Conformational Analysis. XXVII. Solvent Effects in Conformational Equilibria of Heterosubstituted 1,3-Dioxanes[1]

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Abstract: The position of equilibrium between the *cis*- and *trans*-2-isopropyl-5-methoxy- and -5-ethoxy-1,3-dioxanes has been determined in 17 different solvents. In general, solvents of higher dielectric constant shift the equilibrium toward the (more dipolar) axial isomers. Benzene, toluene (but not *tert*-butylbenzene or mesitylene), chloroform, methylene chloride, and methanol behave as more polar solvents in this regard than their dielectric constants would lead one to predict. Possible reasons are discussed. The free energy changes ($\Delta G°$) associated with the above equilibria and some others are plotted against the solvent parameter $E_T(30)$; good straight-line correlations are obtained except for the above-mentioned solvents. Logarithms of rates of quaternization of tertiary amines correlate better with $\Delta G°$ than with $E_T(30)$.

In a previous paper[3] we have discussed acid-catalyzed equilibria of the type shown in Scheme I for X = F, Cl, Br, and OCH_3 in various solvents. It proved possible to predict the variations of $\Delta G°$ with solvent by a treatment[4a] based on Onsager reaction field theory[4b] for the solvents carbon tetrachloride, diethyl ether, chloroform, and acetonitrile, although ether and chloroform gave mediocre agreement in the case of the 5-methoxy compound. No agreement between calculated and observed $\Delta G°$ was obtained in solvent benzene for any of the four substituents. Benzene, in all cases, behaved as if its effective dielectric constant were considerably larger than the bulk dielectric constant of 2.2.

Scheme I

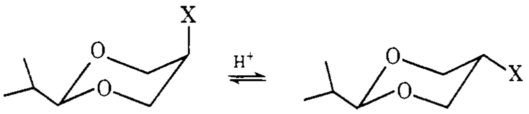

Table I. Equilibria (Scheme I) for X = OCH_3 and OC_2H_5 in Relation to Solvent Parameters

Solvent	ϵ_{20}	$E_T(30)$	$-\Delta G°_{OCH_3}$	$-\Delta G°_{OC_2H_5}$
n-Hexane	1.9	30.9	1.06	1.24
Cyclohexane	2.0	31.2	1.03	1.23
CCl_4	2.24	32.5	0.90	1.09
Mesitylene	2.28	33.1	0.87	1.12
tert-Butylbenzene	2.38	33.7	0.83	1.01
Toluene	2.38	33.9	0.71	0.94
Benzene	2.20	34.5	0.59	0.82
Et_2O	4.33	34.6	0.83	1.05
CH_3CCl_3	7.10	36.2	0.58	0.82
Tetrahydrofuran	8.20	37.4	0.65	0.86
$CDCl_3$	4.80	39.0	0.19	0.51
$CHCl_3$	4.81	39.1	0.16	0.51
CH_2Cl_2	9.01	41.1	0.10	0.34
Nitrobenzene	34.8	42.0	0.20	0.38
Me_2CO	21.4	42.2	0.34	0.56
CH_3CN	37.5	46.0	−0.01	0.19
CH_3OH	33.7	55.5	0.03	
Neat			0.66	1.02

We have now studied the equilibrium shown in Scheme I for X = OCH_3 and OC_2H_5 for a much larger number of solvents[5] with the results shown in Table I. Inspection of Table I discloses that, as might be expected for an equilibrium involving compounds of differing dipole moment (that of the axial cis compound is 2.85 D, that of the equatorial trans compound 1.30 D),[3] the isomer with the higher dipole becomes more favored as the dielectric constant of the solvent increases. In fact, in the highest dielectric solvent studied, acetonitrile, $\Delta G°$ is zero, within experimental error, for the methoxy compound and about 0.2 kcal/mol for the ethoxy compound, suggesting that there is no net O···O repulsion in the conformation shown in Figure 1.[6]

Since our efforts to correlate $\Delta G°$ (Table I) with either ϵ, $1/\epsilon$, or the sometimes used function $(\epsilon - 1)/(2\epsilon + 1)$ were unsuccessful,[7] we looked toward other solvent parameter scales. Of the various existing scales,[8] for example, the Winstein–Grunwald Y scale,[9]

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[1] (a) Paper XXVI: E. L. Eliel and R. Enanoza, *J. Amer. Chem. Soc.*, **94**, 8072 (1972); (b) presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 15, 1971.

