Conformational Analysis of Five-Membered Rings

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Abstract: The conformationally averaged coupling constants between all vicinal pairs of protons have been measured in cyclopentane, tetrahydrofuran, pyrrolidine, and tetrahydrothiophene. The vicinal couplings between the equivalent 3 and 4 protons have also been measured in cyclopentene, cyclopentanone, cyclopentanol, and cyclopentyl bromide. The qualitative R-value analysis of these couplings shows that tetrahydrothiophene and cyclopentanone are somewhat more puckered than cyclopentane, and the remaining molecules are flatter. Quantitative R-value analysis was found to overestimate the magnitude of the internal torsional angles, probably because these five-membered rings do not possess the threefold symmetry in Newman projection that is characteristic of six-membered rings. Torsional angles calculated for the 3,4 segment by a traditional Karplus approach are thought to be more accurate, since a common A factor may be used. Similar quantitative structural analysis for the 2,3 segment is not possible since this A factor is strongly dependent on the electronegativity of the group at the 1 position. The 3,4 vicinal coupling constants for cyclopentene and cyclopentanone have been found to be essentially invariant over a temperature range of 140 and 60°, respectively, whereas those of tetrahydrofuran and tetrahydrothiophene vary gradually with temperature. These results are consistent in the former cases with a single conformation (or group of equal-energy conformations), and in the latter cases with multiple conformers of differing energies.

As the field of conformational analysis of six-membered rings approaches maturity, structural chemists have increasingly turned their attention to studies of other ring systems, both smaller and larger. The conformational problems posed by the saturated five-membered ring are far more complex than those of the six-membered ring. In addition to the two conformations possessing symmetry, 1 (the C_s or envelope form) and 2 (the C_2 or half-chair form),[2] other reasonable
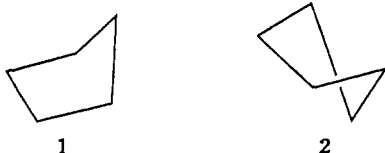
geometries exist along the pseudorotation coordinate for interconversion (1 may be converted to 2 by vertical displacement of two atoms in the flap), and in the case of cyclopentane many of these have approximately the same energy.[3] Conformations increase in energy only as they tend toward planarity or become extremely puckered. Thus, cyclopentane is thought to exist as a mixture of numerous conformations that are interconverted by pseudorotation so that each atom can assume any position of 1 and 2 and the intermediate forms. Introduction of substituents, of unsaturation, or of heteroatoms should perturb this long, smooth potential well so that certain forms are excluded and others become favored, with the extreme possibility that a molecule exists as a single conformation.

Five-membered rings occur frequently in nature, as the D ring of steroids, in furanose sugars, and in proline-containing peptides. In contrast to six-membered rings, for which the chair is almost always the correct

representation, the complex conformational situation described above does not permit a standard depiction for five-membered rings. Nor is X-ray crystallography so powerful an aid. Most six-membered rings assume the same conformation in the solid as in solution (although an axial–equatorial equilibrium in solution will probably crystallize as one form). With a large array of conformational possibilities, each with several different substituent positions, a five-membered ring might yield a structure in the crystal with only a distant relationship to the situation in solution. Independent methods are therefore required for conformational determination in the gas or liquid phase. One of the most successful of these has been electron diffraction, by which the structures of cyclopentane,[4a] cyclopentanone,[4b] tetrahydrofuran,[4c] and tetrahydrothiophene[4d] have been studied in the gas phase. Although accurate data about torsional angles can be obtained by this method when the molecule exists in a single conformation, mixtures of conformations are difficult or impossible to analyze.

For molecules in solution, no more powerful method exists than analysis of vicinal proton–proton coupling constants. Although the major successes of this method have been demonstrated in six-membered rings, a number of applications to five-membered rings have now appeared.[5] Because slow-exchange limits cannot be reached, the vicinal couplings represent averages over all conformations present. The dihedral angle φ

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(2) J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Amer. Chem. Soc.,* **69,** 2483 (1947).

(3) J. B. Hendrickson, *J. Amer. Chem. Soc.,* **83,** 4537 (1961); **85,** 4059 (1963).

(4) (a) W. J. Adams, H. J. Geise, and L. S. Bartell, *J. Amer. Chem. Soc.,* **92,** 5013 (1970); (b) H. J. Geise and F. C. Mijlhoff, *Recl. Trav. Chim. Pays-Bas,* **90,** 577 (1971); (c) A. Almenningen, H. M. Seip, and T. Willadsen, *Acta Chem. Scand.,* **23,** 2748 (1969); (d) Z. Náhlovská, B. Náhlovský, and H. M. Seip, *ibid.,* **23,** 3534 (1969).

(5) (a) R. J. Abraham, *J. Chem. Soc.,* 256 (1965); (b) P. Haake, J. P. McNeal, and E. J. Goldsmith, *J. Amer. Chem. Soc.,* **90,** 715 (1968); (c) J. B. Lambert and F. R. Koeng, *Org. Magn. Resonance,* **3,** 389 (1971); (d) L. A. Sternson, D. A. Coviello, and R. S. Egan, *J. Amer. Chem. Soc.,* **93,** 6529 (1971); (e) R. Steyn and H. Z. Sable, *Tetrahedron,* **27,** 4429 (1971); (f) K. Bergeson, M. Bjorøy, and T. Gramstad, *Acta Chem. Scand.,* **26,** 2156 (1972); (g) P. Albriksten, *ibid.,* **26,** 3671 (1972); (h) D. W. Aksnes and O. Vikane, *ibid.,* **27,** 1337 (1973); (i) D. W. Wertz, *J. Mol. Struct.,* **17,** 163 (1973); (j) G. E. Wilson, Jr., and T. J. Bazzone, *J. Amer. Chem. Soc.,* **96,** 1465 (1974); R. L. Lipnick, *ibid.,* **96,** 2941 (1974).

