Base-catalysed Mutarotation of Glucose in Dimethylformamide and Dimethyl Sulphoxide

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The rate of mutarotation of glucose has been measured in pure dimethylformamide and dimethyl sulphoxide with substituted benzoate ions as catalysts, and in 80 vol % dimethyl sulphoxide–water with acetate and chloroacetate as catalysts. Unlike many other base-catalysed reactions in these solvents, the rates show no subtantial increase over those observed in water. This is interpreted in terms of a strong involvement of water with the transition state in aqueous media, in accordance with earlier suggestions concerning the mechanism of related reactions such as the addition of water and alcohols to carbonyl compounds. In combination with previously reported p*K* values in the appropriate solvents, the results show that there is a good correlation of the catalytic effect of the anion bases with their basic strengths. The observed Brönsted coefficients are slightly higher (β = 0.6 in dimethylformamide and dimethyl sulphoxide) than in water (β = 0.4).

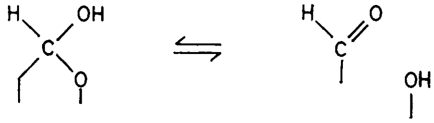
THE solvation of the proton and other ions is of prime importance in determining the position of protolytic equilibria in solution. It can also have a considerable influence on the kinetics of proton transfer reactions.[1] The study of proton transfer reactions in non-aqueous solvents should prove very fruitful in this context, particularly reactions involving anion bases in dipolar aprotic solvents (which cannot act as proton donors). Anions in these solvents are very reactive, and the interpretation of results is frequently more straightforward because of the little specific tendency shown by dipolar aprotic solvents to solvate anions. Valuable insight into the mechanism of a number of reactions, and often results of considerable practical importance, have come from recent kinetic studies in non-aqueous solvents,[2] combined with thermodynamic studies of the properties of ions in the corresponding solvents.[2–6] These latter studies have, in addition, provided many data relevant to the study of proton transfer reactions in non-aqueous solvents.

There are two potentially important sources of information in studies of solvent effects on proton transfer reactions. First, the solvent dependence of the reaction rates can give information on the importance of the changes in solvation which must accompany the redistribution of charge occurring during reaction. Secondly, the variation of substituent effects may help to show the extent to which these are dependent upon solvation. This may have important consequences regarding the interpretation of substituent effects and Brönsted coefficients relating rates and equilibria in terms of the symmetry of transition states, *etc.* This latter point is relevant [7] to the question of anomalous Brönsted coefficients observed for a number of reactions in aqueous solution.[6,8]

The extent to which any resolvation occurring during a reaction precedes or follows other changes (*e.g.* proton transfer) as a system passes along the reaction coordinate has been discussed in some detail recently.[9,10] However, in this context we feel that it is meaningful to distinguish between reactions involving proton transfer to and from oxygen and nitrogen, and those involving proton transfer to and from carbon. In the former case, proton transfer in aqueous solution may involve one or more intervening solvent molecules.[11] In particular, the results of studies of the addition of water to carbonyl compounds of water in non-aquous solvents [12,13] suggest the involvement of several water molecules in the reaction.

In the present paper, we report the results of a study of the mutarotations of glucose, catalysed by substituted benzoate ions in dimethylformamide (DMF) and dimethyl sulphoxide (DMSO). This reaction is related to the addition of water to carbonyl compounds and might be expected to show similar involvement of the solvent in aqueous media. It can, however, be studied under anhydrous conditions, as a water molecule is not formally involved in the stoicheiometry.

The reaction has been studied in considerable detail in aqueous solution,[14] and it has been shown that the interconversion of the cyclic epimers α- and β-glucose takes place through the open-chain aldehydic form. The mutarotation process thus involves the breaking and



re-forming of a hemiacetal link, and has been shown to be subject to general acid–base catalysis.[14] A recent

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[2] A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

[3] B. G. Cox, *Ann. Reports* (*A*), 1973, 249.

[4] I. M. Kolthoff and M. K. Chantooni, *J. Amer. Chem. Soc.*, 1971, **93**, 3843.

[5] E. M. Arnett, D. E. Johnston, L. E. Small, and D. Oancea, *Chem. Soc. Faraday Symposium*, 1975, **10**, 20.

[6] F. G. Bordwell, *Chem. Soc. Faraday Symposium*, 1975, **10**, 100.

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[8] R. P. Bell and S. Grainger, *J.C.S. Perkin II*, 1976, 1367.

[9] See particularly contributions by W. J. Albery, R. A. Marcus, and M. M. Kreevoy in ref. 1.

[10] R. P. Bell and P. E. Sørensen, *J.C.S. Perkin II*, 1976, 1594.

