Conformational Analysis. XXIV. Effect of Dipolar and Eclipsing Forces on Intramolecular Hydrogen Bonding in 3-Hydroxymethyltetrahydropyran and 5-Hydroxymethyl-1,3-dioxane[1]

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Abstract: Whereas no intramolecular hydrogen bond is observed in *cis*-5-hydroxymethyl-2-isopropyl-1,3-dioxane (*cis*-**1**) or its 5-methyl homolog (*cis*-**2**), infrared spectroscopy indicates some bonding in the corresponding tertiary (α,α-dimethyl) alcohol, *cis*-**4**. Considerable (though compared to 3-methoxy-1-propanol, attenuated) hydrogen bonding is found in *r*-2,*cis*-6-dimethyl-*cis*-3-hydroxymethyltetrahydropyran (**9**). The findings are explained on the basis of an interplay of hydrogen bonding, bond eclipsing, and dipolar forces.

Intramolecular hydrogen bonding plays a very important role in both organic and biological chemistry and, as a result, has been studied extensively.[2] One of its aspects which has long attracted interest is the relation between the strength of the hydrogen bond and molecular geometry. Unfortunately, whereas the geometry of intermolecular hydrogen bonds in crystals can often be independently established by X-ray or neutron diffraction studies,[3] corresponding (direct) study of intramolecular hydrogen bonds is possible only rarely, since such bonds tend to be supplanted by intermolecular ones in the crystal and even in concentrated solution.

Indirect approaches, especially approaches employing infrared spectroscopy, have, therefore, been explored over the years. The strength of the hydrogen bond has usually been assessed either in terms of $-\Delta H$, the enthalpy difference between molecules with unbonded and intramolecularly bonded O–H,[4] or $\Delta\tilde{\nu} = \tilde{\nu}_f - \tilde{\nu}_b$, the difference in frequency (generally expressed in terms of wave numbers) between the stretching frequencies of the free (f) and bonded (b) O–H groups.[4] These approaches are fraught with difficulty. An early assumption[5] that there existed a linear relation between $\Delta\tilde{\nu}$ and ΔH was subsequently shown[6,7] to be inapplicable at least in the case of intramolecular hydrogen bonds. A later postulated functional relationship[8] between $\Delta\tilde{\nu}$ and the distance of the hydrogen bond, O–H···O,[9] was also shown to break down both in the case of intermolecular[10] and intramolecular[11] hydrogen bonds, presumably because $\Delta\tilde{\nu}$ depends not only on the O–H···O distance but also on the O–H···O bond angle and perhaps also on the spatial disposition of the acceptor oxygen, *e.g.*, with respect to the direction of the orbitals occupied by the unshared electron pairs.[12] Finally, there has also been an experimental difficulty in the measurement of $\Delta\tilde{\nu}$, for, whereas the value of $\tilde{\nu}_b$ is unequivocal, there is some question about $\tilde{\nu}_f$.[13] It is, therefore, best to use standard frequencies[14–16] for $\tilde{\nu}_f$; these frequencies depend on the primary, secondary, or tertiary nature of the hydroxyl as well as on its conformation.

In summary it appears that whereas $\Delta\tilde{\nu}$ is indeed a measure of the strength of a hydrogen bond, attempted correlations of $\Delta\tilde{\nu}$ with molecular geometry have tended to be empirical.[8,12,17]

From the point of view of *a priori* calculations of molecular geometry and conformational equilibria by semiempirical energy minimization schemes,[18] the ΔH

(1) Paper XXIII: W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 5394 (1970).

(2) For reviews see: (a) M. Tichý, *Advan. Org. Chem.*, **5**, 115 (1965); (b) G. M. Badger, *Rev. Pure Appl. Chem.*, 7, 55 (1957); (c) W. C. Hamilton, *Annu. Rev. Phys. Chem.*, **13**, 19 (1962); (d) J. W. Smith, *Sci. Progr.*, **52**, 97 (1964); (e) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, Chapter 5.

(3) (a) Reference 2e, Chapter 9; (b) J. Donohue in "Structural Chemistry and Molecular Biology," A. Rich and N. Davidson, Ed., W. H. Freeman, San Francisco, Calif., 1968, pp 443–465; (c) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, New York, N. Y., 1968.

(4) The discussion here will be in terms of O–H···O hydrogen bonds, but, *mutatis mutandis*, applies to other X–H···Y hydrogen bonds as well.

(5) R. M. Badger and S. H. Bauer, *J. Chem. Phys.*, **5**, 839 (1937).

(6) E. D. Becker, *Spectrochim. Acta*, **17**, 436 (1961).

(7) L. P. Kuhn and R. A. Wires, *J. Amer. Chem. Soc.*, **86**, 2161 (1964).

(8) L. P. Kuhn, *ibid.*, **74**, 2492 (1952).

(9) The discussion in the literature is often beclouded by the fact that the "hydrogen bonding distance" is stated in terms of the O···O rather than in terms of the H···O distance, presumably because the former can be measured more readily by X-ray diffraction.

(10) K. Nakamoto, M. Margoshes, and R. E. Rundle, *J. Amer. Chem. Soc.*, 77, 6480 (1955).

(11) H. Buc, *Ann. Chim. (Paris)*, [13] **8**, 409 (1963).

(12) *Cf.* M. Tichý, J. Šipoš, and J. Sicher, *Collect. Czech. Chem. Commun.*, **27**, 2907 (1962).

(13) If a compound exists with its molecules partly in O–H bonded and partly in unbonded conformations, one might take $\tilde{\nu}_f$ to be the frequency of the unbonded O–H. However, this procedure is fallacious, since the O–H stretching frequency itself depends on conformation.[14] Similarly, in a molecule such as *trans*-1,2-cyclohexanediol where one OH is free and the other bonded, it cannot be assumed that the (experimentally inaccessible) $\tilde{\nu}_f$ for the bonded hydrogen is equal to the observable $\tilde{\nu}_f$ for the unbonded one, for even apart from hydrogen bonding the two OH groups do not have the same conformation.

(14) *E.g.*, L. Joris, P. v. R. Schleyer, and E. Ōsawa, *Tetrahedron*, **24**, 4759 (1968).