between vicinal protons is related to the three-bond coupling by the Karplus equation (eq 1).[6] The internal

$$J_{vic} = A \cos^2 \varphi \qquad (1)$$

torsional angle Ψ of an $X-CH_2-CH_2-Y$ fragment is given by the R-value expression (eq 2 and 3),[7] in which

$$R = \frac{J_{trans}}{J_{cis}} = \frac{3 - 2 \cos^2 \Psi}{4 \cos^2 \Psi} \qquad (2)$$

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

J_{trans} and J_{cis} are the average vicinal couplings in the bismethylene fragment. Use of eq 3 has given reliable torsional angles in six- and seven-membered rings, ranging from $\Psi = 45°$ ($R = 1.00$) to $74°$ ($R = 8.7$).[8] Out of numerous comparisons between R-value results and torsional angles measured by X-ray crystallography, in only one case has the difference been as large as $3°$.[7]

We have set about to apply these methods to the conformational analysis of all the basic five-membered rings.[9] We report in the present paper the complete or partial analysis of the proton spectra of cyclopentane (3), tetrahydrofuran (4), pyrrolidine (5), tetrahydrothiophene (6), cyclopentanone (7), cyclopentanol (8), cyclopentyl bromide (9), and cyclopentene (10). Interpreta-

X	X
3, CD_2	7, $C=O$
4, O	8, CDOH
5, NH	9, CDBr
6, S	

10
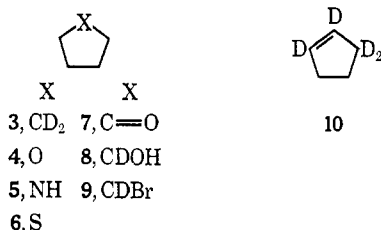
tion of these couplings permits qualitative and quantitative conclusions about the shapes of these rings. The temperature dependence of these couplings gives further information about the multiplicity of conformations. A molecule frozen into a single form will have temperature-independent couplings, as will one that exists as a mixture of more than one form with identical energies. Observation of a temperature dependence of the vicinal couplings, however, can be taken as evidence that the molecule exists in two or more forms of differing energy. We have therefore examined the spectra of tetrahydrofuran, tetrahydrothiophene, cyclopentanone, and cyclopentene as a function of temperature and can report that the first two molecules must exist in at least two forms of different energy, and that the last two probably exist in a single form (or in an equilibrium among forms of equal energy).

Results

In order to effect the complete analysis of the eight-spin system of molecules of the types 3–9, two separate four-spin systems were isolated by deuteration: deuterium in the 2 and 5 positions (a); and deuterium in the 2 and 3 positions (b). The syntheses of these labeled

(6) M. Karplus, J. Chem. Phys., 30, 11 (1959); J. Amer. Chem. Soc., 85, 2870 (1973).

(7) J. B. Lambert, J. Amer. Chem. Soc., 89, 1836 (1967); J. B. Lambert, Accounts Chem. Res., 4, 87 (1971); H. R. Buys, Recl. Trav. Chim. Pays-Bas, 88, 1003 (1969).
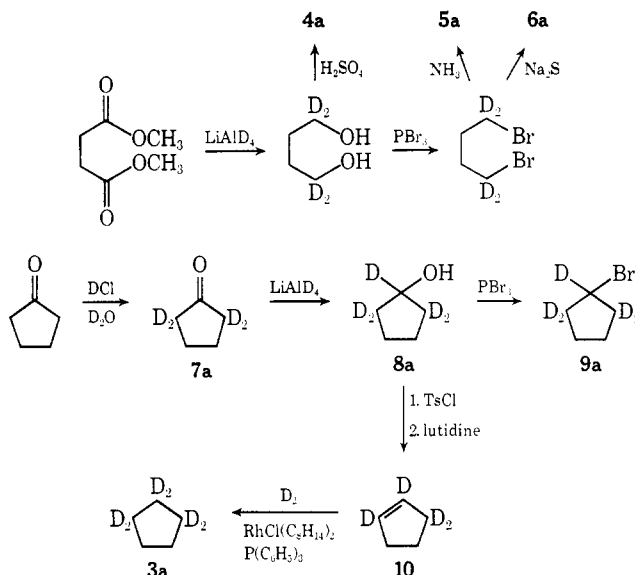
(8) S. F. Nelsen, P. J. Hintz, and R. T. Landis, II, J. Amer. Chem. Soc., 94, 7105 (1972); M. St. Jacques and C. Vaziri, Org. Magn. Resonance, 4, 77 (1972).

(9) J. B. Lambert, J. J. Papay, E. S. Magyar, and M. K. Neuberg, J. Amer. Chem. Soc., 95, 4458 (1973).

a

b

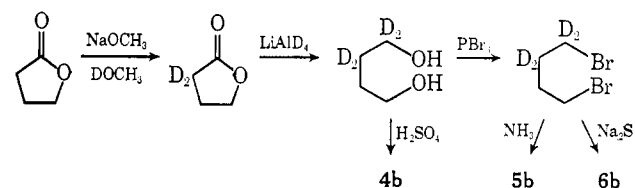systems are given respectively in Schemes I and II.

Scheme I

Scheme II

The $AA'BB'$ or $AA'XX'$ spectra of variant b for compounds 4–6, of variant a for compounds 8 and 9, and of compound 10 are readily analyzed under conditions of double irradiation at the deuterium resonance frequency. The ^{13}C satellites of the spectra of 3a–7a again give analyzable $AA'XX'$ spectra with deuterium irradiation. The vicinal coupling constants were obtained from these spectra by standard iterative techniques. Figure 1 presents the observed and calculated spectra for both isotopic variants of tetrahydrofuran (4a and 4b). Analogous spectra for pyrrolidine (5a and 5b), tetrahydrothiophene (6a and 6b), cyclopentanone (7a), cyclopentanol (8a), cyclopentene (10), and cyclopentane (3a) are given in Figures 2–7,[10] respectively.

