

# Conformational Analysis. XIX. The Conformational Enthalpy and Entropy of the Hydroxyl Group in Various Solvents. Conformational Energy of Methoxyl<sup>1</sup>

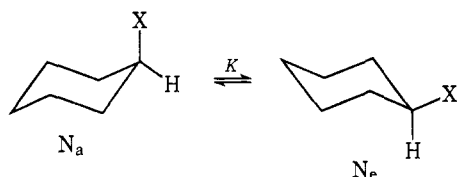
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**Abstract:** *cis*- and *trans*-4-*t*-butylcyclohexanol have been equilibrated by Raney nickel in several solvents over a range of temperatures, and the following thermodynamic parameters (*cis*  $\rightleftharpoons$  *trans*) have been determined. In cyclohexane, 0.05 *M*,  $\Delta H^\circ = -0.58$  kcal/mol,  $\Delta S^\circ = 0.06$  cal/deg mol,  $\Delta G^\circ_{25} = -0.60$  kcal/mol; 0.10 *M*,  $\Delta H^\circ = -0.61$ ,  $\Delta S^\circ = -0.02$ ,  $\Delta G^\circ_{25} = -0.61$  (units as above); 0.20 *M*,  $\Delta H^\circ = -0.63$ ,  $\Delta S^\circ = -0.06$ ,  $\Delta G^\circ_{25} = -0.61$ . In 1,2-dimethoxyethane, 0.1 *M*,  $\Delta H^\circ = -0.83$ ,  $\Delta S^\circ = -0.30$ ,  $\Delta G^\circ_{25} = -0.74$ . In 2-propanol, 0.1 *M*,  $\Delta H^\circ = -1.09$ ,  $\Delta S^\circ = -0.46$ ,  $\Delta G^\circ_{25} = -0.95$ . In *t*-butyl alcohol, 0.1 *M*,  $\Delta H^\circ = -1.18$ ,  $\Delta S^\circ = -0.76$ ,  $\Delta G^\circ_{25} = -0.95$ . Corresponding data for 3,3,5-trimethylcyclohexanol (*trans*  $\rightleftharpoons$  *cis*) are as follows. In cyclohexane, 0.05 *M*,  $\Delta H^\circ = -1.55$  kcal/mol,  $\Delta S^\circ = -0.26$  cal/deg mol,  $\Delta G^\circ_{25} = -1.47$  kcal/mol; 0.10 *M* (same units),  $\Delta H^\circ = -1.59$ ,  $\Delta S^\circ = -0.28$ ,  $\Delta G^\circ_{25} = -1.51$ . In 1,2-dimethoxyethane, 0.1 *M*,  $\Delta H^\circ = -1.90$ ,  $\Delta S^\circ = -0.77$ ,  $\Delta G^\circ_{25} = -1.67$ . In 2-propanol, 0.1 *M*,  $\Delta H^\circ = -2.47$ ,  $\Delta S^\circ = -1.16$ ,  $\Delta G^\circ_{25} = -2.12$ . The conformational free energy of the hydroxyl group determined by the nmr method in cyclohexane at high dilution (0.015 *M*),  $-\Delta G^\circ_{25} = 0.61$  kcal/mol, agrees with the thermodynamic value, but in certain other solvents, even at high dilution, there was neither agreement nor consistency, which confirms earlier doubts regarding the general validity of the nmr method using a *t*-butyl holding group. The conformational energy values for methoxyl, determined by nmr in various solvents, range from 0.34 to 0.63 kcal/mol. Cryoscopic measurements of the degree of association of the cyclohexanols used in this study at various concentrations and two temperatures are reported. The dependence of the conformational thermodynamic parameters on solvent is rationalized in detail. Additional data are reported for the equilibration of 2-methoxy-6-methyloxane.

Conformational equilibria of the type shown in Scheme I have been of interest for some time.<sup>3-5</sup> The soundest method,<sup>6</sup> from the theoretical point of

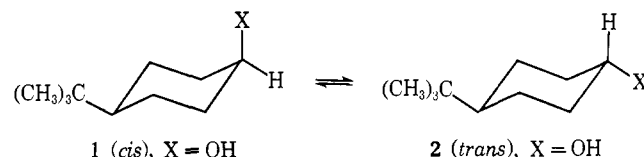
Scheme I



view, for determining the associated free-energy changes is the low-temperature nmr method.<sup>7</sup> Unfortunately, because of the limited temperature range accessible by this method, it has not so far been successfully applied to the determination of conformational enthalpies and entropies. Moreover, the method appeared particu-

larly poorly suited for the objective of the present study, the conformational equilibrium of the hydroxyl group (Scheme I, X = OH), since at the low temperatures required, even at the lowest concentrations conveniently accessible with the use of a computer of average transients, intermolecular association would constitute a strongly disturbing feature.<sup>8</sup> We, therefore, decided to resort to another method, namely the equilibration of compounds biased by a *t*-butyl group in the 4 position (Scheme II). This method, while not entirely free from

Scheme II



theoretical objections<sup>9</sup> (the *t*-butyl group may affect the position of equilibrium), has played a central role in the development of conformational analysis in mobile systems<sup>10</sup> and, at the very least, provides the thermodynamic parameters for a real equilibrium (that shown in Scheme II if not that shown in Scheme I).

We were primarily concerned with the hydroxyl group (Schemes I and II, X = OH). The conformational free energy of hydroxyl has been studied extensively and values ranging from 0.20 to 1.25 kcal/mol have been

(1) (a) Paper XVIII: E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, **91**, 2703 (1969); (b) preliminary publication: E. L. Eliel, D. C. Neilson, and E. C. Gilbert, *Chem. Commun.*, 360 (1968).

(2) Du Pont Teaching Fellow, 1967-1968. This paper is taken from the Ph.D. Dissertation of E. C. Gilbert, University of Notre Dame, 1969.

(3) For general reviews, see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965; (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965; (c) J. McKenna, "Conformational Analysis of Organic Compounds," Lecture Series No. 1, The Royal Institute of Chemistry, London, 1966.

(4) E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965).

(5) For a theoretical interpretation, see I. Ugi and E. Ruch in "Topics in Stereochemistry," Vol. 4, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, New York, N. Y., 1969.

(6) (a) Cf. E. L. Eliel, *Chimia*, **22**, 201 (1968). For a review of the method, see (b) H. Feltkamp and N. Franklin, *Angew. Chem.*, **77**, 798 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965).

(7) (a) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 3251 (1968); (b) F. R. Jensen, C. H. Bushweller, and B. H. Beck, *ibid.*, **91**, 344 (1969). For a related method, see (c) F. R. Jensen and C. H. Bushweller, *ibid.*, **88**, 4279 (1966).

(8) The method can be and has been applied to the determination of the conformational free energy of the methoxyl group, however; cf. ref 7b.

(9) Cf. E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *J. Amer. Chem. Soc.*, **88**, 3327 (1966); F. Shah-Malak and J. H. P. Utley, *Chem. Commun.*, **69**, (1967).

(10) E.g., E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, **79**, 5992 (1957).

**Table I.** Thermodynamic Parameters for 4-*t*-Butylcyclohexanol Equilibrium<sup>a</sup>

Solvent	Molarity, <i>M</i>	$-\Delta H^\circ$ , kcal/mol	$\Delta S^\circ$ , cal/deg mol	$-\Delta G^\circ_{25}$ , kcal/mol	Lit. <sup>b</sup> $-\Delta G^\circ$ , kcal/mol ( $^\circ\text{C}$ )
Cyclohexane	0.05	$0.58 \pm 0.02$	$0.06 \pm 0.04$	$0.60 \pm 0.03$	
	0.10	$0.61 \pm 0.01$	$-0.02 \pm 0.03$	$0.61 \pm 0.02$	0.60 (80) <sup>12</sup>
	0.20	$0.63 \pm 0.01$	$-0.06 \pm 0.03$	$0.61 \pm 0.02$	
1,2-Dimethoxyethane	0.10	$0.83 \pm 0.02$	$-0.30 \pm 0.05$	$0.74 \pm 0.03$	0.63 (80) <sup>c</sup>
2-Propanol	0.10	$1.09 \pm 0.02$	$-0.46 \pm 0.04$	$0.95 \pm 0.03$	0.93–0.96 (82–89) <sup>d</sup>
<i>t</i> -Butyl alcohol	0.10	$1.18 \pm 0.02$	$-0.76 \pm 0.07$	$0.95 \pm 0.04$	0.88 (82) <sup>e</sup>

<sup>a</sup> Scheme II, X = OH. Error limits are standard deviations. <sup>b</sup> Values from literature at temperature indicated. <sup>c</sup> Reference 12. Value at 80° calculated from present results is 0.72. <sup>d</sup> References 10 and 12. Value at 85° calculated from present results is 0.92. <sup>e</sup> Reference 12. Value at 82° calculated from present results is 0.91.