[11] R. P. Bell, *Chem. Soc. Faraday Symposium*, 1975, **10**, 7.

[12] R. P. Bell, J. F. Millington, and J. M. Pink, *Proc. Roy. Soc. A*, 1968, **303**, 1.

[13] R. P. Bell and P. E. Sørensen, *J.C.S. Perkin II*, 1972, 1740.

[14] R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London 1973, 2nd edn., ch. 9.

[15] N. M. Ballash and E. B. Robertson, *Canad. J. Chem.*, 1973, **51**, 558.

study[15] has shown that the reaction proceeds smoothly in DMSO, with the equilibrium constant between the α- and β-forms being the same, within experimental error, as in water.

EXPERIMENTAL AND RESULTS

Materials.—Tetraethylammonium salts of the following acids were prepared by neutralising an ethanolic solution of the acid with aqueous tetraethylammonium hydroxide:[4,16] 3,4-dimethylbenzoic, benzoic, *m*-bromobenzoic, 3,4-dichlorobenzoic, *p*-nitrobenzoic, 4-chloro-3-nitrobenzoic, 3,5-dinitrobenzoic. The salts were purified by recrystallization from ethyl acetate–ethanol. Potentiometric titration of the salts against perchloric acid showed a purity of $\geqslant 99\%$.

DMSO was dried (CaH_2) and distilled under reduced pressure. DMF was passed through a column of basic alumina, purged with nitrogen for 24 h, and fractionally distilled.[17] All other materials were commercial samples used without further purification.

Kinetic Measurements.—The change in rotation at 436 or 537 nm was followed with a Perkin-Elmer 141 digital polarimeter. Reactions were followed for between two and four half-lives and the first-order rate constants were determined by using a program based on the general least-squares program LETAGROP VRID of Sillén.[18]

All reactions were carried out at 25($\pm$0.2) °C.

Reactions in Dimethyl Sulphoxide.—The rate of the base-catalysed mutarotation of glucose was measured in 80 vol % DMSO–H_2O mixtures with acetate and chloroacetate as catalysts, and in pure DMSO with several substituted benzoates as catalysts. Glucose concentrations were *ca.* 0.05 mol dm^{-3} and base concentrations in the range 0.01—0.20 mol dm^{-3}. The reaction is subject to both acid and base catalysis, but in the present work buffers were prepared with buffer ratios ($[B^-]/[BH]$, where B^- and BH refer to the basic and acidic forms of the catalysts) such that catalysis by BH was negligible. Under these conditions, the observed first-order rate constant, k_e, is given by equation (1).

$$k_e = k_0 + k_B[B] \qquad (1)$$

The results for the reactions in 80% DMSO–H_2O are given in Table 1 and those for reactions in pure DMSO in Table 2. Included with the results are values of k_e calculated from equation (1) using values of k_0 and k_B listed in the Tables. The catalytic constants for catalysis by acetate and chloroacetate (80 vol % DMSO–H_2O) and benzoate (pure DMSO) may be compared with the following values obtained in aqueous solution[19] (18 °C):

chloroacetate: $k_B = 2.07 \times 10^{-4}$ mol^{-1} dm^3 s^{-1}
benzoate: $k_B = 5.8 \times 10^{-4}$ mol^{-1} dm^3 s^{-1}
acetate: $k_B = 70.2 \times 10^{-4}$ mol^{-1} dm^3 s^{-1}

TABLE 1

Base-catalysed mutarotation of glucose in 80% DMSO–H_2O at 25 °C

(i) Acetate: $10^4k_B = 46.4$ mol^{-1} dm^3 s^{-1}; pK_a = 8.00 [a]

$10^2[B]$/mol dm^{-3}	1.6	3.2	4.8	6.4	8.0
10^4k_e/s^{-1} (obs.)	0.768	1.54	2.23	3.00	3.66
10^4k_e/s^{-1} (calc.) [b]	0.752	1.50	2.24	2.98	3.72

(ii) Chloroacetate: $10^4k_B = 2.50$ mol^{-1} dm^3 s^{-1}; pK_a = 5.66 [a]

$10^2[B]$/mol dm^{-3}	3.2	6.4	9.6	12.8	16.0
10^5k_e/s^{-1} (obs.)	0.87	1.71	2.52	3.20	4.16
10^5k_e/s^{-1} (calc.) [b]	0.89	1.69	2.49	3.29	4.09

[a] E. H. Baughman and M. M. Kreevoy, *J. Phys. Chem.*, 1974, **78**, 421. [b] Calculated from $k_e = 0.9 \times 10^{-6} + k_B[B]$.

