic substitution at tetracoordinate phosphorus in phosphorus-containing six-membered rings (352).

VI. OVERVIEW

Over the past 25 years the area of conformational analysis has been extensively investigated with respect to aliphatic, alicyclic, and heterocyclic organic compounds (16-23). Recent interest has focused on, among other things, saturated six-membered heterocycles containing main-group elements from the second, third, and fourth rows of the Periodic Table (26,27; this chapter). In this realm new stereochemical and conformational experiences have been encountered. For example, although substituents attached to carbon and nitrogen atoms in saturated, six-membered rings usually prefer an equatorial orientation, the same groups display this tendency to a much weaker degree when attached to atoms such as sulfur, phosphorus, selenium, and arsenic--indeed, axial preferences are often observed. This conformational novelty has stimulated much interest and study, especially on phosphorus-containing cyclohexane systems (phosphorinanes) (26,27; this chapter).

As brought out in this chapter, dipolar interactions, attractive van der Waals forces, and ring distortion have been advanced by different researchers to rationalize the axial favoring (or equatorial disfavoring) phenomena. We believe that, depending on the system under study, various combinations of these three factors are involved.

An exciting revelation is the propensity for certain 1,3,2-dithiaphosphorinane derivatives to assume twist conformations, whereas this does not occur with analogous 1,3,2-dioxaphosphorinanes or phosphorinanes. Importantly, the favoring of the twist form is not apparently caused by molecular constraints; it is naturally adopted. Further study in this area should be fruitful.

The structural and conformational properties of 1,3,2-diazaphosphorinanes are vague at this time. But observations peculiar to this system herald another potentially interesting area for future work. X-Ray data for this class of compounds are long overdue.

For the 1,3,2-dioxaphosphorinanes nucleophilic and electrophilic reactions have furnished a wealth of novel chemistry of stereochemical significance. However, regarding the other phosphorus-containing cyclohexanes, a vast territory remains largely unexplored.

The biological relevance of phosphorus-containing cyclohexanes is evident from Sect. III-D. For example, modification of cyclic nucleotides can lead to derivatives that have different susceptibilities to hydrolysis by phosphodiesterase. Application of some of the chemistry and structural information

derived from simple systems to the cyclic nucleotides could provide new compounds with unusual (and perhaps useful) biological properties.

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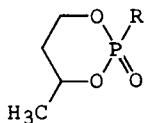
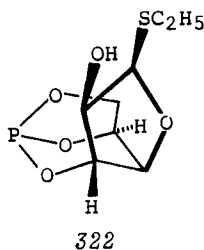
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ADDENDUM

Because of the time gap between manuscript preparation and the publication of monographs of this type, coupled with high activity in this area, we deemed it worthwhile to update this review. Coverage of relevant chemical literature has been extended up to December 1978.

Section I. A review on the Kerr effect and its application to organophosphorus compounds has appeared in print (353). The Kerr effect has been used in the conformational analysis of tri- and tetracoordinate 1,3,2-dioxaphosphorinanes.

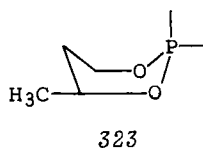
Section III.A.3. Phosphorylation of hexofuranosides with $(C_2H_5N)_3P$ furnished sugar-derived 1-phospha-2,7,8-trioxabicyclo [3.2.1]octane compounds (354). The formation of bicyclic phosphites, such as *D*-glucofuranoside 322, was governed by a *cis* relationship of the vicinal substituents at C-3 and C-4 of the tetrahydrofuran ring.