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[3] R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, *J. Amer. Chem. Soc.*, **94**, 1913 (1972).

[4] (a) R. J. Abraham, L. Cavalli, and K. G. R. Pachler, *Mol. Phys.*, **11**, 471 (1966). The treatment comprises both dipole and quadrupole terms for the solute. (b) L. Onsager, *J. Amer. Chem. Soc.*, **58**, 1486 (1936).

[5] The choice of groups which themselves have rotational conformational isomerism, such as methoxy or ethoxy, is perhaps not wholly felicitous. It was imposed upon us by considerations of synthetic accessibility: the 5-alkoxy compounds are easy to prepare[3] in quantity whereas the corresponding halides are not.

[6] There may actually be a small attraction, for if $\Delta H°$ were zero, the equatorial isomer should be slightly favored by its higher rotameric entropy. There are, presumably, only two populated conformations for axial methoxyl ("Me-out," the "Me-in" conformation being disfavored for steric reasons, *cf.* ref 3) whereas in the equatorial isomer, in addition to the two equally populated enantiomeric rotamers, there will be a third one with a plane of symmetry, albeit probably of low population because of the double C–O–C–C gauche interaction. The slight favoring of the equatorial conformation in the ethoxy compound may be due to extra conformational entropy caused by rotational isomerism about the CH_3–CH_2 bond which may be sterically inhibited in the axial isomer.

[7] Not unexpectedly so; *cf.* K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 385.

[8] For reviews of empirical solvent scales, see: (a) C. Reichardt, *Angew. Chem., Int. Ed. Engl.*, **4**, 29 (1965); (b) C. Reichardt, "Lösungsmittel-Effekte in der organischen Chemie," Verlag Chemie, Weinheim-Bergstr., Germany, 1969, Chapter 7; (c) C. Reichardt and K. Dimroth, *Fortschr. Chem. Forsch.*, **11**, 1 (1968); this review has the most extensive discussion of solvent scales; (d) M. R. J. Dack, *Chem. Brit.*, **6**, 347 (1970); *Chem. Technol.*, 108 (1971); (e) H. F. Herbrandson and F. R. Neufeld, *J. Org. Chem.*, **31**, 1140 (1966).

[9] E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, **70**, 846 (1948).

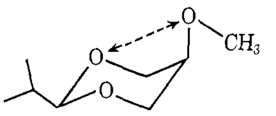

Figure 1. *cis*-5-Methoxy-2-isopropyl-1,3-dioxane.

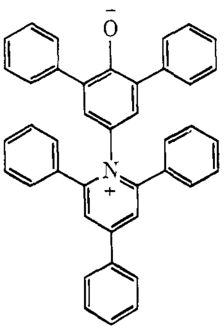

Figure 2. Phenoxypyridinium dye used in $E_T(3)$ determination.

the Kosower Z scale,[10] and the Dimroth–Reichardt $E_T(30)$ scale,[11] the latter has the distinct advantage that parameters for most common solvents are available or can be readily determined.[12] The $E_T(30)$ scale is based on the change in light absorption of the aryl-substituted *p*-phenoxypyridinium dye shown in Figure 2. Because the ground state is stabilized by polar solvents more than the excited state, the energy gap between the two states widens and the dye absorbs at shorter wavelengths (λ) in more polar solvents. $E_T(30)$ is defined as hc/λ in kcal/mol.

Plots of $-\Delta G°$ *vs.* $E_T(30)$ for 5-methoxy- and 5-ethoxy-2-isopropyl-1,3-dioxanes are shown in Figures 3 and 4. (The point for methanol is omitted in Figure 3; it is completely off the plot and to the right of it.) The correlation coefficient is 0.938 for $\Delta G°_{OMe}$ and 0.961 for $\Delta G°_{OEt}$. It is clear from the plot that the data points for benzene and toluene as well as those for chloroform, deuteriochloroform, and methylene chloride are the most deviant. [Omission of these five solvents would improve the correlation coefficients to 0.988 and 0.986, respectively.]