(15) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

(16) W. F. Baitinger and P. v. R. Schleyer, *J. Org. Chem.*, **29**, 989 (1964).

(17) *E.g.*, (a) L. P. Kuhn, *J. Amer. Chem. Soc.*, **80**, 5950 (1958); (b) L. P. Kuhn, P. v. R. Schleyer, W. F. Baitinger, and L. Eberson, *ibid.*, **86**, 650 (1964); (c) R. S. Stolow, P. M. McDonagh, and M. M. Bonaventura, *ibid.*, **86** 2165 (1964); (d) W. F. Baitinger, P. v. R. Schleyer, T. S. S. R. Murty, and L. Robinson, *Tetrahedron*, **20**, 1635 (1964); (e) N. Mori, Y. Takahashi, and Y. Tsuzuki, *Bull. Chem. Soc. Jap.*, **40**, 2720 (1967).

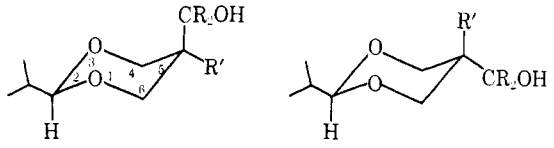
(18) (a) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 12; (b) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7047 (1967), and earlier papers therein cited; (c) K. B. Wiberg, *ibid.*, **87**, 1070 (1965); (d) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **91**, 337 (1969), and earlier papers therein cited; (e) S. Lifson and A. Warshel,

of hydrogen bonding is of particular interest. A limited number of careful determinations of such ΔH values are in the literature.[7b,19,20] It is clear that there can be no relation between ΔH and any *single* molecular parameter, such as the O–H···O bond distance, since the molecule will always dispose itself in such a way that the *sum total* of nonbonded energy, bond and angle deformation energy, torsional energy, dipolar interaction energy, and hydrogen bonding energy is minimized.

In the present study we have endeavored to study the interplay of the various forces by varying, specifically, bond eclipsing and dipolar interactions in predictable fashion and then observing whether or not an intramolecular bond does form.

The starting point of this work was the observation[21] that *cis*-**1** (Chart I) showed no trace of intramolecular

Chart I



cis-1, R = R′ = H
cis-2, R = H; R′ = CH_3
cis-4, R = CH_3; R′ = H

trans-1, R = R′ = H
trans-2, R = H; R′ = CH_3
trans-4, R = CH_3; R′ = H

hydrogen bonding in the infrared spectrum, its O–H stretching frequency, 3643 cm^{-1}, being exactly the same as that of *trans*-**1**. Since it has been established[22] that an isopropyl group in the 2 position of 1,3-dioxane is a good holding or biasing group,[23] its $\Delta G°$ value being 4.2 kcal/mol, *cis*-**1** must be nearly totally in the conformation shown in Chart I, especially since $\Delta G°$ for the CH_2OH group at C-5 is actually 0.27 kcal/mol in favor of the axial form.[21] The boat or twist form of 1,3-dioxane need not be considered, since it is destabilized *vis-à-vis* the chair by well over 5 kcal/mol.[24] Intramolecular hydrogen bonding is also absent in the corresponding 5-methyl compound, *cis*-**2**,[25] whose O–H stretch coincides with that of the epimer *trans*-**2** (Chart I) (*cf.* Table I).

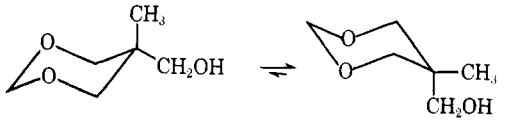
Table I. Hydroxyl Group Stretching Frequencies (cm^{-1})

Compd	$\tilde{\nu}_{free}$	Calcd[a]	$\tilde{\nu}_{bonded}$
cis-**1**	3640	3636–3644[b]	*c*
trans-**1**	3640	3636–3644[b]	*c*
cis-**2**	3641	3636–3644	*c*
trans-**2**	3642	3636–3644	*c*
cis-**4**	3622	3605–3617	3571 (weak)
	3639[d]		
cis-**4**-OD	2570		
	2552		
trans-**4**	3616	3605–3617	*c*
6	3623	3636–3644[b]	*c*
9	3640	3636–3644[b]	3530
10	3641	3636–3644[b]	*c*

[a] Free OH, see ref 14. [b] Alternate possibility, 3623–3627 cm^{-1}. [c] Absent. [d] Shoulder.

An analogous observation has been made by Laszlo[26] and by Delmau[27] in the mobile system 5-hydroxymethyl-5-methyl-1,3-dioxane (Scheme I). Although this system might, *a priori*, exist largely in conformation E with axial methyl in which hydrogen bonding is not feasible, both Laszlo[26] and Delmau[27] have adduced evidence that conformation A is, in fact, the more populous and that the absence of hydrogen bonding is thus due to other causes. In our own work we have found $\Delta G°$ for the equilibrium *trans*-**2** ⇌ *cis*-**2** (Chart I) to be −1.0 kcal/mol; *i.e.*, the axial hydroxymethyl function is indeed preferred.[25]

Scheme I



E A

cis-**1** and *cis*-**2** (Chart I) are cyclic analogs of 3-methoxy-1-propanol if one considers the $HOC_\alpha C_5C_4O_3C_2$ framework of the molecules, and $CH_3OCH_2CH_2$-CH_2OH (**3**) shows substantial intramolecular hydrogen bonding [7b,28] with $\Delta\tilde{\nu}$ = 86–87 cm^{-1} and ΔH = 2.1 kcal/mol. The following seem likely causes for the pronounced difference between *cis*-**1** and *cis*-**2** on one hand and **3** on the other. (1) **3** can enter into hydrogen bonding with little bond eclipsing, whereas *cis*-**1** and -**2** must incur $HOC_\alpha C_5$ eclipsing as well as eclipsing of the CH_2OH group with the groups attached to C_5. This is best seen in a molecular model. (2) Since the cyclic compounds are more constrained than the acyclic one, optimization of the O–H···O distance and angle is more facile in the latter. This factor should be particularly important if the hydrogen bond strength is very sensitive to this distance and angle or if the exact geometric disposition of the lobes of the unshared electrons on the acceptor oxygen is crucial. (3) In the hydrogen bonded form of *cis*-**1** or *cis*-**2** there is a strong unfavorable dipole interaction between the COH dipole and the COC dipole of the ring oxygen which is *not* engaged in bonding[29] (Chart II). (4) Steric factors prevent the hydroxyl group from pointing into the ring.