**Table II.** Thermodynamic Parameters for 3,3,5-Trimethylcyclohexanol Equilibrium<sup>a</sup>

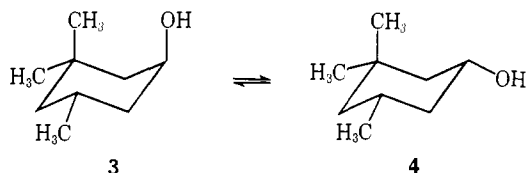
Solvent	Molarity, <i>M</i>	$-\Delta H^\circ$ , kcal/mol	$\Delta S^\circ$ , cal/deg mol	$-\Delta G^\circ_{25}$ , kcal/mol	Lit. <sup>b</sup> $-\Delta G^\circ$ , kcal/mol ( $^\circ\text{C}$ )
Cyclohexane	0.05	$1.55 \pm 0.02$	$-0.26 \pm 0.04$	$1.47 \pm 0.03$	
	0.10	$1.59 \pm 0.03$	$-0.28 \pm 0.08$	$1.51 \pm 0.05$	1.54 (80) <sup>c</sup>
	0.20	$1.63 \pm 0.01$	$-0.06 \pm 0.03$	$0.61 \pm 0.02$	
1,2-Dimethoxyethane	0.10	$1.90 \pm 0.01$	$-0.77 \pm 0.01$	$1.67 \pm 0.01$	
2-Propanol	0.10	$2.47 \pm 0.07$	$-1.16 \pm 0.18$	$2.12 \pm 0.12$	1.96–2.08 (82–84.5) <sup>d</sup>

<sup>a</sup> Scheme III. Error limits are standard deviations. <sup>b</sup> Values from literature at temperature indicated. <sup>c</sup> Reference 12. Value at 80° calculated from present results is 1.49. <sup>d</sup> References 12 and 14. Value at 83° calculated from present results is 2.06 kcal/mol.

tabulated,<sup>11–13</sup> the best values given<sup>11–13</sup> being 0.52 kcal/mol in aprotic solvents and 0.87 kcal/mol in protic ones. Earlier studies of the 4-*t*-butylcyclohexanol equilibrium (Scheme II, X = OH) in our laboratory<sup>12</sup> had yielded values ranging from 0.60 to 0.69 kcal/mol in cyclohexane, benzene, toluene, 1,2-dimethoxyethane, and tetrahydrofuran and a range of 0.88–0.94 kcal/mol in isopropyl and *t*-butyl alcohols.<sup>10,12</sup>

## Results

The principal objective of the present study was to determine  $\Delta H^\circ$  and  $\Delta S^\circ$  for the 4-*t*-butylcyclohexanol equilibrium in various solvents. Equilibration was readily effected by means of Raney nickel. Results are shown in Table I which also includes earlier values of  $\Delta G^\circ$  from the literature. In Table II are shown data for the 3,3,5-trimethylcyclohexanol equilibrium<sup>14</sup> (Scheme III) which was studied concurrently to help

**Scheme III**

throw light on the nature of steric effects which influence  $\Delta H^\circ$  and  $\Delta S^\circ$ . The  $\Delta G^\circ$  values in both Tables I and II are in good agreement with those earlier obtained in our laboratories by both Raney nickel<sup>12</sup> and aluminum isopropoxide<sup>10,14</sup> equilibration.

(11) J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967. We believe that the "best value" of 0.52 kcal/mol tabulated by Hirsch for aprotic solvents is too low, since it puts undue weight on some of the early equilibrium determinations, which were later shown to be in error,<sup>12</sup> and on values obtained by the infrared method which may be theoretically unsound.<sup>13</sup>

(12) E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

(13) J. R. Hall and M. K. Wilson, *Spectrochim. Acta*, **22**, 1729 (1966).

(14) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

A rationalization of the values in Tables I and II should take into account the following factors: (i) nonbonded interactions within the molecules affecting  $\Delta H^\circ$ ; (ii) entropy-of-mixing terms due to the existence of various rotational conformations of (either unbonded or bonded) OH in both the equatorial and axial positions; (iii) possible effects of intermolecular hydrogen bonding on  $\Delta H^\circ$  and  $\Delta S^\circ$ ; (iv) effects of hydrogen bonding to acceptor solvent on  $\Delta H^\circ$  and  $\Delta S^\circ$ ; (v) effects of hydrogen bonding from donor solvent on  $\Delta H^\circ$  and  $\Delta S^\circ$ . Since we are unable, at the present time, to assess intrinsic entropy differences between *cis*- and *trans*-4-*t*-butylcyclohexanol due to differences in vibrational and rotational entropies, we shall make the assumption that such differences are negligible and that the only intramolecular cause for  $\Delta S^\circ \neq 0$  is ii above.

Cyclohexane is a solvent which acts neither as hydrogen donor nor as hydrogen acceptor. Thus, if solutions in this solvent are dilute enough to suppress complications caused by association, the thermodynamic parameters should give a true indication of i (nonbonded interactions) and ii (entropy-of-mixing differences) above.

The predicted entropy-of-mixing differences depend on the assumptions one makes regarding the rotational conformation of axial hydroxyl. There is little doubt that equatorial hydroxyl has three populated (perhaps nearly equally populated)<sup>15,16</sup> rotational conformations and that its entropy of mixing is therefore close to  $R \ln 3$  or 2.2 cal/deg mol. The situation with respect to axial hydroxyl is not so clear-cut. At one time it was believed that the "OH-inside" conformation was sterically disfavored and that only the two "OH-outside" conformations were appreciably populated;<sup>17</sup> in this

(15) L. Joris, P. von R. Schleyer, and E. Osawa, *Tetrahedron*, **24**, 4759 (1968); see, however, ref 16.

(16) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969). Professor Allinger has informed us that the calculation regarding the conformational energy of hydroxyl in cyclohexanol in this paper contains an error. The correct calculated parameters for the change  $\text{OH}_a \rightleftharpoons \text{OH}_e$  are  $\Delta H^\circ = -0.58$  kcal/mol,  $\Delta S^\circ = +0.41$  cal/deg mol. Only about 10% of the axial isomer is calculated to be in the "OH-inside" conformation; the symmetrical conformation of equatorial OH amounts to about 20%.

case, the entropy of mixing of the axial isomer **1** should be  $R \ln 2$  or 1.4 cal/deg mol and the equatorial **2** should thus be favored, entropywise, by 2.2 – 1.4 or 0.8 cal/deg mol. More recently, however, it has been suggested that all three rotamers of axial hydroxyl (in **1**) are nearly equally<sup>15</sup> populated, with the entropy of mixing thus being in the 2.1–2.2-cal/deg mol range<sup>18</sup> giving rise to a  $\Delta S^\circ$  (*cis*  $\rightleftharpoons$  *trans*) of 0.0–0.1 cal/deg mol.

Our experimental data (Table I) at the lowest accessible concentration (0.05 *M*) of alcohol show a slightly positive  $\Delta S^\circ$  which would appear to support the existence of three nearly (though not quite) equally populated conformations, for the axial alcohol as discussed by Schleyer<sup>15</sup> provided that there are also three equally populated conformations of the equatorial alcohol.<sup>19</sup> However, our data *might* be compatible with only two rotational conformations of the axial alcohol if the resulting entropy advantage of the equatorial alcohol of 0.8 cal/deg mol (*vide supra*) were compensated by a corresponding disadvantage caused by intermolecular association which is known (see the later discussion) to lead to an entropy loss. For a variety of reasons, which are summarized in the next paragraph, we consider this possibility unlikely.

It is a fact, which we have confirmed by infrared spectroscopy (see Experimental Section), that both **1** and **2** are intermolecularly hydrogen bonded, to a considerable extent, even at the lowest concentrations (0.05 *M*) achieved in this study.<sup>20</sup> However, although the infrared spectra clearly indicated that such bonding drops off greatly as the concentration is lowered from 0.1 to 0.05 *M*, the data in Table I show but a very small entropy change over the same range of concentration. This suggests that association is not greatly different for **1** and **2** and that any entropy change caused by such association is compensated when the difference between **1** and **2** is considered. The infrared spectra support this suggestion qualitatively. More quantitative support came from a cryoscopic determination of the amount of association of **1** and **2** in 0.1 and 0.05 *M* solutions in cyclohexane at 6.5° and in cyclododecane at 61°. If one assumes that only a monomer–dimer equilibrium comes into play,<sup>21</sup> the associations of **1** and **2** are 50 and 64%, respectively, at 6.5° and 25 and 38%, respectively, at 61°. Clearly, in the temperature range of the equilibration experiments (81–115°) association would be even less, especially considering that, due to the destruction of some of the substrate, the effective concentration of **1** + **2** was less than 0.05 *M*.<sup>22</sup>

(17) H. S. Aaron and C. P. Rader, *J. Amer. Chem. Soc.*, **85**, 3046 (1963).