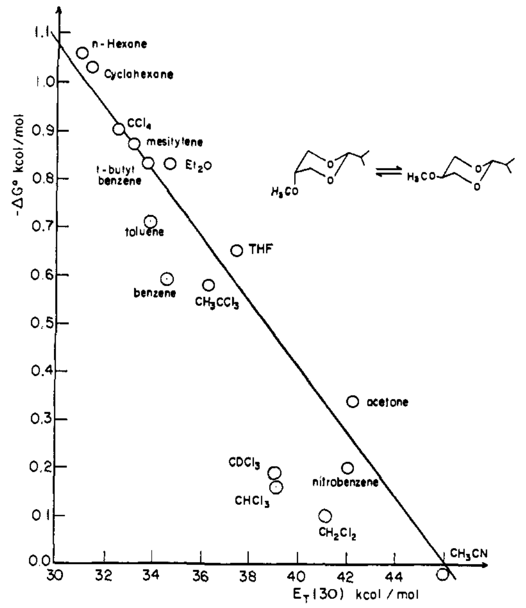

Figure 3. Plot of $-\Delta G°$ for 2-isopropyl-5-methoxy-1,3-dioxane *vs.* $E_T(30)$, $r = 0.938$.

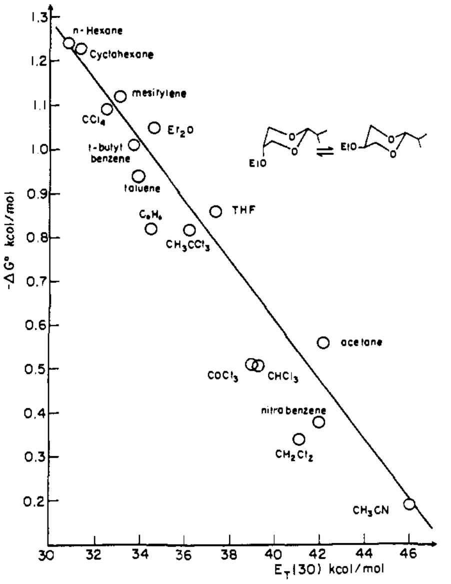

Figure 4. Plot of $-\Delta G°$ for 2-isopropyl-5-methoxy-1,3-dioxane *vs.* $E_T(30)$, $r = 0.961$.

The deviation of the methanol points from straight-line plots is perhaps not surprising, since methanol must function as a strong hydrogen bonding solvent as well as one of relatively high dielectric constant; the two factors combine differently in their effect on light absorption [$E_T(30)$] and conformational equilibria ($\Delta G°$). A two-parameter equation taking separate accounts of these two factors has recently been proposed.[17] The deviation for chloroform might, at first sight, also have been ascribed to specific hydrogen bonding which varies from substituent to substituent. However, we believe such an explanation to be untenable for the following reasons: (1) $\Delta G°$ is the same, within limits of experimental error, for $CHCl_3$ and $CDCl_3$, although the latter is a poorer hydrogen bonding solvent; (2) methylene chloride, CH_2Cl_2, also shows the anomaly although it is a much poorer hydrogen bonding solvent than chloroform; (3) hydrogen bonding should lead to preference of equatorial over axial OCH_3.[18] In fact, however, as is clear from Figures 3 and 4, the equato-

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[10] E. M. Kosower, *J. Amer. Chem. Soc.*, **80**, 3253, 3267 (1958).

[11] K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, **661**, 1 (1963); K. Dimroth and C. Reichardt, *ibid.*, **727**, 93 (1969); C. Reichardt, *ibid.*, **752**, 64 (1971).

[12] Because of the dearth of data for nonpolar solvents in the Z scale, Y scale, log k_{ion} scale,[13] and Ω scale,[14] we did not attempt to correlate our $-\Delta G°$ values with these scales. We did, at the suggestion of Professor Edward M. Arnett, correlate $-\Delta G°$ with the Hildebrand δ parameters[15] (square roots of cohesive energy densities); the correlation is not as good as with $E_T(30)$ but acceptable, whereas an attempted correlation with the "universal" Brownstein S scale[16] was quite poor.