In an attempt to sort out these various factors, we synthesized the tertiary alcohols *cis*-**4** and *trans*-**4** (Chart I). Infrared study did show a low-intensity hydrogen bonded peak in *cis*-**4** (Table I), $\Delta\tilde{\nu}$ = 51–68

J. Chem. Phys., **49**, 5116 (1968), and earlier papers; (f) J. E. Williams, P. J. Stang, and P. v. R. Schleyer, *Annu. Rev. Phys. Chem.*, **19**, 531 (1968).

(19) (a) P. J. Krueger and H. D. Mettee, *J. Mol. Spectrosc.*, **18**, 131 (1965); (b) T. Lin and E. Fishman, *Spectrochim. Acta, Part A*, **23**, 491 (1967); (c) see also ref 2e, Chapter 7 and Appendix B.

(20) A. W. Baker and A. T. Shulgin (a) *Can. J. Chem.*, **43**, 650 (1965); (b) *Spectrochim. Acta*, **22**, 95 (1966); (c) A. W. Baker and D. E. Bublitz, *ibid.*, **22**, 1787 (1966).

(21) E. L. Eliel and M. K. Kaloustian, *Chem. Commun.*, 290 (1970).

(22) F. W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 3050 (1970).

(23) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience-Wiley, New York, N. Y., 1965, pp 48, 71.

(24) K. Pihlaja, *Acta Chem. Scand.*, **22**, 716 (1968); K. Pihlaja and S. Luoma, *ibid.*, **22**, 2401 (1968).

(25) M. K. Kaloustian, Ph.D. dissertation, University of Notre Dame, Notre Dame, Ind., 1970.

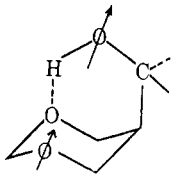
(26) P. Laszlo, personal communication, Oct. 7, 1969; R. Dratler and P. Laszlo, *Tetrahedron Lett.*, 2607 (1970).

(27) J. Delmau, personal communication, Nov 5, 1969, indicating that the interpretation of the position of equilibrium of the system in Scheme I on the basis of assumed hydrogen bonding (J. Delmau, J.-C. Duplan, and M. Davidson, *Tetrahedron*, **23**, 4371 (1967)) was incorrect.

(28) A. B. Foster, A. H. Haines, and M. Stacey, *Tetrahedron*, **16**, 177 (1961).

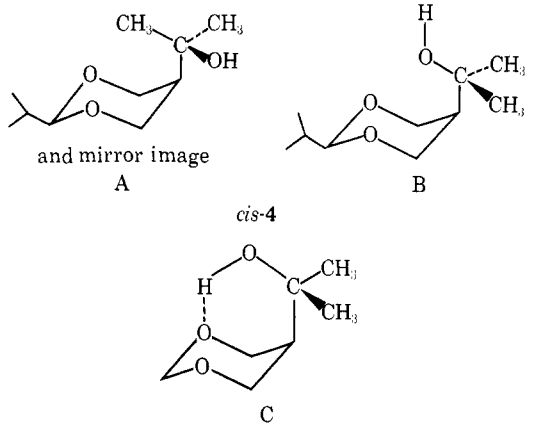
(29) We are disregarding the dipole of the potentially bonded oxygen since that dipole is presumably responsible, at least in part, for the formation of the hydrogen bond.

Chart II



cm^{-1}. The $\Delta\tilde{\nu}$ value[30] suggests formation of a hydrogen bond of reasonable strength, though probably somewhat less strong than in **3**. The small difference implies that improper disposition of the O–H···O bond itself is not a major factor in *cis*-**4**, yet the population of the hydrogen-bonded conformation in *cis*-**4** must be quite small. This is despite the fact that the conformation in which the oxygen is turned outward (A, Chart III) is considerably destabilized by the steric

Chart III

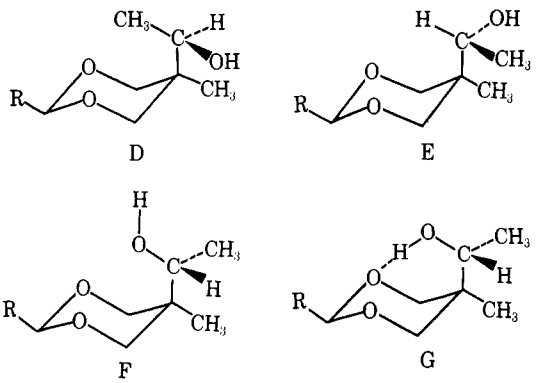


interaction of the methyl pointing into the ring. This interaction has previously been estimated[31] to amount to about 2.3 kcal/mol. Experimentally, we obtained evidence that, whereas A (Chart III) is the preferred conformation in concentrated solution (probably because it is best disposed toward intermolecular H bonding), either B or C must become the major conformations in dilute solution. This was shown by an unusually large concentration effect on the chemical shift of the β methyl groups in *cis*-**4** in the nmr spectrum. Whereas a shift of about 3 Hz (presumably due to anisotropy changes of the medium) occurs in *trans*-**4** and in the isopropyl methyl groups of both *cis*- and *trans*-**4**, the β-CH_3 in *cis*-**4** moves upfield from 82.7 to 68.7 Hz as the concentration is lowered from *ca.* 1 *M* (in CCl_4) to 5.5×10^{-3} *M*. Now 68.7 Hz is just about the chemical shift of β-CH_3 in *trans*-**4** and may thus be assigned to conformations B or C (Chart III). From earlier work[31b] it is known that the downfield shift caused by the placement of the methyl proton of an axial 5-*tert*-butyl group over the ring is about 30 Hz.[32] Thus the 14-Hz shift upon dilution of solutions of *cis*-**4** is very close to the 15 Hz expected if one shifts from an average of one out of two methyls inside the ring (conformation A, Chart III) to both methyls outside (conformations B or C).