The coupling constants derived from these analyses are given in Table I. The smaller vicinal coupling is assigned in all cases but one to J_{trans}. Reversal of this assignment would give geometries that are far too puckered for five-membered rings. For tetrahydrothiophene, however, the larger coupling is assigned to J_{trans} in the 3,4 segment because of the large puckering expected for molecules containing the smaller C–S–C bond angle and to accord with the electron diffraction results.[4d] Table I also contains the R values (eq 2), the torsional angles derived from the R value (eq 3), the torsional angles obtained from application of the Karplus equation (eq 1) to J_{cis} in isotopic variant a, and

(10) Figures 2–4, 6, and 7 appear only in the microfilm edition of this journal. See the paragraph at end of the paper regarding supplementary material.
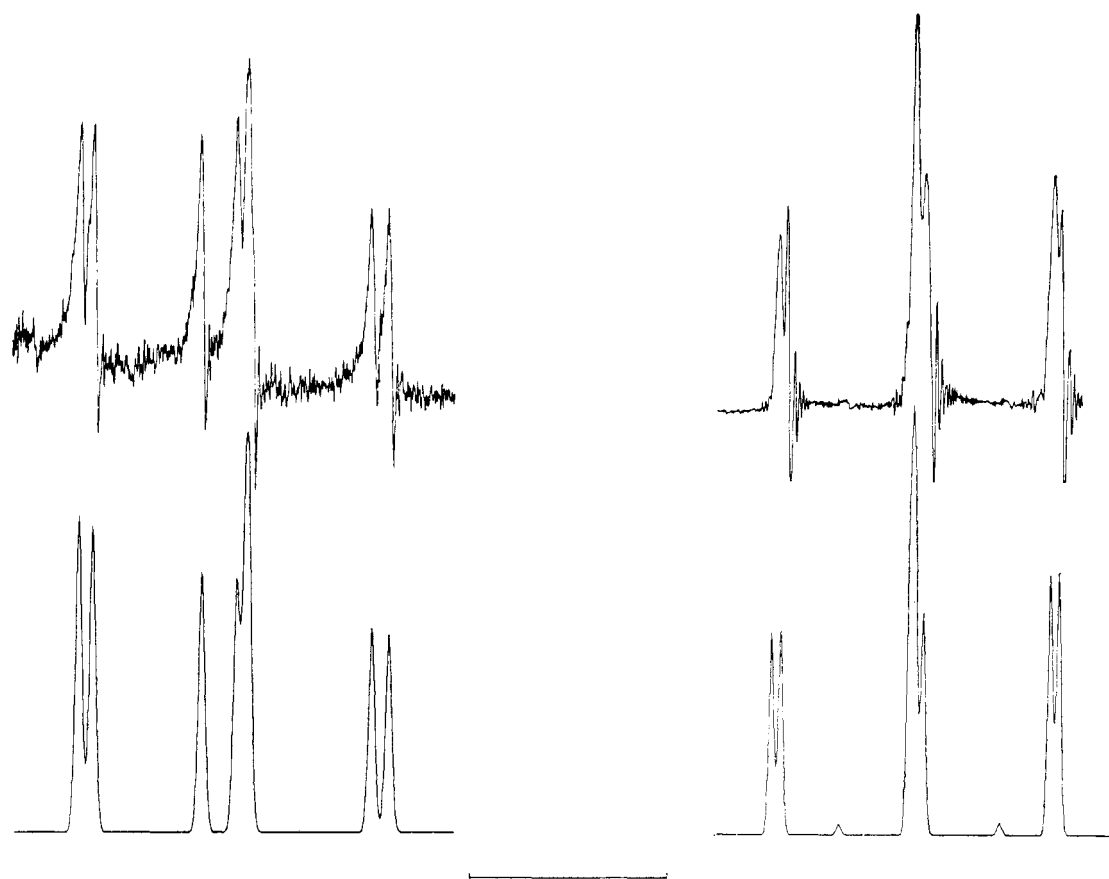
Figure 1. Left: observed (top) and calculated 90-MHz proton spectra of tetrahydrofuran-$2,2,5,5$-d_4 (**4a**) in $CHCl_3$ (upfield ^{13}C satellite). Right: observed (top) and calculated 60-MHz proton spectra of tetrahydrofuran-$2,2,3,3$-d_4 (**4b**) in $CHCl_3$ (downfield half). Both spectra were obtained with deuterium decoupling. The calibration bar represents 10 Hz.

Table I. Coupling Constants and Torsional Angles in Five-Membered Rings (Room Temperature)

Compd	X	J_{trans},[a] Hz	J_{cis},[a] Hz	R	Ψ_r,[b] deg	Ψ_k,[c] deg	Ψ_{lit}, deg
6a	S	7.25	5.45	1.33	50	42	46[d]
7a	CO	6.75	6.75	1.00	45	34.5	37.4[c]
3a	CD_2	6.30	7.90	0.80	40	(27)[f]	27[e]
5a	NH	6.30	8.30	0.76	39	24	
4a	O	6.25	8.65	0.72	38	21	e, g
8a	CDOH	6.02	8.25, 8.25[h]	0.71	38	25	
9a	CDBr	5.76	9.16, 9.55[h]	0.62	35		
6b	S	6.66	6.66	1.00	45		
5b	NH	6.07	7.78	0.78	40		
4b	O	6.14	7.94	0.77	40		
10		5.72	9.36	0.61	35		

[a] The average derivation from the mean is about ±0.04. [b] Calculated from the R value (eq 3). [c] Calculated from the Karplus equation (eq 1) with $A = 9.95$. [d] Calculated by molecular mechanics methods: see G. Allegra, G. E. Wilson, Jr., E. Benedetti, C. Pedone, and R. Albert, *J. Amer. Chem. Soc.*, **92**, 4002 (1970). [c] Reference 4. [f] This observed angle was used to calculate the Karplus A for the remaining determinations. [g] Maximum, rather than average, torsional angles have been reported. [h] The symmetry of this molecule-is such that there are two distinct values of J_{cis}, which are averaged for the R value; for cyclopentanol, however, the values appear to be the same.

torsional angles reported in the literature for the solution or gas phase.