(18) The maximum deviation from equality of the three conformers contemplated in ref 15 corresponds to 20% of the OH-inside conformation and 40% of each of the OH-outside conformations; the corresponding entropy of mixing is 2.1 cal/deg mol.

(19) Our data ( $\Delta H^\circ = -0.58$  kcal/mol,  $\Delta S^\circ = +0.06$  cal/deg mol) are also in good agreement with the corrected values of ref 16. However, the calculation suggests a more sparsely populated "OH-inside" conformation for axial hydroxyl compensated, in part, by the fact that the symmetrical conformation of equatorial OH is also energetically disfavored.

(20) Because of attrition of substrate due to side reactions it was not possible to effect reproducible equilibrium measurements at concentrations below 0.05 *M*.

(21) According to infrared spectra, this assumption is probably reasonably good at room temperature and 0.05 *M* concentration (and therefore, *a fortiori*, at higher temperatures at this concentration); it is undoubtedly not good at 0.1 *M* and we have, therefore, not calculated the per cent association at this concentration.

(22) The fact that good straight lines were obtained for the plots of  $\ln K$  vs.  $1/T$  (see Experimental Section) is additional (if not highly sensi-

It is unlikely that such small differences in association would have a palpable effect on  $\Delta S^\circ$ . In fact, from the (two-point) temperature dependence of association equilibrium constant, we calculated  $\Delta S^\circ$  for the association process to be –11.1 cal/deg mol for **1** and –11.2 cal/deg mol for **2**. Unfortunately, the significance of this finding is marred by the very low precision of an entropy determination of this type of cryoscopic measurement; the nearly perfect agreement of the two  $\Delta S^\circ$  values is no doubt in part fortuitous.

Inspection of Table II would seem to throw immediate doubt on the assumption of negligible differences in entropy of mixing of rotamers for axial and equatorial hydroxyl. For it is clear that in **3** the "OH-inside" conformation cannot be appreciably populated for steric reasons and since the rotamer situation in **4** is similar to that in **2**, **4** should have an entropic advantage of  $R \ln 3 - R \ln 2$  or 0.8 cal/deg mol over **3**. In fact, as Table II shows, the entropy difference is in the other direction, favoring the axial isomer (**3**) slightly. However, this result is probably due to association differences. Infrared spectra once more indicate that **4**, like **2**, is appreciably associated, *but 3, at 0.05 M concentration, is hardly associated at all*. Cryoscopy bears out this finding: the extent of association of **4**, 64% at 6.5° or 44% at 61°, is very similar to that of its conformational analog **2** (*vide supra*), but the extent of association of **3**, 29% at 6.5° or 7% at 61°, is very much less. As a result, one must expect an entropy loss of the equatorial alcohol **4** compared to its axial epimer **3** through much more extensive association, and this entropy loss presumably more than compensates for the expected entropy of mixing gain.<sup>23</sup>

The  $-\Delta H^\circ$  value at the lowest concentration studied, namely 0.58 kcal/mol, is probably very close to the true conformational enthalpy of hydroxyl; it is in perfect agreement with the value of 0.58 kcal/mol computed theoretically using an energy minimization procedure.<sup>16</sup>

We now turn to the effect of hydrogen acceptor and hydrogen donor solvents. We had, at one time, speculated<sup>24</sup> that there would be a progression of  $-\Delta G^\circ_{\text{OH}}$  as one proceeds from aprotic to hydrogen acceptor to hydrogen donor solvents. Subsequent determination of  $\Delta G^\circ$  in hydrogen acceptor solvents<sup>12</sup> did not show such a progression very clearly, however, and, on the basis of other investigations, it was suggested<sup>25</sup> that hydrogen acceptor solvents have no effect on  $\Delta G^\circ$ . The 1,2-dimethoxyethane data in Table I show, however, that the effect, while small, is real; its smallness is due to a partial compensation of more significant changes in  $\Delta H^\circ$  and  $\Delta S^\circ$ . If one accepts that both equatorial and axial cyclohexanols have three populated rotational conformations, it would appear reasonable that the equatorial hydroxyl hydrogen can attach itself to an acceptor solvent molecule in each of its three conformations with a

tive) evidence that differences in degree of association of the two alcohols do not play a major part; since association diminishes as temperature increases, neither  $\Delta H^\circ$  nor  $\Delta S^\circ$  would be constant if such differences played a major role.

(23) This result, unfortunately, means that in the case of **3** and **4** we have not achieved the near-ideal conditions desired for determination of  $\Delta H^\circ$  and  $\Delta S^\circ$ . At infinite dilution in cyclohexane,  $\Delta S^\circ$  should be about 1 cal/deg mol [0.8 – (–0.26)] more positive than indicated in Table II and  $\Delta H^\circ$  should be less negative, by about 0.3 kcal/mol, than indicated there.

(24) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

(25) (a) C. P. Rader, *J. Amer. Chem. Soc.*, **88**, 1713 (1966); (b) see also R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 4378 (1964).

resultant enthalpic stabilization. The axial hydroxyl hydrogen, on the other hand, can probably not bond readily to an acceptor solvent in the "OH-inside" conformation, since in this conformation the solvent molecule would have to occupy space very close to the syn-axial hydrogens. Thus, the bonding of the axial OH is less effective and the equatorial hydroxyl thus gains in stability, -enthalpywise. At the same time, since hydrogen bonding tends to lead to a diminution of rotational and/or translational freedom, the equatorial isomer loses entropy, although this loss, translated into  $\Delta G^\circ$ , is less than the enthalpic stabilization. It is interesting that the change in  $\Delta H^\circ$  from cyclohexane to 1,2-dimethoxyethane in Table I (0.25 kcal/mol) is similar to that in Table II (0.35 kcal/mol); this is to be expected if the cause in the two systems (Schemes II and III) is the same, namely, inability of the acceptor solvent to bond across the ring, whether this be due to difficulties of approach (as in 1) or to absence of the necessary OH-inside conformation (as in 3). The entropy effect is also similar (0.36 vs. 0.51 cal/deg mol).

Stabilization of the equatorial conformation in hydrogen-donor solvents, such as alcohols, has long been recognized.<sup>11,12,25</sup> The data for 2-propanol and *t*-butyl alcohol (Table I) conform to the pattern. That the effect on  $\Delta H^\circ$  for this type of solvent is greater than for the acceptor solvents may be an artifact of the choice of solvents, which are, in fact, both donors and acceptors, with a possible resulting potentiation of the effects. Another, perhaps more likely, possibility, is that hydrogen bonding to axial oxygen is difficult at any angle; this hypothesis is supported by the fact that  $-\Delta H^\circ$  in the sterically more demanding *t*-butyl alcohol is even larger than in 2-propanol, and that the enhancement in  $-\Delta H^\circ$  in going from 1,2-dimethoxyethane to 2-propanol is substantially greater for the sterically more encumbered 3,3,5-trimethyl system (Scheme III and Table II, 0.57 kcal/mol) than for the 4-*t*-butyl system (Scheme II and Table I, 0.26 kcal/mol).<sup>26</sup> The entropy, as expected, shows the reverse trend: the stronger the hydrogen bond, the lower the entropy (*vide supra*).

**Nmr Data.** At a time when approaches to the determination of conformational equilibria were still quite limited, an nmr method based on chemical shifts was devised.<sup>27</sup> This method is based on the fact that the chemical shift of a proton in a conformationally heterogeneous system is the weighted average of the shifts of the same proton in each of the pure conformers in equilibrium. Thus, for the system shown in Scheme I, the shift  $\nu$  of the CHX proton is given by

$$\nu = N_a\nu_a + N_e\nu_e$$

where  $\nu_a$  and  $\nu_e$  are the shifts of the protons shown in Scheme I in the axial and equatorial conformations, respectively (note that  $\nu_e$  refers to an equatorial proton and  $\nu_a$  to an axial proton), and  $N_a$  and  $N_e$  are the mole fractions of the two conformers. Since the shifts  $\nu_a$  and  $\nu_e$  are not readily accessible experimentally,<sup>28</sup> it was sug-

(26) The over-all enhancement in  $-\Delta H^\circ$  in going from cyclohexane to 2-propanol solvent in the 3,3,5-trimethyl system (Scheme III) amounts to nearly 1 kcal/mol. A contributing factor to this very large value may be that the "OH-inside" conformation, which is the one best disposed toward bonding of the oxygen with a hydrogen donor, is nearly absent in 3.

(27) E. L. Eliel, *Chem. Ind.* (London), 568 (1959). For a review, see ref 6b.

