# Conformational Analysis in Saturated Heterocyclic Compounds

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By conformational analysis is meant the analysis of physical and chemical properties of compounds in terms of the "conformation" (rotational arrangement about single bonds) of the ground states, transition states, or excited states of the corresponding molecules. While conformational analysis historically dates back to the classical paper of Sachse[1] on the chair and flexible (boat) forms of cyclohexane, the wide impact of the subject today was initiated by the pioneering paper of Barton[2] relating cyclohexane conformation to stability, physical properties, and reactivity. In the past 12 years cyclohexane and (to a lesser extent) simple alkanes[3,4] have been studied quantitatively as well as qualitatively from the conformational point of view, and several summaries of the extensive body of information in this field are available.[5-8]

The fact that many important cyclic compounds—carbohydrates, many alkaloids, nucleic acids, and even tetrahydrocannabinol—as well as the majority of acyclic compounds (including polymers such as polyoxymethylene and polyoxyethylene) contain elements other than carbon and hydrogen demonstrates the need for extending conformational study to rings and chains with heteroatoms. Although qualitative studies, especially in the alkaloid and carbohydrate area, are available (and, in the case of carbohydrates, sometimes have preceded similar studies in carbocycles)[9] and although some of the pioneering work in the application of proton magnetic resonance has been in the carbohy-

drate field,[10] there has, until very recently, been a dearth of quantitative work concerned with conformation of heterocycles.[11]

The present Account deals primarily with work in this area carried out in the Notre Dame laboratories in the past 4 years. Unfortunately, limitations of space do not permit extensive discussion of the many excellent studies carried out elsewhere, especially by physical techniques (nmr spectroscopy, X-ray study, dipole measurements, etc.); most of this work has been reviewed or cited elsewhere.[12,13]

## A priori Considerations

As long as conformational analysis was merely qualitative, it seemed adequate to draw parallels between carbocyclic and heterocyclic rings. Most known heterocyclic six-membered rings (with the exception of some polysulfur-containing ones[14]) are most stable in the chair form, as is cyclohexane, and the barriers to ring inversion are similar.[15] However, upon quantitative examination, important differences between carbocyclic and heterocyclic systems come to the fore.

(1) The C–X bond distances are often appreciably different from C–C distances. Thus C–O (1.43 Å) and C–N (1.47 Å) are shorter than C–C (1.54 Å), whereas C–S (1.82 Å) is longer. The variation in bond angles is less important for oxygen and nitrogen, but the C–S–C angle of about 100° is substantially different from the near-tetrahedral angles found in other alicyclic and heterocyclic compounds.

(1) H. Sachse, *Ber.*, **23**, 1363 (1890); *Z. Physik. Chem.*, **10**, 203 (1892).

(2) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(3) J. D. Kemp and K. S. Pitzer, *J. Chem. Phys.*, **4**, 749 (1936).

(4) S. Mizushima and K. Higasi, *J. Chem. Soc. Japan*, **54**, 226 (1933).

(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1965.

(6) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965.

(7) E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965); E. L. Eliel, *Chimia*, **22**, 201 (1968).

(8) J. McKenna, "Conformational Analysis of Organic Compounds," The Royal Institute of Chemistry Lecture Series, London, 1966, No. 1.

(9) For a historical discussion of the contributions to conformational analysis from carbohydrate chemistry, see ref 5, p 362.
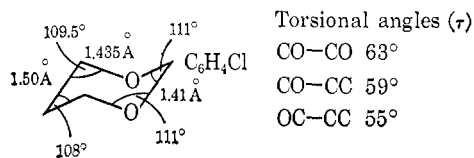
(10) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **79**, 1005 (1957); **80**, 6098 (1958).

(11) For a notable exception see R. U. Lemieux and N. J. Chu, Abstracts of Papers, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, p 31N.

(12) (a) Reference 5, p 243; (b) F. G. Riddell, *Quart. Rev.* (London), **21**, 364 (1967); (c) C. Romers, C. Altona, H. R. Buys, and E. Havinga in "Topics in Stereochemistry," Vol. IV, E. L. Eliel and N. L. Allinger, Ed., Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1969.

(13) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(14) C. H. Bushweller, *ibid.*, **89**, 5978 (1967); **90**, 2450 (1968).

(15) H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, *Tetrahedron Letters*, 683 (1962); H. G. Schmid, H. Friebolin, S. Kabuss, and R. Mecke, *Spectrochim. Acta*, **22**, 623 (1966); H. Friebolin, H. G. Schmid, W. Faisst, and S. Kabuss, personal communication; J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, **62**, 39 (1966).

Torsional angles $(\tau)$

CO—CO 63°
CO—CC 59°
OC—CC 55°

Figure 1.



1          $-\Delta G° = 4.0\,\text{kcal}/\text{mol}$          2

Figure 2. Equilibration of the 2,4-cis-6-trimethyl-1,3-dioxanes.[13,21b]

(2) Hetero atoms engender appreciable dipole moments. If there is only one such atom, the dipole has no effect on conformation, but when there is more than one hetero atom in the ring or when there is a hetero substituent (such as OH or OR) on a heterocyclic ring, dipole–dipole interactions do affect conformation. Such interactions are solvent dependent (being inversely proportional to effective dielectric constant), so conformation may vary with solvent.

(3) The van der Waals radii of oxygen, nitrogen, and especially sulfur are different from those of carbon. Moreover, carbon bears four ligands whereas nitrogen bears only three and oxygen, and often also sulfur, bear two. The "absent ligand" tends to diminish nonbonded interactions, since it is now known[13] that an unshared pair does not engender as much nonbonded repulsive interaction as a hydrogen atom.

(4) The bending force constants for C–X–C and X–C–C angles and the torsional potentials about the C–X bond are different depending on whether X is carbon or a hetero atom.

Additional factors may come into play. Thus when a heterocycle bears a hydroxyl group, intramolecular hydrogen bonding may affect conformation, as may intermolecular hydrogen bonding in cases where such a heterocycle is dissolved in a hydrogen-donor solvent. The rather facile nitrogen inversion[16] plays an important part in the conformational analysis of nitrogen-bearing heterocycles, and so does the fact that these heterocycles are converted to salts in acidic solvents.

## Specific Heterocycles

We shall deal in detail with the 1,3-dioxane and 1,3-dithiane and more briefly with the 1,3-diazane and the tetrahydropyran systems.

