Conformational Analysis of Pentamethylene Heterocycles

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Contents

I. Introduction

Replacement of a single methylene unit in cyclohexane by a heteroatom (and its attendant substituents or lone pairs) provides a system **1** with a rich variety of conformational properties. The purpose of the first part of the present review

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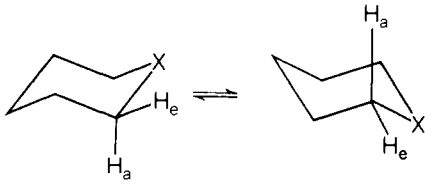
(section II) is to discuss each of these properties in turn and to summarize the current status of their analysis. The scope of the field is then explored (section III) by surveying these results according to the location of the heteroatom in the Periodic Table. This review will be restricted to systems that either are entirely unsubstituted or bear substituents only on the heteroatom (**1**). The conformational properties of substituents on carbon are very much like those of alicyclic systems and therefore are not of interest for the purpose of this review. Substituents on carbon may also alter the system sufficiently that changes in conformational properties cannot be interpreted entirely in terms of the heteroatom component. Additional heteroatoms in the ring give rise to new and interesting problems that go beyond the scope of the present review.

Heterocycles of the type **1** have been named according to four distinct systems. (1) The nitrogen (**1**, X = NH) and oxygen (X = O) molecules and their derivatives are usually referred to by the trivial names, piperidine and tetrahydropyran. (2) Any of these heterocycles can be named by prefixing the appropriate heteroatom abbreviation to "cyclohexane", as in silacyclohexane, germacyclohexane, phosphacyclohexane, arsacyclohexane, thiacyclohexane, and magnesiacyclohexane. This method is preferred only for the group IV heterocycles for reasons given below, although there is widespread usage in some group V and group VI heterocycles. (3) The word "pentamethylene" followed by the functional group term ending in "-ide" or "-ine" for the fully alkylated, neutral heteroatom is frequently used, particularly for the group VI heterocycles: pentamethylene oxide, pentamethylene sulfide, pentamethylenephosphine, pentamethylenearsine. The names are a single word for the group V compounds, because the functional group term is also the parent compound, e.g., PH_3 (phosphine). This system is probably the most awkward and will not be used in this article. (4) The preferred heterocyclic nomenclature indicates ring size, saturation, identity and number of heteroatoms, and presence of nitrogen by the structure of the compound name. For these saturated, six-membered rings with one heteroatom (only piperidines contain nitrogen), the compound name consists of the heteroatom prefix appended directly to the suffix "-ane," with some adjustments for assonance. In certain ambiguous situations, the full stem and suffix "-inane" is used; thus, arsenane, antimonane, oxane, thiane, selenane, tellurane, but borinane, silinane, germinane, phosphorinane, to be distinguished from borane (BH_3), silane (SiH_4), germane (GeH_4), and phosphorane (PH_5). This review will subscribe to this usage, except in the cases of the group IV compounds and metallocycles (silacyclohexane, etc., will be used in preference) and for the nitrogen and oxygen heterocycles, whose common names will be used.

II. Conformational Properties

We will consider four general conformational properties of pentamethylene heterocycles: the barrier to ring reversal, the conformational preference of substituents on the heteroatom, the shape of the ring, and conformationally dependent magnetic resonance parameters (chemical shifts and coupling constants). (1) The process of chair–chair ring reversal (eq 1)



(1)

converts the ring (disregarding substitution) to its mirror image and interchanges the axial or equatorial nature of all substituents. The barrier to this process is normally obtained by examination of the NMR spectrum as a function of temperature. (2) When the heteroatom bears a substituent, ring reversal provides a mechanism for the rapid interconversion of the two conformers. If ring reversal can be "frozen out" on the

TABLE I. Activation Parameters for Ring Reversal in Pentamethylene Heterocycles

Hetero group	Method[a]	Solvent	E_a, kcal/mol	Log A	$\Delta H^{\ddagger}$,[b] kcal/mol	$\Delta S^{\ddagger}$,[b] eu	$\Delta G^{\ddagger}(T_c)$,[c] kcal/mol	Ref
$Si(CH_3)_2$	CLS	$CBrF_3$	6.1	13.6[d]	5.5	1.7	5.5 (−162)	36, 37
NH	CLS	CD_3OD	14.5	16.9	13.9	16.8	10.4 (−62.5)[d]	1, 14
NH	CT	CD_3OD					10.3 (−62.5)[d]	1, 14
NH	CT	$(CH_2)_3$					10.7 (−55)	e
NH	CT	$C_6D_5CD_3$					10.2 (−65)	e
$\overset{+}{N}H_2\bar{C}l$	CT	SO_2					9.7 (−75)	e
NCH_3	CLS	CD_3OD	14.4	14.8	13.8	7.2	12.0 (−28)[d]	1, 14
NCH_3	CT	CD_3OD					11.8 (−28)	e
N–t-C_4H_9	CLS	CD_3OD	14.0	15.2	13.4	9.1	11.2 (−40)[d]	1, 14
N–t-C_4H_9	CT	CD_3OD					11.2 (−40)	e
N–t-C_4H_9	CT	$(CH_2)_3$					11.0 (−45)	e
N–t-C_4H_9	CT	$C_6D_5CD_3$					10.7 (−50)	e
N–Cl	CLS	CH_2Cl_2	17.0	15.5	16.4	10.4	13.6 (−1)[d]	46, 47
N–O·	ESR	CH_2Cl_2	6.4[d]	13.7[d]	5.8	2.2	5.1 (25)[d,f]	48
N–O·	ESR	H_2O	5.6		5.0			49
N–O·	ESR	CH_2Cl_2	6.0		5.4			50
P–CH_3	CT	$(CH_3)_2C{=}CHCH_3$					8.5 (−109)	22, 23
P–CH_3	CT	$CH_2{=}CHCl$					8.7 (−87)	22, 23
P–C_2H_5	CT	$CH_2{=}CHCl$					8.4 (−96)	23
P–C_2H_5	CLS	$CH_2{=}CHCl$	8.4, 9.1[d,g]	13.1, 13.8[d,g]	7.8, 8.5[d,g]	−0.6, 2.6[d,g]	7.9, 8.0 (−96)[d,g]	23
P–i-C_3H_7	CT	$CH_2{=}CHCl$					8.6 (−104)	23
P–C_6H_5	CT	$CH_2{=}CHCl$					9.3 (−65)	23
As–CH_3	CT	CBr_3F					6.8 (−128)	89
O	CT	$CD_3OD/CHClF_2$					10.3 (−61)	9
O	CLS	CD_3OD	10.7	13.9	10.1	3.1	9.5 (−80)[d]	5, 10
O	CT	CD_3OD					9.4 (−80)	10, e
O	ALS	CS_2	10.5	13.2	10.1	−0.1	10.0 (−65)[d]	2
S	CT	$CD_3OD/CHClF_2$					9.4 (−81)	9
S	CLS	CH_2Cl_2	11.6	15.7	11.0	11.3	9.0 (−93)[d]	5, 10
S	CT	CH_2Cl_2					8.8 (−93)	10, e
SO	CT	CH_2Cl_2					9.8, 10.0 (−70)[d,g]	9
SO	CLS	CH_2Cl_2	14.2[h]	17.1[h]	13.6[h]	17.7[h]	10.0 (−70)[h]	5, 12
SO_2	CT	CH_2Cl_2					10.3 (−63)	19
SO_2	CLS	CH_2Cl_2	14.9	17.3	14.3	18.7	10.4 (−63)[d]	5, 10
SO_2	CT	CH_2Cl_2					10.2 (−63)	10, e
S(NH)	CLS	$CH_2Cl_2/CHClF_2$	13.9[h]	16.1[h]	13.3[h]	13.2[h]	10.5 (−59)[h]	12, 13
S(NTs)	CLS	$CHClF_2$	14.2[h]	16.4[h]	13.6[h]	14.5[h]	10.5 (−57)[h]	12, 13
S(O)(NH)	CLS	CH_2Cl_2	14.1[h]	16.7[h]	13.5[h]	15.9[h]	10.2 (−65)[h]	12, 13
S(O)(NTs)	CLS	$CHClF_2$	12.6[h]	15.0[h]	12.0[h]	8.1[h]	10.3 (−58)[h]	12, 13
Se	CT	$CHClF_2$					8.2 (−105)	9
Se	CLS	$CHClF_2$	11.2	16.3	10.6	14.1	8.3 (−105)	9
SeO	CLS	$CHClF_2$	8.2, 8.2[g]	12.2, 12.9[g]	7.6, 7.6[g]	−4.7, −1.5[g]	8.4, 7.9 (−102)[g]	9, 11
SeO_2	CT	$CH_2Cl_2/CHClF_2$					6.7 (−133)	9, 11
Te	CT	$CHClF_2/CHCl_2F$					7.3 (−119)	9, 11

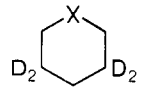
[a] CLS (complete NMR line shape), ESR (electron spin resonance), CT (NMR coalescence temperature), ALS (approximation NMR line shape). [b] These activating parameters have been calculated from literature data for a common temperature of 25°. [c] The coalescence temperature (°C) is given in parentheses. [d] Calculated from literature data. [e] Unpublished results of J. B. Lambert and R. G. Keske. [f] The published temperature does not correspond to coalescence. [g] Activation parameters for both directions of the equilibrium. [h] Data for only one direction, or average data were reported for this equilibrium.

NMR time scale (vide infra), the equilibrium constant may be obtained by direct integration. Otherwise, indirect methods must be used. The conformational preference of the substituent on the heteroatom has proved to be a sensitive probe of atom–atom interactions. (3) The torsional arrangements of the ring atoms in cyclohexane are altered by the replacement of a methylene group with a heteroatom. The overall result may be a ring that is more flattened or one that is more puckered than cyclohexane. In some cases, certain portions of the ring are flattened while others within the same ring are puckered. The analysis of proton spectra can describe these conformational deformations in great detail. (4) Finally, introduction of a heteroatom can alter the basic magnetic resonance parameters (chemical shifts and coupling constants) considerably, because of changes in the electronegativity of X, changes in the magnitude and sign of the diamagnetic anisotropy of the C–X bond, changes in the shape of the ring, and the introduction of lone pairs that are capable of new electronic interactions. In the next sections each of these conformational properties will be discussed in turn.

A. Barriers to Ring Reversal

Piperidine (**1**, X = NH) was the first pentamethylene heterocycle in which ring reversal was studied (1966).[1] Since that time a host of other systems have been examined (Table I). The greater number of these studies has used dynamic nuclear magnetic resonance methods. At room temperature rapid ring reversal interchanges the axial and equatorial substituents on a given carbon (eq 1). As a result, these protons, in the absence of substitution on the heteroatom, are spectrally equivalent. As the temperature is lowered, the rate of ring reversal is decreased, and the singlet resonance from the protons α to the heteroatom (ignoring coupling to the β protons) broadens and splits into an AB quartet. This simple A_2-to-AB

spectral process may be realized in practice by removal of the couplings to the β protons, either by chemical substitution with deuterium (**2**)[1] or by double irradiation.[2]



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The rate of ring reversal may be obtained most easily at the coalescence temperature by eq 2, in which $\Delta\nu$ is the chemical-shift difference between two uncoupled nuclei at slow exchange. Alternatively, eq 3 may be used for exchange processes between coupled nuclei, as in piperidine. The free energy of activation is then obtained from the rate by eq 4.