In order to probe for the presence of multiple conformations, the spectra of variant a of tetrahydrofuran, tetrahydrothiophene, and cyclopentanone and the spectrum of cyclopentene were measured as a function of temperature (Table II). Some variation was observed in the spectra of the first two molecules, but the last two exhibited essentially no change.

Discussion

The primary objective of vicinal coupling constant analysis is to derive dihedral angle information. In addition to its dependence on the dihedral angle, as represented by eq 1, the vicinal coupling, however, also varies with the C–C bond length, the H–C–C bond angle, and the electronegativity of substituents.[6] Fortunately, these dependencies are multiplicative, so that division of J_{trans} by J_{cis} gives a ratio that depends only on conformation.[7] The dependence of vicinal couplings on the orientation of substituents is removed by the use of averaged J_{trans} and J_{cis}. Because the R value (eq 2) is independent of all these additional factors, the torsional angles Ψ obtained by eq 3 have been extremely accurate.

The specific aim of this work was to derive the tor-

Table II. Temperature Dependence of Vicinal Couplings (Hz) in Five-Membered Rings

Temp, °K	Tetrahydrofuran (4a) J_{trans}	J_{cis}	Tetrahydrothiophene (6a) J_{trans}	J_{cis}	Cyclopentanone (7a) J_{trans}	J_{cis}	Cyclopentene (10) J_{trans}	J_{cis}
365			7.25	5.75				
360	6.10	8.90					5.66	9.39
350							5.71	9.39
340	6.12	8.88						
335			7.30	5.60	6.73	6.73		
330							5.70	9.40
320	6.14	8.86						
305			7.35	5.50	6.75	6.75		
300	6.15	8.75					5.68	9.44
280	6.25	8.75					5.69	9.43
275			7.35	5.45	6.74	6.74		
260	6.24	8.64						
250							5.67	9.46
245			7.30	5.30				
240	6.32	8.62						
220	6.40	8.60					5.70	9.53
215			7.35	5.15				

sional angles of the two ring segments that are undeuterated respectively in isotopic variants a and b. Knowledge of two torsional angles in a five-membered ring can determine the shape of the entire ring.[11] Initial qualitative examination of the data given in Table I is useful. Cyclopentane, with an R value of 0.80, can be taken as the point of reference, just as cyclohexane ($R = 2.16$) was for six-membered rings.[7] The larger R value (1.00) for the 3,4 portion of cyclopentanone is best explained in terms of the half-chair conformation (2), with the carbonyl group at the central position of the three coplanar carbons. The 3,4 methylene groups are then placed in a position of maximal puckering. The small C–S–C bond angle causes considerable puckering in both the 2,3 and 3,4 portions of the tetrahydrothiophene ring ($R = 1.00, 1.33$). Both the 2,3 and the 3,4 R values in tetrahydrofuran (0.77, 0.72) and in pyrrolidine (0.78, 0.76) are slightly smaller than that of cyclopentane. The shorter C–O and C–N bonds probably bring about this slight flattening. A similar deformation is observed for the alcohol ($R = 0.71$) and the bromide (0.63), probably because certain points along the pseudorotational itinerary have been excluded. For example, if the substituent is on the carbon at the center of the flap of the envelope conformation (1), the protons reside in portions of the ring that are flatter on the average than in cyclopentane.

Useful though these qualitative comments are, quantitative torsional angles would be far more revealing. Contrary to the situation in six-membered rings,[7] the present quantitative results are not good. The R-value torsional angles (Ψ_r in Table I) are 10 and 13° larger than the respective angles measured by electron diffraction (Ψ_{1it}) for cyclopentanone and cyclopentane.[12] This overestimation by the R-value method may be due at least in part to a breakdown of the pseudo-three-fold symmetry assumed in the derivation of eq 3. In six-membered rings and larger, the projection angle

(11) C. Altona, H. J. Geise, and C. Romers, Tetrahedron, 24, 13 (1968). Unfortunately, this relationship breaks down when bond lengths and bond angles are extremely unequal. Additional bond angles and bond lengths must be specified for unsymmetrical cases such as heterocycles. See G. E. Wilson, Jr., J. Amer. Chem. Soc., 96, 2426 (1974).