**1,3-Dioxane[13] (Figure 1).** Recent X-ray study[17] of 2-p-chlorophenyl-1,3-dioxane has disclosed the bond angles and bond lengths shown in Figure 1. The molecule is slightly puckered in the $O_1$–$C_2$–$O_3$ region ($\tau = 63°$)[17] and flattened in the $C_4$–$C_5$–$C_6$ region ($\tau = 55°$), as had been anticipated on the basis of model study[13] and nmr investigation.[18,19] Barrier measurements[15] indicate the ring inversion barrier to be similar to that in cyclohexane ($\Delta G^{\ddagger} = 9.0$–9.9 kcal/mol compared to 10.2 kcal/mol in $C_6H_{12}$) with a notable drop (to 7.8–8.0 kcal/mol) in 2,2-dimethyl-1,3-dioxane. The skew-boat form is 7.1 kcal/mol less stable than the chair[20,21a] (the
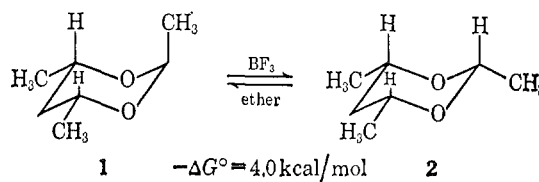
corresponding enthalpy difference for cyclohexane is 5.9 kcal/mol[5]).

Equilibration of the 2,4-cis-6-trimethyl-1,3-dioxanes (Figure 2)[13,21b] indicates that the axial methyl group at C-2 is disfavored by 4.0 kcal/mol ($-\Delta G°$ value); a corresponding value of $-\Delta H° = 4.1 \pm 0.5$ kcal/mol has been obtained[21a] from heats of combustion,[21c] and the considerable instability of an axial 2-methyl group is also implied by the earlier mentioned low inversion barrier in 2,2-dimethyl-1,3-dioxane compared to that of the parent compound (ground-state compression). The large $-\Delta G°$ value for Me-2 in 1,3-dioxane compared to axial methyl in cyclohexane (1.7 kcal/mol[22]) is probably mainly a manifestation of the short axial–axial distance in the dioxane (cf. Figure 2), the (Me–H)–H-4 distance being 1.94 Å compared to 2.29 Å in cyclohexane.[23] A contributing factor is most likely the puckering of the dioxane ring in the C-2 region which would push the axial methyl group further into the region of the syn-axial hydrogens. This is borne out by comparison of the 1,3-dioxane with the 1,3,5-trioxane system (which, for reasons of symmetry, does not possess the same puckering); $-\Delta G°$ for the cis–trans equilibration in 2,4,6-trimethyl-1,3,5-trioxane (paraldehyde) is 3.05 kcal/mol (after correction for symmetry),[13] i.e., less than in 2-methyl-1,3-dioxane.

The equilibrium shown in Figure 2 corresponds to 99.7% of the equatorial (cis,cis) isomer at room temperature, and since the synthesis of 1,3-dioxanes from diols and aldehydes in the presence of mineral acid (with azeotropic distillation of the water formed) proceeds largely under thermodynamically controlled conditions, it was very tedious to isolate the trans,trans isomer. Fortunately a very convenient synthesis of the axial isomers, summarized in Figure 3, has since been discovered.[24] The required 2-alkoxy-1,3-dioxane is readily synthesized from the appropriate diol and trimethyl orthoformate;[25] for reasons to be discussed later, the equilibrium favors the axial isomer by about 2:1, separation of the isomers is easily achieved by fractional

(16) Cf. M. Saunders and F. Yamada, J. Amer. Chem. Soc., 85, 1882 (1963).

(17) A. J. deKok and C. Romers, Rec. Trav. Chim., in press.

(18) H. R. Buys, ibid., 88, 1003 (1969); ref 12c, p 66.

(19) Cf. J. B. Lambert, J. Amer. Chem. Soc., 89, 1836 (1967).

(20) K. Pihlaja, Acta Chem. Scand., 22, 716 (1968).

(21) (a) K. Pihlaja and J. Heikkilä, ibid., 21, 2390, 2430 (1968), K. Pihlaja and S. Luoma, ibid., 22, 2401 (1968). (b) F. W. Nader and E. L. Eliel, unpublished observations. (c) The near-equality of $\Delta G°$ and $\Delta H°$ implies that $\Delta S \approx 0$. We have measured $\Delta S°$ for the cis–trans equilibration in 2-t-butyl-5-methyl-1,3-dioxane and find it to be zero within limits of experimental error (M. C. Knoeber, unpublished observations).

(22) J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1967.

(23) F. G. Riddell and M. J. T. Robinson, Tetrahedron, 23, 3417 (1967).

(24) E. L. Eliel and F. Nader, J. Amer. Chem. Soc., 91, 536 (1969).

(25) E. L. Eliel and C. A. Giza, J. Org. Chem., 33, 3754 (1968).

(major product)

+ cis isomer

(major product)

Figure 3.



3     $-\Delta G^\circ = 2.9\ \text{kcal/mol}$     4
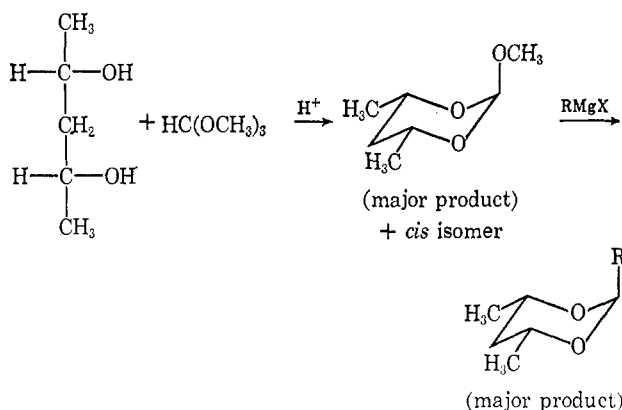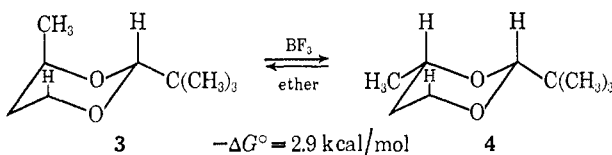
Figure 4.

distillation, and the reaction of the axial isomer is 85–95% stereospecific to give the product with axial alkyl, presumably for stereoelectronic reasons. (Actually, separation of the isomers of the starting material is not even necessary, since the equatorial alkoxy compound is unreactive toward the Grignard reagent under mild conditions.) By the method shown in Figure 3, trans-2-ethyl- and trans-2-isopropyl-cis-4,6-dimethyl-1,3-dioxanes have been synthesized; equilibration (cf. Figure 2) gives $-\Delta G^\circ$ values of 4.0 and 4.15 kcal/mol, respectively, for Et-2 and i-Pr-2.[21b]