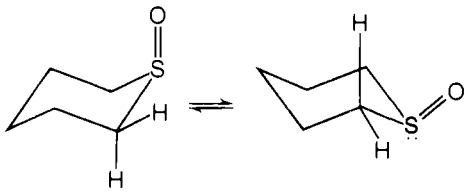
$$k_c = \pi\Delta\nu/\sqrt{2} \quad (2)$$

$$k_c = \left(\frac{\pi}{\sqrt{2}}\right)(\Delta\nu^2 + 6J^2)^{1/2} \quad (3)$$

$$\Delta G_c^{\ddagger} = 2.3RT_c(10.32 + \log T_c/k_c) \quad (4)$$

Although the coalescence temperature method is very easy to apply and provides exceptionally accurate values of $\Delta G^{\ddagger}$, it is restricted to very simple spin systems and gives only the free energy of activation, which is temperature dependent. Line-shape computer programs are available that can provide the rates of ring reversal at any temperature in the range over which spectral changes occur. Plots of log k *vs.* $1/T$ or of log (k/T) *vs.* $1/T$ can provide the Arrhenius activation parameters (E_a and A) or the enthalpy and entropy of activation, respectively. This complete line-shape method has the advantage of utilizing all available temperatures and all the spectral points at a given temperature. It is, of course, more troublesome to use than the coalescence temperature method, but it provides a richer set of activation parameters. Its most serious drawback is sensitivity to systematic errors such as changes in the line width of the slow-exchange chemical-shift difference. When these errors can be avoided, it is the method of choice. Approximate line-shape methods have also been developed, but they have been largely abandoned. The activation parameters in Table I have all been obtained by one of these methods,[3,4] except in the case that used electron spin resonance.

If the heteroatom bears a substituent, as in thiane 1-oxide, the two partners in the equilibrium may be unequally populated (eq 5).[5] The fast-exchange spectrum of the α protons is



(5)

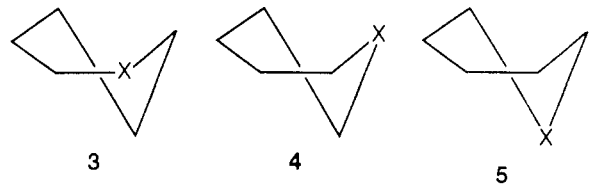
an AB quartet, since the cis/trans relationship between the protons and the oxide functionality is not altered by ring reversal. At slow exchange, each of the conformers produces its own AB quartet, so that the four-line spectrum is transformed into an eight-line spectrum. This more complicated set of spectral changes is best analyzed by the complete line-shape method.

The transition state for chair–chair ring reversal is generally considered to be the half-chair conformation, in which four ring atoms are coplanar. A pentamethylene heterocycle has the choice of three such conformations (**3–5**). The increase in energy in going from the ground-state chair to the transition-state half chair comes primarily from increased torsional interactions, although contributions from nonbonded interactions and angle-bending strain may be significant.[6,7] If the C–X torsional barrier is considerably different from the C–C barrier, then the barrier for ring reversal in the pentamethylene heterocycle can be expected to be different from that of cyclohexane ($\Delta H^{\ddagger}$ = 10.8 kcal/mol; $\Delta S^{\ddagger}$ = 2.8 gibbs; $\Delta G^{\ddagger}$ = 10.3 kcal/mol).[8] Because the number of ring protons is constant within a pentamethylene heterocycle series, barriers can probably be compared better from heterocycle to heterocycle than from heterocycle to cyclohexane. As a first approximation, it can be said that for molecules in which the C–X torsional barrier is lower than that of the C–C bond, transition state **3** is preferred, since the heteroatom relieves the greatest amount of eclipsing strain. If the C–X torsional barrier is higher, then transition state **5** is preferred, since the heteroatom is in the least eclipsed portion of the ring. If there is little difference between the C–X and C–C torsional barriers, then any of the transition states **3–5** might be utilized, or other factors may become dominant.

TABLE II. Torsional Barriers in CH_3–X–CH_3[a]

X	V_0, kcal/mol	X	V_0, kcal/mol
CH_2	3.3	S	2.13
NH	3.28	Se	1.50
NCH_3	4.40	Te	(1.2)
PH	2.22	SO	2.94
O	2.50	SiH_2	1.65

[a] The references for these barriers may be found in Table IV of ref 9.

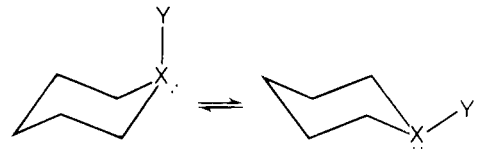


3 **4** **5**

If the barrier to ring reversal arises predominantly from torsional interactions, then variations between systems can be explained by examining the CH_3–X rotation barrier in molecules of the type CH_3–X–CH_3 (Table II).[9] The barrier to ring reversal should depend directly on the magnitude of the C–X torsional energy. Individual cases are discussed in the survey of pentamethylene systems found in section III.

B. Conformational Preferences of Substituents on the Heteroatom

For pentamethylene heterocycles that bear substituents at the 1 position, a simple equilibrium exists between axial and



(6)

equatorial forms (eq 6). A number of such systems have now been studied, and the results are enumerated in Table III. Equilibrium constants are most accurately determined when resonances from both isomers are observed in the slow-exchange NMR spectrum. Direct integration gives K_e, from which ΔG° is readily calculated ($-RT$ ln K_e). Failure to observe distinct resonances can arise because only one isomer is present (a "biased" equilibrium), because the slow-exchange limit is not obtainable, or because the spectra are fortuitously superimposed. Separate bands from axial and equatorial isomers can also sometimes be observed in the vibrational spectrum. The vibrational time scale is such that ring reversal does not average peaks, as in the NMR spec-

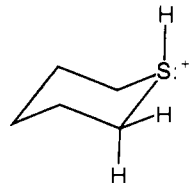
TABLE III. Conformational Preferences of 1-Substituents in Pentamethylene Heterocycles

Hetero group	Solvent	Method	Preference	$\lvert\Delta H^\circ\rvert$, kcal/mol	$\lvert\Delta G^\circ\rvert$, kcal/mol[a]	Ref
$SiHCH_3$	None	Calc.	ax (CH_3)	0.04		38
$SiHCH_3$	None	Calc.	ax (CH_3)	0.3		39
$SiH-t-C_4H_9$	None	Calc.	eq (t-C_4H_9)	1.6		39
$:SiH^-$	None	Calc.	ax (H)	0.25		39
:NH	CD_3OD	NMR	ax (H)			1, 14
:NH	$CDCl_3$	NMR	ax (H)		1.2 (24)	18–21
:NH	CCl_4	NMR	ax (H)			51
:NH	None	Calc.	ax (H)	0.6		45
:NH	CCl_4	Ir	eq (H)	0.4		54
:NH	None	Ir	eq (H)	0.53		25, 26
:NH	CCl_4	Ir	eq (H)	0.6		25, 26
:NH	CCl_4	Ir	eq (H)		0.5 (23)	52
:NH	CCl_4	Ir	eq (H)		0.47 (23)	53
:NH	None	MW	eq (H)	0.25		44
$:NCH_3$	CD_3OD	NMR	eq (CH_3)			1, 14
$:NCH_3$	$CDCl_3$	NMR	eq (CH_3)			18–21
$:NCH_3$	CCl_4	NMR	eq (CH_3)			51
$:NCH_3$	$CDCl_3$	NMR	eq (CH_3)		1.65 (31)	24
$:NCH_3$	None	Calc.	eq (CH_3)	0.8		45
$:NCH_3$	CCl_4	Ir	eq (CH_3)		1.61 (21)	53
$:NCH_3^\bullet$	Cyclohexane	NMR	eq (CH_3)		2.70 (15)	108
$:N-t-C_4H_9$	CD_3OD	NMR	eq (t-C_4H_9)			1, 14
$^+NCH_3(O^-)$	CH_2Cl_2	NMR	eq (CH_3)		0.68 (28)	73
$^+NCH_3(O^-)$	$CDCl_3$	NMR	eq (CH_3)		0.65 (28)	73
$^+NCH_3(O^-)$	D_2O	NMR	eq (CH_3)		0.28 (28)	73
$^+NCH_3(O^-)$	CF_3CO_2H	NMR	eq (CH_3)		1.1 (28)	73
:PH	$CFCl_3$	NMR	ax (H)			69, 70
:PH(S)	$CFCl_3$	NMR	ax (H)			70
$:PCH_3$	CH_2=CHCl	NMR	eq (CH_3)	0.68	0.12 (−110)	22, 23
$:PCH_3$	CH_2=CHCl	NMR	ax (CH_3)	0.68	0.35 (27)	22, 23
$:PC_2H_5$	CH_2=CHCl	NMR	eq (C_2H_5)	0.71	0.18 (−110)	23
$:PC_2H_5$	CH_2=CHCl	NMR	ax (C_2H_5)	0.71	0.26 (27)	23
$:P-i-C_3H_7$	CH_2=CHCl	NMR	eq (i-C_3H_7)		0.5 (−110)	23
$:PC_6H_5$	CH_2=CHCl	NMR	eq (C_6H_5)	0.58	0.16 (−110)	23
$:PC_6H_5$	CH_2=CHCl	NMR	ax (C_6H_5)	0.58	0.19 (27)	23
$:AsCH_3$	CBr_3F	NMR			0.0 (−130)	89
$^+$:SH	FSO_3H/SO_2	NMR	ax (H)			10
$^+:SCH_3$	CH_2Cl_2/SO_2	NMR	eq (CH_3)			9
$^+:SCH_3$	$CHCl_3$	Equil.	eq (CH_3)		0.275 (100)	94
:SO	CH_2Cl_2	NMR	ax (O)		0.175 (−90)	5
:SO	None	Calc.	ax (O)	0.37		98
:S(NH)	$CH_2Cl_2/CHClF_2$	NMR	eq (NH)		0.075 (−85)	12, 13
:S(NTs)	$CHClF_2$	NMR	ax (NTs)		0.145 (−89)	12, 13
:S(NBzs)	$CHClF_2$	NMR	ax (NBzs)		0.070 (−89)	12, 13
S(O)(NTs)	$CHClF_2$	NMR			0.25 (−89)	13
$^+$:SeH	FSO_3H/SO_2	NMR	ax (H)			10
$^+:SeCH_3$	CH_2Cl_2/SO_2	NMR	ax (CH_3)			9
:SeO	$CHClF_2$	NMR	ax (O)		0.48 (−130)	9, 11
$^+$:TeH	FSO_3H/SO_2	NMR	ax (H)			10

[a] The temperature (°C) is given in parentheses.

trum. Direct integration cannot be carried out on vibrational bands, because extinction coefficients may be unequal. Determination of the intensity ratio as a function of temperature, however, can produce the enthalpy difference (ΔH°) between isomers. If a reference substituent is placed elsewhere in the ring, classical chemical equilibration can be used to measure an axial–equatorial equilibrium constant. Thus the *cis*- and *trans*-4-*tert*-butyl-*S*-methylthianium salts, when equilibrated, give the value of K_e directly, since the 4-*tert*-butyl is assumed to be entirely equatorial. The principal drawback to this method is the assumption that the reference substituent does not perturb the equilibrium.

Although very accurate values of ΔG° or ΔH° can be obtained spectrally, it is an entirely separate problem to make a reliable isomer identification. Since NMR has been the dominant structural tool in studies of pentamethylene heterocycles, we shall first consider the various magnetic resonance criteria that have been developed for isomer identification. Because of the well-defined dependence of the vicinal coupling constant on the H–C–X–H dihedral angle, such couplings can be used to identify whether a proton on the heteroatom is axial or equatorial. The first such example was protonated thiane (**6**), in which the couplings between the proton on sulfur and the protons on the α carbon were measured to be



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14.1 and 2.3 Hz.[10] The large coupling requires that the proton on sulfur be axial. This method is applicable, of course, only to systems in which the heteroatom bears a proton. Furthermore, the proton cannot be undergoing intermolecular proton exchange at a rate that is faster than the NMR time scale.