TABLE 2

Base-catalysed mutarotation of glucose in dimethyl sulphoxide at 25 °C

(i) 3,4-Dimethylbenzoate: $10^5k_B = 162$ mol^{-1} dm^3 s^{-1}; pK_a = 11.4 [a]

[B]/mol dm^{-3}	0.011 4	0.022 7	0.034 1	0.045 5	0.056 7
10^5k_e/s^{-1} (obs.)	2.26	4.56	5.43	7.41	9.13
10^5k_e/s^{-1} (calc.) [b]	2.02	3.86	5.70	7.55	9.36

(ii) Benzoate: $10^5k_B = 102$ mol^{-1} dm^3 s^{-1}; pK_a = 11.0 [a]

[B]/mol dm^{-3}	0.009 87	0.019 7	0.029 6	0.039 4	0.049 4
10^5k_e/s^{-1} (obs.)	1.20	2.27	3.26	4.05	5.24
10^5k_e/s^{-1} (calc.) [b]	1.19	2.19	3.20	4.20	5.22

(iii) *m*-Bromobenzoate: $10^5k_B = 31.8$ mol^{-1} dm^3 s^{-1}; pK_a = 9.7 [a]

[B]/mol dm^{-3}	0.043 7	0.091 5	0.131	0.146	0.183
10^5k_e/s^{-1} (obs.)	2.03	2.94	4.53	4.82	5.36
10^5k_e/s^{-1} (calc.) [b]	1.57	3.09	4.34	4.82	6.00

(iv) 3,4-Dichlorobenzoate: $10^5k_B = 7.50$ mol^{-1} dm^3 s^{-1}; pK_a = 9.2 [a]

[B]/mol dm^{-3}	0.032 2	0.125	0.166	0.201
10^5k_e/s^{-1} (obs.)	0.81	1.06	1.48	1.65
10^5k_e/s^{-1} (calc.) [b]	0.80	1.12	1.43	1.69

(v) *p*-Nitrobenzoate: $10^5k_B = 5.9$ mol^{-1} dm^3 s^{-1}; pK_a = 9.0 [a]

[B]/mol dm^{-3}	0.04	0.08	0.12	0.16	0.20
10^5k_e/s^{-1} (obs.)	0.38	0.55	0.95	1.22	1.26
10^5k_e/s^{-1} (calc.) [b]	0.41	0.65	0.89	1.12	1.36

[a] Ref. 4. [b] Calculated from $k_e = 0.18 \times 10^{-5} + k_B[B]$.

Reactions in Dimethylformamide.—The rate of the mutarotation reaction was measured in pure DMF, with substituted benzoates as catalysts. Buffer ratios were again such that catalysis by the corresponding benzoic acid was negligible. At low base concentrations the reactions were of the first order, with the observed first-order rate constant being given by equation (1). At higher base concentrations, depending upon the basicity of the anion, there was evidence of specific interactions between the base and glucose. Thus there was a non-linear dependence of k_e upon [B], the overall equilibrium constant for interconversion of α- and β-glucose (as measured by the change in rotation) varied with the concentration of base present, and the observed first-order rate constants also depended upon the total glucose concentration. This could be explained in terms of H-bond formation between glucose and the benzoate anions. Similar phenomena involving H-bonding between carboxylate anions and neutral molecules containing acidic protons have been observed frequently in dipolar aprotic solvents.[4,20,21] Evidence for the presence of small amounts (*ca.* 2%) of glucofuranose in solutions of glucose in pure DMF has recently been reported,[22] and it is also possible that substantial increases in

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[16] I. M. Kolthoff and M. K Chantooni, *J. Phys. Chem.*, 1966, **70**, 856.

[17] N. S. Moe, *Acta Chem. Scand.*, 1967, **21**, 1389.

[18] L. G. Sillén, *Acta Chem. Scand.*, 1962, **16**, 159; 1964, **18**, 1085.

[19] J. N. Brönsted and E. A. Guggenheim, *J. Amer. Chem. Soc.*, 1927, **49**, 2554.

[20] O. Vilkane and J. Songstad, *Acta Chem. Scand.*, 1973, **95**, 4768.

[21] M. K. Chantooni and I. M. Kolthoff, *J. Phys. Chem.*, 1973, **77**, 527.

[22] A. Reine, J. A. Hveding, O. Kjolberg, and O. Westbye, *Acta Chem. Scand.*, 1974, **B28**, 690.

its concentration in the more concentrated base solutions could account for the observed behaviour. The results reported (Table 3) refer to rates obtained at low base concentrations, where the rate constants were independent of the glucose concentration, and the equilibrium constant was independent of the added base. Also in Table 3 are values of k_e calculated from equation (1) using values of k_0 and k_B listed.