Various 4-methyl-2-alkyl-1,3-dioxanes were synthesized from 1,3-butanediol and appropriate aldehydes and equilibrated with boron trifluoride etherate, the most significant case being that of 2-t-butyl-4-methyl-1,-3-dioxane shown in Figure 4. Since methyl at C-2 already finds it difficult to fit into the axial position (cf. Figure 3), t-butyl at C-2 is presumably a good equatorial "holding group," and it may safely be assumed that the equilibration shown in Figure 4 corresponds to a change from axial to equatorial methyl at C-4. The corresponding $-\Delta G^\circ$, 2.9 kcal/mol, is in reasonable agreement with the thermochemical value, $-\Delta H^\circ = 2.8 \pm 0.5$ kcal/mol, measured by Pihlaja.[21a] That $-\Delta G^\circ$ for Me-4 is less than for Me-2 is reasonable, for, unlike Me-2 which interacts with two close-by syn-axial hydrogens across the (short) C–O–C link, Me-4 has only one correspondingly close syn-axial hydrogen (at C-2) and one more remote one (across a C–C–C link) at C-6. If one equates the Me-2–H-4 (or Me-4–H-2) syn-axial interaction with one-half the total interaction of axial methyl at C-2, or $4.0/2 = 2.0$ kcal/mol, and the Me-4–H-6 interaction with one-half the axial methyl interaction in cyclohexane, or $1.7/2 = 0.85$ kcal/mol, then the calculated interaction of axial Me-4 (with syn-axial



5, $R_1 = CH_3$;   $R_2 = (CH_3)_3C$
6, $R_1 = C_2H_5$;   $R_2 = (CH_3)_3C$
7, $R_1 = (CH_3)_2CH$;   $R_2 = (CH_3)_3C$
8, $R_1 = (CH_3)_3C$;   $R_2 = CH_3$
9, $R_1 = (CH_3)_3C$;   $R_2 = C_2H_5$
10, $R_1 = (CH_3)_3C$;   $R_2 = (CH_3)_2CH$
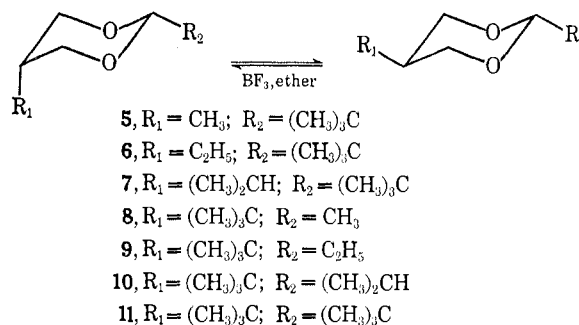11, $R_1 = (CH_3)_3C$;   $R_2 = (CH_3)_3C$

Figure 5.

H-2 and H-6) is $1.8 + 0.85 = 2.85$ kcal/mol, in good agreement with the experimental value of 2.9 kcal/mol.

Probably the most interesting system studied[13,23] in the dioxane family is represented by the 2,5-dialkyldioxanes 5–11 (Figure 5). Stereoisomers of 5, 6, and 7 differ in the conformation (equatorial or axial) of the 5-alkyl substituent, since it may safely be assumed that the 2-t-butyl group remains equatorial. The corresponding $\Delta G^\circ$ values, summarized in Table I, are appreciably smaller than corresponding values in cyclohexane (Table I). This is a very strong indication that interaction of the axial alkyl at C-5 with the ring oxygens at positions 1 and 3, including their unshared electron pairs, is less than the corresponding interaction of an axial alkyl group with C-3 and C-5 and the attached syn-axial hydrogen atoms. Since more than half of the interaction in axially substituted cyclohexane is ascribed to the syn-axial hydrogens,[26a] and since the interaction in the axially 5-substituted dioxane is less than half that in cyclohexane, the conclusion is almost inescapable that the axial electron pair on oxygen produces a considerably smaller syn-axial nonbonded repulsion than does an axial hydrogen on carbon.[26b] The same conclusion is reached, a fortiori, from the data for the 2-alkyl-5-t-butyl-1,3-dioxanes (8–11, Table I and Figure 5). The independence of the position of equilibrium, in these isomer pairs, of the 2 substituent was at first puzzling but finds a natural explanation when one assumes that the 2 substituents rest in the equatorial position (cf. Figure 2) and the 5-t-butyl group moves from the equatorial to the axial position in the equilibration (Figure 6). This assumption—at first sight startling if one keeps in mind that axial t-butyl in t-butylcyclohexane is thermochemically unstable, vis-

(26) (a) Cf. J. B. Hendrickson, J. Amer. Chem. Soc., 84, 3355 (1962). (b) The apportionment of nonbonded interactions is of necessity somewhat arbitrary. In axial methylcyclohexane the interaction of the methyl hydrogen with the syn-axial hydrogens at C-3 and C-5 may be assumed to amount to about two-thirds of the total of 1.7 kcal/mol or 1.1 kcal/mol.[26a] The total interaction in axial 5-methyldioxane is about 0.8 kcal/mol; presumably this value may be ascribed to the interaction of axial methyl hydrogen with the oxygen atoms plus their unshared electrons. It follows that the interaction with the unshared electrons alone amounts to considerably less than 1.1 kcal/mol, unless one ascribes a considerable attractive interaction to the "bare oxygen core." (The assumption is made in this argument that steric interactions in equatorial methylcyclohexane and 5-methyldioxane are either negligible or at least equal.)

**Table I**

**Conformational Energies of Alkyl Groups at C-5 in 1,3-Dioxane (Figure 5)**

| Compound | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|
| Alkyl group[a] | $CH_3$ | $C_2H_5$ | $(CH_3)_2CH$ | $(CH_3)_3C$ | $(CH_3)_3C$ | $(CH_3)_3C$ | $(CH_3)_3C$ |
| $-\Delta G°$, kcal/mol | 0.80 | 0.67 | 0.98 | 1.46 | 1.43 | 1.40 | 1.36 |
| $-\Delta G°(C_6H_{12})$, kcal/mol[b] | 1.70 | 1.75 | 2.15 | c | c | c | c |

[a] In position 5.   [b] For cyclohexane values, see ref 22.   [c] Estimated value $\geq 4.9$ kcal/mol.[27,28]

**Table II**

**Chemical Shift of 5-t-Butyl Group and Coupling Constants ($J_{4,5}$) in 2,5-Dialkyl-1,3-dioxanes (Figure 5)**

| | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|
| | | | | *trans* | | | |
| $\nu_{t-Bu}$, cps[a] | | | | 52.6 | 52.5 | 52.6 | 53.0 |
| $J_{4a,5}$, cps | 10.1 | 12.7 | 10.2 | 10.6 | 11.2 | 11.3 | 12.1 |
| $J_{4e,5}$, cps | 4.3 | 4.7 | 4.9 | 5.6 | 4.4 | 4.6 | 4.7 |
| | | | | *cis* | | | |
| $\nu_{t-Bu}$, cps[a] | | | | 62.3 | 63.1 | 63.1 | 62.7 |
| $J_{4a,5}$, cps | b | b | 3.0 | 4.0 | 3.9 | 4.3 | 3.9 |
| $J_{4e,5}$, cps | b | b | 2.3 | 1.3 | 1.1 | 1.4 | 1.1 |

[a] At 60 Mcps, downfield from TMS.   [b] Not determined, spectrum degenerate.