Studies of the oxides and imides of thianes and selenanes resulted in the development of three spectral criteria for the differentiation of axial and equatorial isomers in sulfur and selenium systems.[5,9,11-13] These compounds are of the type (eq 5) that give two AB quartets for the α-proton resonances at the slow-exchange limit. It was found that the AB quartet for the axial-oxide or axial-imide isomer invariably has the smaller chemical-shift difference, the larger coupling constant, and the higher field midpoint. The equatorial isomer, conversely, has the larger chemical-shift difference, the smaller coupling constant, and the lower field midpoint. For example, the axial isomer of thiane 1-oxide has $\Delta\nu$ = 0.48 ppm and J = 13.7 Hz, and the equatorial isomer has $\Delta\nu$ = 0.87 ppm and J = 11.7 Hz.[5] Because the nature of the heteroatom and its substituents alters the absolute value of these spectral parameters, the criteria cannot be applied unless both isomers are observed. If the carbon atoms bear substituents, in exceptional cases the chemical-shift criteria can be overridden.[13] All three criteria have invariably been valid in pentamethylene heterocycles without carbon substituents, and the coupling constant criterion has been found to hold regardless of substitution elsewhere in the ring. The relative merits of the criteria have been reviewed recently.[106]

A related method has been applied to the conformational problem of the nitrogen substituent in piperidines.[1,14] The chemical-shift difference (δ_{ae}) between the axial and equatorial protons of cyclohexanes is 0.4–0.5 ppm,[15] with the axial protons at higher field. In 1964, considerably larger values of δ_{ae} were observed for methylene groups adjacent to a tertiary ring nitrogen.[16] These authors suggested that interaction between axial CH groups and a vicinal axial lone pair leads to shielding of the proton. Thus an enhanced value of δ_{ae} should occur only for compounds with an equatorial substituent on nitrogen (axial lone pair). The observed δ_{ae} values of 0.44 ppm for the α protons of piperidine but 0.94 ppm for those of *N*-methylpiperidine indicated that the NH group is predominantly axial and the NCH_3 group equatorial.[1,14] Significantly, protonation of both piperidine and *N*-methylpiperidine in methanol gave values of $\delta_{ae}(\alpha)$ (0.40, 0.44 ppm, respectively) close to that of cyclohexane. The method suffers from the fact that $\delta_{ae}(\alpha)$ may be affected by the N substituent as well as by the lone pair. Examination of the difference ($\Delta\delta_{ae}$) between the values of δ_{ae} in the unprotonated and protonated forms therefore serves as a control to distinguish lone-pair and N-alkyl effects.[17] Protonation removes the lone pair but has no effect on the presence of an N-alkyl group. The value of $\Delta\delta_{ae}(\alpha)$ = 0.04 for piperidine confirms that the lone pair is equatorial (NH axial), and $\Delta\delta_{ae}(\alpha)$ = 0.50 ppm for *N*-methylpiperidine indicates a predominantly axial lone pair (methyl equatorial). Because of the requirement that δ_{ae} be measured in the same solvent for both the amine base and the ammonium salt, $\Delta\delta_{ae}$ has so far only been measured in methanol. Thus the method is highly restricted with respect to solvent possibilities, and gives only qualitative results. Further discussion of this method can be found in the nitrogen section of the Survey.

The effect of shift reagents such as nickel(II) acetylacetonate has also provided a qualitative tool for the differentiation of axial and equatorial isomers.[18-21] The effect of shift reagents on both the proton and the carbon-13 chemical shifts was found to depend on whether the nitrogen lone pair was axial or equatorial. The method is valid only insofar as the shift reagent does not alter the equilibrium constant for the free base.

Phosphorus chemical shifts and coupling constants have provided useful criteria in configurational studies of phosphorinanes.[22,23] Rigid model compounds indicate that the two-bond coupling between ^{31}P and the protons on the α carbon of the substituent is always larger when the P substituent is axial (3.2 *vs.* 1.8 Hz). The phosphorus-31 resonance for the axial isomer is always found at higher field than that of the equatorial isomer.

Carbon-13 NMR is now being applied to configurational problems. The use of model compounds to determine the resonance position of axial and equatorial *N*-methyl has yielded a quantitative determination of ΔG° for *N*-methylpiperidine.[24] The C–C–X–H and C–X–C–H couplings may provide useful configurational information.[107]

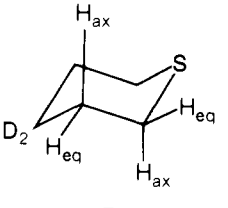
Assignment of isomers from the first overtone bands of the NH-stretch region in the infrared spectrum has been accomplished by band-shape contour analysis.[25,26] The stretching of bonds parallel to the largest moment of inertia is expected to give the broadest band. For cyclohexane, $I_A = I_B$ = 117.1 and I_C = 205.1, so that the largest moment of inertia is perpendicular to the average plane of the ring. If cyclohexane is a valid model for piperidine, then an axial NH-stretch band should be broader than that of an equatorial NH stretch. The higher frequency, higher intensity band was therefore assigned to the equatorial NH isomer.[25,26] Analysis of the temperature dependence of the band area indicated that the equatorial isomer is enthalpically favored. Discussion of the discrepant piperidine results can be found in the nitrogen section of the Survey.

C. The Shape of the Ring

Vicinal NMR coupling constants have provided the most useful information with regard to the shapes of ring systems. Direct application of the Karplus equation

$$^3J = A\cos^2\varphi + C \qquad (7)$$

which relates the H–C–C–H dihedral angle φ to the vicinal coupling, is frequently thwarted by the inability to evaluate the constant A for a specific case (C is small and generally neglected). The method of coupling constant ratios circumvents this problem by using two coupling constants that contain identical multiplicative dependencies on the electronegativity and other factors included in the Karplus A.[27,28] A mobile ring system such as **7** permits the measurement of two averaged coupling constants in a CH_2–CH_2 fragment, $J_{trans} = \frac{1}{2}(J_{aa} + J_{ee})$ and $J_{cis} = \frac{1}{2}(J_{ae} + J_{ea})$. The same averaged coupling



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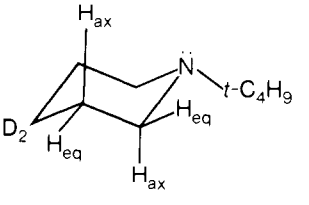

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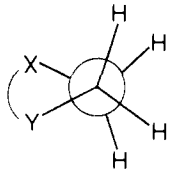
constants may be obtained for a rigid or biased ring such as **8** by arithmetic manipulation of the four measured couplings. The ratio, $R = J_{trans}/J_{cis}$, was found to be free of all dependence on the electronegativity and orientation of substituents attached to the CH_2–CH_2 fragment, and therefore to depend only on conformation.[27] Molecules with approximately the same dihedral relationships as unsubstituted cyclohexanes (**10**) were found to have ratios (R) in the range 1.9–2.2. A flattened distortion (**9**), in which the methylene groups are more nearly eclipsed, results in a decrease in the R value; and a puckering distortion (**11**) causes an increase in the R value. The coupling constant ratio therefore gives a direct measure

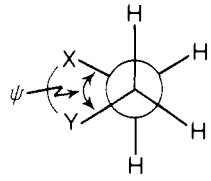
TABLE IV. Ring Shapes as Determined by the *R*-Value Method

Hetero group	Segment	J_{trans}, Hz	J_{cis}, Hz	*R*	Ψ	Ref
:NH	α, β	7.88	3.77	2.07	57	10
:NCH_3	α, β	7.52	3.65	2:06	57	28
O	α, β	7.41	3.87	1.91	56	10
S	α, β	8.15	2.96	2.65	61	32
S	β, γ	8.47	3.28	2.58	60	32
$^+$:SH	α, β	8.5	3.9	2.2	58	10
$^+$:SCH_3I^-	α, β	8.63	3.24	2.66	61	28
$^+$:SCH_3I^-	β, γ	8.30	3.59	2.31	59	28
Se	α, β	8.24	3.09	2.66	61	32
Se	β, γ	8.63	3.14	2.75	61	32
$SeBr_2$	α, β	7.75	4.70	1.65	53.5	32
$SeBr_2$	β, γ	8.88	2.90	3.07	63	32
SeI_2	α, β	8.33	3.32	2.51	60	32
SeI_2	β, γ	8.44	3.04	2.78	61.5	32
Te	α, β	8.62	3.12	2.76	61	10
$TeBr_2$	α, β	7.8	5.2	1.5	52	31, 32
$TeBr_2$	β, γ	9.21	2.56	3.60	64	31, 32

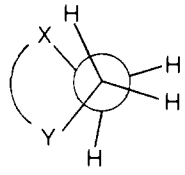
of the deviation of the fragment conformation from that of undistorted cyclohexane.



9 ($R < 1.8, \Psi < 55°$)



10 ($R = 1.9–2.2$, $\Psi = 56–58°$)



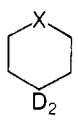
11 ($R > 2.3, \Psi > 59°$)

The *R* value is related to the internal torsional angle Ψ (see **10**) by eq 8.[29]

$$\cos \Psi = [3/(2 + 4R)]^{1/2} \quad (8)$$

Thus the undistorted *R* value of 1.9–2.2 corresponds to a torsional angle of 56–58°, in agreement with the nontetrahedral geometry of cyclohexane.[30] The flattened geometry ($R < 1.8$) corresponds to $\Psi < 55°$, and the puckered geometry ($R > 2.3$) corresponds to $\Psi > 59°$. The straightforward determination of two averaged coupling constants can thus lead to very accurate torsional descriptions of the conformational state in solution. Comparisons with X-ray data on crystals show general agreement to within 1–2°.[28,29]

To determine the shape of a pentamethylene heterocycle, two deuterated variants are required (**12** and **13**).[31,32] Deuter-



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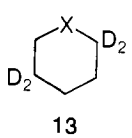

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ation at the γ position results in an AA′BB′ or AA′XX′ spectrum from the α and β protons (ABCD or ABXY if X carries a noninverting substituent), from which J_{trans} and J_{cis} can be readily obtained. The corresponding *R* value produces the torsional angle Ψ for this segment of the molecule. Similarly, deuteration at the α and β′ positions (**13**) isolates the β and γ protons. Irradiation at the deuterium resonance frequency produces an AA′BB′ spectrum (ABCD for X substituted), whence *R* and Ψ for this segment of the molecule. The entire conformation of the molecule is thus determined, except at the heteroatom itself. A number of *R*-value analyses of pentamethylene heterocycles have been reported (Table IV). The individual examples are discussed in the Survey that follows.

D. Magnetic Resonance Parameters

Nuclear magnetic resonance spectroscopy has proved to be by far the most useful tool in the conformational analysis of pentamethylene heterocycles, and many such applications have already been described. The four principal measurables in the nmr experiment are the chemical shift, the coupling constant, the relaxation time, and line-shape changes. The effect of line-shape changes has already been treated in full in the section on ring reversal. The relaxation time has only just begun to assume its place in the repertoire of the organic spectroscopist, and no extensive conformational applications have yet been made to the present subject. Thus it is the chemical shift and the coupling constant that have supplied most of the conclusions that have gone before. Table V lists the important spectral parameters that have been reported.

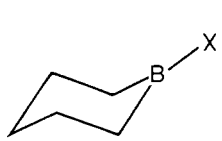
The absolute proton chemical shifts have proved to be less useful than the relative shifts between particular protons in the molecule. The chemical-shift difference between the axial and equatorial protons that are α to the heteroatom [$\delta_{ae}(\alpha)$] has been described above as a useful criterion for the configuration of the heteroatom substituents. Both $\delta_{ae}(\alpha)$ and $\delta_{ae}(\gamma)$, which are obtained from studies of β-deuterated derivatives (**2**), provide information about the diamagnetic anisotropy ($\chi_L - \chi_T$) of the ring bonds, particularly of the carbon–heteroatom bond,[33] and about the overall geometry of the ring. The vicinal coupling constants also provide information about the ring shape, as discussed in the previous section. The geminal coupling constants at the α position furnish one criterion for the configuration about the heteroatom. The geminal coupling constants for the γ protons are generally uninformative.

The study of nuclei other than the proton has been largely ignored in this field. In one study of phosphorinanes,[22,23] to be discussed in the Survey, both carbon-13 and phosphorus-31 resonance measurements play an important part in configurational assignments. The presence of phosphorus also supplies another nucleus of spin ½, the couplings to which can be structurally significant. Carbon-13 spectra have also been used in some studies of piperidines.[18,21,24] The carbon-13 data that are available are included in Table V. Because many of the heterocycles contain magnetically active nuclei, in addition to carbon-13, it is likely that this area will continue to expand.