141 R = OCH₃

142 R = N(CH₃)₂

151 R = CH₃

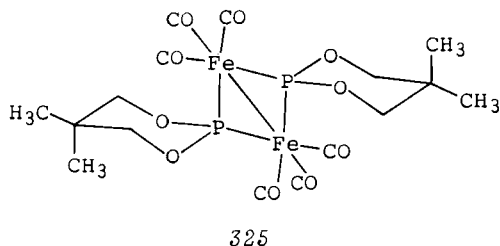
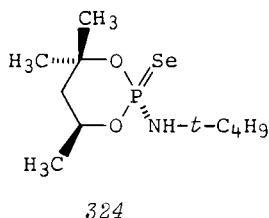


Section III.B.1.a. Dipole moment data indicated that $N(CH_3)_2$ and $N(C_2H_5)_2$ strongly prefer an equatorial orientation in 2-dialkylamino-2-oxo-1,3,2-dioxaphosphorinanes with no biasing substituents on ring carbons 4, 5, and 6 (355).

220-MHz ^1H NMR data for both isomers of 141, 142, and 151 were analyzed in depth (356). Compounds 141a (*trans*), 142b (*cis*), 151a (*cis*), and 151b (*trans*) each exist as a single chair conformation ($\geq 95\%$) with the 4-methyl group equatorial. Both 141b and 142a, which with an equatorial 4-methyl group in a chair conformer have an unfavorable orientation of the phosphorus substituents, exist as conformational mixtures. Mosbo, using vicinal coupling constants, suggested that 141a contained 60% equatorial chair, 20% axial chair, and 20% boat (*viz.* 323) conformers; and that 142b contained 68% equatorial chair, 16% axial chair, and 16% boat (323) conformers. Small amounts (10–20%) of boat (or twist) conformers may be present in conformational mixtures of 1,3,2-dioxaphosphorinanes, which are reported to be composed of two interconverting chair conformers (e.g., 144b and 301).

Section III.B.1.b. Investigation of 324 by X-ray crystallography revealed a twist conformation in the solid state (357).

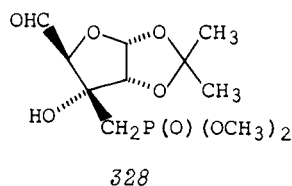
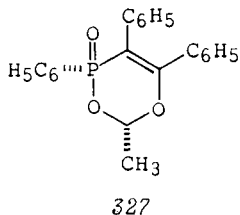
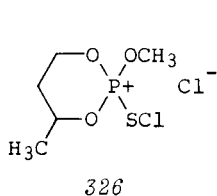
This is not unreasonable since both possible chair forms of **324** suffer severe 1,3 syn-axial interactions.



Section III.B.1.c. Bis[μ-5,5-dimethyl-1,3,2-dioxaphosphorinano]hexacarbonyldiiron, in the solid state, has a "butterfly" geometry, typical of such complexes, and contains chair dioxaphosphorinane rings (**358a**). The rings are tilted with respect to the Fe-Fe axis, so that one iron atom is axial and the other is equatorial with respect to a single phosphorinane ring. Given the approximate C_2 symmetry (**325**), each iron atom is axial in one ring and equatorial in the other. ^1H NMR of **325** showed a single resonance for the 5,5-dimethyl groups (from -75 to 100°C), reflecting fluxional properties in solution (phosphorinane ring inversion) (**358b**). Observation of the ring methylene signals (60 MHz, $26-79^\circ$) disclosed a loss of $^5\text{J}_{\text{PH}}$ attributable to fluxion of the Fe-P-Fe-P ring at higher temperatures.

Section III.B.2.a. Nucleophilic displacement of 4-nitrophenoxide from **165a** ($\text{R} = \text{NO}_2$) and **165b** ($\text{R} = \text{NO}_2$) by 4-methylphenoxide was studied (**359**). Substitution occurred with both inversion and retention at phosphorus, the relative amount of which was dependent on the cation and solvent involved. A high degree of association between the cation (e.g., lithium) and oxy-anion favored retention.

Stereospecific chlorinolysis (Cl_2 or SO_2Cl_2) of phosphorothionates **138a** and **138b** was shown to involve diastereomeric phosphonium intermediates (viz. **326**) by ^{31}P NMR (**360**).