Thus in dilute solution, *cis*-**4** must exist in either conformation B or conformation C. The very low population of the H-bonded ir stretch clearly shows that B is greatly preferred over C. This suggests that steric factors preventing the hydroxyl group from turning into the ring are not responsible for the weak hydrogen bonding in *cis*-**4** and therefore probably not in *cis*-**1** and *cis*-**2** either.[33] This leaves dipolar and/or eclipsing interactions as possible factors responsible.

The secondary alcohols **5** resemble the tertiary *cis*-**4** rather than the primary *cis*-**2** in that a weak intramolecular hydrogen bond is formed.[34] Here, presumably, conformations D and E, Chart IV, are destabilized by

Chart IV



5, R = CH_3, $(CH_3)_3C$, or C_6H_5

the methyl-inside and double-gauche interactions, respectively. Between conformations F and G, F is preferred but G contributes measurably, as for *cis*-**4**.

To test the hypothesis that dipolar repulsion (Chart II) might be the major cause for the absence or near absence of hydrogen bonding in *cis*-**1**, *cis*-**2**, and *cis*-**4**, we synthesized a 3-hydroxymethyltetrahydropyran in which such dipolar repulsion would not be present. 3-Hydroxymethyltetrahydropyran (**6**) itself[35] did not show an intramolecular hydrogen bond, in contrast to its lower homolog 3-hydroxytetrahydropyran,[36] probably because the population of the axial conformation is low in this case (Scheme II)).[37] It was, therefore, necessary to synthesize a conformationally homogeneous homolog, as shown in Scheme III.

Condensation of crotonaldehyde with water and acid gave aldehyde **7**,[38] contaminated with its positional

(30) Since there seems to be no standard frequency for $\tilde{\nu}_f$ in *cis*-**4** we used the measured frequency of the unbonded OH peak. There are two such frequencies, corresponding, presumably, to two different rotational arrangements (*vide infra*). $\Delta\tilde{\nu}$ depends on which of the two is used for $\tilde{\nu}_f$.

(31) (a) Footnote 43 in ref 31b; (b) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

(32) The shift difference between an equatorial and axial 5-*tert*-butyl group in a 5-*tert*-butyl-1,3-dioxane is *ca.* 10 Hz. Since, in the axial conformation, on the average one out of three Meβ's of the tertiary butyl is inside the ring, close to the oxygen, the gross shift of moving a single methyl close to the ring oxygens is estimated as $3 \times 10 = 30$ Hz, assuming that the shifts of the methyl groups outside the ring are the same as those of the equatorial tertiary butyl group.

(33) We can*not* with confidence conclude that the conformation of *cis*-**1** corresponding to B, Chart III (H instead of CH_3), is more stable than that corresponding to A. However, it does seem very likely that the order of stability C < B would hold for the primary alcohol as well.

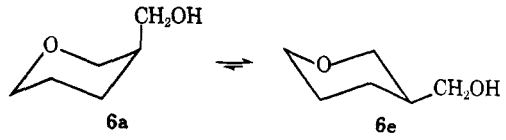
(34) T. A. Crabb and R. F. Newton, *Tetrahedron*, **26**, 693 (1970). Professor Crabb has kindly informed the authors in a personal communication that the hydrogen bond in *cis*-**5** also corresponds to a very low intensity peak in the infrared.

(35) J. Falbe and F. Korte, *Chem. Ber.*, **97**, 1104 (1964); for the (modified) method of synthesis see the preliminary communication, E. L. Eliel and H. D. Banks, *J. Amer. Chem. Soc.*, **92**, 4730 (1970).

(36) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen, and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).

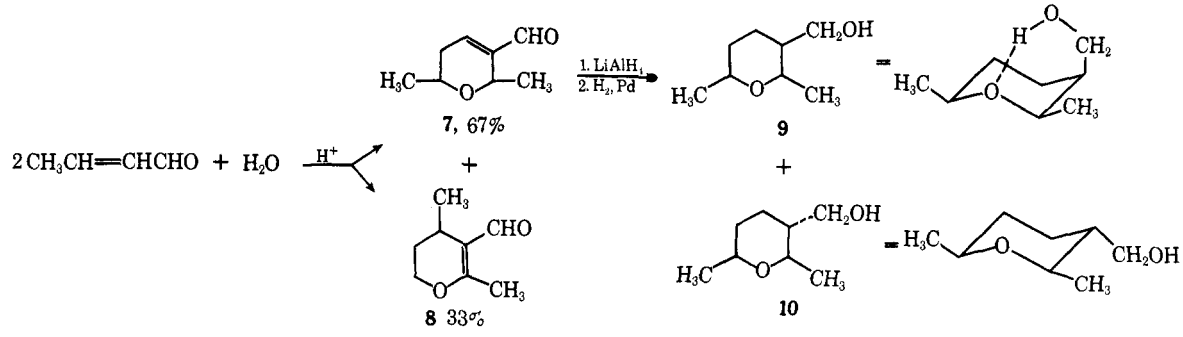
(37) $-\Delta G°$ for the CH_2OH group in cyclohexylcarbinol is 1.65 kcal/mol: E. L. Eliel, D. G. Neilson, and E. C. Gilbert, *Chem. Commun.*, 360 (1968). $-\Delta G°$ in **6** should be somewhere intermediate between this value and the −0.27 kcal/mol value in cis-**1**.