$R = CH_3$, $C_2H_5$, $(CH_3)_2CH$, $(CH_3)_3C$

$R = (CH_3)_3C$: $\Delta G° = 1.4$ kcal/mol
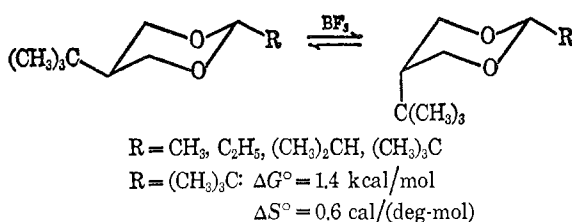
$\Delta S° = 0.6$ cal/(deg·mol)

Figure 6.

*d-vis* equatorial *t*-butyl, by over 5 kcal/mol[27,28]—is convincingly borne out by nmr spectroscopy as shown in Table II. The chemical shifts of the 5-*t*-butyl groups in *cis*-**8**, **-9**, **-10**, and **-11** are all nearly the same, as are the 4,5 coupling constants; both the shifts and the coupling constants differ from those in the corresponding *trans* isomers. The coupling constants furthermore rule out the possibility that the *cis* isomers are in the skew-boat form, since for this form the coupling constant would be of the order of 7 cps;[29] the actual coupling constants (Table II) are much smaller. A twist (skew-boat) form for *cis*-2,5-di-*t*-butyl-1,3-dioxane is also excluded by measurement[13] of $\Delta S°$ for the process depicted in Figure 6 [**11**, R = $(CH_3)_3C$] which is 0.6 cal/(deg mol); a value of at least 3.5 cal/(deg mol) would be expected for a chair–skew-boat equilibrium.[28]

**1,3-Dithiane.**[28] The basic structure of the 1,3-dithiane system has been determined through an X-ray analysis of 2-phenyl-1,3-dithiane[30] shown in Figure 7.

(27) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960); N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tymenski, and F. A. Van Catledge, *ibid.*, **90**, 1199 (1968).

(28) R. O. Hutchins and E. L. Eliel, *ibid.*, **91**, 2703 (1969).

(29) H. Booth and G. C. Gidley, *Tetrahedron Letters*, 1449 (1964); K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

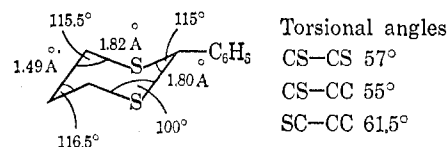(30) H. T. Kalff and C. Romers, *Acta Crystallogr.*, **20**, 490 (1966).

| Torsional angles | |
|---|---|
| CS–CS | 57° |
| CS–CC | 55° |
| SC–CC | 61.5° |

Figure 7.

The small C–S–C angle and the long C–S distances are as expected; the enlargement of the C–C–C and C–C–S angles to 115–116° is of note. The torsional angles are normal for a chair.

We have studied[28] the conformational preferences of alkyl groups in the 2, 4, and 5 positions of the 1,3-dithiane ring. Conformational energies for the 2 position, obtained by the equilibration procedure shown in Figure 8, are summarized in Table III. It is note-
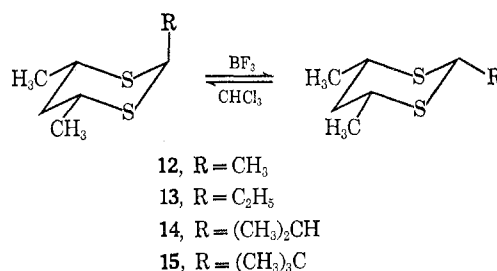


12, R = $CH_3$
13, R = $C_2H_5$
14, R = $(CH_3)_2CH$
15, R = $(CH_3)_3C$

Figure 8.

**Table III**

**Conformational Energies in 2-Alkyl-cis-4,6-dimethyl-1,3-dithianes**

| Compound[a] | 12 | 13 | 14 | 15 |
|---|---|---|---|---|
| Alkyl group | $CH_3$ | $C_2H_5$ | $(CH_3)_2CH$ | $(CH_3)_3C$ |
| $-\Delta G°$, kcal/mol[b] | 1.77 | 1.54 | 1.95 | 2.72 |
| $-\Delta G°(C_6H_{12})$, kcal/mol[c] | 1.70 | 1.75 | 2.15 | $\geq 4.9$ |

[a] Figure 8.   [b] At 69°.   [c] For cyclohexane values, see ref 22.

worthy that the values for methyl, ethyl, and isopropyl are similar to the corresponding values in cyclohexane and the value for methyl is much smaller than the corresponding value at C-2 in 1,3-dioxane (Figure 2). In a model constructed according to the dimensions of Figure 7 it appears that the distance from H–CR$_2$ attached at C-2 to the *syn*-axial hydrogen atoms at C-4 and C-6 is very similar to the corresponding distance in axial methyl-, ethyl- or isopropylcyclohexanes, because of a fortuitous counterbalancing of the longer C–S–C bond distances and smaller bond angles. This compensation is no longer seen for the *t*-butyl (H$_3$C–CR$_2$) group at C-2; its $-\Delta G°$ value of 2.7 kcal/mol is considerably less than the value ($\geqslant 5$ kcal/mol) in cyclohexane. One might perhaps have assumed that *trans*-4,*trans*-6-dimethyl-2-*t*-butyl-1,3-dithiane (*trans*-15) exists in the skew-boat form (*vide infra*), but comparison of the coupling constants of *trans*-15 ($J_{4a,5a} = 11.2$ cps, $J_{4a,5e} = 3.2$ cps) with those of the other *trans* isomers (12–14) (11.0–12.0 and 2.3–2.6 cps) shows substantial similarity; there is little evidence for the large (*ca.* 7 cps) coupling constant found in the twist form. One must conclude either that *trans*-15 exists largely in the chair form, with the interaction of the methyl appendages of the axial *t*-butyl group and the *syn*-axial hydrogen atoms being attenuated by the long C–S–C distances (the small C–S–C angle not producing a compensation in this situation), or else that *trans*-15 exists in the classical boat form (which would leave the coupling constant in the C$_4$–C$_5$–C$_6$ region much the same as in the chair form). It will probably require X-ray study to decide this matter.