(12) The value of Ψ_{1it} for cyclopentane is obtained by averaging the five Ψ for each form of cyclopentane calculated by Hendrickson.[3] For all low-energy forms, the average torsional angle is 27–28°. Similarly, the average torsional angle found by Adams, et al.,[4b] is close to 27° and does not depend significantly on the assumed geometry.
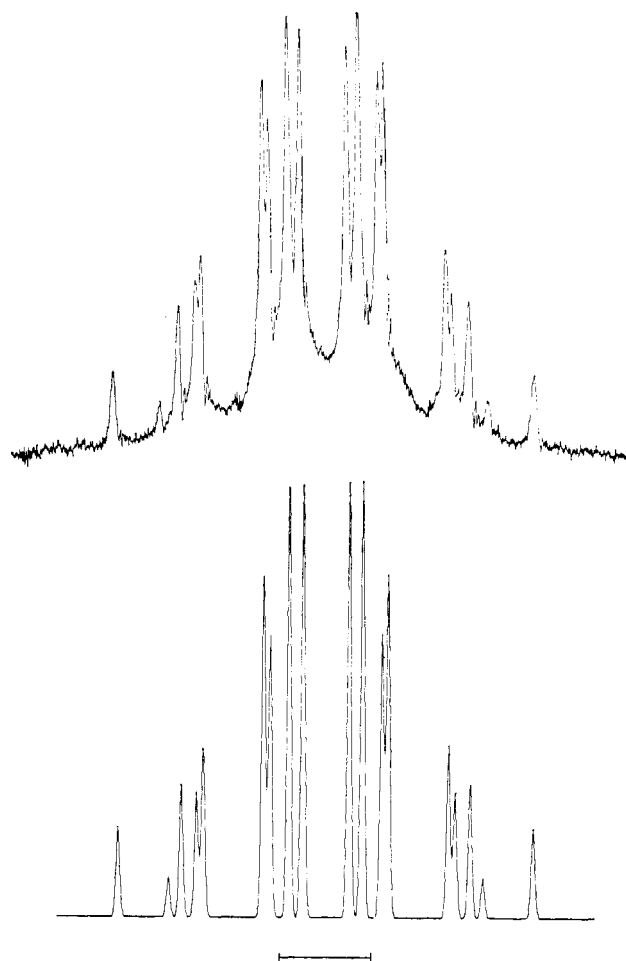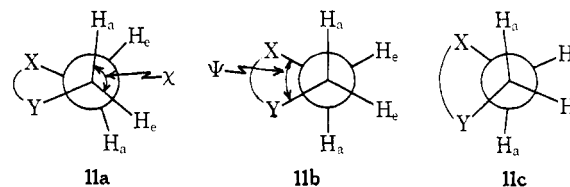

Figure 5. Observed (top) and calculated 90-MHz proton spectra of cyclopentanol-1,2,2,5,5-d_5 (8a) in $CHCl_3$. The observed spectrum was obtained with deuterium decoupling. The calibration bar represents 10 Hz.

χ of the H–C–H group is very close to 120° in flattened (11a), normal (11b), and puckered (11c) molecules.


11a   11b   11c

The H–C–C–H dihedral angles are then related to the internal torsional angle Ψ by eq 4. Substitution of the

$$\varphi_{aa} = 120° + \Psi$$
$$\varphi_{ae} = \varphi_{ea} = \Psi \qquad (4)$$
$$\varphi_{ee} = 120° - \Psi$$

Karplus equation (eq 1), expressed in terms of Ψ, into the definition of the R value (eq 2) gives eq 5,

$$R = \frac{{}^1/_2(A \cos^2 (120 + \Psi) + A \cos^2 (120 - \Psi))}{A \cos^2 \Psi} \qquad (5)$$

which reduces to eq 3 on cancellation of A and expansion with trigonometric identities. Rings with appreciable angle strain lack trigonal projection symmetry, so that χ becomes greater than 120° (**12**). A more general set of

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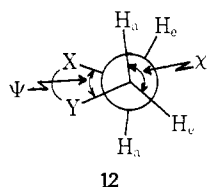
expressions is then necessary to relate φ and Ψ (eq 6).

$$\varphi_{aa} = \chi + \Psi$$
$$\varphi_{ae} = \varphi_{ea} = \chi \qquad (6)$$
$$\varphi_{ee} = \chi - \Psi$$

Substitution of these values into the Karplus equation gives eq 7, from which it can be seen that an increase in

$$J_{trans} = {}^1/_2(A \cos^2 (\chi + \Psi) + A \cos^2 (\chi - \Psi)) \qquad (7a)$$
$$J_{cis} = A \cos^2 \Psi \qquad (7b)$$

χ increases J_{trans} but has no effect on J_{cis}. Wilson and Bazzone[5j] have reduced the general expression for the R value (division of eq 7a by 7b) to eq 8 by trigonometric

$$\Psi = \cos^{-1}\left[\frac{1 - \cos^2 \chi}{2(R - \cos^2 \chi)}\right]^{1/2} \qquad (8)$$

manipulation. When χ is greater than 120°, as in these five-membered rings, the increase in J_{trans} and the constancy of J_{cis} produce an inflated R value for a given Ψ. If eq 3 is applied to such situations, the resulting Ψ_r is larger than the actual angle. Since there is no accurate and reliable method to evaluate χ for the entire series, eq 8 cannot be used. We are by no means sure that changes in χ comprise the only factor that causes the overestimation of Ψ, but it is probably the dominant one. Equation 3 at any rate is not applicable to molecules in which χ is distorted by angle strain. This conclusion does not alter the qualitative conclusions about ring shapes given above.

The Karplus approach provides an alternative method to obtaining torsional angles. According to eq 7b, the magnitude of Ψ can be obtained from J_{cis} without reference to the projection angle χ. The J_{trans} would not give useful information because of its complex dependence on Ψ and χ. The major drawback to any application of the Karplus equation has been the evaluation of the constant A, which depends on bond angles, bond lengths, and substituent electronegativities. The advantage of the R-value method is the removal of this

constant. In an homologous series the A factor should remain relatively constant. Evaluation of A in a standard compound can then permit the determination of Ψ from J_{cis} and eq 7b for the entire series.