III. Survey of Pentamethylene Heterocycles

A. Group III

Pentamethylene heterocycles containing boron (borinanes) are known with quite a wide variety of substituents on the heteroatom: B–H (as the diborane), B–alkyl, B–aryl, and B–alkoxy, among others.[34] As yet there have been no conformational studies reported.[35] Because the boron atom is sp^2 hybridized, the substituent has no conformational preference (**14**). For the same reason, the barrier to ring reversal should be quite low, like that of cyclohexanone. The shape of the ring could be examined without problem by the *R*-value method.



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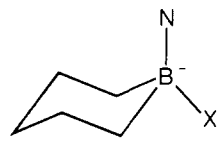

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Borinanes should react with Lewis bases to form quaternary salts of the type **15**. Studies of conformational preferences and of ring reversal should be possible in this system.

It may be possible to prepare heterocycles of other group III elements (aluminum, gallium), but to our knowledge none has yet been reported.

B. Group IV

The ring reversal of 1,1-dimethylsilacyclohexane has been studied by low-temperature NMR methods.[36,37] The very low barrier (Table I, $\Delta G^{\ddagger}$ = 5.5 kcal/mol at −162°) is probably a reflection of the low barrier to torsion about the C–Si bond (Table II). Unless the methyl groups provide unusual interactions, the transition state to reversal is **3**, in which the heteroatom assumes the position of greatest eclipsing.

Although no other systems have been examined experimentally, theoretical studies have provided insight into the conformational properties of the parent silacyclohexane and several monosubstituted derivatives.[38,39] Force-field calculations have shown that the SiH_2, $SiHCH_3$, $Si(CH_3)_2$, SiH-*t*-C_4H_9, and :$\bar{S}iH$ systems all prefer the chair form. There is a small preference in 1-methylsilacyclohexane for the methyl-axial form, in surprising contrast to the well-known situation in methylcyclohexane. This preference is apparently a result of the fact that the $H_3C–CH_2–SiH_2–CH_3$ gauche interaction is attractive. Because of the greater size of the *tert*-butyl group, 1-*tert*-butylsilacyclohexane again prefers the equatorial conformation.[39] The anion produced by removing a proton from silicon in silacyclohexane (analogous in structure to piperidine, phosphorinane, and protonated thiane) has a small preference for the axial-proton (equatorial-lone pair) conformation.[39] Calculations on the three transition states (**3**–**5**) confirmed that **3** ("6123 planar") has the lowest energy and **5** ("2345 planar") the highest.[38] Interestingly, form **4** ("1234 planar") is at an energy maximum compared to the corresponding classic boat form, which is intermediate in energy between **3** and **5**. It is not clear why the half-chair form **4** is not at a minimum. Silicon-29 magnetic resonance studies have been reported for some silacyclohexanes.[40]

Germacyclohexanes are known with numerous geminal substituents at the 1 position: Cl, Br, I, H, CH_3, C_2H_5, and C_6H_5, among others.[41] The same may be said of stannacyclohexanes (Br, I, CH_3, C_2H_5, C_6H_5, etc.) and, to a lesser extent, of plumbacyclohexanes (C_2H_5, C_6H_5).[41] By analogy with silacyclohexane, the barrier to ring reversal should be quite low, so that conformational studies would be difficult. The proton spectrum of 1,1-dimethylgermacyclohexane remained unchanged down to −130° at a field corresponding to 270 MHz.[42] The C–C–Ge–C gauche interaction may become more attractive than the C–C–Si–C, so that axial preferences will be even more prevalent.

C. Group V

1. Nitrogen

More work has probably been carried out on piperidine and its derivatives than on most of the other pentamethylene heterocycles combined. The ring system is easily accessible, and is of importance because of its widespread occurrence in alkaloids and other natural products. Piperidines with substituents only on nitrogen are all considered to exist in the chair conformation. A crystallographic study of the silver iodide salt of piperidine[43] and a microwave study of piperidine itself[44] have substantiated the chair conformation. Force-field calculations have also led to the conclusion that the chair form is favored.[45] The *R*-value analysis of both piperidine (R = 2.09) and its *N*-methyl derivative (R = 2.06)[10,28] (Table IV) indicates that the ring (Ψ = 57°) is essentially undistorted from the shape of the cyclohexane chair, despite the slightly different C–N bond length and C–N–C bond angle.

The barrier to ring reversal in piperidine and its N-alkyl derivatives (Table I) is slightly higher than that in cyclohexane.[1,14] There is no theoretical calculation like that on dimethylsilacyclohexane to indicate which transition state is preferred. The higher barrier to C–N torsion found in trimethylamine suggests that **5** ("2345 planar") may be preferred. The barrier to ring reversal is clearly higher for *N*-chloropiperidine than for any of the alkyl derivatives.[46,47] Whether this result arises because of an increased barrier to C–NCl torsion or to an increased difficulty in deforming the C–NCl–C angle cannot be determined until more information is obtained on acyclic chloramines. The barrier to ring reversal in the nitroxide of piperidine (N–O·) has been measured by several groups using electron spin resonance techniques.[48–50] The very low barrier (5–6 kcal/mol) results from the sp^2 hybridization of nitrogen, similar to the situation in cyclohexanones.

The most challenging question in piperidine conformational analysis has been the axial/equatorial preference of the N substituent, and the simplest system, the parent piperidine, has proved to be the most controversial. As discussed in section II, considerable evidence has been amassed in support of preference for both the NH-axial and the NH-equatorial conformation. On the axial side, the $\Delta\delta_{ae}(\alpha)$ method led to the qualitative conclusion that the proton is predominantly axial.[1,14] An empirical correlation of the absolute chemical shift with the number of skew lone pair/hydrogen interactions led to the same conclusion.[51] Changes in the proton and carbon-13 shieldings on the addition of paramagnetic shift reagents were interpreted in terms of an axial preference.[18–21] These conclusions were substantiated by force-field calculations.[45] On the other hand, several vibrational studies have indicated a clear preference for the equatorial form.[25,26,52–54] The same conclusion was reached by a calorimetric study[55] and by a tentative microwave study.[44] There are at least four possible explanations for the considerable difference of opinion represented by these various works.

(1) *There is a fundamental flaw in one of the methods.* The earliest information on the piperidine problem came from Kerr-constant measurements, which favored the NH-axial form,[56,57] and from dipole-moment measurements, which favored the equatorial form.[58–63] The reliability of both these methods proved insufficient to differentiate the subtleties of structure represented by NH-axial and -equatorial, so that they are now generally disregarded.[24] Likewise, the results of both methods with NCH_3 have proved to be incorrect.[24] The dipole moment method, for example, must use an additional polar group in the molecule, such as *p*-chlorophenyl, to make a quantitative determination of the conformation. Such polar groups, however, have been found to influence the conformation. Thus the probe used to determine the conformation can alter it. There is also the problem of how to treat the lone pair in designating the direction of the nitrogen dipoles. Furthermore, several authors used an incorrect reference moment for their calculations,[58–60] although it has been corrected in one case.[61]

The $\Delta\delta_{ae}(\alpha)$ method has been criticized because the value of $\delta_{ae}(\alpha)$ can be enhanced not only by an axial lone pair but also by an equatorial alkyl group. Analysis of the lone-pair and the alkyl contributions to the enhancement in $\delta_{ae}(\alpha)$, however, showed that the former was considerably larger.[17] The

TABLE V. Magnetic Resonance Parameters[a]

Hetero group	Solvent	$\delta_{ae}(\alpha)$	$\delta_{ae}(\gamma)$	$J_{ae}(\alpha)$	$J_{ae}(\gamma)$	$\delta_C(\alpha)$	$\delta_C(\beta)$	$\delta_C(\gamma)$	Ref
$Si(CH_3)_2$	Neat					14.3	24.4	30.1	109
$Ge(CH_3)_2$	Neat					15.4	25.9	30.6	109
:NH	CD_3OD	0.44	0.41	11.9	13.1				1, 14
	$(CH_2)_3$	0.46		10.2					1, 14
	CH_2Cl_2	0.48	0.45	12.3	13.4				14
	$C_6D_5CD_3$	0.54	0.49	11.2	12.4				14
	$CD_3(CO)CD_3$	0.51	0.52	12.0	13.1				*b*
	Neat					47.7	27.5	26.1	75
$:NCH_3$	CD_3OD	0.94	0.52	11.4	12.9				1, 14
	$(CH_2)_3$	1.06		11.2					14
	CH_2Cl_2	1.02	0.57	11.2	13.1				14
	$C_6D_5CD_3$	1.10	0.66	11.0	12.9				14
	Neat					57.0	26.6	24.6	76
	Neat					56.7	26.2	24.3	75
$:NC_2H_5$	Neat					54.9	26.8	25.4	76
$:N-t-C_4H_9$	CD_3OD	1.00	0.53	10.7	12.6				1, 14
	$(CH_2)_3$	1.06		10.5					1, 14
	CH_2Cl_2	1.08		11.4					14
	$C_6D_5CD_3$	1.06	0.56	10.2	11.3				14
	Neat					47.0	27.2	26.0	109
:NCl	CH_2Cl_2	0.62	0.40	10.2	12.0	64.0	27.8	23.2	47, 109
$^+NH_2$	CD_3OD	>0.37	0.27	13.1	13.3				14
	FSO_3H/SO_2	0.47	0.34	12.1	13.5				14
	H_2O					45.8	23.2	22.4	109
$\overset{+}{N}HCH_3$	CD_3OD	0.44	0.29	12.0	13.7				14
	FSO_3H/SO_2	0.60	0.38	12.4	14.2				14
	H_2O					55.9	24.1	21.7	109
$\overset{+}{N}H-t-C_4H_9$	CD_3OD	0.64	0.28	12.0	13.3				14
	FSO_3H/SO_2	0.80	>0.42	12.3	13.5				14
$\overset{+}{N}HC_6H_5$	FSO_3H/SO_2	0.16	0.35	12.7	14.3				14
$\overset{+}{N}(CH_3)_2I^-$	H_2O or dioxane					63.3	20.6	21.0	75
$\overset{+}{N}(O^-)CH_3$	C_6H_6					66.1	21.1	21.7	75
$:PCH_3$	Neat					26.7	23.4	28.3	80
$:PC_2H_5$	Neat					24.9	23.7	28.4	80
$:P-i-C_3H_7$	Neat					24.1	23.9	28.3	80
$:P-t-C_4H_9$	Neat					21.4	25.0	28.4	80
$:PC_6H_5$	Neat					24.6	23.4	27.9	80
$P(S)CH_3$	$CHCl_3$					32.7	22.4	26.2	80
$P(S)C_2H_5$	$CHCl_3$					30.3	21.9	26.4	80
$P(S)-i-C_3H_7$	$CHCl_3$					28.8	21.2	26.5	80
$P(S)-t-C_4H_9$	$CHCl_3$					24.6	20.8	26.9	80
$P(S)C_6H_5$	$CHCl_3$					31.9	21.8	26.6	80
$P(O)C_2H_5$	$CHCl_3$					26.5	22.5	26.5	80
$P(O)C_6H_5$	$CHCl_3$					28.7	22.5	27.0	87
$:AsCH_3$	Neat					22.4	23.9	29.3	109
O	CD_3OD	0.50	0.30	11.1	12.9				10, *b*
	$CD_3OD/CHClF_2$	0.50	0.32	11.2	13.2				9
	CS_2	0.55		12.0					2
	Neat					69.7	27.9	25.1	74
S	CH_2Cl_2		0.52		13.9				10, *b*
	$CD_3OD/CHClF_2$	0.187	0.50	13.6	13.9				9
	Neat					29.3	28.2	26.9	109
:SO-ax	CH_2Cl_2	0.48	0.40	13.7	14.3				5
:SO-eq	CH_2Cl_2	0.87	0.34	11.7	14.0				5
SO_2	CH_2Cl_2	<0.1	0.45		14.0				10, *b*
	$CDCl_3$					52.6	25.1	24.3	109
:S(NH)-ax	$CH_2Cl_2/CHClF_2$	0.16	0.44	13.8	13.8				12, 13
:S(NH)-eq	$CH_2Cl_2/CHClF_2$	0.55	0.38	12.0	14.0				12, 13
:S(NTs)-ax	$CHClF_2$	0.022	0.46	14.4	14.2				12, 13
:S(NTs)-eq	$CHClF_2$	0.37	0.44	12.0	14.4				12, 13
:S(NBzs)-ax	$CHClF_2$	0.036	0.46	14.7	14.0				12, 13
:S(NBzs)-eq	$CHClF_2$	0.34	0.44	12.4	14.0				12, 13
S(O)(NH)[c]	CH_2Cl_2	<0.1	0.45		14.1				13
S(O)(NH)[c]	CH_2Cl_2	<0.1	0.45		14.1				13
S(O)(NTs)[c]	$CHClF_2$	0.53	0.50	14.8	14.4				13
S(O)(NTs)[c]	$CHClF_2$	0.83	0.45	13.7	14.8				13