[13] S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Amer. Chem. Soc.*, **83**, 618 (1961).

[14] J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, **84**, 297 (1962).

[15] J. H. Hildebrand and R. L. Scott, "The Solubility of Non-electrolytes," Reinhold, New York, N. Y., 1950, p 419; "Regular Solutions," Prentice-Hall, Englewood Cliffs, N. J., 1962, Appendix 5; see also ref 8e.

[16] S. Brownstein, *Can. J. Chem.*, **38**, 1990 (1960).

[17] F. W. Fowler, A. R. Katritzky, and R. J. D. Rutherford, *J. Chem. Soc. B*, 460 (1971).

[18] E. L. Eliel and E. C. Gilbert, *J. Amer. Chem. Soc.*, **91**, 5487 (1969).

rial isomer is *less* favored in chloroform than the correlation with $E_T(30)$ would have led one to predict. Thus the salient factor cannot be hydrogen bonding[19] but must lie in the fact that chloroform favors the more polar isomer to a greater extent than predicted on the basis of $E_T(30)$ (in other words, chloroform behaves as a "more polar" solvent in the equilibrium of compounds here studied than it does in the transition of the dye on which the $E_T(30)$ scale is based); this despite the fact that $E_T(30)$ of chloroform is already larger than might have been predicted on the basis of its bulk dielectric constant (Table I). The reason must, in some way, lie in the as yet unknown solvent structure of $CHCl_3$; it is, of course, a well-known fact in organic chemistry that chloroform is a much better solvent for highly polar solutes than is diethyl ether, despite the fact that the two solvents have similar dielectric constants.

The situation relating to the aromatic solvents may be analyzed more readily. As seen in Figures 3 and 4, the data points for benzene deviate substantially from the correlation line, those for toluene less so, and the points for mesitylene and *tert*-butylbenzene are right on the line.[21,25] It is generally believed[20,26] that the enhanced "polar nature" of aromatic solvents is due to their ready polarizability by polar solutes; the polarized solvent then stabilizes the polar solute. This explanation is clearly inadequate, since benzene, toluene, *tert*-butylbenzene, and mesitylene all have nearly the same polarizabilities; yet where $-\Delta G°$ (for either methoxy or ethoxydioxane; *cf.* Table I) in mesitylene is nearly the same as in the less polarizable carbon tetrachloride and that in *tert*-butylbenzene is only slightly lower, the values for benzene and toluene are appreciably smaller (all five solvents have nearly the same dielectric constant).[27] Our best hypothesis to explain this nonmonotonic solvent behavior rests on the fact that the polarizability on aromatic solvents is anisotropic, being largely confined to the plane of the aromatic ring. Therefore the orientation of the solvent molecules with respect to the dipole moment of the solute is crucial: only if the solute dipole is parallel to the plane of the nearby solvent molecules can the polarizability of the solvent be fully called into play.[28] Presumably the bulky side chains in mesitylene and *tert*-butylbenzene prevent optimal orientation of these solvents *vis-à-vis* the solute; thus the polarizability of these solvents is not called upon, in contrast to that of benzene. Toluene, with its less bulky side chain, occupies an intermediate position.

Table II. Chemical Shifts in 5-Methoxy-1,3-dioxane (in ppm, δ scale)

Solvent	Cis compd $H_{4,6}$ (ax)	 H_5 (ax)	 OCH_3	Trans compd OCH_3
CCl_4	3.66	2.92	3.33	3.30
Benzene	3.35	2.38	3.05	2.90
Toluene	3.40	2.48	3.09	2.94
Mesitylene	3.40	2.50	3.12	2.98

Attempts were made to correlate the supposedly closer association of benzene (as compared to, say, mesitylene) with solute molecules by investigation of the proton nmr signals of the latter. The results are summarized in Table II; unfortunately, there is no correlation. Whereas in solvent properties mesitylene resembles carbon tetrachloride, while toluene and benzene are increasingly "anomalous," in the effect on nmr spectra the three aromatic solvents are quite similar and all three are substantially different from CCl_4. This may simply be a reflection of the fact that the well-known anisotropy effect of aromatic solvents on proton chemical shifts of solute molecules operates at an appreciably longer distance than the microscopic dielectric effects discussed above. In fact, the trends in the variation in chemical shifts are in the right direction even though the magnitudes of the changes are too small.