Section III.C.1. One of the two isomers (**327**, E configuration) formed in the reaction of $(\text{C}_2\text{H}_5)_2\text{P}(\text{O})\text{C}(\text{N}_2)\text{C}(\text{O})\text{C}_6\text{H}_5$ with acetaldehyde was identified by X-ray crystallography (**361**). The unsaturated heterocyclic ring adopts a flattened half-chair con-

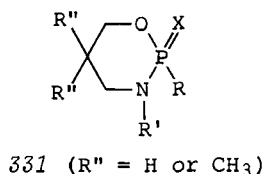
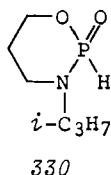
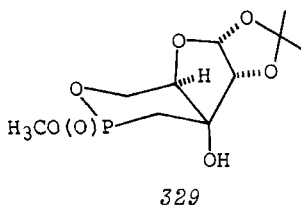
formation with pseudoaxial *P*-phenyl and pseudoequatorial methyl groups.

Sodium borohydride reduction of **328** afforded sugar-derived oxaphosphorinane **329**, which has a chair phosphorinane ring; the configuration at phosphorus was not established (362).

Section III.C.2. An NMR study of **330** indicated one predominant chair conformation with an axial P-H bond (363). Dipole moment measurements on several derivatives of **331** ($X = O$) indicated chair conformers with axial *P*-substituents (364).

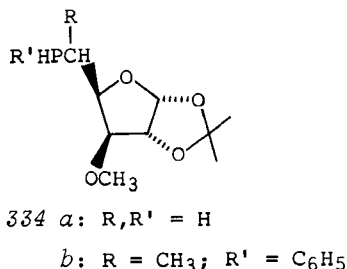
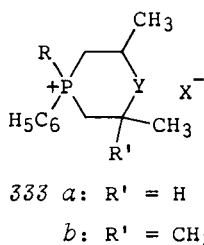
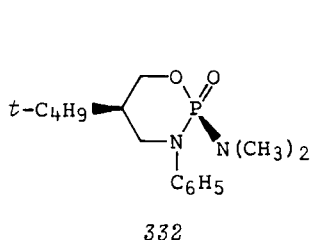
X-Ray analysis of **332** revealed a twist structure in the solid state (365). ^1H NMR studies indicated the preference of a twist conformer in solution as well. The trans isomer related to **332** is also a twist conformer in the solid state, but favors a chair conformer in solution [equatorial *t*-C₄H₉ and N(CH₃)₂] (365).

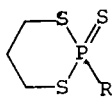
X-Ray analysis of **331** ($R = \text{OC}_6\text{H}_5$, $R' = \text{CH}_3$, $R'' = \text{H}$, $X = \text{S}$) showed a chair structure with the $\text{P} = \text{S}$ bond equatorial; the ring nitrogen was nearly planar (366a).



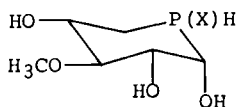
Section III.C.4. ^1H , ^{13}C , and ^{31}P NMR data for 2-thiono-1,3,2-dithiaphosphorinanes **219a-219e** and **219** [$R = \text{OCH}_3$, C_6H_5 , *t*-C₄H₉, 2,2-dimethylaziridinyl (DMA), and *t*-C₄H₉NH] were analyzed (226b). When $R = \text{Cl}$, OCH_3 , or DMA, the molecule adopts a chair conformation, with an axial *R* group; when $R =$ bulky R_2N (as in **219c-219e**), the molecule adopts a chair conformation with an equatorial *R* group; and when $R = \text{C}_6\text{H}_5$, CH_3 , $\text{N}(\text{CH}_3)_2$, or $\text{NH-}t\text{-C}_4\text{H}_9$, the molecule exists as a chair-chair mixture.

Section III.C.6. A large series of 1,4-heterophosphorinanium salts **333** ($Y = \text{O}$, S , NH , NCH_3) were prepared by Samaan (366b). The configuration and conformation of the salts, formed as iso-



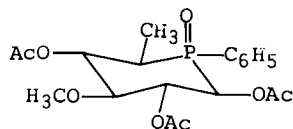


219



335 a: X = lone pair (lp)

b: X = O

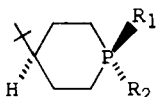
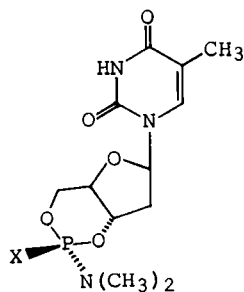


336

meric mixtures from divinylphosphonium compounds and H_2Y , were studied by ^1H and ^{13}C NMR spectroscopy.