An analysis of this type can be carried out for the isotopic variant a to obtain the torsional angle of the 3,4 portion of the molecule. The changing X group (CD_2, O, S, NH, etc.) is far enough from the coupling protons that electronegativity effects on J_{cis} are absent. The changes in J_{cis} therefore come entirely from conformational differences. Since the average torsional angle is known to be about 27° in cyclopentane both by calculation[3] and by electron diffraction,[4a,12] the constant A may be calculated from eq 7b to be 9.95. This value in turn gives the entire array of torsional angles labeled Ψ_k in Table I. It is seen that the Ψ_r are uniformly larger than the Ψ_k by 12–17°. The only values that can be independently compared are those for cyclopentanone, and the agreement between the calculated Ψ_k (34.5°) and the observed Ψ_{lit} (37.4°)[4b] is good. We therefore believe that the values of Ψ_k are reasonably accurate. It should be emphasized again that the nmr-determined torsional angles are averages over all populated conformations, since the coupling constants from which they are measured are similar averages. Only when the molecule exists in a single form do the nmr torsional angles correspond to hard structural parameters. The temperature dependence of the vicinal couplings in tetrahydrofuran and tetrahydrothiophene demonstrate that multiple conformations are present for these molecules. The values of Ψ_k therefore cannot be compared to a Ψ_{lit} determined by any method that assumes a single conformation.[4c,d]

Unfortunately, the Karplus approach cannot be applied to the isotopic variant b of **4–6** or to cyclopentene **10**, since the X group strongly influences the magnitude of the couplings beyond the perturbations caused by conformation. For this reason, the A factor varies from system to system, and values of Ψ_k cannot be calculated. One can only suggest that the true values of Ψ are probably about 15° lower than the Ψ_r listed in Table I.

Substantiation of the use of eq 7b for determining torsional angles can be obtained by application to six membered rings, in which the R value is known to give reliable values of Ψ. In the system **13** the coupled
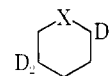
13, X = CD_2, $\overset{+}{S}CH_3$, S, Se, SeI_2, $SeBr_2$, TeI_2

portion (the 3,4 protons) again is sufficiently far from the changing X group that the coupling constants depend only upon conformation. The series should have a common Karplus A factor, which is calculated to be 13.28 from J_{cis} and the known value of Ψ in cyclohexane. The values of Ψ_k calculated from this quantity and eq 7b are listed in Table III, along with the values of Ψ_r calculated from the R value and eq 3.[13] It is seen that the largest deviation is 1°. The methods can therefore be considered to be equivalent in systems without angle strain. The large deviations between Ψ_r

(13) J. B. Lambert, D. H. Johnson, R. G. Keske, and C. E. Mixan, *J. Amer. Chem. Soc.*, 94, 8172 (1972).

Table III. Torsional Angles in Six-Membered Rings (13)

X	J_{trans},[a] Hz	J_{cis},[a] Hz	R	Ψ_r,[b] deg	Ψ_k,[c] deg
CD_2	8.07	3.73	2.16	58	58[d]
CH_3S^+	8.30	3.59	2.31	59	59.5
S	8.47	3.28	2.58	60	60
Se	8.63	3.14	2.75	61	61
SeI_2	8.44	3.04	2.78	61.5	61
$SeBr_2$	8.88	2.90	3.07	63	62
TeI_2	9.21	2.56	3.60	64	64

[a] Data from ref 13. [b] Calculated from the R value and eq 3. [c] Calculated from J_{cis}, eq 7b, and $A = 13.28$. [d] Assumed.

and Ψ_k for five-membered rings (Table I) indicate a systematic error in one procedure. For the reasons given above, we believe that the systematic error is in the R-value method, and is present only in systems containing angle strain.

Summary and Conclusions

It is worthwhile to summarize the preferred methods for determining torsional angles in solution for various systems. (1) For molecules without angle strain (six-membered rings and larger), the R-value method gives accurate torsional angles without evaluation of other factors, such as electronegativity of substituents. (2) For strained molecules that form an homologous series with a constant Karplus A (as in isotopic variant a), the Karplus approach provides the best torsional angles, provided that one member of the series has a known angle for evaluation of A. (3) For strained molecules in which the Karplus A is either variable (as in isotopic variant b) or for which there is no system with a known torsional angle to serve as the standard, the qualitative R-value method provides the only procedure for comparing torsional differences between systems.

We have found that in comparison to cyclopentane ($\Psi = 27°$), cyclopentanone ($\Psi = 34.5°$) and tetrahydrothiophene ($42°$) exhibit increased puckering in the 3,4 portion of the ring, whereas pyrrolidine ($24°$) and tetrahydrofuran ($21°$) are flatter. Cyclopentanol and cyclopentyl bromide also are flatter than cyclopentane. The saturated portion of cyclopentene is the flattest fragment examined ($R = 0.61$), but the torsional angle cannot be calculated since there is no A factor available.

The constancy of the vicinal couplings with temperature in cyclopentene and cyclopentanone indicates that the molecules probably exist in a single conformation, the former in an envelope and the latter in a half chair. Multiple conformations with equal energy cannot be excluded. The variation of the vicinal couplings with temperature in tetrahydrofuran and tetrahydrothiophene is consistent with the presence of multiple conformations of unequal energy.

Experimental Section

The 60-MHz nmr spectra were taken on Varian Associates Model T-60 and A-60 spectrometers. The 90-MHz spectra were recorded on a Bruker HFX-10 spectrometer with variable-temperature probe, deuterium decoupler, and Fabri-Tek (Nicolet) Model 1074 computer for signal averaging. Infrared spectra were taken on a Beckman IR-5 spectrophotometer. Mass spectra were obtained by Dr. Leo Raphaelian of the departmental Analytical Services Laboratory on a Consolidated Electrodynamics Corp. Model 21-104 instrument. Preparative vapor-phase chromatography was performed on an F & M Model 700 instrument, utilizing 10% silicone gum rubber (SE-30) and 10% Carbowax 20M on Chromosorb W in copper columns (0.25 in. × 5 ft). Analytical vapor-phase chro-

matography was performed on a Varian Aerograph Series 1520B instrument. Computer-simulated nmr spectra were obtained using NMRPLOT and ENIT programs on a Control Data Corp. Model 6400 computer with a Calcomp Model 565 plotter. Iterations resulted in rms errors of less than 0.05 Hz on calculated energy levels.