That there is no specific, stoichiometric association of benzene with 5-methoxy-2-isopropyl-1,3-dioxane is shown by the data in Table III which gives $-\Delta G°$ values in benzene–carbon tetrachloride mixtures as a function of solvent composition. Had there been a stoichiometric solute–benzene complex, we should have seen a discontinuous change of $-\Delta G°$ after the addition of 1 (or perhaps 2 or 3) molar equiv of benzene to the carbon tetrachloride solvent. In fact, however, $-\Delta G°$ changes smoothly as a function of the mole fractions of the two solvents in the mixture, suggesting that the presence or absence of a benzene molecule in the vicinity of the solute is entirely a matter of statistics.

Table III. Equilibria (Scheme I) for X = OCH_3 and OC_2H_5 in Benzene–Carbon Tetrachloride Mixtures

Mole fraction of benzene in CCl_4	$-\Delta G°_{OCH_3}$	$-\Delta G°_{OC_2H_5}$
0.00	0.90	1.09
0.20	0.85	1.06
0.52	0.74	0.97
0.77	0.67	0.89
1.00	0.59	0.82

Comparison with the Amine Quaternization (Menshutkin) Reaction

One of the more widely studied reactions from the point of view of the effect of solvent on reaction rate is

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(19) The same conclusion had been reached in ref 20 with less extensive experimental support.

(20) M. H. Abraham, *J. Chem. Soc. B*, 299 (1971).

(21) It may be of heuristic interest that "adjustment" of the $E_T(30)$ value for benzene from 34.5 to 37.1 improves not only the correlations shown in Figures 3 and 4 (obviously!) but also brings the $\Delta G°$ values in benzene into line for the equilibration of the 2-isopropyl-5-fluoro-, -5-chloro-, and -5-bromo-1,3-dioxanes discussed earlier.[3] Appropriate plots are shown in Figure 7.[22] The adjusted benzene value also improves the correlation of $\Delta G°$ for 2-methoxy-6-methyloxanes[23,24] with $E_T(30)$ as shown in Figure 8.[22] The corresponding "adjustment" for toluene would be from 33.9 to 35.3.

(22) See paragraph at end of paper regarding supplementary material.

(23) *Cf.* E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968); additional data in solvents chloroform and benzene were obtained in the present investigation; see Experimental Section.

(24) Regarding 2-methoxyoxane itself, see the polarimetric and nmr study by R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe [*Can. J. Chem.*, **47**, 4427 (1969)] in which chloroform also shows strongly deviant behavior.

(25) Similar observations have been made for conformational equilibria of 1,2-dihalocyclohexanes as a function of solvent by D. J. Sikkema, Ph.D. Thesis, University of Leiden, The Netherlands, 1969. We thank Professor E. Havinga for bringing this thesis to our attention.

(26) C. Lassau and J. C. Jungers, *Bull. Soc. Chim. Fr.*, 2878 (1968).

(27) The $E_T(30)$ values in the series carbon tetrachloride–mesitylene–*tert*-butylbenzene–toluene–benzene do rise, but they rise nearly monotonically and thus do not reflect the discontinuously greater solvent power of toluene and benzene.

(28) We are not concerned here with bulk solvent properties; solvent–solute interactions are largely governed by the solvent molecules in the immediate vicinity of the solute.