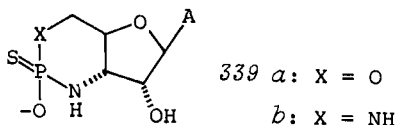
Interesting sugar analogs with phosphorus as the ring heteroatom have been synthesized (367). Treatment of 334a with aqueous HCl gave 335a, which was directly oxidized to 335b; the configuration at phosphorus in 335b was not established (367b). Treatment of 334b with aqueous HCl, followed by acetylation, gave a mixture of D-glucopyranose and L-idopyranose compounds (367a). A crystalline material, identified as 336 by X-ray crystallography (368), was isolated from the sugar mixture (367a).

^{13}C (and ^{31}P) NMR data (369) for 337a-337d reinforced original stereochemical assignments (43f). An X-ray analysis of 337c displayed a chair conformation with t-butyl and phenyl groups equatorial (369). Equilibration of 337c and 337d with 6N HCl at 125° produced a 25/75 mixture, respectively, indicative of the conformational preference for equatorial phenyl vs. $P=O$ (43f). Alkaline cleavage of stereoisomerically pure benzylphosphonium salts from 337a and 337b gave mixtures of oxides 337c/337d (66/34 and 21/79, respectively) (43f). The corresponding 4-methyl series gave corresponding oxide ratios of 48/52 and 22/78 (252). Hydroxide-induced cleavage of methylphosphonium salts from 337a and 337b (by displacement of phenyl) gave mixtures of oxides 337f and 337e (62/38 and 25/75, respectively) (43f) and cleavage of the phenylphosphonium salt from 337a (337b) gave oxides 337c and 337d (40/60).

337 a: $R_1 = C_6H_5$; $R_2 = lp$ b: $R_1 = lp$; $R_2 = C_6H_5$ c: $R_1 = C_6H_5$; $R_2 = O$ d: $R_1 = O$; $R_2 = C_6H_5$ e: $R_1 = CH_3$; $R_2 = O$ f: $R_1 = O$; $R_2 = CH_3$ 

338 a: X = lp

b: X = O



Hydroxide cleavage of methoxyphosphonium salts obtained by methylation of *337c* and *337d* occurs with complete inversion of configuration, if homogeneous conditions are employed (370). Under heterogeneous conditions, some attack at carbon (giving retention) is observed (352b,370).

Section III.D.1. Condensation of thymidine with hexamethylphosphorus triamide yielded cyclic nucleotide *338a*, having an equatorial amino group (371). Stereospecific oxidation with N_2O_4 gave *338b*. Methanolysis of *338a* at 70° afforded a mixture (60/40) of diastereomeric triesters. An X-ray analysis of *338b* shows the dioxaphosphorinane in a chair conformation with the dimethylamino group equatorial (262b,371).