(28) In principle, as pointed out in ref 7a, measurement of the shifts at

gested that the corresponding shifts in the 4-*t*-butyl-substituted compounds (Scheme II) be used instead. This procedure, while often giving data of a reasonable order of magnitude,<sup>11</sup> can no longer be recommended in the light of subsequent experience.<sup>7a,29</sup> Nevertheless, we attempted to use this method, with a modification devised by Winstein<sup>30</sup> and extensively used by Reisse,<sup>31</sup> using 2,2,6,6-tetradeuterated substrates (to avoid broadening of the pertinent CHX signal by vicinal proton coupling), both because it is a convenient one to use at high dilution and because we wanted to obtain a comparison with the equilibration method. The nmr results are summarized in Table III which also contains earlier

**Table III.** Apparent Conformational Energies of Hydroxyl Obtained by the Nmr Method

Solvent	Concn, <i>M</i>	$-\Delta G^\circ_{41}$ , kcal/mol	Lit. <sup>a</sup> $-\Delta G^\circ$ , kcal/mol
Cyclohexane	1.5-2.0	0.85	0.84, <sup>c,i</sup> 0.82, <sup>j</sup> 0.88, <sup>c,k</sup> 0.88 <sup>d,k</sup>
	0.15-0.20	0.72	0.73 <sup>d,k</sup>
	0.075-0.10	0.64	
	0.015	0.61	
Carbon tetrachloride	0.015	0.61	0.78, <sup>l</sup> 0.83, <sup>i</sup> 0.65, <sup>j</sup> 0.72 <sup>e,k</sup>
Nitrobenzene	0.015	0.73	
Chloroform- <i>d</i>	0.015	0.82	1.00 <sup>j</sup>
<i>t</i> -Butyl alcohol	0.025	0.83	1.05, <sup>i</sup> 0.88, <sup>j</sup> 0.94 <sup>f,k</sup>
Dimethyl- <i>d</i> <sub>6</sub> sulfoxide	0.025	0.84 <sup>b</sup>	0.84, <sup>k</sup> 0.61 <sup>i</sup>
Acetonitrile	0.015	0.88	0.94 <sup>j</sup>
Pyridine	0.015	0.89	0.84, <sup>i</sup> 0.91, <sup>j</sup> 0.94 <sup>k</sup>
Benzene	0.015	0.87	1.00, <sup>j</sup> 0.98 <sup>o,i</sup>
Acetone- <i>d</i> <sub>6</sub>	0.015	0.93	0.81 <sup>h,k</sup>
Acetic acid			0.82 <sup>j</sup>
<i>t</i> -Butylamine			0.73 <sup>j</sup>
2-Propanol-2- <i>d</i>			0.88 <sup>l</sup>
Dimethylformamide			1.00 <sup>k</sup>

<sup>a</sup> Values from the literature, obtained at considerably higher concentration (>0.1 *M*) near room temperature. <sup>b</sup> At 59°. <sup>c</sup> In isoctane. <sup>d</sup> In decalin. <sup>e</sup> This value refers to a 0.67 *M* solution. The value at 0.13 *M* is 0.65 kcal/mol. <sup>f</sup> In 3,5-dimethylhexanol-3. <sup>g</sup> In bromobenzene. <sup>h</sup> In cyclohexanone. <sup>i</sup> See ref 31. <sup>j</sup> See ref 32. <sup>k</sup> See ref 33. <sup>l</sup> See ref 30.

data from the literature<sup>31</sup> and from our own laboratories.<sup>32</sup>

The usefulness of the data in Table III is distinctly limited, but the following points may be made. (i) In aprotic or weakly bonding solvents, such as cyclohexane, carbon tetrachloride, chloroform, and benzene, the values in dilute solution (0.015 *M*) obtained by the nmr method tend to be considerably lower than those earlier obtained<sup>31,32</sup> at ten times higher concentration without the benefit of a computer of average transients.<sup>33</sup> (ii) The data in strongly hydrogen bonding

low temperatures coupled with a temperature extrapolation may solve this problem. In the case of alcohols, however, low-temperature measurements are unattractive for the reasons discussed earlier.

(29) Cf. E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962); E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, 90, 682 (1968); S. J. Wolfe and J. R. Campbell, *Chem. Commun.*, 872 (1967).

(30) A. H. Lewin and S. Winstein, *J. Amer. Chem. Soc.*, 84, 2464 (1962).

(31) J. Reisse, J. C. Celotti, D. Zimmermann, and G. Chiurdoglu, *Tetrahedron Lett.*, 2145 (1964).

(32) T. H. Williams, unpublished observations.

(33) J. Reisse, J. Celotti, R. Ottinger, and G. Chiurdoglu, *Chem. Commun.*, 752 (1968).

solvents, such as *t*-butyl alcohol, DMSO, acetonitrile, and pyridine, seem to be much less concentration dependent, as is to be expected when solute-solvent interactions swamp solute-solute interactions. (iii) Whereas the results in cyclohexane at the lowest concentration and in *t*-butyl alcohol are in good agreement with the equilibrium values (Table I), giving the impression that the nmr method might be applicable for the case of 4-*t*-butyl-substituted cyclohexanols, the same, unfortunately, cannot be said for the benzene value which is in strong disagreement with that found earlier<sup>12</sup> by equilibration ( $0.69 \pm 0.03$  kcal/mol). Since it is difficult to see how the 4-*t*-butyl groups could affect the shifts of the *CHOH* protons in the cyclohexanols by a direct magnetic anisotropy effect in one solvent but not in another, we are inclined to speculate that the orientation of the solvent molecules around the solute is what affects the shift; this orientation may not be the same for **1** and **2** (Scheme II) as it is for the axial and equatorial conformers of cyclohexanol itself (Scheme I). Such differences in orientation would have a particularly serious disturbing effect in the case of a highly magnetically anisotropic solvent, such as benzene. Unfortunately, since the same effect may come into play with other solvents listed in Table III, the data given in that table must be considered quite suspect, despite the good agreement with other methods in the case of cyclohexane and *t*-butyl alcohol. This may explain why, contrary to earlier assertion,<sup>31</sup> the nmr data do not show any kind of reasonable dependence on solvent type.

**The Conformational Energy of Methoxyl.** Application of the nmr method to 2,2,6,6-tetradeuteriocyclohexyl methyl ether and its *cis*- and *trans*-4-*t*-butyl analogs (Scheme II, X = OCH<sub>3</sub>, deuterated in positions adjacent to CHX) yielded the data shown in Table IV.

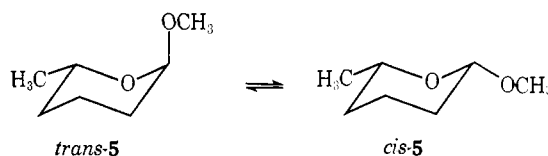
**Table IV.** Conformational Free Energies (kcal/mole) for Methoxyl by the Nmr Method

	Solvent			
	Cyclohexane	CCl <sub>4</sub>	Nitrobenzene	<i>p</i> -Dioxane
$-\Delta G^\circ$	0.34	0.35	0.40	0.45
	DMSO- <i>d</i> <sub>6</sub>	<i>t</i> -Butyl alcohol	Chloroform- <i>d</i>	Acetonitrile
$-\Delta G^\circ$	0.45	0.56	0.57	0.63

While the validity of the nmr method remains to be established in these cases, we wish to point out that the value obtained in aprotic solvents (other than acetonitrile),  $0.40 \pm 0.05$  kcal/mol, is appreciably lower than the value previously accepted.<sup>11</sup> The increase to *ca.* 0.55 kcal/mol in hydrogen-donor solvents may be real and can be explained in similar fashion as the analogous (though more substantial) increase for hydroxyl (*vide supra*). The value in acetonitrile is clearly anomalous; it is not clear whether this is due to a failure of the method in a strongly magnetically anisotropic solvent (as discussed earlier) or whether it is a real effect on the position of conformational equilibrium due to specific solvation. The low-temperature nmr value for OCD<sub>3</sub> found by Jensen and coworkers<sup>7b</sup> in carbon disulfide is 0.55 kcal/mol.