Conformational equilibria of 4-methyl-substituted 1,3-dithianes (Figure 9) are summarized in Table IV.
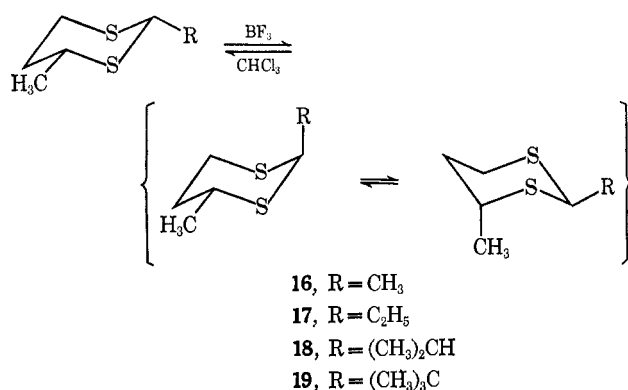


Figure 9.

**Table IV**
**Conformational Energies in**
**2-Alkyl-4-methyl-1,3-dithianes (Figure 9)**

| Compound | 16 | 17 | 18 | 19 |
|---|---|---|---|---|
| Alkyl group | CH$_3$ | C$_2$H$_5$ | (CH$_3$)$_2$CH | (CH$_3$)$_3$C |
| $-\Delta G°$, kcal/mol[a] | 1.26 | 1.15 | 1.45 | 1.69[c] |
| $-\Delta G°$ (calcd), kcal/mol[b] | 1.32 | 1.20 | 1.40 | |

[a] Experimental value at 25° unless noted. [b] Calculated from value for 19 and values in Table III. [c] At 69°.
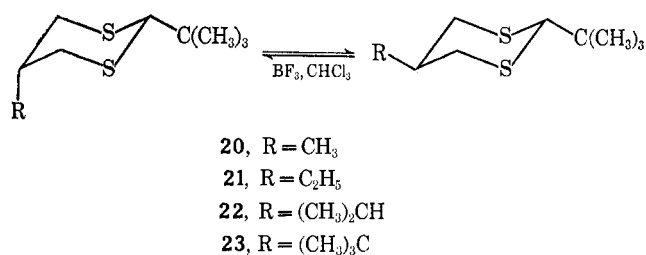


Figure 10.

Assuming that a 2-*t*-butyl substituent (in **19**) serves as a holding group, the conformational energy of a 4-methyl group is seen to be 1.7 kcal/mol, *i.e.*, substantially the same as that of a 2-methyl group (Table III) or of an axial methyl group in cyclohexane (1.7 kcal/mol). Knowing the conformational energy of a 4-methyl group and of various alkyl groups in the 2 position, one may, *a priori*, calculate[28,31] the expected position of equilibrium for a 2-alkyl-4-methyl-1,3-dithiane; the computed $\Delta G°$ values are compared with the observed ones in Table IV. The agreement is satisfactory.

Conformational free energies for 5-alkyl-substituted 1,3-dithianes (Figure 10) are summarized in Table V.

**Table V**
**Conformational Energies in**
**2-*t*-Butyl-5-alkyl-1,3-dithianes (Figure 10)**

| Compound | 20 | 21 | 22 | 23 |
|---|---|---|---|---|
| Alkyl group | CH$_3$ | C$_2$H$_5$ | (CH$_3$)$_2$CH | (CH$_3$)$_3$C |
| $-\Delta G°$, kcal/mol[a] | 1.04 | 0.77 | 0.85 | 1.85[c] |
| $-\Delta G°$(C$_6$H$_{12}$), kcal/mol[b] | 1.70 | 1.75 | 2.15 | $\geqslant 4.9$ |

[a] Experimental value at 69° unless noted. [b] For cyclohexane values, see ref 22. [c] Value at 25°. The compound is not in the chair form; see text.

The values are slightly higher than those in the dioxane series (Table I), perhaps because of the larger van der Waals radius of sulfur compared to oxygen; they are still substantially smaller than values in axially substituted cyclohexanes. That the values for ethyl and isopropyl are smaller than those for methyl may imply that the terminal methyl groups in the ethyl and isopropyl groups interfere with ring constituents (C, H, or S) more when the substituent is equatorial than when it is axial.

While the $\Delta G°$ value for the 5-*t*-butyl substituent (**23**) at first sight appears unexceptional, the average $J_{4,5}$ for *cis*-**23** (7.3 cps as compared to 3.3–3.9 cps for *cis*-**20**, -**21**, and -**22**) suggests that this compound exists in the skew-boat form, and the measured $\Delta S°$ value (Figure 11) derived from the temperature dependence of the equilibrium constant confirms this assumption. A possible reason why *cis*-**23** avoids the chair form may be steric: the larger van der Waals radius of sulfur as
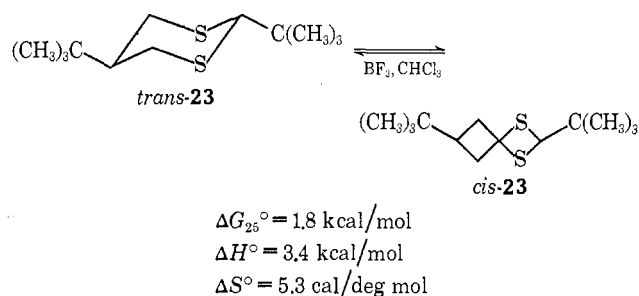
(31) *Cf.* ref 5, pp 23–25.

$$\Delta G_{25}° = 1.8 \text{ kcal/mol}$$
$$\Delta H° = 3.4 \text{ kcal/mol}$$
$$\Delta S° = 5.3 \text{ cal/deg mol}$$

Figure 11.



24, 25: $\Delta G° = +0.4$ kcal/mol
24, $R_1 = H$; $R_2 = H$
25, $R_1 = CH_3$; $R_2 = H$
26, $R_1 = CH_3$; $R_2 = CH_3$

Figure 12.

compared to oxygen (Figure 6) would tend to engender a strong repulsion with one of the methyl substituents of the axial $t$-butyl group. However, another, and perhaps more important, reason for the preference for the twist conformation in $cis$-23 lies in the relatively ready accessibility of this conformation, clearly implied by the thermodynamic parameters indicated in Figure 11.