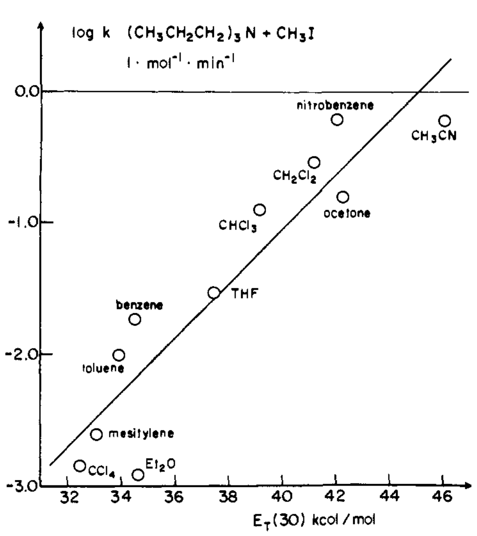


Figure 5. Plot of log k (amine quaternization) *vs.* $E_T(30)$ (data of ref 26), $r = 0.909$, including the data point for cyclohexane (not shown).

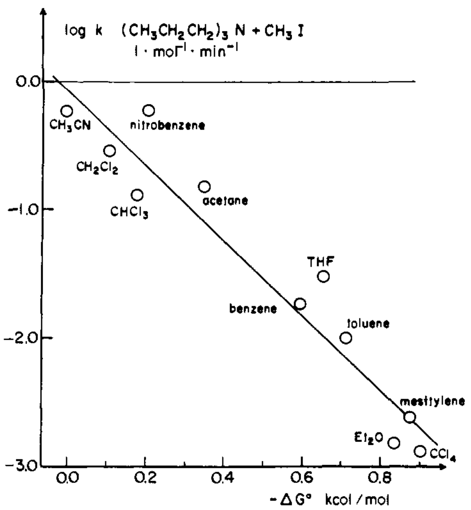


Figure 6. Plot of log k (amine quaternization) *vs.* $-\Delta G°_{OCH_3}$, $r = 0.947$, including the data point for cyclohexane (not shown).

the amine quaternization (Menshutkin) reaction.[29] The reaction of tri-*n*-propylamine with methyl iodide

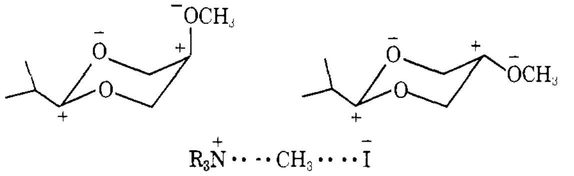
$$(CH_3CH_2CH_2)_3N + CH_3I \longrightarrow (CH_3CH_2CH_2)_3NCH_3{}^+I^-$$

has recently been studied in a wide variety of solvents.[26] The correlation with $E_T(30)$ is only modest,[8c] the correlation coefficient (r) being 0.879. In fact, if one confines oneself to the set of solvents comprised in the present investigation (Table I) for which quaternization data are also available,[26] the correlation becomes very much worse ($r = 0.622$). As it turns out, the poor correlation is largely caused by the data points for methanol and for *n*-hexane. Methanol, as has already been pointed out, cannot be expected to correlate, since its strong hydrogen bonding to the dye (Figure 3) contributes substantially to its high $E_T(30)$ value.[30] In the case of hexane (see below) there is some question on the quality of the Menshutkin data. In fact, elimination of these two solvents improves r to 0.909.

Inspection of the log $k_{\text{quaternization}}$ *vs.* $E_T(30)$ plot (Figure 5) suggests that the correlation is impaired largely by the data points for the aromatic solvents benzene, toluene, and nitrobenzene and the halocarbon solvents chloroform and methylene chloride, *i.e.*, the same solvents which caused difficulty in the $\Delta G°$ *vs.* $E_T(30)$ correlations (Figures 3 and 4). It occurred to us that a better correlation might be obtained by plotting log $k_{\text{quaternization}}$ *vs.* $\Delta G°_{OMe}$; the appropriate plot (omitting points for methanol and *n*-hexane[31]) is shown in Figure 6; indeed, the correlation coefficient, 0.947, is considerably better than that with $E_T(30)$.