**Equilibrium of 2-Methoxy-6-methyloxane (5).** In a previous study<sup>34</sup> we had reported the equilibration of *cis*- and *trans*-**5** (Scheme IV) in carbon tetrachloride and

**Scheme IV**



$$\Delta G_{25}^\circ (\text{CCl}_4) = +0.73 \text{ kcal/mol}^{34}$$

$$\Delta G_{25}^\circ (\text{MeCN}) = +0.35 \text{ kcal/mol}^{34}$$

in acetonitrile and had interpreted the substantially lessened preference for the *trans* (axial) isomer (*cf.* Scheme IV) in acetonitrile to a dielectric effect of the solvent, since the preference for the axial conformation is due to dipole interactions which should be lessened in a high-dielectric solvent. It was subsequently pointed out to us that the effect in acetonitrile might be a specific solvent effect and the results with methoxycyclohexane shown in Table IV increased our concern in this regard. We have, therefore, studied the equilibrium shown in Scheme IV in several other solvents, with the results shown in Table V. It is clear that, except for an

**Table V.** Equilibrium in 2-Methoxy-6-methyloxane (**5**) as a Function of Solvent

Solvent	Dielectric constant	$\Delta G_{25}^\circ$ , kcal/mol <sup>a</sup>
Carbon tetrachloride	2.238 <sup>b</sup>	$0.74 \pm 0.01^c$
<i>p</i> -Dioxane	2.209 <sup>d</sup>	$0.60 \pm 0.01$
Tetrahydrofuran	8.200 <sup>b</sup>	$0.60 \pm 0.01$
Nitrobenzene	34.82 <sup>d</sup>	$0.43 \pm 0.01$
Acetonitrile	37.5 <sup>b</sup>	$0.35 \pm 0.01^e$

<sup>a</sup> For equilibrium as shown in Scheme IV. Error limits are standard deviations. <sup>b</sup> At 20°. <sup>c</sup> Reference 34 reports  $0.73 \pm 0.01$ . <sup>d</sup> At 25°. <sup>e</sup> Data from ref 34.

anomaly in the case of dioxane (whose dielectric constant is lower than that normal for an ether),  $\Delta G^\circ$  does in fact decrease with increasing dielectric constant of the solvent; there is no appreciable specific solvent effect in acetonitrile. The conclusions previously reached<sup>34</sup> thus remain valid.

## Experimental Section

**Starting Materials. 4-*t*-Butylcyclohexanols.** The *cis* alcohol (96% pure) was prepared in 97% yield by reduction of 4-*t*-butylcyclohexanone with hexachloroiridic acid-trimethyl phosphite-2-propanol.<sup>35</sup> Recrystallization from 60% aqueous ethanol gave over 99% pure *cis*-4-*t*-butylcyclohexanol, mp 82–83.5° (lit.<sup>36</sup> mp 82–83°). The *trans* isomer<sup>37</sup> (~100% pure by glpc) melted at 78–79.5° (lit.<sup>36</sup> mp 80–81°).

**3,3,5-Trimethylcyclohexanols.** Commercial *cis*-3,3,5-trimethylcyclohexanol (Aldrich Chemical Co.) was found to be 97% pure by glpc. Low-temperature (0°) recrystallization from petroleum ether (bp 30–60°) gave material of over 99% purity, mp 37–38.5° (lit.<sup>38</sup> mp 37.3°). The *trans* alcohol was prepared as previously

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

(35) Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. B. Mitchell, *Proc. Chem. Soc.*, 361 (1964); E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Syn.*, in press.

(36) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

(37) E. L. Eliel, R. J. L. Martin, and D. Nasipuri, *Org. Syn.*, **47**, 16 (1967).

(38) E. G. Peppiatt and R. J. Wicker, *J. Chem. Soc.*, 3122 (1955).

described<sup>14</sup> in an over-all yield of 83%; recrystallized from petroleum ether (bp 30–60°) it was 99.5% pure, mp 56.5–57.5° (lit.<sup>88</sup> mp 57.3°).

**Cyclohexanone-2,2,6,6-*d*<sub>4</sub>.** Cyclohexanone (20 g), 0.5 g of dry sodium carbonate, and 2.0 g of sodium chloride in 20 ml of deuterium oxide were refluxed for 24 hr.<sup>89</sup> The cooled reaction mixture was then extracted with dry ether, and the ether was carefully evaporated on a rotary evaporator. The residue was treated with fresh sodium chloride, sodium carbonate, and deuterium oxide, and set to reflux for another 24 hr. This process was repeated eight or nine times for each of three samples of ketone. The deuterium oxide used in the series of deuterations of the first ketone sample was reused for the second and third series, except for the last two deuterations in each series, for which fresh deuterium oxide was used.

The ketone collected from the three runs was shown to be more than 95% deuterated by comparison of the integrated peaks due to the hydrogens  $\alpha$  to the carbonyl group (doublet, –127 to –143 cps) and the remaining ring hydrogens (singlet, –101 to –122 cps).

**4-*t*-Butylcyclohexanone-2,2,6,6-*d*<sub>4</sub>** was prepared in the same manner as described for cyclohexanone-2,2,6,6-*d*<sub>4</sub> above. The recovered ketone was shown to be 95% deuterated by comparison of the integrated peaks due to the *t*-butyl group (singlet, –56 cps) and the ring hydrogens (multiplet, –70 to –135 cps).

**Cyclohexanol-2,2,6,6-*d*<sub>4</sub>** was obtained by reduction of 24.5 g (0.24 mol) of cyclohexanone-2,2,6,6-*d*<sub>4</sub> in 250 ml of ether with 2.75 g of lithium aluminum hydride in 100 ml of ether. After the usual work-up (10% H<sub>2</sub>SO<sub>4</sub>), the crude product was distilled to yield 19.7 g (79%) of cyclohexanol-2,2,6,6-*d*<sub>4</sub>, bp 60–62° (12 mm), *n*<sup>20</sup><sub>D</sub> 1.4610, 99.4% pure by glpc analysis. Deuterium content was estimated to be in excess of 96% by comparison of the integrated peaks due to the carbinol hydrogen (singlet, –210 cps) and remaining ring hydrogens (multiplet –50 to –120 cps).

**trans-4-*t*-Butylcyclohexanol-2,2,6,6-*d*<sub>4</sub>** was prepared by mixed hydride reduction of 4-*t*-butylcyclohexanone-2,2,6,6-*d*<sub>4</sub>.<sup>37</sup> From 43.0 g (0.27 mol) of the ketone was obtained 44.0 g (96%) of the crude product which was recrystallized from petroleum ether (bp 60–70°), mp 80–81°, 99.1% pure (glpc analysis). Deuterium content was estimated to be 94% by comparison of the integrated peaks due to the *t*-butyl group (singlet, –52 cps) and the ring hydrogens other than the carbinol hydrogen (multiplet –65 to –120 cps).

**cis-4-*t*-Butylcyclohexanol-2,2,6,6-*d*<sub>4</sub>**.<sup>40</sup> In a cooled, three-necked, 2-l. flask equipped with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser, were placed 17.1 g (0.451 mol) of lithium aluminum hydride (LAH) and 400 ml of cold tetrahydrofuran (THF), added slowly. The flask was cooled to 0° and 46 ml of methanol (1.07 mol) in 200 ml of THF was added, with stirring, over a period of 1 hr, followed by 60 g (0.38 mol) of 4-*t*-butylcyclohexanone-2,2,6,6-*d*<sub>4</sub> in 200 ml of THF also added over a 1-hr period. The reaction mixture was stirred for 1.25 hr at 0° to complete the reduction, enough ethylene glycol was added to the mixture to destroy excess hydride, the solution was diluted by addition of *ca.* half its volume of water, and ether was added until one could easily discern two layers of liquid. After separation the bottom layer was extracted three times with 150-ml portions of ether and the combined ether layers were dried over anhydrous magnesium sulfate. Filtration and concentration yielded 57.5 g (94.6%) of a mixture of *cis*-4-*t*-butylcyclohexanol-2,2,6,6-*d*<sub>4</sub> (45.9%) and *trans*-4-*t*-butylcyclohexanol-2,2,6,6-*d*<sub>4</sub> (54.1%).

Chemically pure *cis*-4-*t*-butylcyclohexanol-2,2,6,6-*d*<sub>4</sub> was obtained by chromatographic separation of the alcohols using an alumina column. In a typical example, 130 g of commercial activated alumina (80/20 mesh, Matheson Coleman and Bell) was employed for the separation of a 4.0-g sample of the alcohol mixture. Approximately 45 fractions of 200 ml each were collected as follows: fractions 1–34 (100% benzene), fraction 35 (70% benzene–30% chloroform), fraction 36 (50% benzene–50% chloroform), fraction 37 (30% benzene–70% chloroform), fractions 38–40 (100% chloroform), fractions 41–45 (100% ether). Pure *cis* alcohol was obtained from *ca.* fraction 10 to *ca.* fraction 37. A typical yield was 1.37 g (74% recovery) of virtually 100% chemically pure *cis*-4-*t*-butylcyclohexanol-2,2,6,6-*d*<sub>4</sub>, mp 78–79°. The alcohol was shown to be 95% deuterated by comparison of the integrated peaks due to

the *t*-butyl group (singlet, –52 cps) and the ring hydrogens other than the carbinol hydrogen (multiplet –65 to –120 cps).