TABLE V (Continued)

Hetero group	Solvent	$\delta_{ae}(\alpha)$	$\delta_{ae}(\gamma)$	$J_{ae}(\alpha)$	$J_{ae}(\gamma)$	$\delta_C(\alpha)$	$\delta_C(\beta)$	$\delta_C(\gamma)$	Ref
$^+$:SH	FSO_3H/SO_2	0.25	0.33	15.0	15.0	31.2	24.1	21.8	10, 109
$^+$:SCH_3I^-	SO_2	0.38	0.11	13.0	14.9				28, *b*
$^+$:SCH_3I^- (27°)	CH_2Cl_2/SO_2	0.31		12.3					9
Se	$CHClF_2$	0.30	0.47	12.3	13.9				9
	Neat					20.2	29.1	28.4	109
:SeO-ax	$CHClF_2$	0.25		12.9					9, 11
:SeO-eq	$CHClF_2$	0.80		10.0					9, 11
SeO_2	$CH_2Cl_2/CHClF_2$	<0.1	0.39		14.0				9, 11
$^+$:SeH	FSO_3H/SO_2	0.27	0.39	13.0	15.0	41.8	23.8	22.5	10, 109
$^+$:$SeCH_3I^-$	SO_2	0.22	0.11	12.8	15.5				*b*
$^+$:$SeCH_3I^-$ (27°)	CH_2Cl_2/SO_2	0.31		12.4					9
Te	$CHClF_2/CHCl_2F$	0.75	0.68	11.0	13.0				9
	Neat					−2.1	29.9	30.9	109
$^+$:TeH	FSO_3H/SO_2	0.27	0.50	13.5	15.0	24.0	25.0	25.8	10, 109

[a] Chemical-shift differences (δ_{ae}) are in ppm and coupling constants (J_{ae}) are in Hz; carbon-13 shifts are in ppm downfield from TMS. [b] Unpublished results of J. B. Lambert, C. E. Mixan, and R. G. Keske. [c] Identification of the isomers has not been made.

use of $\Delta\delta_{ae}(\alpha)$, the difference between the chemical-shift differences in the free base and the protonated form, automatically gives only the lone-pair contribution, so that this problem can be circumvented. In 3,3-dimethylpiperidines, the 3-axial methyl group should drive the equilibrium toward the NH-equatorial form.[64,65] The $\Delta\delta_{ae}(\alpha)$ clearly indicated such a shift in equilibrium. Thus no flaw has yet been found in this method, but it suffers from being only qualitative.

There is the possibility of a serious flaw in the use of paramagnetic shift reagents to determine conformation.[18-21] The shifts in the proton and carbon-13 resonance positions occur in the complex between free base and paramagnetic reagent. It must be assumed that complexation does not favor one form over the other, so that the axial/equatorial equilibrium constant is the same in the free base and in the complex. One study has shown that the axial form of *N*-methylpiperidine complexes much more strongly than the equatorial form, so that the method may not be valid in this case.[66] For the more critical parent piperidine, however, both forms appeared to complex much more closely to equal extents ($K_e/K_a \sim 2/1$), so that the method may have produced a valid conclusion,[66] that NH-axial is favored.

An NMR method based on protonation of the free base has been questioned seriously,[67] although the conclusion has been reaffirmed that piperidine is almost 1:1 axial to equatorial.[68] This method requires that salt formation occur much more rapidly than nitrogen inversion, that it take place stereospecifically with retention, and that it be irreversible. Otherwise the product does not give a valid picture of the starting material.

Vibrational methods using the first overtone of the NH stretch have not been questioned.[25,26] Other methods, which use the Bohlmann bands (2500–2820 cm^{-1}), are much less reliable, because these spectral areas have considerable background absorption from other causes.[52,53]

The predominant peaks in the microwave spectrum are from the NH-axial form, by a factor of about 6/1.[44] In order to correct peak intensity for extinction coefficient, it had to be assumed that the overall dipole mcment of the axial and equatorial forms are the same, an assumption that is unwarranted. The resulting conclusion, that NH-equatorial is favored, therefore is in doubt. More work is necessary before firm conclusions can be drawn from this method.

Although some of the work from both the NH-axial and -equatorial points of view is dubious, it must be concluded that entirely valid methods, nonetheless, have arrived at contradictory conclusions. The possibility that all of the work supporting one contention is faulty must be rejected.

(2) *The method is correct but the conformational assignment is wrong.* It is possible that an entirely valid ΔH° or ΔG° can be determined but that the sign is incorrectly deduced by a false spectral assignment. The NMR methods that favor NH-axial probably are not susceptible to this criticism. Spectral properties for the lone pair-axial form can be reliably deduced from the *N*-methyl analog, so that assignments are not in doubt. In studies of the first overtone of the NH stretch, the higher frequency peak was assigned to the NH-equatorial form on the basis of band contours.[25,26] The assignment is only as reliable as the band-shape theory, which utilized cyclohexane as a vibrational model for piperidine. The validity of this assumption is not known. Thus the sign of the accurately determined ΔH° may be in doubt. Although the misassignment of isomers remains a problem, we do not favor this explanation for the disagreement.

(3) *The conformational preference is a function of solvent.* It may be more than coincidence that studies favoring NH-axial have generally been carried out in highly polar solvents, whereas those favoring NH-equatorial used nonpolar solvents or none at all (gas phase). The $\Delta\delta_{ae}(\alpha)$ method has relied entirely on data from methanol, since $\delta_{ae}(\alpha)$ must be measured in the same solvent for both the free base and the protonated form. A comparison between different solvents would be invalid, so that only highly polar media can be used for the method. Under such conditions, the solvent will most likely interact with the lone pair on nitrogen. Since solvation is probably more effective when the lone pair is equatorial, an NH-axial preference could arise. The studies of proton and carbon-13 shifts in the presence of paramagnetic reagents[18-21] were carried out in chloroform, another highly polar solvent. On the other hand, the NH-stretch overtone studies were carried out in the gas phase and in carbon tetrachloride,[25,26] and the microwave study, of course, was in the gas phase.[44] These four methods provide the most reliable results for the respective points of view. The role of the solvent in determining the direction of the equilibrium must be clarified.

(4) *Enthalpy favors NH-equatorial but entropy favors NH-axial.* The NMR studies give a direct indication of the relative amounts of species present in solution, since resonance absorption is directly proportional to the number of protons present. It is noteworthy that essentially all the methods that favor NH-axial have used NMR techniques (Table III). Vibrational and microwave studies on the other hand must evaluate ratios of extinction coefficients. These methods have favored NH-equatorial. As a result, the NMR methods have dealt essentially with free-energy differences, whereas the vibrational methods have produced enthalpy differences. It was a stated assumption in the vibrational studies that enthalpy is taken as a measure of free energy by assuming that entropy differ-

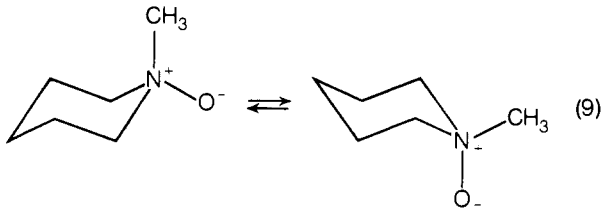
ences are negligible.[25,26] In light of the recent work on *P*-methylphosphorinane[22,23] (vide infra), this assumption can no longer be made without proof. This work showed that enthalpy favors the equatorial-methyl form (ΔH° = 0.68 kcal/mol, equatorial preponderance at −109°), but that entropy favors the axial form (ΔS° = 3.4 eu, same sign as ΔH°, axial preponderance at room temperature). If entropy can be important in phosphorinanes, it cannot be ruled out in piperidines without accurate experimental justification. The possibility therefore remains that the NMR results, based on free-energy considerations, and the vibrational results, based on enthalpy considerations, are compatible.

Theory at present favors the NH-axial form. The axial proton on nitrogen has attractive interactions with the β-axial protons and the β carbons.[45] The strong axial preference for the heteroatom protons in phosphorinane[69,70] and protonated thiane[10] were attributed to these attractive interactions. Calculations have shown the 1,3-axial–axial proton–proton interaction to be attractive even in cyclohexane. It has recently been suggested that the equatorial preference in methylcyclohexane results more from attractive interactions of the 1-axial proton (particularly with the antiperiplanar axial protons) than from repulsive interactions of the equatorial methyl group.[71] The NH-axial form is also favored by the gauche effect.[72] The axial conformation (equatorial lone pair) maximizes the number of gauche interactions between the lone pair on nitrogen and the vicinal polar C–H bonds.

As yet there is no unambiguous experimental answer to the question of the conformational preference of the proton on nitrogen in piperidine. No experiment reported to date is without some problem. The answer must ideally come from an experiment that is carried out directly on piperidine so there is no reliance on model compounds, that provides a direct measure of the relative amounts of both isomers, that can unambiguously assign the observable to the appropriate isomer, that leads to the free-energy difference rather than the enthalpy difference, and that can be carried out in both polar and nonpolar solvents. Until all these criteria can be met in a single experiment or set of experiments, the piperidine problem must be considered unsolved.

With the exception of one early report based on Kerr-constant measurements,[57] there has been universal agreement that the methyl group in *N*-methylpiperidine has a decided preference for the equatorial position.[1,14,18–21,24,45,59–61,63,68] Some controversy has developed over whether the preference is about the same as for the methyl group in cyclohexane ($\Delta G^\circ \sim$ 1.7 kcal/mol) or considerably less (~0.8 kcal/mol). Attempts to observe both isomers at the slow-exchange limit for ring reversal failed, even at −150° (90 MHz).[47] Thus indirect methods have had to be used. Dipole-moment studies by one research group gave a free-energy difference between conformers of about 0.6 kcal/mol,[61,63] whereas another group obtained 1.7 kcal/mol.[59,60] More recent evidence has favored the larger value: infrared studies of the Bohlmann bands,[53] protonation under controlled conditions,[68,108] and correlation of carbon-13 chemical shifts with model compounds.[24] Unfortunately, none of these methods is without flaw, but the preponderance of evidence does indicate that the conformational preference of an *N*-methyl group in piperidine is similar to that of a methyl group in cyclohexane, and possibly much larger.[108]

Studies of *N*-chloropiperidine at the slow-exchange limit for ring reversal found resonances for only a single isomer.[46,47] Either the chlorine is entirely equatorial, or the resonances for two isomers are superimposed. This question is still unresolved. The conformational preference for the substituents on nitrogen has been determined for *N*-methylpiperidine oxide (eq 9) by comparison of the chemical shifts of the unsubstituted compound with those of the two diastereomeric 4-*tert*-butyl derivatives.[73] The axial-oxide, equatorial-methyl form was favored in a variety of solvents (Table III). These are the only two examples of conformational studies of piperidine possessing polar substituents on nitrogen, although there remains a wealth of possibilities.