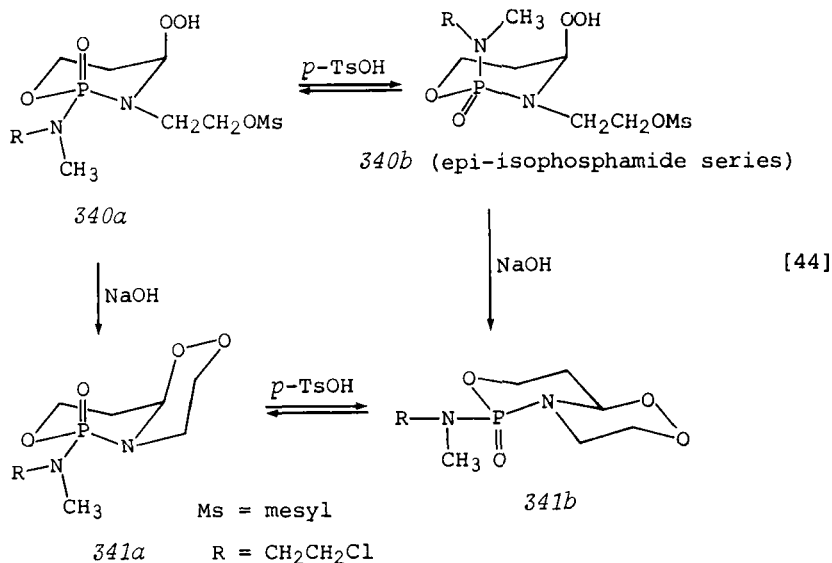
Analogous of c-AMP, *339a* and *339b*, were prepared as mixtures of diastereomers which were separated by chromatography (372). Reaction of *339a* with CH_2N_2 resulted in ring cleavage, but reaction of *339b* furnished a stable methylthio derivative. The P-N bonds in *339a* and *339b* were more stable to acid hydrolysis than those in the corresponding compounds with the P=O group. The diastereomers were stereochemically assigned using ^{13}C and ^{31}P NMR data. A diastereomeric pair of 2',3' cyclic nucleotides was also prepared, separated, and stereochemically identified.

Benkovic and co-workers utilized snake-venom phosphodiesterase to destroy one stereoisomer of adenosine monophosphorothioate *p*-nitrophenylester (AMPS-NPE). The intact AMPS-NPE isomer was cyclized under base catalysis to a single diastereomer of cAMPS (272), assignment of which is in progress (373a).

Section III.D.2. Optical resolution of cyclophosphamide (275a) was accomplished by recrystallization of diastereomeric α -naphthylphenylmethylsilyl derivatives, and cleavage of the endocyclic Si-N bond with cyclohexylammonium fluoride (373b).

Several 4-hydroperoxyisophosphamide analogs were synthesized by ozonolytic cyclization of 3-butenylphosphorodiamidates (374a), a reaction employed earlier to make 4-hydroperoxycyclophosphamide (276b) (374b), an active metabolite of 275a. Two stereoisomers were obtained for the isophosphamide series (281, 374a), whereas only a *cis* isomer was isolated in the synthesis of 276b (374b). Treatment of the unfractionated mixture of 340a and 340b with dilute NaOH produced cyclic peroxides 341a and 341b in a 5:1 ratio (eq [44]). Both 340a/340b and 341a/341b were interconvertible by the action of acid, giving equilibrium mixtures of 5:1 and 3:4, respectively (374a). High antileukemic activity *in vivo* was observed for the hydroperoxy analogs (374a).

Separate incubation kinetic studies with (+)- and (-)-275a in microsomal preparations gave nearly the same V_{max} and K_m values (375a). Other experiments also suggested an unusually low



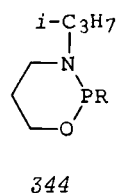
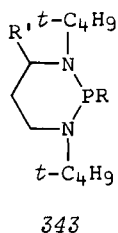
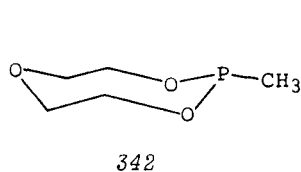
degree of biological stereoselectivity associated with metabolism of (+)- and (-)-275a. Animal testing of the enantiomers against mouse L1210 leukemia showed little therapeutic difference.

A synthesis of (+)- and (-)-226 from separable diastereomers in analogy to work with 275a (283) was reported by Zon's group (375b).

Verkade and co-workers studied the solution stereochemistry of 275a and its (pairs of) *cis*- and *trans*-4,6-dimethyl derivatives (375c). Using the two anomeric *cis*-4,6-dimethyl compounds as models, they concluded that the dominant conformer of 275a in solution has an equatorial amino group.

Zon's group has reported on some 5-bromocyclophosphamide compounds, which undergo interesting base-induced intramolecular cyclizations to 3,5-dehydro derivatives (375d).