**Cyclohexyl-2,2,6,6-*d*<sub>4</sub> Methyl Ether.** In a 100-ml two-necked flask equipped with a magnetic stirrer, a dropping funnel, and a condenser fitted with a calcium chloride drying tube, was placed 3.0 g (0.029 mol) of cyclohexanol-2,2,6,6-*d*<sub>4</sub> in 15 ml of dried (LAH distilled) 1,2-dimethoxyethane (DME).<sup>41</sup> Next 1.38 g (0.058 mol) of sodium hydride in 15 ml of 1,2-DME was added with stirring, followed by the slow addition of 8.2 g (0.058 mol) of methyl iodide dissolved in 10 ml of 1,2-DME. After 1 hr, 1 ml of methyl iodide was added and the solution was stirred overnight. It was then extracted with three 15-ml portions of dry ether, and the ether solution dried by passage through a sintered glass crucible covered with a 0.5-in. layer of anhydrous magnesium sulfate.

Distillation through a spinning-band column yielded 2.43 g (71%) of cyclohexyl-2,2,6,6-*d*<sub>4</sub> methyl ether, bp 132° (746 mm), *n*<sup>20</sup><sub>D</sub> 1.4263, 99.5% chemically pure (by glpc). Deuterium content was estimated as over 96% by comparison of the integrated peaks due to the CHOMe hydrogen (singlet, –183 cps) and the remaining ring hydrogens (multiplet, –55 to –120 cps).

**trans-4-*t*-Butylcyclohexyl-2,2,6,6-*d*<sub>4</sub> Methyl Ether.** By the same method described above for the cyclohexyl methyl ether,<sup>10</sup> 3.0 g (0.019 mol) of *trans*-4-*t*-butylcyclohexanol-2,2,6,6-*d*<sub>4</sub> yielded 2.29 g (71%) of *trans*-4-*t*-butylcyclohexyl-2,2,6,6-*d*<sub>4</sub> methyl ether, bp 31° (1 mm), *n*<sup>20</sup><sub>D</sub> 1.4460. The alcohol was virtually 100% pure and was shown by nmr analysis to have a deuterium content of over 99% as estimated from a comparison of the integrated peaks due to the *t*-butyl group (singlet, –51 cps) and the ring hydrogens other than the CHOMe hydrogen (multiplet, –70 to –120 cps).

**cis-4-*t*-Butylcyclohexyl-2,2,6,6-*d*<sub>4</sub> Methyl Ether.** By the same procedure 2.0 g (0.013 mol) of *cis*-4-*t*-butylcyclohexanol-2,2,6,6-*d*<sub>4</sub> yielded 1.62 g (75%) of the *cis* ether, bp 50° (1 mm), *n*<sup>20</sup><sub>D</sub> 1.4474. Its purity was greater than 99% as evidence by glpc, and nmr analysis showed it to be over 99% deuterated estimated by comparison of the integrated peaks due to the *t*-butyl group (singlet, –51 cps) and the ring hydrogens other than the CHOMe hydrogen (multiplet, –70 to –120 cps).

**cis- and trans-2-Methoxy-6-methyloxane.** Both of these compounds were obtained from a previous study;<sup>34</sup> glpc analysis showed them to be virtually 100% pure.

**Equilibration Procedures.** Alcohol equilibrations were carried out using the sealed ampoule technique previously described<sup>42</sup> using Raney nickel as the catalyst.<sup>12</sup> The method used for the oxane equilibrations was that employed earlier.<sup>34</sup> Solvents were purified as follows: cyclohexane, distilled over sodium; 2-propanol, redistilled; *t*-butyl alcohol, redistilled; 1,2-DME, distilled over LAH; carbon tetrachloride, spectral grade; *p*-dioxane, dried over sodium; THF, dried over sodium; nitrobenzene, dried over anhydrous magnesium sulfate.

The equilibrated solutions were analyzed by gas chromatography using an F & M Model 810-29 research gas chromatograph with a thermal conductivity detector. A Honeywell Electronic 15 recorder, equipped with a disk integrator, was used to obtain the peak areas. Columns employed were 9-ft 20% Carbowax 20M on 45/60 mesh Firebrick, or on 45/60 mesh Chromosorb W, 5% Carbowax 20M on 45/60 mesh Chromosorb G and 20% THEED (tetrahydroxyethylethylenediamine) on 45/60 mesh Chromosorb P for the alcohols and 20-ft 25% FFAP or silicon (Fluoro) QF-1 on 45/60 mesh Chromosorb W for the oxanes.

**Thermodynamic Parameters.** Evaluation of thermodynamic parameters ( $\Delta G^\circ$ ,  $\Delta S^\circ$ , and  $\Delta H^\circ$ ) was accomplished from least-squares plots of  $\ln K_{eq}$  vs.  $1/T$  as previously described.<sup>42</sup> The equilibrium constants obtained in the alcohol studies are presented in Table VI, those for the oxane study in Table VII. Each equilibrium constant is the average of at least 12 analytical determinations; errors are expressed as the standard deviation from the mean.

**Cryoscopic Molecular Weight Determination Study.** The cryoscopic molecular weight determination was carried out using the cooling curve method.<sup>43</sup> Temperature readings were taken every 30 sec once the temperature was within 1–2° of the freezing point. The study was carried out using 0.10 and 0.05 *M* solutions of **1**, **2**, **3**, and **4** in cyclohexane as well as 0.05 *M* solutions of each of the above alcohols in cyclododecane. The freezing point depressions

(39) Cf. A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(40) Cf. H. C. Brown and P. M. Weissman, *ibid.*, **87**, 5614 (1965). The application to 4-*t*-butylcyclohexanone is due to Dr. Y. Senda, University of Notre Dame, 1967 (unpublished results).

(41) U. E. Diner, F. Sweet, and R. K. Brown, *Can. J. Chem.*, **44**, 1591 (1966).

(42) E. L. Eliel and M. C. Reese, *J. Amer. Chem. Soc.*, **90**, 1560 (1968).

(43) Cf. A. Findlay, "Practical Physical Chemistry," Longmans Green and Co., Ltd., New York, N. Y., 1941, p 125.

Table VI. Alcohol Equilibrium Constants

Compound <sup>a</sup> ( <i>M</i> )	Temp, °C	Time, hr <sup>b</sup>	<i>K</i> (eq./ax.) <sup>c</sup>
ROH in cyclohexane (0.05)	81	24	2.353 ± 0.024
	95	20	2.284 ± 0.018
	115	19	2.189 ± 0.021
ROH in cyclohexane (0.10)	79	24	2.383 ± 0.031
	94	24	2.309 ± 0.021
	114	24	2.206 ± 0.026
	135	11	2.112 ± 0.030
	155	6	2.043 ± 0.026
ROH in cyclohexane (0.20)	81	26	2.380 ± 0.018
	96	24	2.298 ± 0.018
	116	21	2.193 ± 0.013
	137	13	2.108 ± 0.007
ROH in 2-propanol <sup>d</sup> (0.10)	80	96	3.734 ± 0.038
	95	96	3.519 ± 0.021
	116	96	3.233 ± 0.031
	138	96	3.005 ± 0.040
ROH in <i>t</i> -butyl alcohol (0.10)	81	99	3.640 ± 0.041
	96	58	3.403 ± 0.058
	115	47	3.133 ± 0.029
	122	24	3.054 ± 0.037
	138	47	2.381 ± 0.027
ROH in 1,2-DME (0.10)	80	58	2.812 ± 0.033
	95	49	2.692 ± 0.033
	116	49	2.527 ± 0.029
R'OH in cyclohexane (0.05)	80	24	7.93 ± 0.09
	95	20	7.23 ± 0.20
	105	14	6.86 ± 0.18
	123	10	6.24 ± 0.13
	138	9	6.07 ± 0.14
R'OH in cyclohexane (0.10)	80	24	8.38 ± 0.23
	96	21	7.56 ± 0.18
	116	14	6.82 ± 0.11
	138	9	6.07 ± 0.14
R'OH in 2-propanol (0.10) <sup>d</sup>	80	41	18.6 ± 0.4
	95	36	16.4 ± 0.4
	116	35	13.6 ± 0.4
	137	24	11.4 ± 0.3
R'OH in 1,2-DME (0.10)	81	64	10.0 ± 0.2
	96	45	8.98 ± 0.26
	114	38	7.96 ± 0.22
	137	30	6.93 ± 0.07

<sup>a</sup> R is 4-*t*-butylcyclohexyl (Scheme II), R' is 3,3,5-trimethylcyclohexyl (Scheme III). <sup>b</sup> Equilibration time. The time allowed was probably longer than needed in most instances. <sup>c</sup> Corrected for response ratios. Response ratios for the *cis-trans* isomer pairs ranged from 0.973 to 1.011 depending on the system and detector temperature. <sup>d</sup> Caution must be taken when equilibrating alcohols in 2-propanol over Raney nickel since hydrogen pressure builds up in the ampoules and an explosion may occur.