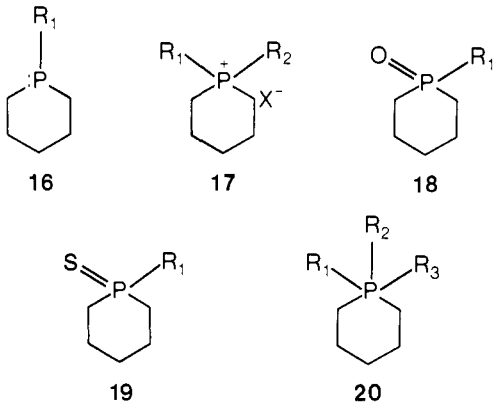

(9)

Carbon-13 studies of piperidines are beginning to appear,[24,74–76] although conformational conclusions are not necessarily a part of them. The carbon-13 study of *N*-methylpiperidines alluded to above[24] is one of the few examples to date that has yielded important conformational results.

2. Phosphorus

The derivatives of phosphorinane have received much stereochemical attention.[77] The multiplicity of valence states of phosphorus and its high barrier to pyramidal inversion, which makes it configurationally stable on the NMR time scale (unlike nitrogen), contribute to its popularity. Also ^{31}P, with 100% natural abundance, has a spin of ½ and thus does not suffer from problems associated with quadrupolar relaxation. As a result, NMR spectroscopy (^{31}P, ^{1}H, ^{13}C) has been the principal method for the study of these systems. The coupling of ^{31}P with other elements has been particularly useful because of its frequent dependence on molecular geometry.

The known types of phosphorinane derivatives are given by **16–20.** The trivalent phosphorus atom of **16** has a hybrid-


16 17 18 19 20

ization between p and sp^3, and thus the angles about phosphorus have been found to be significantly less than tetrahedral. The internal ring angle (C–P–C) in some C-substituted phosphorinanes has been found to be around 98° by X-ray crystallographic analyses,[78] so that the cycle is more puckered around phosphorus than in "normal" cyclohexanes. Some examples of **16** have R_1 = H, CH_3, *t*-C_4H_9, C_6H_5, $C_6H_5CH_2$, cyclohexyl, *p*-tolyl, and Cl.[77,79,80]

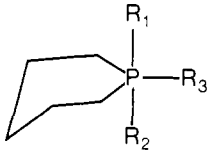
The tetravalent phosphorus atom has a hybridization close to sp^3 in phosphonium salts (**17**), and thus ring shape and angles should approach those of cyclohexane. Phosphonium salts of the type **17** have substituents (R_1 and R_2) such as H, CH_3, C_2H_5, cyclohexyl, C_6H_5, or *p*-tolyl, and typical anions (X) such as Cl, Br, or I.[70,77,78]

Also included in **17,** although not phosphonium salts, are the adducts formed between phosphorinanes and boranes,[81] e.g., R_1 = H, R_2 = BF_3; R_1 = H, R_2 = $B(CH_3)_3$, and the complexes formed between phosphorinanes and $HgCl_2$[77] or $NiCl_2$,[82] e.g., R_1 = C_6H_5, R_2 = $HgCl_2$; R_1 = C_6H_5, R_2 = $NiCl_2$.

In this type of compound the phosphorus acts as a Lewis base and thus acquires some positive charge.

The tetravalent phosphine oxides and sulfides, **18** and **19,** are intermediate between **16** and **17** in their hybridization, so that the heterocycle would be required by angular constraint to be flatter around phosphorus than **16.** Some of the oxides of type **18** have as a substituent (R_1) H, CH_3, C_2H_5, $C_6H_5CH_2$, C_6H_5, Cl, $(C_2H_5)_2N$, HO, or C_2H_5O.[77,83] The sulfides of **19** include R_1 = H, CH_3, C_2H_5, $(CH_3)_3C$, C_6H_5, $P(S)(CH_2)_5$, and HS.[70,77,80]

The pentavalent phosphorus in phosphoranes (**20**) is sp^3d hybridized, with the result that compounds have a trigonal-bipyramidal shape (**21**). Thus the ring carbons attached to



21

phosphorus have the option of being diequatorial or apical-equatorial. In the two known pentavalent phosphorinanes the ring is in the equatorial plane and electronegative substituents are in their preferred apical positions. Ideally the internal ring angle at phosphorus in these systems would be 120°, so the ring would be extremely flattened (**21**). The known compounds corresponding to **20** have $R_1 = R_2 = R_3 = F$[84] and $R_1 = R_2 = OC_2H_5$, $R_3 = C_6H_5$.[85]

The parent phosphorinane (**16,** R_1 = H) and its 1-sulfide and methiodide have been investigated by proton NMR spectroscopy.[69,70] The proton on phosphorus exchanges with the medium more slowly than does the proton on nitrogen in piperidine, so that couplings with the ring protons can be observed. Also the phosphorus atom is nearly p hybridized in this secondary phosphine, and thus the lone pair resides in an orbital of very high s character and must have little directionality. Thus P-proton interactions, rather than lone-pair interactions, should be the major factor in the determination of the preferred conformer.

Because of the large coupling between phosphorus and its attached proton (200 ± 5 Hz), the low-field subspectrum of the P-proton resonance appears well downfield of the ring-proton region. When proton exchange is slow on the NMR time scale (−50° in $CFCl_3$), this subspectrum appears as a triplet of triplets. Such a pattern is consistent with an axial proton that has a large J_{aa} with the two adjacent α axial protons and a smaller J_{ae} with the two α equatorial protons. A computer-simulated spectrum resulted in the best fit when J_{aa} = 12 Hz and J_{ae} = 2.5 Hz, values that are consistent with a P-proton that is almost entirely axial. No more than 10% of the equatorial conformer could have been present. On lowering the temperature to −80° the subspectrum remained unchanged, in accord with an equilibrium that is strongly biased toward one conformer.

This extreme preference of the P-proton for the axial position is consistent with results for the protonated heterocycles of group VI (vide infra) and is thought to result from attractive interactions of the heteroatom proton with the axial 3,5 protons. The 1-sulfide of phosphorinane shows a similar preference in $CFCl_3$ for the proton-axial (sulfide-equatorial) conformation.[70] The pmr spectrum of the methiodide salt of phosphorinane in $CHCl_3$ yielded ambiguous results concerning the position of the proton because of second-order spectral complications caused by a small chemical-shift difference between the axial and equatorial α protons.

The barriers to ring reversal of P-substituted phosphorinanes given in Table I were determined by variable-temperature proton and phosphorus nmr spectroscopy.[23] The chemical-shift difference between conformers is enhanced in the ^{31}P spectra relative to proton nmr, thus yielding a more convenient coalescence temperature. Also the simplicity of having one resonance at fast exchange and two resonances under slow exchange considerably assists the analysis. The free energies of activation for ring reversal were calculated to be about 8.5 kcal/mol for all substituents. This value is intermediate between that of thiane 1-oxide (10.0 kcal/mol)[5,12] and that of 1,1-dimethylsilacyclohexane (5.5 kcal/mol)[37] and thus reflects the torsional barriers of the C–X bonds (see Table II). The values are also significantly lower than those in the analogous piperidines. With this relatively low barrier the preferred transition state is probably **3**, in which the heteroatom relieves the greatest amount of eclipsing strain.

The conformational preference of the substituent in *P*-methylphosphorinane was initially studied by observing the methyl signal in the proton spectrum.[22] At slow exchange the spectrum consisted of two doublets for $P-CH_3$ ($^2J_{PCH}$ = 3.2 and 1.8 Hz), separated by 0.09 ppm. The doublet with the larger coupling constant was assigned to the axial conformer by comparison with model compounds. At higher temperatures these doublets merged into a broad "singlet", and at room temperature a coupling (3 Hz) again became resolved. Phosphorus decoupling at slow exchange simplified the spectrum to singlets, of relative ratio 2:1 with the equatorial substituent predominating. Variable-temperature ^{31}P NMR yielded more accurate equilibrium constants by direct electronic integration. The smaller signal (axial conformer) at the slow-exchange limit gave the further upfield of the two ^{31}P signals. Axial isomers of isomeric phosphorinanols[80] have been found to have higher field ^{31}P chemical shifts than equatorial isomers.

Equilibrium constants were determined in this way by ^{31}P NMR spectroscopy for *P*-methyl-, *P*-ethyl-, *P*-isopropyl-, and *P*-phenylphosphorinanes for temperatures below the coalescence temperature. The equatorial conformer was found to predominate for all of the above substituents, but by a much smaller margin than equatorial conformers in cyclohexanes or piperidines. Linear plots of log K *vs.* $1/T$ for the *P*-methyl, *P*-ethyl, and *P*-phenyl systems yielded enthalpies favoring the equatorial conformer by 0.5 − 0.7 kcal/mol (see Table III).

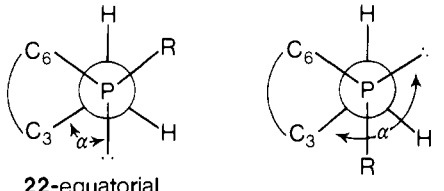
Extrapolation of these graphs to room temperature for R_1 = CH_3, C_2H_5, and C_6H_5 yielded the surprising result that the axial conformers predominate. Support for this conclusion is found in the room-temperature coupling constant for $P-CH_3$ ($^2J_{PCH}$) of 3 Hz, which is closer to the axial limit of 3.2 Hz than the equatorial limit of 1.8 Hz. Room-temperature ^{13}C NMR spectra of these compounds also lend credence to this conclusion (vide infra).

In contrast to the proton on phosphorus, these larger substituents have an enthalpic preference for the equatorial conformer. The sign and the magnitude of the enthalpy change suggest that these alkyl and aryl substituents have repulsive nonbonded interactions, although the magnitude is much smaller than similar interactions in cyclohexanes or piperidines. These interactions may be reduced by the longer C–P bond (1.87 Å) and by opening of the P–C–C ring angles in the axial conformer. The *S*-methyl salt of thiane has also been found to prefer the equatorial conformer (vide infra).

In P-substituted phosphorinanes (R_1 = C_6H_5, CH_3, C_2H_5), it was found that a relatively small enthalpy change and a non-negligible entropy change of the same sign (2–4 eu), favoring the axial conformer for reasons unknown, are sufficient to cause axial predominance at room temperature. It would therefore seem from this work that loose correlation of $\Delta H°$ with the "conformational preference" of a compound ($\Delta G°$) without experimental justification could be hazardous.

Conformational analysis of phosphorinanes by proton-decoupled ^{13}C NMR spectroscopy has been fairly successful

because of the sensitivity of carbon chemical shifts and $^{31}P-^{13}C$ coupling constants to stereochemistry. Table V• gives the ^{13}C NMR data for phosphorinanes (**16**) and their sulfides (**19**) for $R_1 = CH_3$, C_2H_5, $(CH_3)_2CH$, $(CH_3)_3C$, and C_6H_5. The two-bond $^{31}P-^{13}C$ coupling has been found to be dependent on the dihedral angle (α) between the lone pair of electrons of ^{31}P and the carbons β to phosphorus. The Newman projection along the $P-C_2$ bond for equatorial and axial substituents of phosphorinanes is given by **22**. Thus in a series of



rigid phosphorinane derivatives $^2J_{PC_{3,5}}$ for the equatorial isomers, in which the dihedral angle is small, was found to be around 7 Hz, whereas this coupling in axial isomers was 0–1 Hz.[86] From these limits, $^2J_{PC}$ of 5.0 and 7.0 Hz for isopropyl and *tert*-butyl substituents suggests a strong preference for the equatorial conformer. Values of $^2J_{PC}$ around 3.0 Hz for methyl, ethyl, and phenyl substituents, however, suggest a largely unbiased equilibrium or a slight excess of axial conformer for these substituents, in agreement with the extrapolation of low-temperature ^{31}P NMR results. The axial predominance of *P*-methyl, -ethyl, and -phenyl is further reflected in the upfield chemical shifts for carbons 3,5 relative to that of *P*-*tert*-butyl, which lacks the γ-shielding effect of an axial substituent.