The good correlation of rate of quaternization (a reaction involving neutral starting material and a dipolar transition state in which the effect of solvent probably largely asserts itself in the transition state) with conformational equilibria involving two ground states of differing dipole–dipole interaction might, at first sight, seem surprising and even fortuitous. We believe[32] that the rationale lies in the nature of dipole–dipole interaction on the molecular scale; because of the very close proximity of the dipoles, they should more properly be viewed in terms of interactions of charged atoms. Seen in that light, the analogy between the "dipole–dipole interaction" and a charged transition state becomes more plausible, as shown in Scheme II;

Scheme II



both cases involve interaction of (like or unlike) charged atoms over short distances. It must be stressed that for other types of reactions this kind of analogy may not hold and a better correlation may be obtained with $E_T(30)$ rather than $\Delta G°_{OMe}$, or $\Delta G°_{OEt}$ (*cf.* ref 8c). It is in those cases where reaction rates in solvents benzene, toluene, nitrobenzene, chloroform, and methylene chloride are higher than predicted on the basis of the E_T-

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(29) N. Menshutkin, *Z. Phys. Chem.*, **6**, 41 (1890); see also the discussion by E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 2, p 70.

(30) All solvents with $E_T(30)$ values above 47 (the upper limit is 63.1, for water) are hydrogen donors; ref 8a. In a recent correlation of ^{19}F nmr chemical shift in various solvents with $E_T(30)$, the alcohol solvents gave rise to a correlation line different from that for all other solvents: C. S. Giam and J. L. Lyle, *J. Amer. Chem. Soc.*, **95**, 3235 (1973).

(31) The poor correlation of *n*-hexane (and to a lesser extent cyclohexane) for the Menshutkin data caused us some initial concern, since it seemed to suggest that the $-\Delta G°_{OMe}$ *vs.* $-\log k$ correlation might break down in aliphatic hydrocarbons. However, inspection of data for other Menshutkin reactions discloses no particular problem with hydrocarbons. Thus for quaternization of triethylamine with ethyl bromoacetate [Y. Drougard and D. Decroocq, *Bull. Soc. Chim. Fr.*, 2972 (1969)], $r = 0.983$, including the cyclohexane point. For quaternization of *p*-nitrobenzyl chloride with trimethylamine [H. von Halban, *Z. Phys. Chem.*, **84**, 129 (1913)], $r = 0.932$; these data include methanol (which deviates badly) and *n*-hexane (which does not deviate). The less extensive data of H. G. Grimm, H. Ruf, and H. Wolff [*Z. Phys. Chem., Abt. B*, **13**, 301 (1931)] for the reaction of triethylamine with ethyl iodide and those of H. Hartman, H. D. Brauer, and G. Rinck [*Z. Phys. Chem.* (*Frankfurt*), **61**, 47 (1968)] for the same reaction also yield good straight line correlations of log k *vs.* $\Delta G°_{OMe}$; the former series includes *n*-hexane and the latter *n*-heptane. It would appear that there may have been experimental difficulties affecting the quaternization rates in *n*-hexane and possibly cyclohexane reported in ref 26; nevertheless, we chose this particular set of data for illustration because it includes more solvents than any of the other available sets.

(32) *Cf.* E. L. Eliel and S. A. Evans, *J. Amer. Chem. Soc.*, **94**, 8587 (1972).

(30) scale that the existence of a better correlation with $\Delta G^\circ_{\mathrm{OMe}}$ may be suspected, and such a correlation may be useful, from the practical point of view, for predicting the effect of changing solvents on a reaction involving a charged transition state.

Experimental Section

The synthesis and equilibration by means of Amberlyst-15 (beaded polystyrenesulfonic acid) of the 2-isopropyl-5-alkoxy-1,3-dioxanes have been described previously.[3] Plots of $-\Delta G^\circ$ *vs.* E_T (30) were drawn by computer through a least-squares fitting program and correlation coefficients were computed by the standard formula.[33] The 6-methyl-2-methoxyoxanes were prepared and equilibrated as previously described;[18,23] $-\Delta G^\circ$ in carbon tetrachloride was found to be 0.74 kcal/mol (previous values, 0.74[18] and 0.73 kcal/mol[23]). The newly determined values were 0.55 kcal/mol in benzene and 0.46 kcal/mol in chloroform.

Acknowledgments. Financial support of this investigation through award of a postdoctoral fellowship to O. H. by the University of Notre Dame under an National Science Foundation Science Development Grant is gratefully acknowledged. We are greatly indebted to Professor Christian Reichardt for supplying us with an extensive amount of unpublished data and a number of references; both Dr. Reichardt and Professor Edward M. Arnett provided us with much helpful advice. We are thankful to them and also to Professors R. J. Abraham and Kenneth Wiberg for a critical reading of the first draft of the manuscript.