are listed in Table VIII. The molecular weight of the alcohols could be calculated directly as

$$\text{mol wt} = 1000K_f(g/G)\Delta T_f \quad (i)$$

(*g* = weight of solute, *G* = weight of solvent) or more accurately but indirectly from the mole fraction of solvent

$$\ln x_1 = (\Delta H_f/R)(T - T_0)/(T T_0) \quad (ii)$$

where *T*<sub>0</sub> is the freezing point of the pure solvent and *T* that of the solution. Since  $\Delta H_f$  was not available for cyclododecane, only eq i could be used for molecular weight calculations in that solvent. Both equations were used for the calculation of the molecular weights of the alcohols in cyclohexane for comparative purposes. The ratio of the observed to the theoretical molecular weight will be called  $\gamma$ ; it is the reciprocal of the conventional *i* factor. Since its spectra showed that the hydrogen bonded species were mostly dimers at 0.05 *M* concentration, the data obtained at this concentration were used to calculate *P* (per cent association) and *K*<sub>eq</sub> (equilibrium constant) based on a monomer-dimer equilibrium, where  $P = 200(\gamma - 1)/\gamma$  and  $K_{eq} = (1/M)((\gamma - 1)/\gamma)^2$ .<sup>3</sup> The derived parameters are listed in Table IX.

Table VII. Oxane Equilibrium Constants

Solvent	Temp, °C	Time, hr <sup>a</sup>	<i>K</i> (ax./eq.)
Carbon tetrachloride	28	48	3.442 ± 0.049
<i>p</i> -Dioxane	27	154	2.724 ± 0.034
Tetrahydrofuran	31	84	2.686 ± 0.060
Nitrobenzene	29	48	2.061 ± 0.041

<sup>a</sup> Equilibration time. See footnote *b*, Table II.

Table VIII. Freezing Point Depressions

Substrate	Molarity, <i>M</i>	$\Delta T_f$ , °C
In cyclohexane <sup>a</sup>	0.10	2.680
In naphthalene		
3	0.10	1.841
3	0.05	1.136
4	0.10	1.379
4	0.05	0.898
1	0.10	1.575
1	0.05	0.993
2	0.05 <sup>b</sup>	0.900
In cyclododecane <sup>c</sup>	0.10	1.150
In naphthalene		
3	0.05	0.536
4	0.05	0.428, 0.432 <sup>d</sup>
1	0.05	0.488
2	0.05	0.448, 0.449 <sup>d</sup>

<sup>a</sup> The freezing point of cyclohexane is 6.554° and the freezing point depression constant *K*<sub>f</sub> is 20.00°/(mol 1000 g); "International Critical Tables," Vol. 4, McGraw-Hill Book Co., Inc., New York, N. Y., 1928. <sup>b</sup> Compound 2 was insufficiently soluble in cyclohexane at 6.5° for study in 0.10 *M* solution. <sup>c</sup> The freezing point of cyclododecane is 61.0° [L. Ruzicka, Pl. A. Plattner, and H. Wild, *Helv. Chim. Acta*, 29, 1425 (1946)]; its freezing point depression constant, *K*<sub>f</sub>, was determined to be 8.87°/(mol 1000 g). <sup>d</sup> Repeated determinations.

**Spectroscopic Hydrogen Bonding Studies.** By Infrared Spectroscopy. The instrument employed in this study was a Perkin-Elmer Model 521 infrared analytical spectrometer. A variable path length potassium bromide cell, adjustable to give path lengths from 0.00 to 5.00 mm, was used for the analysis. Solutions of 1, 2, 3, and 4 were analyzed, the alcohol concentrations being 0.05, 0.075, and 0.10 *M* in spectral grade carbon tetrachloride. At all concentrations the free hydroxyl peaks centered at 3630 cm<sup>-1</sup> were sharp and intense, the hydrogen bonded ones more broad and diffuse, the latter became less broad and more symmetrical as the alcohol concentration was lowered. This effect, however, was much less for the equatorial than the axial alcohols. The hydrogen bonded peak (lowest tip of unsymmetrical peak) was found at approximately 3490 cm<sup>-1</sup> in all of the spectra studied. Comparison of band areas suggested that 4 was over 2.3 times as hydrogen bonded as 3, whereas 2 was only approximately 1.6 times as hydrogen bonded as 1 on the assumption (which is certainly at best qualitatively correct) that the extent of hydrogen bonding was proportional to the ratio of the bonded to the unbonded peak.

**By Nuclear Magnetic Resonance.** Studies similar to those carried out of Ouellette<sup>25b</sup> confirmed that substantial hydrogen bonding persisted in 1 and 2 even in the 0.10–0.03 *M* range of concentration in carbon tetrachloride.

**Nmr Determination of Equilibrium Constants.** A. Hydroxyl Group. The instrument was a Varian A-60A spectrometer equipped with a C-1024 computer of average transients. The scan time used was 25 sec over a 50-cps region using 2% TMS as internal standard and trigger. The probe temperature was 41° in all cases except for the study in DMSO-*d*<sub>6</sub> for which the probe temperature was set at 59°, to eliminate solute interaction with a very small amount of residual water in the system. The alcohols used were tetradeuterated in the 2 and 6 positions of the ring to decrease coupling with the carbinol hydrogen. Two alcohol mixtures were prepared for each solvent studied, one containing the appropriately deuterated cyclohexanol and *cis*-4-*t*-butylcyclohexanol ("cis-mixture"), the other the appropriately deuterated cyclohexanol and *trans*-4-*t*-butylcyclohexanol ("trans-mixture"). The equilibrium

Table IX. Data Obtained from Cryoscopic Molecular Weight Study

Solutes	Molarity, <i>M</i>	Mol wt		$\gamma$ factor	<i>P</i> <sup>d</sup>	<i>K</i> <sub>eq</sub> <sup>d</sup>
		Calcd	Obsd <sup>c</sup>			
1	0.05 <sup>a</sup>	156.3	178.9	1.15	25.3	4.54
2	0.05 <sup>a</sup>	156.3	192.4	1.23	37.5	9.62
			193.8	1.24	38.7	10.3
3	0.05 <sup>a</sup>	142.2	147.4	1.04	6.95	0.80
4	0.05 <sup>a</sup>	142.2	183.6	1.29	45.1	15.0
			180.6	1.27	42.5	12.9
Naphthalene	0.10 <sup>b</sup>	128.2	126.7, 127.6			
1	0.10 <sup>b</sup>	156.3	262.1, 265.7	1.68, 1.70		
			209.5, 205.9	1.32, 1.34	48.2, 50.9	18.0, 21.1
2	0.05 <sup>b</sup>	156.3	231.6, 227.3	1.46, 1.48	62.5, 65.1	44.6, 53.2
3	0.10 <sup>b</sup>	142.2	206.9, 204.4	1.44, 1.45		
3	0.05 <sup>b</sup>	142.2	167.0, 164.4	1.16, 1.17	27.6, 29.6	3.96, 4.43
4	0.10 <sup>b</sup>	142.2	276.3, 272.3	1.91, 1.94		
4	0.05 <sup>b</sup>	142.2	211.0, 207.3	1.46, 1.48	62.7, 65.1	45.2, 53.6

<sup>a</sup> In cyclododecane at 61°. <sup>b</sup> In cyclohexane at 6.5°. <sup>c</sup> The first figure is the molecular weight calculated using eq i; the second figure is the molecular weight calculated using eq ii. <sup>d</sup> Values were not calculated for the 0.10 *M* solutions since a significant amount of polymeric hydrogen bonded species was present (ir evidence).