The relatively small $\Delta H°$ for the chair–twist equilibrium in 1,3-dithiane and the high $\Delta S°$ imply that even moderately crowded substituted 1,3-dithianes will exist in the twist form to a substantial extent at temperatures not much above 25°, provided that whatever crowding of substituents exists in the chair form is relieved in the skew-boat. $cis$-2-$t$-Butyl-5-isopropyl-1,3-dithiane (22, Figure 10 and Table V) is a case in point: the temperature dependence of the sum of $J_{4,5}$ (Table VI) indicates a change from nearly all chair at $-100°$ to an almost 1:1 chair–twist mixture at $+150°$. From these data one calculates $\Delta S°_{\text{chair-twist}} = 4.9 \pm 0.4$ cal/(deg mol) and $\Delta H° = 2.4 \pm 0.1$ kcal/mol. These values are in excellent agreement with those shown in Figure 11, the calculated $\Delta H°$ being $3.4 - 0.85$ or 2.55 kcal/mol, where 3.4 kcal/mol is the value from Figure 11 and 0.85 kcal/mol is the interaction of the axial isopropyl group in the chair form ($cf$. Table V) which is assumed to be relieved in the skew-boat.

The differences in the chair–twist equilibria (Table VII) between 1,3-dithiane, 1,3-dioxane, and cyclohexane are of interest. The dioxane skew-boat is the
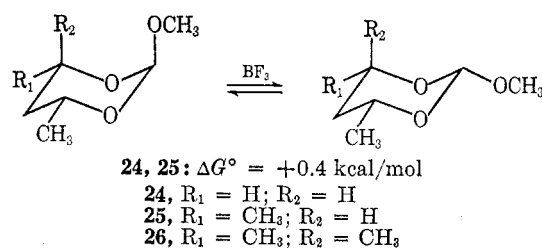
"most compact" and probably suffers from hydrogen–hydrogen transannular nonbonded interactions which make it the least stable. Such interactions are not very important in cyclohexane.[32] The lesser instability of the dithiane twist form may be due to lesser eclipsing interactions; it is known that eclipsing in dimethyl sulfide (barrier[33] $= 2.1$ kcal/mol) is less severe than in propane (barrier[34] $= 3.4$ kcal/mol).

**Polar Factors.** When the 2-methyl group in the dioxane shown in Figure 2 is exchanged for a methoxy group, the position of equilibrium changes dramatically (Figure 12), lying now on the side of the axial isomer, the difference in $\Delta G°$ between the case shown in Figure 12 ($R_2 = H$) and that in Figure 2 amounting to over 4 kcal/mol. Part of this difference is no doubt due to the much lesser nonbonded interaction of the methoxy oxygen and its unshared pair of electrons compared to the methyl carbon and its attached hydrogens. However, this is not the entire explanation, for $\Delta G°$ in methoxycyclohexane is 0.4 kcal/mol favoring the *equatorial* conformation.[35] The nonbonded interaction of axial methoxyl in 24 and 25 should be greater than that because of the shorter $syn$-axial O–H distance, as discussed earlier. Even in 4,4,6-trimethyl-2-methoxy-dioxane (26, Figure 12) the equatorial and axial isomers are nearly equally stable ($\Delta G° = -0.05$ kcal/mol), though the nonbonded interaction between the $syn$-axial methyl and methoxy must be substantial. (The $syn$-axial Me–O interaction in cyclohexane amounts to about 2 kcal/mol.[36]) Clearly an important factor stabilizing the axial methoxyl group in compounds 24–26 is the interaction of the dipole of the C–O–C groups in the ring with the dipole of the substituent. Perhaps the best way of visualizing these dipole interactions[25,37,38] is to look at the lobes of the unshared $p$ electrons, which are probably the principal sources of the dipoles. When two such lobes are in the parallel orientation, as

**Table VI**

**Change in Sum of Coupling Constants ($J_{4,5}$) with Temperature in $cis$-2-$t$-Butyl-5-isopropyl-1,3-dithiane (22)**

| Temp, °C | $-100$ | $-48.5$ | $-2$ | 59 | 102 | 152 |
|---|---|---|---|---|---|---|
| $J_{4,5}$, cps | 6.26 | 6.76 | 7.24 | 8.08 | 8.80 | 9.64 |
| $K^a$ | 139 | 17.8 | 7.08 | 3.47 | 2.23 | 1.44 |

$^a$ Computed equilibrium constant for twist $\rightleftharpoons$ chair process.

**Table VII**

**Thermodynamic Parameters for Chair–Twist Equilibria**

| System | $\Delta G_{25}°$, kcal/mol | $\Delta H°$, kcal/mol | $\Delta S°$, cal/(deg mol) | Ref |
|---|---|---|---|---|
| Cyclohexane | 4.9 | 5.9 | 3.5 | 27$^a$ |
| 1,3-Dioxane | 5.7 | 7.1 | 4.8 | 20, 21a |
| 1,3-Dithiane | 1.8 | 3.4 | 5.3 | 28 |

$^a$ See also ref 28 for treatment of data.

(32) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961).
(33) L. Pierce and M. Hayashi, *J. Chem. Phys.*, **35**, 479 (1961).
(34) K. S. Pitzer, *ibid.*, **12**, 310 (1944).
(35) E. L. Eliel and E. C. Gilbert, *J. Amer. Chem. Soc.*, **91**, 5487 (1969).
(36) E. L. Eliel and S. H. Schroeter, *ibid.*, **87**, 5031 (1965).
(37) (a) *Cf.* R. U. Lemieux in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1964, p 726, 739; (b) M. Kabayama and D. Patterson, *Can. J. Chem.*, **36**, 563 (1958).
(38) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).

shown in Figure 13, the dipole repulsion is at its maximum. We have given the name "rabbit-ear effect" to this unfavorable interaction;[38,39] thus, the most stable conformations will be the ones with the least number of rabbit-ear effects. Inspection of a model of cis-4,6-dimethyl-2-methoxy-1,3-dioxane (Figure 14) shows that one of the rotational conformations of the equatorial isomer has two rabbit-ear interactions and the other two conformations have three, whereas the two sterically favored "methyl-outside" conformations of the axial methoxy compound have only a single rabbit-ear interaction, thus explaining the greater stability of the axial isomer.