Carbon-13 NMR studies have found that in phosphorinane 1-sulfides the carbon substituents prefer the equatorial position, in contrast to the axial preference of the smaller proton in phosphorinane 1-sulfide.[70,80] The chemical shift of carbons 3,5 moves upfield as the R_1 group increases in size and the amount of equatorial conformer increases. The axial sulfide exerts a greater shielding at $C_{3,5}$ than does an axial methyl. This effect is also present in phosphine oxides as demonstrated by the increased shielding at $C_{3,5}$ in the oxides of *P*-ethyl- and *P*-phenylphosphorinane in comparison to the trivalent compounds (see Table V) and suggests an axial orientation of the oxide function.[80,87]

A recent study found that ^{31}P chemical shifts are sensitive to the same β and γ effects that influence ^{13}C chemical shifts.[88] Thus the ^{31}P chemical shifts of *P*-ethyl-, -isopropyl-, and -*tert*-butylphosphorinane can be predicted quite accurately by adding successive β deshielding effects (−13.5 ppm for tertiary phosphines) to the ^{31}P chemical shift of *P*-methylphosphorinane.

Phosphorus-31 nmr spectroscopy was used to verify the structure of phosphorane **20**: $R_1 = R_2 = OC_2H_5$, $R_3 = C_6H_5$. The relatively high ^{31}P chemical shift of 48 ppm (upfield of 85% phosphoric acid) is consistent with a pentavalent phosphorus. This structure appears to be in equilibrium with the phosphonium salt formed by the ionization of ethoxide.[85]

Fluorine-19 NMR spectroscopy was used very effectively in conjunction with infrared spectroscopy to prove the structure of the trifluorophosphorane **20**, $R_1 = R_2 = R_3 = F$.[84] The preferred conformer has the ring in two equatorial positions and the electronegative fluorine atoms in one equatorial and two apical positions (see **21**). Phosphorus–fluorine infrared stretching frequencies suggested that apical bond lengths are greater than equatorial in $(CH_2)_5PF_3$, as apical PF stretching frequencies are significantly lower (~730 cm^{-1}) than the equatorial frequencies (840–900 cm^{-1}). This geometry is also reflected in the ^{19}F NMR data for this compound. Apical $^1J_{PF}$ are about 200 Hz less than the equatorial (800 and 1005 Hz, respectively), and the equatorial fluorine is 64 ppm to higher field than the apical fluorines.

3. Arsenic, Antimony, and Bismuth

Few conformational studies have been reported for group V pentamethylene heterocycles below phosphorus. Numerous such heterocycles, however, exist.[77] 1-Substituted arsenanes are known, including methyl, ethyl, phenyl, *p*-tolyl, chloro, and bromo. In addition, the methiodide and the dichloride are known for the methyl compound, and the arsenic acid (As(O)OH) has been prepared. The barrier to ring reversal of 1-methylarsenane is even lower than that of the corresponding phosphorinane (Table I).[89] The methyl group has a nearly equal preference to be axial or equatorial at −130°. The trend of strong equatorial preference (NCH_3) to less preference (PCH_3) to no preference probably results from decreased repulsive or increased attractive interactions as the C–X bond length increases.

Among the known 1-substituted antimonanes are the methyl, phenyl, chloro, methyl dichloride, and phenyl dichloride compounds.[77] The only known bisminane is the 1-ethyl derivative.[77]

D. Group VI

1. Oxygen

Tetrahydropyran has a chair conformation[90] that is slightly flattened from the shape of cyclohexane (R = 1.91, Table IV).[28] The somewhat larger C–O–C bond angle and shorter C–O bond length cause this distortion, which becomes more pronounced in 1,3-dioxane.[28] The barrier to ring reversal was first reported in 1966 in a study of the deuterated derivative **2** (X = O).[5,10] A method utilizing homonuclear double irradiation was reported in 1967,[2] and an accurate coalescence temperature measurement in 1973.[9] All results point to an Arrhenius activation energy ($E_a \sim$ 10.5 kcal/mol) very close to that of cyclohexane and significantly lower than those of piperidines.

The oxygen of tetrahydropyran can serve as a nucleophile in reactions to form oxonium salts. The simple protonated form has been prepared,[10] but exchange of the O-proton is too rapid to permit determination of coupling constants and hence the conformational preference. The *O*-methyloxonium salt could provide an interesting analog to the isoelectronic *N*-methylpiperidine. Unfortunately, oxygen inversion is extremely rapid and ring reversal could not be frozen out down to −70°, the limit of solubility.[91] The conformational preference of the methyl group and of the proton on trivalent oxygen in tetrahydropyran is potentially as interesting as the analogous problem in piperidines, but the systems are less easily studied. Tetrahydropyran forms complexes readily with iodine. Although equilibrium constants between free and complexed forms have been measured,[92,93] no conformational studies have been reported. From experiments to be discussed in the next section, it can be deduced that the iodine complex probably has a nearly undistorted tetrahydropyran ring, rather than a trigonal bipyramid.[32]

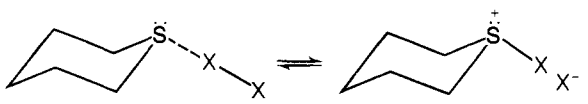
2. Sulfur

The longer C–S bond and the smaller C–S–C angle cause the thiane ring to be distinctly puckered ($R_{\alpha\beta}$ = 2.65, $R_{\beta\gamma}$ = 2.58, Table IV) with respect to the shape of cyclohexane.[10,28,31] This property and the ability of the sulfur atom to expand its valence shell give rise to a distinctly different and richer conformational analysis than is possible for tetrahydropyran and its derivatives. The lower barrier to ring reversal for

thiane ($\Delta G^{\ddagger}$ = 9.4 kcal/mol) than for tetrahydropyran (10.3) is probably due to the lower barrier to torsion for the C–S bond, as compared with the C–O bond (Table II).[9,10] The value of $\delta_{ae}(\alpha)$ is smaller than and probably of opposite sign to that of tetrahydropyran (Table V). Aside from local effects caused by directed lone-pair interactions, as in *N*-methylpiperidine, the chemical-shift difference between axial and equatorial protons is determined primarily by the anisotropy of the bonds β to the attached carbon. Thus in thiane, $\delta_{ae}(\alpha)$ is determined for the most part by the 6,1 C–S and the 3,4 C–C bond anisotropies. The value of $\delta_{ae}(\alpha)$ is reduced because the C–S anisotropy, $(\chi_L - \chi_T)$, has the opposite sign to that of the C–C bond, so the contributions oppose each other.[33] It is thought that the C–S contribution is dominant, so that $\delta_{ae}(\alpha)$ has the opposite sign (equatorial resonance higher than axial) to that of tetrahydropyran or cyclohexane (axial resonance higher field than equatorial). Because $\delta_{ae}(\gamma)$ is determined almost entirely by two C–C bonds, its sign and magnitude are normal (Table V).[33]

Protonated and methylated thiane, the analogs of piperidine and *N*-methylpiperidine, are more amenable to study than are the oxonium systems. The vicinal couplings between the proton on sulfur and the vicinal α protons, J = 14.1 and 2.3 Hz, are clearly indicative of an axial conformation,[10] like that of phosphorinane. *S*-Methylthianium iodide has no such simple handle. *R*-Value analysis indicates that the shape of the ring is similar to that of thiane.[28] The spectrum of the β-deuterated derivative reveals only one AB spectrum for the α protons down to −88°.[9] Either ring reversal is not yet frozen out or the molecule exists entirely as one conformation. The magnitude of the geminal coupling constant between the α protons is suggestive of an equatorial conformation, but the presence of only one isomer renders the method unreliable.[9] Equilibration of the *cis*- and *trans*-4-*tert*-butyl-*S*-methylthianium perchlorates indicates a preference for the equatorial form of 275 cal/mol at 100° (K = 1.45).[94] Comparison of the weighted-average carbon-13 methyl resonance from the *tert*-butyl systems with that of *S*-methylthianium perchlorate itself suggests that the equilibrium constant is similar in the substituted and unsubstituted systems. The greatly reduced equatorial preference for methyl on sulfur, when compared with methyl on carbon or nitrogen, can be attributed to smaller repulsive interactions with the β-axial protons. The greater proton–methyl distance, due to the longer C–S bonds and opening of the S–C–C bond angles, contribute to these reduced interactions. The situation is similar to that in *P*-methylphosphorinane, in which there is actually an axial preference for the methyl group at room temperature.[22,23]

Thiane forms 1:1 complexes with chlorine, bromine, and iodine.[32,95–97] The dark violet iodine complex is indefinitely stable in a closed container, the bright orange bromine complex is moderately stable, and the chlorine complex is only briefly stable. The nmr spectra of the bromine and iodine complexes are essentially identical with that of thiane itself, except for shifts in resonance positions, so the shape of the ring is unaltered.[32] A trigonal-bipyramid structure can therefore be excluded. Either a simple molecular complex or an *S*-halothianium halide structure is present (eq 10). The con-



(10)

ductance of the bromine adduct is about a fifth that of the entirely ionic *S*-bromothianium fluoroborate, so that the ionic form furnishes a significant portion of the equilibrium. The conductance of the iodine adduct is less than 0.5% that of the *S*-iodothianium fluoroborate, so that the ionic component is much smaller. In both cases the equilibrium can be driven to the side of the ionic species by the addition of excess halogen.[32]

The low-temperature nmr spectrum of thiane 1-oxide reveals the presence of two isomers in the ratio 62/38 (ΔG° = 175 cal/mol at −90°).[5] Complete line-shape analysis indicated that the Arrhenius activation energy is slightly higher than that of thiane itself (Table I). On the basis of the chemical-shift difference and coupling constant between the α protons, the major isomer was assigned the axial structure. This unusual preference was attributed to an attractive interaction between the axial oxide and the syn-axial 3,5 protons. Force-field calculations supported this explanation.[98] Subsequent experiments with thiane-1 imide (S=NH instead of S=O) and its derivatives indicated that the parent imide has a slight preference for the equatorial conformation (75 cal/mol, 55/45), whereas the *N*-tosyl (S=NTs) and *N*-benzenesulfonyl (S=NBzs) derivatives retain the axial preference (150 cal/mol, 60/40; 70 cal/mol, 55/45, respectively).[12,13] Although the general rule for the oxide and the imides is probably an axial preference, the reversal for the parent imide may result from its ability to hydrogen bond better in the equatorial conformation. The barriers to ring reversal in the imides are about the same as in the oxide (Table I).[12,13] The axial preference of the oxide may be entirely reversed by introduction of a 3-axial methyl group.[99] It is interesting that the axial preference of the proton in protonated thiane is retained even in the presence of a 3-axial methyl group.[99] The anisotropy of the C–(SO) bond appears to have the same sense as that of the C–C bond, and hence the opposite sense to that of the C–S bond.[33] As a result, the α-axial protons resonate at higher field than the equatorial protons. The sulfur lone pair clearly exerts an influence on the overall anisotropy of the C–(SO) bond, since $\delta_{ae}(\alpha)$ is significantly different in magnitude in the two isomers, although with the same sign. This reliable difference is the basis for the $\delta_{ae}(\alpha)$ configurational criterion in sulfoxides. The C–(SNR) bond appears to have the same anisotropic properties as the C–(SO) bond, and all configurational criteria identically hold.[12,13]

Thiane 1,1-dioxide, thiane 1-oxide 1-imide, and thiane 1-oxide 1-(*N*-tosyl)imide have similar barriers to those of the sulfoxides and sulfimides (Table I).[5,10,13] In all three systems, the α protons in the β-deuterated derivative fail to split into an AB quartet at low temperature ($\delta_{ae}(\alpha) < 0.1$ ppm), whereas the γ protons produce a normal quartet spectrum, on which the complete line-shape analyses were carried out. The value of $\delta_{ae}(\gamma)$ is determined by the anisotropy of two C–C bonds in all these cases and therefore should be similar from one molecule to another, unless there is a radical change in geometry. The value of $\delta_{ae}(\alpha)$, on the other hand, is determined by one C–C bond and one C–(SO_2) or C–(SONR) bond. The anisotropies of these bonds are similar in magnitude but opposite in sign, so that their contributions cancel and there is essentially no chemical-shift difference between the axial and equatorial α protons.[33]