Scheme II



6a 6e

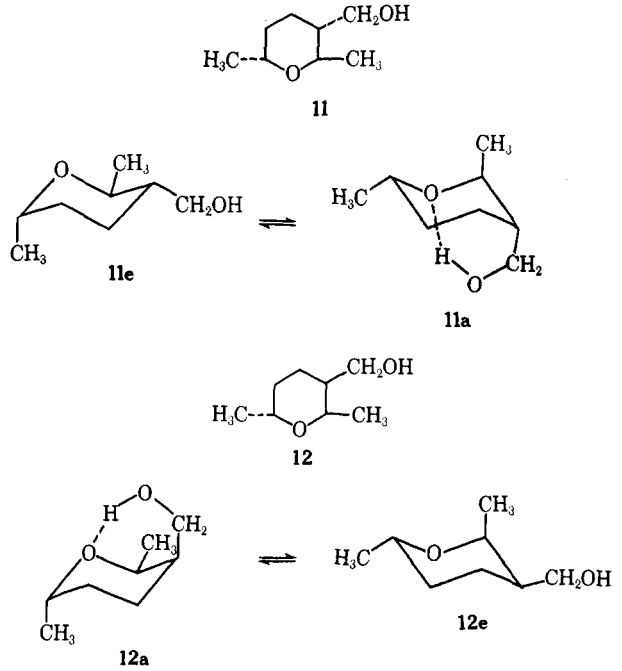
Scheme III



7, 67% 9 10 8 33%

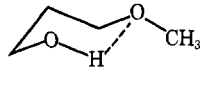
isomer **8**, but according to gas chromatographic and nmr evidence configurationally homogeneous. It thus appears that the more stable cis diastereoisomer is formed exclusively in the condensation; further evidence for this assumption will be presented below. Reduction of purified **7** with $LiAlH_4$ followed by hydrogen over palladium gave two alcohols, **9** and **10**, separated by gas chromatography, which, having been formed from a common precursor, must be diastereoisomeric. One of these alcohols, **9**, showed intense intramolecular hydrogen bonding in the infrared ($\Delta\tilde{\nu}$ = 110 cm^{-1}), whereas the other, **10**, showed no intramolecular hydrogen bond at all (*cf.* Table I). This finding strongly supports the configurational assignment made in Scheme III, for, were the methyl groups in the two alcohols trans to each other (Scheme IV, structures **11** and **12**), both alcohols should be conformationally heterogeneous and both should thus show similar degrees of hydrogen bonding (or lack thereof), the only difference being that of an extra gauche interaction (CH_3–CH_2OH) in hydrogen-bonded structure **12a**. In fact, since **6** (Scheme II) exists largely as **6e**, it would seem reasonable that both **11** and **12** should exist largely as **11e** and **12e**, in which case neither stereoisomer would display a hydrogen bond. Additional evidence for the configuration of **9** and **10** came from the nmr signal of the methyl groups at 1.10, 1.13 and 1.13, 1.15 ppm, respectively, which are very similar to each other, and to those in 2-methyl-6-alkoxytetrahydropyrans[39] (1.12–1.17 ppm) and 4-methyl-1,3-dioxane[31b] (1.15 ppm) and different from those of an axial 4-methyl group in 1,3-dioxane (1.28 ppm).[31b]

Scheme IV



11 11e 11a 12 12a 12e

The fact that hydrogen bonding is intense in **9** whereas it is absent in the geometrically similar *cis*-**1** means that bond eclipsing is not the major factor in blocking the hydrogen-bonding conformation in *cis*-**1**; presumably dipolar repulsion (Chart II) is principally responsible. Nevertheless bond eclipsing does seem to play some role. Although the hydrogen bond in **9** ($\Delta\tilde{\nu}$ = 110 cm^{-1}) seems to be stronger than that in 3-methoxypropanol (**3**) ($\Delta\tilde{\nu}$ = 87 cm^{-1}), the ratio of intensities of the unbonded and bonded O–H stretching bands in the infrared is nearly the same (about unity) in both cases. Thus, assuming similarity in relative extinction coefficients of the two bands, the populations of the bonded and unbonded conformations about OH stand in about the same ratio in **9** and **3**, despite the fact that the bond in **9** is stronger and that entropy considerations should make for more hydrogen bonding in **9** [rotation about only two bonds (C_3–C_α and C_α–O) is inhibited in the hydrogen bonded conformation in **9** but rotation about four bonds, CH_3O–CH_2–CH_2–CH_2–OH, is inhibited in **3**]. A likely source of the counterbalancing factor in **9** is bond eclipsing of the C_3–C_α–O–H bonds and of the C_α–O and C_α–H bonds with C_3–C_2, C_3–C_4, and C_3–H. In contrast, **3** can form a hydrogen bond in a nearly completely staggered, cyclohexane-like conformation with an "equatorial" CH_3 group:



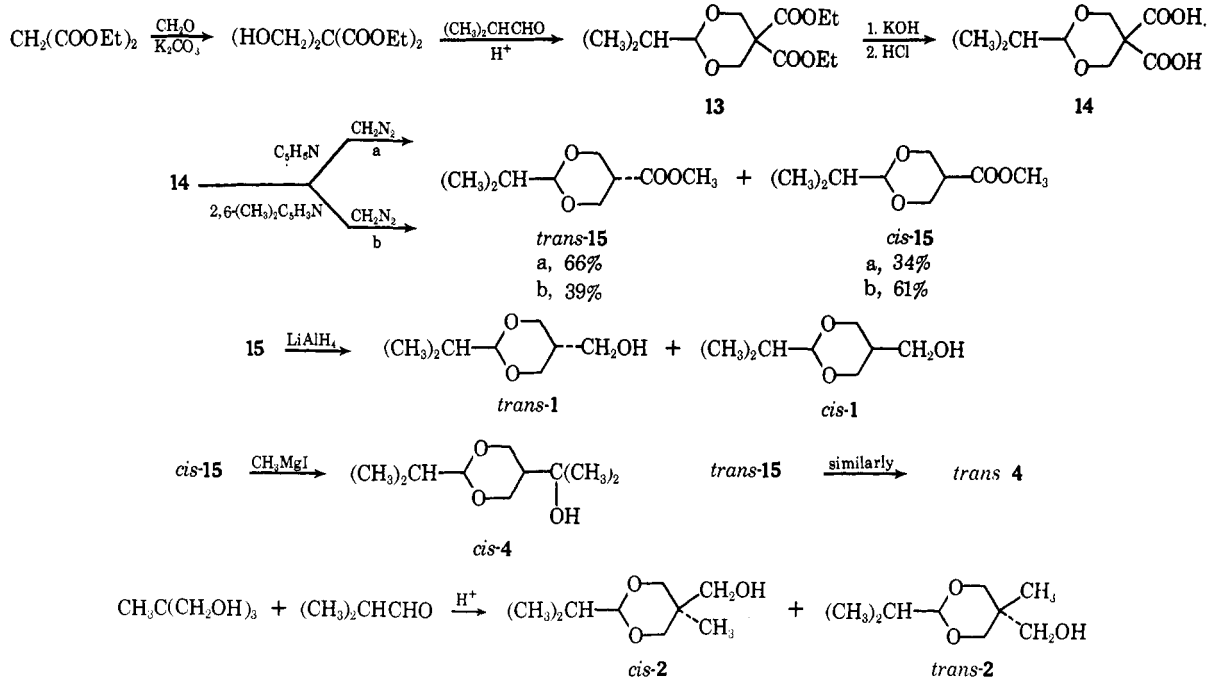
3

It had previously been observed that hydrogen bonding may be inhibited when the hydrogen-bonding con-

(38) (a) F. E. Bader, *Helv. Chim. Acta*, **36**, 215 (1953); (b) A. Losse, *Chem. Ber.*, **100**, 1266 (1967).