The preference of axial over equatorial alkoxyl in a 2-alkoxy-1,3-dioxane is a manifestation of the well-known "anomeric effect" which leads to enhanced stability of axial as compared to equatorial alkoxy (and other polar) substituents in the 2 position of a pyranose sugar or of a simple tetrahydropyran.[11,25,40,41] Thus the greater stability of $\alpha$-glycosides as compared to their $\beta$ isomers may be explained as first hinted by Edward[40a] and later elaborated by Kabayama and Patterson[37b] as involving the repulsions between lone-pair orbitals of the ring and exocyclic oxygens, referred to above as the rabbit-ear effect.[42] As expected, in 2-alkoxy- and 2-thioalkoxy-tetrahydropyrans the effect is solvent dependent, being largest in solvents of lowest dielectric constant.[25]

Other manifestations of the effect are seen in six-membered rings containing an N–R group and another hetero atom in positions 1,3 with respect to each other (Figure 15). The R group tends to prefer the axial position so as to avoid the rabbit-ear interaction of the syn-axial electron pairs on the hetero atoms. Examples are seen in N-alkyloxazanes (axial alkyl),[43,44] in 1,2,4,5-tetramethyl-1,2,4,5-tetrazane,[45] and in 1,3-dimethyl-diazanes.[38] In the case of the 1,3-diazanes, the presence of a substantial fraction of the conformation with axial substituents (H or methyl) on one of the nitrogens may be gleaned from the nmr data summarized in Table VIII and Figure 16. The chemical shift of H-2 in the N–H compounds 27 and 28 is not greatly altered by the

(39) E. L. Eliel, Kemisk Tidskrift, 81, No. 6/7, 22 (1969). It would appear that the rabbit-ear effect is in no way different from the electrostatic effect engendered by the bond dipoles of the C–X and C–Y bonds; it is merely an alternative (and perhaps more convenient) way of envisaging these dipoles.

(40) (a) J. T. Edward, Chem. Ind. (London), 1102 (1955); (b) S. J. Angyal, Aust. J. Chem., 21, 2737 (1968).

(41) For reviews see ref 37, pp 733–743; ref 5, pp 375–377 and 406–413; S. J. Angyal, Angew. Chem., 81, 172 (1969); Angew. Chem. Intern. Ed. Engl., 8, 157 (1969).

(42) Professor R. U. Lemieux has suggested to the author that this effect be included in the definition of "anomeric effect." The anomeric effect normally covers exocyclic–endocyclic dipolar interactions; thus "generalized anomeric effect" might be used to include endocyclic-endocyclic interactions (Figure 15) or exocyclic–exocyclic ones (Figure 17).

(43) Y. Allingham, R. C. Cookson, T. A. Crabb, and S. Vary, Tetrahedron, 24, 4625 (1968); see also D. Gürne and T. Urbanski, J. Chem. Soc., 1912 (1959); D. Gürne, L. Stefaniak, T. Urbanski, and M. Witanowski, Tetrahedron Suppl., 6, 211 (1963).

(44) F. G. Riddell and J. M. Lehn, J. Chem. Soc., B, 1224 (1968).

(45) J. E. Anderson and J. D. Roberts, J. Amer. Chem. Soc., 90, 4186 (1968); R. A. Y. Jones, A. R. Katritzky, and A. C. Richards, Chem. Commun., 708 (1969).
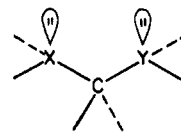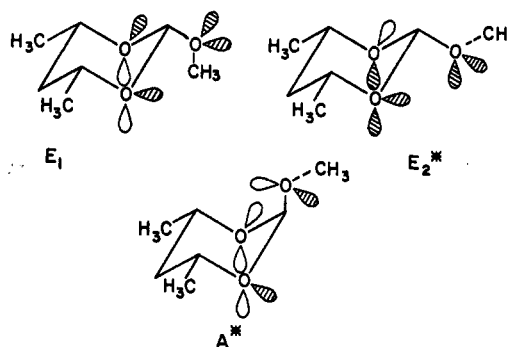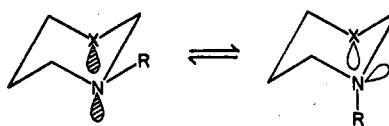
Figure 13.



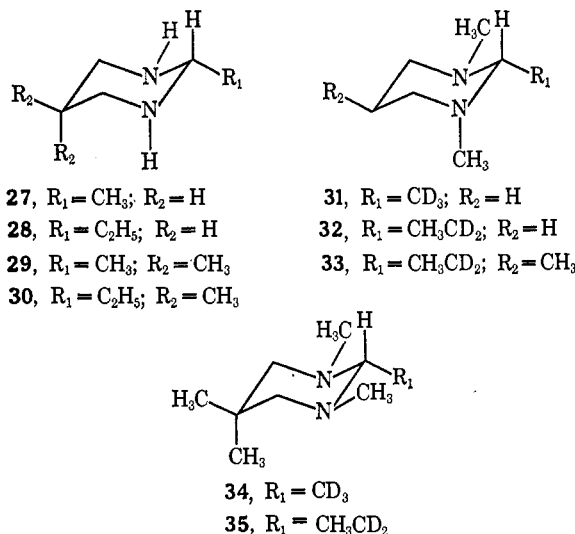Figure 14. Asterisked structures exist as mirror images.



Figure 15.



27, $R_1 = CH_3$; $R_2 = H$
28, $R_1 = C_2H_5$; $R_2 = H$
29, $R_1 = CH_3$; $R_2 = CH_3$
30, $R_1 = C_2H_5$; $R_2 = CH_3$

31, $R_1 = CD_3$; $R_2 = H$
32, $R_1 = CH_3CD_2$; $R_2 = H$
33, $R_1 = CH_3CD_2$; $R_2 = CH_3$

34, $R_1 = CD_3$
35, $R_1 = CH_3CD_2$

Figure 16.

introduction of methyl groups at C-5 (compounds 29 and 30). On the other hand, the chemical shift of H-2 in the N-methyl compounds 31 and 32, while largely unaffected by the introduction of a single (presumably equatorial) methyl group at C-5 (compound 33), is drastically altered (by about 35 cps) by the introduction of a second (axial) methyl group at C-5 (compounds 34 and 35). Since it is known[46a] that an anti-axial unshared electron pair on nitrogen produces a substantial upfield shift on an adjacent axial proton, it may be inferred that 34 and 35 have such a pair[46b] whereas 29–33

**Table VIII**

**Chemical Shifts of H-2 in 2-Alkyl-1,3-diazanes (Figure 16)**

| Compound | 27 | 29 | 28 | 30 | 31 | 34 | 32 | 33 | 35 |
|---|---|---|---|---|---|---|---|---|---|
| $\nu_{H-2}$, cps | 213.7 | 211.4 | 202.9 | 196.8 | 168.9 | 132.7 | 157.1 | 148.5 | 121.6 |



Figure 17.