Section IV.B. Eight-membered-ring heterocycle 342 was suggested as having a chair-chair conformation with an equatorial *P*-methyl group (376a). This contrasts with the preferred axial orientation in the 1,3,2-dioxaphosphorinane system.



Section IV. C. Borisenko and co-workers (376b) reported ^1H , ^{13}C , and ^{31}P NMR spectra for a variety of trivalent 1,3,2-dithia-phosphorinanes.

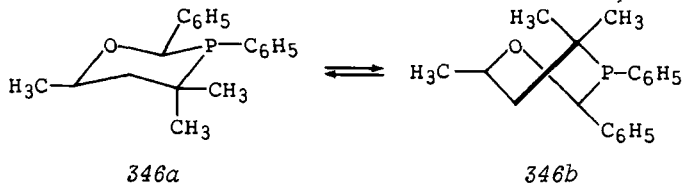
Section IV. D. The synthesis and stereochemistry of series 343 was reported (377); ^{31}P NMR chemical shifts were correlated with conformation.

An NMR study of the stereochemistry of series 344 was reported (363); 344 ($\text{R} = \text{H}, \text{Cl}, \text{C}_6\text{H}_5, \text{OC}_2\text{H}_5, \text{N}(\text{CH}_3)_2$) were claimed to exist in a chair conformation with axial R.

Section IV. E. Pyramidal inversion at phosphorus in 337a and 337b was used to obtain thermodynamic mixtures (from both sides of the equilibrium) at three temperatures (369). At 417°K , K_{eq} was 1.44 ($\Delta G^\circ = -0.30$ kcal/mol) and at 454°K , K_{eq} was 1.21 ($\Delta G^\circ = -0.17$ kcal/mol), corresponding to a preference for trans isomer 337b. This result contrasts with results of Featherman and Quin (324), which for 1-phenylphosphorinane indicated an axial preference for phenyl at 300°K ($\Delta G^\circ = 0.20$ kcal/mol) and exhibited a trend toward less positive ΔG° values at lower temperatures. The barrier to pyramidal inversion at 454°K was 36.0 kcal/mol; a $\Delta G^\ddagger$ (448°K) of 36.6 kcal/mol was found for the corresponding 1,3,2-dithiaphosphorinane 44 (51).

Semi-empirical force-field calculations on phosphorinanes were published (378). For phosphorinane itself (229) the calculated energy difference was 1.2 kcal/mol, favoring the axial proton on phosphorus. This preference was attributed to torsional energetics and "gauche hydrogen" interaction. Calculated values for *P*-methyl (-0.5), ethyl (-0.5), *i*-propyl (-0.6), and phenyl (0.2) were in reasonable agreement with experimental values, save for *P*-phenyl which was more strongly favored equatorially in the calculations.

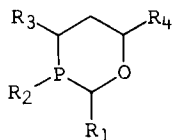
Diastereomers of substituted 1,3-oxaphosphorinanes (345), prepared by condensation of hydroxyphosphines and aldehydes, were studied by ^{13}C and ^{31}P NMR (379). Conformational equilibria were dominated by the equatorial preference of R_1 (phenyl or *t*-butyl). Trans, trans isomer 346 was suggested to exist as a mixture of chair (346a) and twist (346b) conformers, a sign of instability for the equatorial disposition of *P*-phenyl in 346a.



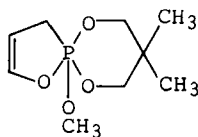
Section IV. F. Allinger and Voithenberg (378) reported molecular mechanics computations on phosphorinanes (*vide supra*).

CNDO/2 calculations for conformations of 2-R-1,3,2-dioxaphosphorinanes ($\text{R} = \text{H}, \text{Cl}, \text{dimethylamino}$) and 2-R-2-thiono analogs ($\text{R} = \text{H}, \text{Cl}, \text{OCH}_3$) were reported (380).

Section V. Permutational isomerization of 347 (observed above 35°) was studied by variable temperature NMR (381).



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