Table X. Equilibrium Constants Obtained for the Deuterated Alcohols at Low Concentration in Ten Solvents<sup>a</sup>

Solvent <sup>b</sup>	<i>K</i> <sub>OH</sub> (eq iii)	<i>K</i> <sub>OH</sub> <sup>c</sup> (eq iv)	<i>K</i> <sub>OH</sub> <sup>d</sup> (comparative values)
Cyclohexane	2.67		3.75, 3.97 <sup>o</sup>
CCl <sub>4</sub>	2.65	2.77	3.02, 3.84
Nitrobenzene	3.21		
DMSO- <i>d</i> <sub>6</sub> <sup>e</sup>	3.59		2.78
Chloroform- <i>d</i> <sub>1</sub>	3.72		5.40
<i>t</i> -Butyl alcohol	(3.78) <sup>f</sup>	3.95	4.37, 5.54
Acetonitrile	4.08		4.85
Pyridine	4.14		4.64, 3.90
Benzene	4.31	4.03	5.44
Acetone- <i>d</i> <sub>6</sub>	4.43		

<sup>a</sup> Owing to drift in the signals relative to TMS during scanning, as well as to the uncertainty in the point of triggering, a table of chemical shifts observed is not given. For the *trans* mixture an average of about 160 scans were employed using filter 1, and an amplitude setting from 10 to 30. For the *cis* mixture an average of about 130 scans was employed using filter 2 and an amplitude setting from 10 to 30. <sup>b</sup> Each solution was 0.015 *M* in each of the two alcohols present, except in the case of *t*-butyl alcohol and DMSO-*d*<sub>6</sub>, for which 0.025 *M* solutions were used. <sup>c</sup> As can be seen from this table, values obtained using eq iv are in fairly good agreement with those obtained using eq iii. <sup>d</sup> First figures, Table III, footnote *j*; second figure, ref 31. These data were obtained at much higher concentrations (ca. 0.1 *M*). <sup>e</sup> Study carried out at 59°. <sup>f</sup> Estimated value. <sup>o</sup> In isooctane.

constants were obtained making use of the equation<sup>27</sup>

$$K_{eq} = (\delta_{ax} - \delta) / (\delta - \delta_{eq}) \quad (iii)$$

in the usual manner. For the *trans* mixture in *t*-butyl alcohol only a large broad solute peak was observable making it impossible to assign chemical shifts to the individual solute alcohols. For this case eq iv was derived to bypass the difficulty, making use now of the *cis* mixture (to give  $\delta_{ax} - \delta$ ) as well as a mixture of the appropri-

$$K_{eq} = \frac{(\delta_{ax} - \delta) / (\delta_{ax} - \delta_{eq})}{1 - [(\delta_{ax} - \delta) / (\delta_{ax} - \delta_{eq})]} \quad (iv)$$

ately deuterated *cis*- and *trans*-4-*t*-butylcyclohexanols (to give

$\delta_{ax} - \delta_{eq}$ ) The equilibrium constants obtained in this study are presented in Table X.

The equilibrium constants obtained from the study of the deuterated alcohols as a function of concentration in carbon tetrachloride are given in Table XI.

Table XI. Equilibrium Constants Obtained for the Concentration Study of the Deuterated Alcohols in Carbon Tetrachloride

Approx molarity in each alcohol	<i>K</i> <sub>OH</sub> <sup>a</sup>
0.015	2.65
0.075-0.10	2.80
0.15-0.20	3.16
1.5-2.0	3.85 ± 0.10

<sup>a</sup> CAT scans were used to arrive at the first three results, whereas the fourth result was obtained from a normal nmr run and is the average of sweeps to increasing and decreasing field. All scans used TMS as internal standard at a temperature of 41°.

**B. Methoxyl Group.** For the nmr study of the deuterated ethers, 40 mg each of cyclohexyl-2,2,6,6-*d*<sub>4</sub> methyl ether and *cis*-4-*t*-butylcyclohexyl-2,2,6,6-*d*<sub>4</sub> methyl ether, as well as 50 mg of *trans*-4-*t*-butylcyclohexyl-2,2,6,6-*d*<sub>4</sub> methyl ether were dissolved in 0.20 ml of solvent. More of the *trans* ether was employed in making up these solutions since the nmr signal of its hydrogen of interest was broader and weaker than that of the other two components. The solutions used in this study were of relatively high concentration (~1.0 *M*) since solute-solute interactions were of no consequence. The equilibrium constants obtained are given in Table XII. The solvents used were *t*-butyl alcohol (chromatography grade, distilled over calcium hydride), acetone-*d*<sub>6</sub> (99.5% deuterated), nitrobenzene (chromatography grade, dried and redistilled), carbon tetrachloride (spectral grade), cyclohexane (spectral grade), benzene (spectral grade), pyridine (reagent grade, distilled over solid sodium hydroxide), *p*-dioxane (chromatography grade, dried and redistilled), acetonitrile (chromatography grade, dried and redistilled), and chloroform-*d*<sub>1</sub> (99.8% deuterated).

All deuterated solvents were obtained from Diaprep Inc., Atlanta, Ga. Nmr CAT scans of all the solvents employed for the alcohol study were made prior to use, to check the purity of the solvents and to ensure that the signals attributed to the alcohols were not due to impurities in the solvents.

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Table XII. Conformational Equilibrium Constants Derived from the Nmr Study of the Cyclohexyl-2,2,6,6-*d*<sub>4</sub> Methyl Ethers

Solvent	Chemical shifts, cps <sup>a</sup>						Equilibrium constants		
	Increasing field <sup>b</sup>			Decreasing field <sup>b</sup>			Inc field	Dec field	Av K
	<i>trans</i>	<i>cis</i>	Unsubstd	<i>trans</i>	<i>cis</i>	Unsubstd			
Cyclohexane	-175.7	-198.0	-183.9	-174.5	-197.7	-183.0	1.72	1.73	1.73 ± 0.01
CCl <sub>4</sub>	-175.9	-198.7	-184.3	-174.4	-198.0	-182.9	1.71	1.78	1.75 ± 0.04
Nitrobenzene	-175.3	-198.5	-183.4	-176.6	-199.4	-184.4	1.86	1.92	1.89 ± 0.03
<i>p</i> -Dioxane	-177.2	-199.5	-184.5	-176.5	-199.0	-183.8	2.05	2.08	2.07 ± 0.02
DMSO- <i>d</i> <sub>6</sub>	-179.0	-201.4	-186.2	-177.7	-200.1	-185.2	2.11	1.99	2.05 ± 0.06
Acetonitrile	-179.0	-200.9	-184.6	-178.0	-200.5	-184.3	2.91	2.57	2.74 ± 0.17
Chloroform- <i>d</i> <sub>1</sub>	-180.6	-202.9	-187.0	-179.9	-202.2	-186.2	2.48	2.54	2.51 ± 0.03
<i>t</i> -Butyl alcohol	-179.6	-200.8	-185.8	-179.3	-200.6	-185.4	2.42	2.49	2.46 ± 0.04

<sup>a</sup> The chemical shifts are relative to TMS (2% v/v of solvent) at 41°. <sup>b</sup> The values given are the average of a minimum of four sweeps.

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## Electrochemical Behavior of Trifluoromethyl-Substituted Nitrobenzene

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**Abstract:** The electrochemical behavior of *o*- and *m*-trifluoromethylnitrobenzene in *N,N*-dimethylformamide was investigated employing cyclic voltammetric, polarographic, and potentiostatic techniques. These compounds undergo reduction *via* two polarographic steps. The first is a diffusion-controlled, one-electron transfer producing a stable anion radical. The second is an ece process producing a trifluoromethyl-substituted nitrosobenzene anion radical. Mass electrolysis experiments show the long-term electrolysis product to be trifluoromethyl-substituted azoxybenzene. Addition of hydroquinone as a source of protons enhances the formation of the nitroso intermediate.

Numerous electron spin resonance studies on the electrochemically generated anion  $\pi$  radicals of substituted nitrobenzenes in aprotic media have been reported.<sup>2-4</sup> The major attention has been focused on the study of anion radicals prepared by the one-electron reduction of the parent molecule. Through these studies a great amount of data has been accumulated on  $\pi$ -electron densities, bonding, and structure. ESR has also proved to be a useful tool in characterizing reactions of nitro-substituted aromatic radical ions in solution.<sup>5,6</sup> However, there are only a very few reported studies on the reduction products of aromatic nitro compounds in which the ESR information is coupled with a complete electrochemical characterization of the system.<sup>7</sup>

In most cases the product of the first reduction step of a nitroaromatic in aprotic solvent is the paramag-

netic monoanion radical of the parent molecule.<sup>3-5</sup> In general, an electron-transfer step occurring at a potential more negative than that necessary to produce the monoanion results in a diamagnetic dianion or electroinactive products produced by subsequent chemical reactions of the dianion. Paramagnetic species produced at reduction potentials more negative than the second polarographic half-wave potential have been reported in a few cases.<sup>6,7</sup> Rogers and Watson have observed the ESR spectrum of a paramagnetic species generated from 2-trifluoromethylnitrobenzene in *N,N*-dimethylformamide (DMF) at a potential corresponding to the second polarographic reduction wave of the parent compound.<sup>8</sup> This system proved to be particularly interesting since *in situ* controlled-potential reduction of 2-trifluoromethylnitrobenzene in dry DMF at -2.0 V vs. saturated calomel electrode (sce) produced species yielding an ESR spectrum characteristic of a combination of the hyperfine splittings of the anion radical and a second paramagnetic substance. Although loss, or decrease, in coupling to the <sup>14</sup>N nucleus was reported, the exact nature of the high potential reduction product was not determined.

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