Methanol-d. Dimethyl carbonate (500 g, 5.55 mol), 99.9% deuterium oxide (120 g, 6.0 mol), and dimethyl sulfate (20 g, 0.18 mol) were refluxed for 96 hr. Methanol-d was removed by distillation (65–68°) and dried by successive distillation from sodium, magnesium, and magnesium methoxide. Gas-chromatographic analysis on a $^1/_8$ in. × 3 ft Chromosorb 102 column (100°, 60 ml/min) indicated less than 1% deuterium oxide impurity.

γ-Butyrolactone-2,2-d_2.[14] γ-Butyrolactone (15 g, 0.017 mol) and sodium metal (0.003 g, 1.3 × 10^{-5} mol) were added to 60 ml of methanol-d in a thick-walled tube. The solution was degassed by three successive freeze-thaw cycles, and the sealed tube was heated in a tube furnace at 180° for 8 hr. The tube was cooled and the partially exchanged lactone was purified by distillation. The procedure was repeated three additional times, and the exchanged lactone was purified by distillation: bp 78–80° (10 mm); nmr ($CHCl_3$) δ 1.5 (t, 2), 3.5 (t, 2).

Butane-1,4-diol-$1,1,2,2$-d_4. γ-Butyrolactone-2,2-d_2 (5.75 g, 0.065 mol) in 25 ml of anhydrous ethyl ether was added slowly to a stirred suspension of 2.75 g (0.065 mol) of lithium aluminum deuteride in 50 ml of anhydrous ethyl ether at 0°. The reaction mixture was refluxed 3.5 hr. Water (2.5 ml) and 10% NaOH (2 ml) were added slowly at 0°, and the reaction mixture was stirred overnight. The solids were separated by filtration and extracted with boiling tetrahydrofuran (3 × 100 ml). Removal of the solvent from all organic portions afforded 4 g of crude diol: nmr (neat) δ 1.0 (t, 2), 2.9 (t, 2), 4.3 (s, 2).

1,4-Dibromobutane-$1,1,2,2$-d_4. Butane-1,4-diol-$1,1,2,2$-d_4 (4.0 g, 0.04 mol) was added slowly to 11 ml (0.115 mol) of PBr_3 at 0° with stirring. The reaction mixture was heated in a steam bath overnight. Water (6 ml) was added slowly at 0°, and the dibromide was extracted into CH_2Cl_2. The organic layer was washed with NaHCO$_3$ and water and dried over anhydrous MgSO$_4$. The dibromide was isolated by distillation: 6.1 g (70%); bp 83–85° (10 mm); nmr (CH_2Cl_2) δ 1.3 (t, 2), 2.7 (t, 2).

Methyl Succininate. Diazomethane, generated by the slow addition of nitrosomethylurea (50 g, 0.5 mol) to 120 ml of 50% KOH under 400 ml of ether, was added slowly to a suspension of 15 g (0.127 mol) of succinic acid in 200 ml of ether at 0°. The solution was allowed to stir for 2 hr, and the excess diazomethane was consumed by addition of glacial acetic acid. The ethereal solution was extracted with NaHCO$_3$ and dried over anhydrous MgSO$_4$. The product was isolated by distillation: 10.4 g (56%); bp 78–80° (10 mm); nmr (neat) δ 2.0 (s, 4), 3.0 (s, 6).

Butane-1,4-diol-$1,1,4,4$-d_4. Methyl succinate (11.7 g, 0.08 mol) was dissolved in 25 ml of anhydrous ethyl ether and added dropwise to a suspension of 6.6 g (0.16 mol) of lithium aluminum deuteride in 125 ml of anhydrous ethyl ether at 0°. The reaction mixture was refluxed 2 hr. Water (6.6 ml) and 10% NaOH (5.8 ml) were added slowly at 0°, and the reaction mixture was stirred overnight. The solids were separated by filtration and extracted with boiling tetrahydrofuran (4 × 10 ml). Removal of the solvent afforded 4.5 g of crude diol: nmr (neat) δ 1.0 (s, 4), 4.4 (s, 2).

1,4-Dibromobutane-$1,1,4,4$-d_4. Treatment of butane-1,4-diol-$1,1,4,4$-d_4 with PBr$_3$, as with the previous diol, afforded this dibromide: 5.5 g (70%); bp 84–85° (10 mm); nmr (CH_2Cl_2) δ 1.3 (s).

Tetrahydrofuran-2,2,3,3-d_4 (4b). Butane-1,4-diol-$1,1,2,2$-d_4 (1 g, 0.011 mol), isolated from the ethereal solution of the above reduction of the lactone, was allowed to react with 0.2 ml of concentrated H$_2$SO$_4$ in a flask fitted with a short-path distillation apparatus. The flask was heated to 140° and the product collected as it distilled: bp 67–68°; nmr ($CHCl_3$) δ 1.2 (t, 2), 2.9 (t, 2).

Tetrahydrofuran-2,2,5,5-d_4 (4a). Analogous treatment of butane-1,4-diol-$1,1,4,4$-d_4 afforded this material: nmr ($CHCl_3$) δ 1.2 (s).