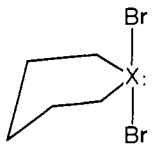
3. *Selenium and Tellurium*

The conformational analysis of selenanes and telluranes has proved to be very similar, so they will be considered together in this section. The puckering noted in thiane becomes more pronounced in the selenium ($R_{\alpha\beta}$ = 2.66) and tellurium ($R_{\alpha\beta}$ = 2.76) heterocycles (Table IV).[32] In selenane the β,γ portion has also been examined and found to be puckered ($R_{\beta\gamma}$ = 2.75) to about the same extent as the α,β portion.[32] The barrier to ring reversal (Table I) in selenane (ΔG° = 8.3 kcal/mol) is slightly lower than that in thiane, and the barrier in tellurane continues the trend (ΔG° = 7.3 kcal/mol).[9] This monotonic decrease in the barrier in going down group VI can

be related directly to the similar decrease observed in the CH_3–X–CH_3 series (Table II). The fact that the barrier becomes lower as the degree of puckering increases provides further evidence that angle bending is much less important than bond torsion in determining the barrier to ring reversal. Although nothing is known directly about the anisotropy of the C–Se and C–Te bonds, it can be inferred from the increase in $\delta_{ae}(\alpha)$ on passing from thiane (0.187 ppm) through selenane (0.295) to tellurane (0.75) that the diamagnetic anisotropy of all three C–X bonds is opposite in sign to that of the C–C and C–O bonds and is increasing in magnitude through the series.[33] The large increase from selenane to tellurane in particular cannot be explained in terms of a geometry change, since the rings are only slightly different in shape.

Protonated selenane and tellurane clearly have a preferred axial conformation, as indicated by the vicinal coupling constants (J_{aa} = 13.0, J_{ae} = 2.1; J_{aa} = 11.2, J_{ae} = 2.4 Hz, respectively).[10] The conformation of *Se*-methylselenanium iodide is less clear. Only one form is observed in the proton spectrum down to −88°, which temperature, however, may still be above coalescence.[9] The value of the geminal coupling constant between the α protons is characteristic of an axial conformation. Although it is reasonable that the small equatorial preference observed in the *S*-methylthianium salt is reversed in the selenanium salt, use of the coupling constant criterion in the absence of both isomers is not without ambiguity.[9] This problem therefore requires further scrutiny.

Both selenane and tellurane form very stable adducts with chlorine, bromine, and iodine. The bromine and iodine complexes have been studied by the *R*-value method and by conductance.[31,32] The iodine complex of selenane is similar to that of thiane. The α,β and β,γ *R* values of selenane are little changed on iodination (Table IV). The conductance is about 1% that of the fully ionic *Se*-iodoselenanium fluoroborate, and increases when excess iodine is added. The structure therefore is a simple molecular complex, with some ionic character (eq 10).[32] The results for the bromine complex of selenane are in considerable contrast. The value of $R_{\alpha\beta}$ (Table IV) indicates that the ring is very flattened around the heteroatom ($\Psi_{\alpha\beta}$ = 53.5°). This is the result expected for a trigonal bipyramid (**23**), because of the very large C–Se–C



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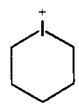
angle. The β,γ portion of the molecule puckers as a response to this distortion ($\Psi_{\beta\gamma}$ = 63°). There is essentially no conductance from this complex, so the bonds must be covalent.[32] The tellurane complex with bromine has a similar but even more extreme trigonal-bipyramidal structure ($\Psi_{\alpha\beta}$ = 52°, $\Psi_{\beta\gamma}$ = 64°).[31,32] Although no NMR experiments were carried out on the tellurane diiodide, it probably also is a trigonal bipyramid.[32] Thus the crossover from simple molecular complex to trigonal bipyramid occurs at tellurium for iodine but at selenium for bromine. It may be hypothesized that all the chlorine adducts are trigonal bipyramids, but there is no experimental evidence as yet.[32]

The preference of the oxide for the axial position is even larger in selenane 1-oxide (84/16, $\Delta G°$ = 475 cal/mol) than in thiane 1-oxide.[9,11] Because of the slightly longer C–Se bonds, the attractive interaction between the axial oxide and the syn-axial 3,5 protons must be even greater. All three configurational criteria developed for thiane oxides were found to hold for the selenium analog. The axial conformer has the smaller $\delta_{ae}(\alpha)$, the larger $J_{ae}(\alpha)$, and the higher field quartet midpoint. Therefore, the C–(SeO) anisotropy must have the same sign as that of C–C, C–(SO), and C–O, but opposite to that of C–S and C–Se.[33] The lone pair plays an important role in differentiating the C–(SeO) anisotropies for the axial and equatorial conformations.

The slow-exchange spectrum of selenane 1,1-dioxide is very similar to that of the analogous sulfone.[5,9–11] In both cases the α resonance is an unresolved, broad singlet, and the γ resonance is a normal quartet. The explanation is the same as for sulfur. The anisotropy of the C–(SeO_2) bond must be similar in magnitude but opposite in sign to that of the C–C bond, so the contributions cancel and the axial and equatorial α protons are not differentiated. The γ protons, however, have the usual relationship with the two C–C bonds.[33] The barrier to ring reversal in the selenone ($\Delta G°$ = 6.7 kcal/mol, Table I) is clearly smaller than that of selenane (8.3) or the selenoxide (7.9 or 8.4, depending on the direction). In the sulfur series, the sulfone barrier is slightly higher than the sulfoxide, and both are clearly higher than the thiane barrier (Table I). The latter data parallel the known torsional barriers for the C–X bonds (Table II), since the barrier in dimethyl sulfoxide is higher than that in dimethyl sulfide. To the extent that ring reversal reflects this property, it would be expected that the torsional barrier for dimethylselenone would be less than that of dimethylselenoxide, which would be about the same as that for dimethylselenide (1.5 kcal/mol). Significant contributions from angle-bending strain would negate these predictions.[9]

E. Group VII

Not until 1973 were pentamethylene heterocycles containing halogens prepared.[100] The iodonium heterocycle (**24**) was obtained in a pure form in solution, but the bromonium ion (**25**) could only be prepared in the presence of the 2-methyltetramethylene isomer. No conformational studies have yet to



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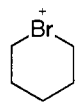

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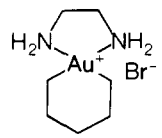
be reported, but the mode of preparation is amenable to the introduction of deuterium and application of principles already discussed in this article.

F. Metallic Heterocycles

Attachment of the pentamethylene group to a metal atom opens the possibility of a wealth of new heterocyclic systems. The synthetic problems here could be considerable, since the introduction of two metal–σ bonds is difficult. At least four such systems have already been reported. The gold heterocycle **26** was reported in the 1930's,[101] but no more recent substantiation of the synthesis has been made. Magnesiacyclohexane has been reported by two groups.[102,103] The com-



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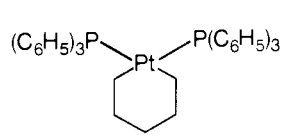

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pound favors dimerization, although preparation in hexamethylphosphoramide produces a monomeric species.[103] Mercuriacyclohexane also favors a dimeric or polymeric structure, although one study has reported the monomer.[104] Finally, the recent preparation of the platinum heterocycle **27** indicates that transition metals can be bonded to penta-

methylene system.[105] No conformational studies have been reported on any of these metallic heterocycles.

IV. Status of the Field

There is still considerable room for work in the areas of borinanes, metallic heterocycles, group IV systems, and possibly the halonium salts. The group VI area has been thoroughly examined, although some gaps still exist, such as the conformation of the methyl and protonated oxonium ions and of the oxides of tellurium. Although more work has been carried out on the group V heterocycles than on any others, much still remains. The piperidine problem still awaits an unambiguous answer, and numerous N-substituted systems have not even been examined. Phosphorinanes have now been the subject of several extended studies, although many unexamined systems remain. Group V heterocycles below phosphorus are essentially unstudied.

V. Addendum

A number of developments have taken place since this manuscript was submitted.

General. An extensive carbon-13 NMR study has now been completed on the pentamethylene heterocycles, including data on chemical shifts[109] and spin-lattice relaxation times.[110] The chemical shifts of the α carbons depend mainly on the electronegativity of the heteroatom, with some perturbations due to substituents at the 1 position (a "β effect"). The β-carbon resonance positions are also dependent on the heteroatom electronegativity, but in addition they are very sensitive to the axial or equatorial orientation of 1 substituents. Thus the β chemical shift may be added to the list of useful configurational criteria. The γ-carbon resonance, like that of the α carbon, is primarily dependent on the electronegativity of X. The partial charges induced at the α, β, and γ carbons by σ induction of the heteroatom, as determined from the slopes of plots of the carbon-13 chemical shift vs. heteroatom electronegativity, are in the ratio 1 to -0.05 to -0.1.[109] The decrease in magnitude with a change in sign between the α and β positions is in agreement with the Pople–Gordon theory of charge polarization.[111] The increase in magnitude without a change in sign between the β and γ carbons results from a special mechanism of σ induction associated with the antiperiplanar relationship between X and the γ carbon. These results[109] provide a more general picture of the phenomenon termed the "γ-anti effect".[112] Contrary to the earlier report, however, the effect does not require the presence of lone pairs, since it applies equally to the group IV heterocycles. Spin-lattice relaxation times have been measured for the $Si(CH_3)_2$, NH, NCH_3, PCH_3, $AsCH_3$, O, S, Se, and Te pentamethylene heterocycles and have been found to be directly proportional to the molecular weight.[110] Anisotropic tumbling of the heterocycles of groups IV and V is indicated by a consistently lower relaxation time for the γ carbon. Tumbling must be more nearly isotropic for the group VI heterocycles, since all three carbons have similar relaxation times. Plots of T_1 as a function of reciprocal temperature indicate that the dominant relaxation mechanism is probably dipole–dipole, although behavior at higher temperatures is indicative of increased importance of the spin-rotation mechanism.[110]

Group V. A full report has appeared on the carbon-13 spectra of decahydroquinolines and *N*-alkylpiperidines.[113] The equatorial form of *N*-methylpiperidine is favored by at least 1.35 kcal/mol, and conformational biasing is even greater in the *N*-ethyl and *N*-isopropyl compounds. These authors[113] presented evidence that the substituted phenyl groups used to obtain erroneous results by the dipole moment method[61] appear to alter the conformational equilibrium constant. Carbon-13 chemical shift data on *N*-chloropiperidine have suggested that the favored conformation is the equatorial.[109] Ultraviolet photoelectron spectroscopy has been applied to pentamethylene heterocycles for the first time.[114] In this study the photoelectron spectra of piperidine and *N*-methylpiperidine were compared with those of their β,γ-dehydro derivatives. Whereas introduction of the double bond causes no change in the ionization potential of the lone pair electrons in piperidine (8.64 eV), in the *N*-methyl case the unsaturation increases the ionization potential from 8.29 to 8.67 eV. The authors conclude that in the unsaturated compounds an axial lone pair (equatorial substituent) is more delocalized than is an equatorial lone pair and hence is harder to ionize. They attribute the absence of a change in the ionization potential in the N–H case to the presence of an equatorial lone pair (axial proton) and the increase in ionization in the $N–CH_3$ case to an axial lone pair (equatorial methyl). On the other side of the controversy, a review article strongly advocating an equatorial preference for the proton in piperidine has appeared.[115]

Group VI. The carbon-13 spectra of the separate axial and equatorial isomers have been observed at low temperatures for thiane 1-oxide.[116] The chemical shifts are significantly different for the α and β carbons and may be a useful configurational criterion when two isomers are in hand. A review of tellurane heterocycles has appeared.[117]

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