(39) E. L. Eliel and C. Giza, *J. Org. Chem.*, **33**, 3754 (1968); C. Giza, Ph.D. Dissertation, University of Notre Dame, Notre Dame, Ind., 1968.

Scheme V



formation is depopulated by steric factors. A case in point is *meso*-$(CH_3)_3CCHOHCHOHC(CH_3)_3$ which shows no intramolecular hydrogen bonding[17a] because the bonding conformation would have the bulky tertiary butyl groups gauche to each other. Another case is 2-ferroceneethanol[20c] in which the conformation with an intramolecular H bond to the π system is more populous ($\Delta H = -0.94$ kcal/mol) than that with an H bond to iron ($\Delta H = -0.86$ kcal/mol), even though the hydrogen bond to iron ($\Delta\tilde{\nu} = 98$ cm^{-1}) is stronger than that to the π system ($\Delta\tilde{\nu} = 29$ cm^{-1}). The present study shows that not only nonbonding interactions, but also other unfavorable intramolecular interactions, such as dipole repulsion, bond eclipsing, and presumably also angle deformation, must be pitted against the energy gained by formation of an intramolecular hydrogen bond, if one wants to predict if a hydrogen-bonded conformation is more stable than alternative, nonbonded conformations of a given molecule.

Synthesis. Schemes III and V summarize the synthetic procedures employed in this investigation.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 457 grating instrument except where noted otherwise. Nmr spectra were recorded on a Varian A-60A instrument at 60 MHz; shifts are reported in parts per million downfield from tetramethylsilane. Preparative gas chromatographic separations were achieved with a Nester-Faust Model 850 Prepkromatik instrument equipped with 3-ft "bi-wall" $^3/_4$-in. annular columns. Elemental analyses are by Midwest Microlab, Indianapolis, Ind.

2-Isopropyl-5,5-dicarbethoxy-1,3-dioxane (13) and 2-Isopropyl-5,5-dicarboxy-1,3-dioxane (14). Diethyl bis(hydroxymethyl)malonate,[40] $(HOCH_2)_2C(COOEt)_2$, mp 48–50° (lit.[40] 50–52°), and isobutyraldehyde were condensed in the usual manner[31] except that petroleum ether (bp 30–60°) was used as solvent instead of benzene (see also below). The product **13** boiled at 99–102° (0.4 Torr): n^{25}D 1.4390; yield 77%; ir strong bands at 2940–2990 (four peaks), 1720–1755 (broad), 1300–1050 (multiple, broad), 920–940 (three peaks, sharp), and 860 cm^{-1}, among others; nmr ($CDCl_3$) δ 0.88 (d, 6 H, J = 7 Hz), 1.22 (t, 3 H, J = 7 Hz), 1.28 (t, 3 H, J = 7 Hz), 1.5–2.0 (m, 1 H), 4.15 (9, J = 7 Hz; also additional peak at 3.75–4.75; total 9 H).

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 56.89; H, 8.29.

Saponification was effected by adding 137 g (0.5 mol) of the above ester to 120 g of KOH in 1 l. of 95% EtOH, boiling for 1 hr, concentrating to remove 250 ml of EtOH, adding an equal amount of water, and alternating distillation and water addition until a 1-l. distillate had been collected. The final volume was 850 ml; a 350-ml aliquot was cooled in an ice–salt bath and acidified with 84.0 ml of concentrated hydrochloric acid, added dropwise with vigorous stirring. The acidified solution was extracted with three 100-ml portions of ether which were combined, dried over $MgSO_4$, decolorized with charcoal, and concentrated to yield 34.35 g (87.3%) of the dicarboxylic acid **14**, mp 141–143° with decarboxylation.

Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.53; H, 6.56.

5-Carbomethoxy-2-isopropyl-1,3-dioxane (15). A. Trans Isomer. A magnetically stirred mixture of 20.0 g (92 mmol) of 5,5-dicarboxy-2-isopropyl-1,3-dioxane (**14**) and 20 ml of anhydrous pyridine was refluxed for 1.5 hr. The evolution of carbon dioxide was virtually complete in 15 min. The solution was cooled in an ice–salt bath, and 100 ml of 20% HCl was added dropwise. The acidic solution was extracted three times with 150-ml portions of ether, and the combined ether extracts were washed with 100 ml of 10% HCl, 100 ml of H_2O, and 100 ml of saturated NaCl solution, dried over $MgSO_4$, decolorized with Norit A, filtered, and concentrated on the rotary evaporator to give 13.9 g (87%) of 5-carboxy-2-isopropyl-1,3-dioxane. Treatment with excess ethereal diazomethane gave 13.0 g (86%) of 5-carbomethoxyl-2-isopropyl-1,3-dioxane (**15**) which glpc analysis (10 ft × 0.25 in. 20% FFAP on Chromosorb N, 60–80 mesh, 135°, 45 ml of He/min) showed to consist of 66% trans and 34% cis isomer. The cis isomer has a considerably longer retention time. The trans ester was purified by dry column chromatography.[41] To 400 g of silica gel (chromatographic grade, 60–200 mesh) was added 50 g of H_2O and 50 g of benzene. The mixture was shaken in a 2000-ml flask, and was allowed to stand overnight to ensure uniform absorption. To 50 g of the resulting mixture was added a solution of 10.0 g of the ester mixture in 50 ml of chloroform. The chloroform was evaporated, and the column was packed at the top with the ester-impregnated absorbent. Development was effected with benzene; in fractions that contained ester, 3.6 g (36% recovery) of pure *trans*-**15** was obtained. The intermediate fractions contained mixtures while the final fractions contained 0.4 g of pure *cis*-**15**.