Pyrrolidine-2,2,3,3-d_4 (5b).[15] 1,4-Dibromobutane-$1,1,2,2$-d_4 (1 g, 0.005 mol) was dissolved in 5 ml of methanol saturated with ammonia, sealed in a tube, and heated at 120° for 5 hr. The tube was cooled and opened, and the solvent removed by bulb-to-bulb dis-

(14) J. A. Magnuson, Ph.D. Dissertation, California Institute of Technology, 1968.
(15) W. L. Oliver, Jr., Ph.D. Dissertation, Northwestern University, 1970.

tillation. The amine hydrobromide that remained was dissolved in a minimum volume of water and the amine liberated by the addition of KOH pellets. The amine was decanted, dried over $CaSO_4$, and dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over molecular sieves: nmr $(CHCl_3)$ δ 1.5 (t, 2), 2.6 (t, 2).

Pyrrolidine-2,2,5,5-d_4 (5a). Analogous treatment of 1,4-dibromobutane-1,1,4,4-d_4 afforded this material: nmr $(CHCl_3)$ δ 1.5 (s).

Tetrahydrothiophene-2,2,3,3-d_4 (6b).[16] 1,4-Dibromobutane-1,1,-2,2-d_4 (2.14 g, 0.01 mol) and sodium sulfide nonahydrate (2.0 g, 0.008 mol) in 50 ml of ethanol–water (50% v/v) were added simultaneously to a solution of 2.0 g of sodium sulfide nonahydrate in 50 ml of ethanol–water. The reaction mixture was refluxed for 2 hr. The product was codistilled with ethanol and water and extracted into CH_2Cl_2. The organic portion was washed with water and dried over anhydrous $MgSO_4$. The product was isolated by distillation: bp 119–121°; nmr $(CHCl_3)$ δ 1.6 (t, 2), 2.4 (t, 2).

Tetrahydrothiophene-2,2,5,5-d_4 (6a). Analogous treatment of 1,4-dibromobutane-1,1,4,4-d_4 afforded this material: nmr $(CHCl_3)$ δ 1.6 (s).

Cyclopentanone-2,2,5,5-d_4 (7a). A solution of deuterium chloride was prepared by careful addition of 12.5 g (0.06 mol) of PCl_5 to 100 g (5 mol) of deuterium oxide.[17] Cyclopentanone (4.2 g, 0.05 mol) was added to 15 ml of this mixture and stirred overnight in a sealed flask. The aqueous solution was saturated with NaCl; the ketone was decanted to 15 ml of fresh DCl solution and stirred overnight in a sealed flask. The new solution was saturated with NaCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and the fully exchanged ketone was isolated by distillation: 3.5 g (83%); bp 128–130°; nmr (benzene) δ 1.4 (s).

Cyclopentanol-1,2,2,5,5-d_5 (8a). Cyclopentanone-2,2,5,5-d_4 (1.7 g, 0.02 mol) was dissolved in 20 ml of anhydrous ethyl ether and added slowly to 1.0 g (0.024 mol) of lithium aluminum deuteride suspended in 40 ml of anhydrous ethyl ether at 0°. The reaction mixture was refluxed 6 hr, and deuterium oxide (2.3 ml) containing half a pellet of NaOH was added slowly at 0°. The solution was stirred overnight, and the solids were separated by filtration and washed with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and the product isolated by distillation: bp 137–138°; nmr $(CHCl_3)$ δ 1.4 (m).

Cyclopentyl-1,2,2,5,5-d_5 Bromide (9a). Cyclopentanol-1,2,2,-

5,5-d_5 (0.8 g, 0.00835 mol) was added dropwise to a three-necked flask equipped with a condenser and charged with 1.66 g (0.0106 mol) of PBr_3. The mixture was stirred 1 hr at room temperature and heated overnight at 100°. Water (2 ml) was added to the solution and the layers were separated. The aqueous portion was extracted four times with CH_2Cl_2. The combined organic portions were neutralized with aqueous $NaHCO_3$, washed with water, and dried over $MgSO_4$. The filtered solution was distilled to give about 0.45 g of the bromide: nmr (CCl_4) δ 1.8 (m).

Cyclopentyl-1,2,2,5,5-d_5 Tosylate. Cyclopentanol-1,2,2,5,5-d_5 (1.1 g, 0.012 mol) was added to 10 ml of cold pyridine (distilled from BaO) containing freshly recrystallized p-toluenesulfonyl chloride (2.85 g, 0.015 ml). The solution was placed in the freezer (−15°) overnight. The reaction mixture was diluted with 20 ml of water, and the tosylate was extracted into ether (4 × 25 ml). The ether extracts were washed with dilute HCl and dried over anhydrous $MgSO_4$. The ether was removed on a rotary evaporator and the tosylate used without further purification.

Cyclopentene-1,2,3,3-d_4 (10).[18] A solution of cyclopentyl-1,2,2,5,5-d_5 tosylate in 20 ml of 2,6-lutidine was heated at 150–160° for 2 hr. Cyclopentene-1,2,3,3-d_4 was distilled through a 10-cm glass-helix fractionating column and collected in a water-cooled condenser by slowly raising the pot temperature to 175°: 0.25 g (30%); nmr $(CHCl_3)$ δ 1.7 (m, 2), 2.6 (m, 2).

Cyclopentane-1,1,2,2,3,3-d_6 (3a) was prepared for this study by Mallory K. Neuberg. The procedure involved the addition of deuterium gas to cyclopentene-1,2,3,3-d_4 over $RhCl(C_8H_{14})_2/P(C_6H_5)_3$ catalyst.[19] The labeled cyclopentane was isolated from the ethanol–benzene solution by distillation and preparative vapor-phase chromatography: nmr $(CHCl_3)$ δ 1.4 (s).

Supplementary Material Available. Figures 2–4, 6, and 7 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, nega, tives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 Sixteenth St., N.W., Washington-D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-6112.

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