Supplementary Material Available. Figures 7 and 8 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-73-8041.

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(33) Documenta Geigy, Scientific Tables, 1956, p 42.

Stereochemistry of Base-Catalyzed Hydrogen Exchange in Cyclic Sulfonium Salts

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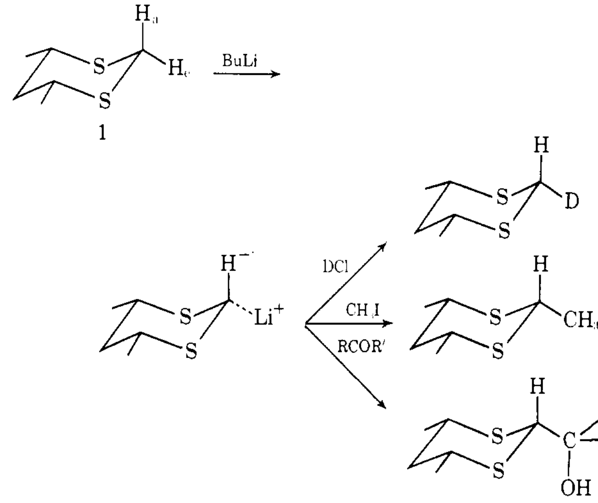
Abstract: The relative rate constants of successive H/D exchange at carbons next to sulfur for the four α-methylene hydrogens in thiacyclohexylmethylsulfonium iodide (**3**) and thiacyclopentylmethylsulfonium iodide (**2**) with sodium deuterioxide in D_2O have been measured. The reactivity ratio for the two pairs of diastereotopic hydrogens in the six-membered ring (**3**) is near 1 : 1 but in the five-membered ring (**2**) it is *ca.* 12 : 1. The corresponding ratio for the two diastereomeric 2-methylthiacyclohexylmethylsulfonium salts **4** and **5** at the methylene carbon is about the same as for the parent compound **3**. The results for the thiacyclohexyl compound **3** agree with those found by others but those for the thiacyclopentyl compound **2** are only in qualitative agreement, the selectivity being less by a factor of over 30 than reported earlier. The findings are discussed in relation to the present status of the gauche effect.

In earlier work[2] we had found a ratio of well over 200 for formation of the equatorial lithium derivative of *cis*-4,6-dimethyl-1,3-dithiane (**1**) over the axial isomer, as gauged by nearly exclusive formation of further transformation products (H/D exchange products,[2] methylation products,[2] carbinol formation[3]) at the equatorial site (Scheme I). However, subsequent work[4] indicated that the high equatorial preference of the lithium derivative is the result of a thermodynamic preference and the difference in rate of abstraction between the equatorial and axial proton at C-2 (kinetic preference) in **1** (k_{H_e}/k_{H_a}) is only by a factor of *ca.* 9.[5]

Scheme I



Our interest in highly stereoselective hydrogen exchanges stemmed from our thinking that such exchanges might possibly be involved in certain highly stereoselective enzyme-catalyzed syntheses of compounds

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(2) A. A. Hartmann and E. L. Eliel, *J. Amer. Chem. Soc.*, **93**, 2572 (1971).

(3) E. L. Eliel and A. A. Hartmann, Abstracts, 165th National Meeting of the American Chemical Society, Dallas, Texas, Apr 1973, No. ORGN-64.

(4) E. L. Eliel, A. Abatjoglou, and A. A. Hartmann, *J. Amer. Chem. Soc.*, **94**, 4786 (1972).

(5) Much more substantial kinetic preferences for diastereotopic hydrogens have been found in a bridged biphenyl-derived sulfoxide [R. R. Fraser and F. J. Schuber, *Chem. Commun.*, 397 (1969); *Can. J. Chem.*, **48**, 633 (1970)] and in benzyl *tert*-butyl sulfoxide: R. Viau and T. Durst, *J. Amer. Chem. Soc.*, **95**, 1346 (1973) (see also ref 19).