The trans isomer, alternatively purified by gas chromatography (6-ft 20% FFAP on Chromosorb W, 45–60 mesh at 145°, He flow

(40) P. Block, *Org. Syn.*, **40**, 27 (1960).

(41) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

375 ml/min), retention time 29 min, had: $n^{25}D$ 1.4377; ir bands (neat) 1730–1740 (s), 1473, 1455 (sh), 1391 (s), 1325 (s), 1292 (s), 1234 (s), 1190–1205 (broad), 1145–1160, 1108, 1090–1100 (s), 1039, 1010–1020, 990–910 (six sharp bands), 858, 778 cm^{-1}; nmr ($CDCl_3$) 0.91 (d, 6 H, J = 6.5 Hz), 1.5–2.0 (m, 11 H), 2.65–3.25 (m, 1 H), 3.66 (s, 3 H), 3.5–4.25 (several peaks, *ca.* 4 H), 4.39 ppm (d, 1 H, J = 5.0 Hz).

B. Cis Isomer. Decarboxylation of 5,5-dicarboxy-2-isopropyl-1,3-dioxane (**14**) as described above but using 2,6-lutidine instead of pyridine, followed by esterification, gave a 75% yield of ester which was *ca.* 61% *cis*-**15** and 39% *trans*-**15**. Crystallization from hexane at −20° gave pure *cis*-**15**: mp 72–73°; 43% yield; retention time 50 min; ir (CCl_4) 1741 (s), 1470–1270 (multiple sharp bands), 1241 (s), 1190–1205, 1150 (s), 1118, 1080 (s), 993–1020, 945–870 cm^{-1} (four bands); nmr ($CDCl_3$) 0.89 (d, 6 H, J = 6.5 Hz, 1.4–1.9 (m, 1 H), 2. 2–2.4 (m, 1 H), 3.75 (s, 3 H), 3.7–3.8, 3.85–4.0, 4.4–4.5, 4.6–4.7 (AB, split, *ca.* 4 H), 4.22 ppm (d, 1 H, J = 5.0 Hz).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found for the cis isomer: C, 57.33; H, 8.59. For the trans isomer: C, 57.52; H, 8.55.

***cis*- and *trans*-2-Isopropyl-5-hydroxymethyl-1,3-dioxane (1).** The mixture of isomeric 2-isopropyl-5-carbomethoxy-1,3-dioxanes, prepared as described above, was reduced with excess lithium aluminum hydride in ether solution. The reaction mixture was worked up by precipitating lithium and aluminum salts with the minimum amount of water and aqueous NaOH. Concentration of the dried ether solution gave a mixture of the two stereoisomers which was separated by gas chromatography on a 3-ft column packed with 16.6% THEED on Chromosorb P at 125°, He flow 670 ml/min, retention times, cis isomer, 36 min, trans isomer, 67 min. The cis isomer had: $n^{25}D$ 1.4507; ir (neat) 3450 (broad), 1239, 1151, 1100, 1033 cm^{-1}; nmr ($CDCl_3$) 0.875 (d, 6 H, J = 7 Hz), 1.3–1.9 (m, 2 H), 2.5–2.8 (m, 1–2 H), 3.8–4.35 (m, 6 peaks, 7 H). The trans isomer had: $n^{25}D$ 1.4521; ir (neat) 3455 (broad), 1276, 1235, 1190, 1150, 1100–1115, 1023–1042 cm^{-1}; nmr ($CDCl_3$) 0.93 (d, 6 H, J = 6.5 Hz), 1.5–2.6 (m, 2 H), 3.2–3.7 (5 peaks, 6 H), 4.0–4.35 (4 peaks, 2–3 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found for the cis isomer: C, 59.78; H, 10.00. For the trans isomer: C, 60.20; H, 10.19.

***cis*- and *trans*-2-Isopropyl-5-hydroxymethyl-5-methyl-1,3-dioxane (12).**[42] In a 200-ml round-bottomed flask were placed 8.3 g (0.069 mol) of 2-methyl-2-hydroxymethyl-1,3-propanediol, 6.3 ml (0.069 mol) of isobutyraldehyde, 50 ml of petroleum ether (bp 30–60°), and 0.8 g of *p*-toluenesulfonic acid monohydrate. The flask was fitted with a Dean-Stark trap connected to a reflux condenser. The mixture was stirred magnetically and refluxed until 1.3 ml of water was collected in the trap (2 hr). The mixture was cooled to room temperature and 0.7 g of anhydrous NaOAc was added. Stirring was continued for 20 min. The mixture was taken up in 100 ml of ether and washed with two 50-ml portions of water. The ethereal solution was filtered through anhydrous $MgSO_4$ and the ether was removed by flash evaporation. Distillation yielded 8.0 g (67%) of 5-methyl-5-hydroxymethyl-2-isopropyl-1,3-dioxane, bp 79–80° (0.3 mm).

The stereoisomers were obtained pure by preparative glc on a 5 ft 3/4 in. annular "bi-wall" column of 20% FFAP on Chromosorb W (40–60 mesh) at 148°, and with a helium flow of 5 ml/sec, retention time, isomer A (90%), 36 min; isomer B (10%), 56 min.

The nmr spectrum ($CDCl_3$) of isomer A (*cis*-hydroxymethyl) showed signals at δ 0.72 (s, 3 H), 0.95 (d, 6 H, J = 6.5 Hz), 1.75 (m, 1 H), 3.05 (s, 1 H), 3.75 (s, 2 H), 3.63 (AA'BB', 4 H), 4.20 (D, 1 H, J = 4.5 Hz); $n^{20}D$ 1.4527.