36, R = CH$_3$: $\Delta G_{50}^\circ = -0.8$ kcal/mol (ether)

37, R = H: $\Delta G_{80}^\circ = +0.8$ kcal/mol (C$_6$H$_{12}$)
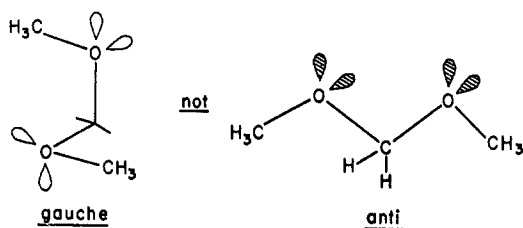
Figure 18.

do not. Thus **29–33** presumably exist largely in the conformation in which one methyl group or hydrogen atom on nitrogen is axial, whereas in **34** and **35**, because of the severe *syn*-axial methyl–methyl interaction, the N-methyl group is forced into the equatorial position and a rabbit-ear interaction is thus necessarily engendered.[46b]

Several other manifestations of the rabbit-ear effect (or "generalized anomeric effect") have been summarized elsewhere.[39]

We have seen that the anomeric effect (interaction of an exocyclic polar substituent with an endocyclic hetero atom) as well as the interaction of endocyclic hetero atoms in 1,3 locations with each other (Figure 15) represent manifestations of the rabbit-ear effect. In addition, as seems first to have been stated clearly by Lemieux,[37] herero atoms in chains may also manifest the effect. Thus dimethoxymethane (Figure 17) exists[47] in the *gauche* rather than in the *anti* form and the related polymer, polyoxymethylene, also exists in helical (*i.e.*, all-*gauche*) conformations rather than in the zigzag (all-*anti*) conformation seen in crystalline polyethylene.[48] It is evident from Figure 16 that in the *anti* conformation two rabbit-ear effects are engendered by each pair of adjacent oxygen atoms, whereas no such interactions occur in the *gauche* conformation.

An interesting paradox is found in 5-methoxy-2-isopropyl-1,3-dioxane (**36**, Figure 18) where the equatorial isomer is preferred by 0.8 kcal/mol,[49] the preferred O–CH$_2$–CH$_2$–O arrangement thus being *anti*. Yet in 1,2-dimethoxyethane[50] and in polyoxyethylene[50a,51] the O–CH$_2$–CH$_2$–O *gauche* arrangement appears to be preferred for reasons which are not entirely clear at the moment. A similar situation exists in 5-chloro- and 5-bromo-2-isopropyl-1,3-dioxane, but not in the 5-fluoro analog.[49] In 5-hydroxy-2-isopropyl-1,3-dioxane (**37**, Figure 18) we find a preference of 0.8 kcal/mol for the *cis* (OH axial) isomer in solvent cyclohexane;[49] the axial preference is in accord with earlier findings.[52] It is not in accord, however, with the assumption[53] that *trans*-**37** exists to an appreciable extent in the skew-boat form and therefore exhibits intramolecular hydrogen bonding in the infrared. As mentioned earlier, the skew-boat form in dioxane is disfavored by about 5.7 kcal/mol (Table VII) and the hydrogen-bonding energy clearly does not suffice to overcome this handicap. Our own measurement in *trans*-**37** confirms the existence to two OH stretching frequencies, one (intense) at 3636 cm$^{-1}$ and one (about one-quarter to one-half as intense) at *ca.* 3605 cm$^{-1}$, but it is possible that the second band is due to an alternative rotational conformation of the equatorial OH group[54] rather than due to intramolecular hydrogen bonding.

(46) (a) *E.g.*, F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Letters*, 2705 (1965). (b) Strictly speaking, these arguments apply to the major conformations of the respective molecules. In the absence of more quantitative data, *e.g.*, regarding the shift of H-2 in model compounds where either both nitrogen substituents are clearly axial or one is clearly equatorial, the presence of minor fractions of conformations other than those shown in Figure 16 is not excluded. Regarding a quantitative assessment of the situation in the N-methyl-1,3-oxazane series, see ref 44 which indicates approximately equal mole fractions in the axial and equatorial conformations (Figure 15, R = methyl; X = O).

(47) T. Uchida, Y. Kurita, and M. Kubo, *J. Polym. Sci.*, **19**, 365 (1956); S. Mizushima, Y. Morino, and M. Kubo, *Physik. Z.*, **38**, 459 (1937); see also ref 37.

(48) E. Sauter, *Z. Phys. Chem.*, **B21**, 186 (1933); M. L. Huggins, *J. Chem. Phys.*, **13**, 37 (1945); A. Novak and E. Whalley, *Trans. Faraday Soc.*, **55**, 1484 (1959); H. Tadokoro, T. Yasumoto, S. Murahashi, and I. Nitta, *J. Polym. Sci.*, **44**, 266 (1960); T. Miyazawa, *J. Chem. Phys.*, **35**, 693 (1961); G. Carazzolo and M. Mammi, *J. Polym. Sci., A*, **1**, 965 (1963); P. de Santis, E. Giglio, A. M. Liquori, and A. Ripamonti, *ibid., A*, **1**, 1383 (1963); G. A. Carazzolo, *ibid., A*, **1**, 1573 (1963); P. J. Flory and J. E. Mark, *Makromol. Chem.*, **75**, 11 (1964); M. Tadokoro, *J. Polym. Sci., Part C*, **15**, 1 (1966); T. Uchida and M. Tadokoro, *ibid., Part A-2*, **5**, 63 (1967).
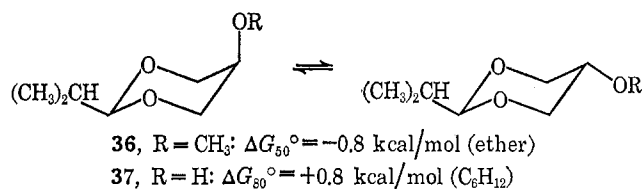
(49) M. Kaloustian, unpublished observations. The value refers to solvent ether and is solvent dependent.

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(51) J. E. Mark and P. J. Flory, *J. Amer. Chem. Soc.*, **87**, 1415, (1965); **88**, 3702 (1966).

(52) N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey, and D. H. Whiffen, *J. Chem. Soc.*, 2574 (1960).

(53) N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, and J. M. Webber, *ibid.*, 4157 (1963).

(54) *Cf.* L. Joris, P. von R. Schleyer, and E. Osawa, *Tetrahedron*, **24**, 4759 (1968).