Isomer B (*trans*-hydroxymethyl) showed: nmr ($CDCl_3$) δ 0.95 (d, 6 H, J = 6.5 Hz), 1.16 (s, 3 H), 1.75 (m, 1 H), 2.78 (s, 1 H), 3.27 (s, 2 H), 3.65 (s, 4 H), 4.16 (d, 1 H, J = 4.5 Hz), $n^{20}D$ 1.4515.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found for isomer A: C, 62.19; H, 10.42. For isomer B: C, 61.90; H, 10.41.

***cis*-5-(2-Hydroxy-2-propyl)-2-isopropyl-1,3-dioxane (*cis*-4).** By means of a syringe, 2.69 g (19 mmol) of methyl iodide was injected into a three-necked flask equipped with a dry nitrogen inlet adapter, condenser, and rubber septum, containing 0.32 g (13 mg-atoms) of magnesium turnings and 8 ml of anhydrous ether. After the initial exothermic reaction had subsided, the reaction mixture was refluxed for 15 min and cooled to room temperature, and 1.03 g (5.4 mmol) of *cis*-**15** in 11 ml of anhydrous ether was added dropwise by means of a syringe. After 1 hr of reflux, 5 ml of saturated NH_4Cl solution was added. The layers were separated and the ethereal solution was dried over $MgSO_4$. After filtration and concentration on a rotary evaporator, the residue was distilled to give 0.52 g (51%) of pure *cis*-**4**: bp 60–61° (0.2 Torr); nmr (CCl_4) δ 0.90 (d, 6 H, J = 7 Hz), 1.23 (m, 1 H), 1.38 (s, 6 H), 1.78 (m, 1 H), 2.63 (s, 1 H), 3.67–4.57 (5 H).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.30; H, 10.72.

***trans*-5-(2-Hydroxy-2-propyl)-2-isopropyl-1,3-dioxane (*trans*-4).** Using *trans*-**15** and the procedure described above for *cis*-**4**, *trans*-**4** was prepared in 53% yield: bp 88–89° (0.7 Torr); nmr (CCl_4) δ 0.92 (d, 6 H, J = 7 Hz), 1.18 (s, 6 H), 1.48–2.27 (m, 3 H), 3.40–4.40 (7 peaks, 5 H).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.35; H, 10.61.

***cis*-2,6-Dimethyl-3-formyl-5,6-dihydro-2*H*-pyran (7).**[38] A mixture of 200 g of crotonaldehyde, 1000 ml of H_2O, and 200 ml of concentrated HCl was refluxed for 1.5 hr. The mixture was cooled and extracted three times with a total of 700 ml of ether. The combined ether extracts were washed twice with 200 ml of H_2O and the black ethereal solution was dried over $MgSO_4$, filtered, and concentrated on the rotary evaporator. The residue was distilled to give 37.7 g of product, bp 63–72° (2 Torr). Glpc analysis (10 ft × 0.25 in. 20% FFAP on Chromosorb W, 60–80 mesh, 105°, 45 ml of He/min) showed the distillate to be *ca.* 67% **7** and 33% 2,4-dimethyl-3-formyl-2,3-dihydro-4*H*-pyran (**8**). Crystallization from pentane at −78° gave **7**, dinitrophenylhydrazone, mp 179–179.5°, from ethanol (lit.[38a] mp 180.5°).

***r*-3-Hydroxymethyl-*cis*-2,*cis*-6-dimethyltetrahydropyran (9) and *r*-3-Hydroxymethyl-*trans*-2,*trans*-6-dimethyltetrahydropyran (10).** Reduction of **7** with excess $LiAlH_4$ in ether gave the corresponding alcohol **16** in 90% yield: bp 85–86° (1.2 Torr); nmr (CCl_4) δ 1.07 (d, 3 H, J = 6.5 Hz), 1.09 (d, 3 H, J = 6.5 Hz), 1.92 (m, 2 H), 3.26–4.49 (m, 5 H), 5.66 (m, 1 H). A mixture of 1.80 g of **16**, 100 mg of 5% Pd/C, and 100 ml of absolute ethanol was hydrogenated at 44 psi on a Parr apparatus. When the calculated amount of hydrogen had been consumed, the reaction mixture was filtered through a Celite pad and concentrated on the rotary evaporator. Glpc analysis (10 ft × 0.25 in. 20% FFAP on Chromosorb W, 60–80 mesh, 140°, 45 ml of He/min.) showed the product to be composed of *ca.* 44% **9** and 56% **10**. The pure compounds were obtained by preparative glpc (10 ft × 0.38 in. 18% Carbowax 20 M on Chromosorb W, 45–60 mesh, 160°, 550 ml of He/min): **9**, nmr (CCl_4) δ 1.10, (d, 3 H, J = 6 Hz), 1.13 (d, 3 H, J = 7 Hz), 0.94–2.29 (m, 5 H), 2.96 (s, 1 H), 3.24–3.86 (m, 4 H); **10**, nmr (CCl_4) δ 1.13 (d, 3 H, J = 6 Hz), 1.15 (d, 3 H, J = 6.5 Hz), 0.90–2.06 (m, 5 H), 3.11 (s, 1 H), 2.96–3.68 (m, 5 H).

Anal. Calcd for $C_8H_{16}O_2$: C, 66.61; H, 11.19. Found: for **9**: C, 66.11; H, 11.15. **10**: C, 66.46; H, 11.15.

Infrared Spectral Determinations in the O–H Stretching Region. The hydroxyl stretching frequencies were determined using a Perkin-Elmer 521 double beam grating spectrophotometer and matched cells of 10-cm path length with quartz windows. The spectra were scanned at a rate of 25 cm^{-1}/min and calibrated by the absorption peaks of *cis*-cyclohexane-1,2-diol[43] at 3626 and 3588 cm^{-1}. The concentration of substrate was 5.0×10^{-4} M in spectral grade CCl_4. In the case of *cis*-**4**, OH was replaced by OD through exchange with D_2O. The OD stretching frequencies appeared at 2570, 2552, and 2498 cm^{-1}; the intensity of the 2498-cm^{-1} peak (presumably O–D···O) was very weak, in accordance with expectation.[19b]

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(42) R. Enanoza, Ph.D. Dissertation, University of Notre Dame, 1971. The configurational assignment of the isomers is discussed there.

(43) L. P. Kuhn, *J. Amer. Chem. Soc.*, **76**, 4323 (1954).