TABLE 3

Base-catalysed mutarotation of glucose in dimethylformamide at 25 °C

(i) 3,4-Dimethylbenzoate: 10^4k_B = 161 mol^{-1} dm^3 s^{-1}; pK_a = 13.0 [a]					
10^2[B]/mol dm^{-3}	0.249	0.499	0.748	0.759	0.998
10^5k_e/s^{-1} (obs.)	5.00	8.52	12.0	12.3	17.0
10^5k_e/s^{-1} (calc.) [b]	4.64	8.66	12.7	12.8	16.7
10^2[B]/mol dm^{-3}	1.01	1.12			
10^5k_e/s^{-1}(obs.)	15.8	17.3			
10^1k_e/s^{-1}(calc.) [b]	16.9	18.6			
(ii) Benzoate: 10^4k_B = 83.7 mol^{-1} dm^3 s^{-1}; pK_a = 12.3 [a]					
10^2[B]/mol dm^{-3}	0.299	0.395	0.599	0.790	0.900
10^5k_e/s^{-1} (obs.)	3.65	4.22	5.98	6.70	7.79
10^5k_e/s^{-1} (calc.) [b]	3.13	3.94	5.64	7.24	8.14
(iii) *m*-Bromobenzoate: 10^4k_B = 24.3 mol^{-1} dm^3 s^{-1}; pK_a = 11.3 [a]					
10^2[B]/mol dm^{-3}	0.54	1.08	1.62	1.98	2.16
10^5k_e/s^{-1} (obs.)	1.77	2.83	4.76	5.51	5.74
10^5k_e/s^{-1} (calc.) [b]	1.94	3.25	4.57	5.44	5.88
(iv) *p*-Nitrobenzoate: 10^4k_B = 10.2 mol^{-1} dm^3 s^{-1}; pK_a = 10.6 [a]					
10^2[B]/mol dm^{-3}	0.88	1.10	1.80	2.20	3.40
10^5k_e/s^{-1} (obs.)	1.42	1.82	2.13	3.08	4.63
10^5k_e/s^{-1} (calc.) [b]	1.53	1.76	2.47	2.88	4.12
10^2[B]/mol.dm^{-3}	3.60	3.60			
10^5k_e/s^{-1} (obs).	4.00	4.26			
10^5k_e/s^{-1} (calc.) [b]	4.31	4.31			
(v) 4-Chloro-3-nitrobenzoate: 10^4k_B = 3.51 mol^{-1} dm^3 s^{-1}; pK_a = 10.0 [a]					
10^2[B]/mol dm^{-3}	2.00	4.00	6.00	8.00	10.00
10^5k_e/s^{-1} (obs.)	1.30	2.18	2.76	3.22	4.32
10^5k_e/s^{-1} (calc.) [b]	1.33	2.03	2.74	3.44	4.14
(vi) 3,5-Dinitrobenzoate: 10^4k_B = 0.85 mol^{-1} dm^3 s^{-1}; pK_a = 8.9 [a]					
10^2[B]/mol dm^{-3}	3.66	7.33	11.0	14.6	
10^5k_e/s^{-1} (obs.)	0.72	1.38	1.49	1.90	
10^5k_e/s^{-1} (calc.) [b]	0.94	1.26	1.57	1.88	

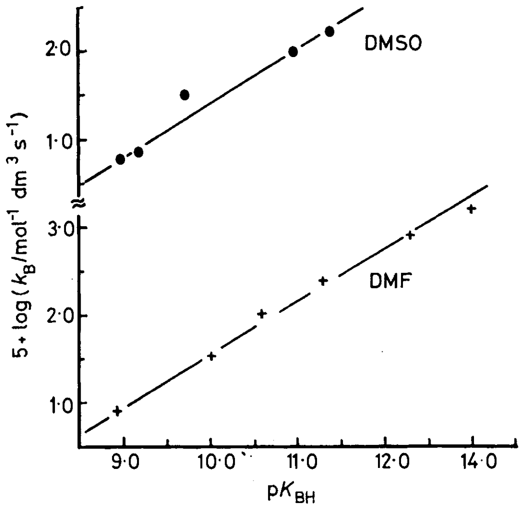
[a] Ref. 4. [b] Calculated from $k_e = 0.63 \times 10^{-5} + k_B[B]$.

The Figure shows the Brönsted plots [equation (2)] obtained for the reactions in DMSO and DMF, in which log k_B is plotted against the acidity constant, pK_{BH}, of the catalyst in the corresponding solvent. For clarity, the two plots, which are practically coincident, have been separated in the Figure.

$$\log k_B = \beta \mathrm{p}K_{BH} + \text{const.} \qquad (2)$$

DISCUSSION

Comparison of the results in Tables 1—3 with earlier results for reactions in water [19] shows that there is almost no rate increase on going from water to DMSO or DMF as solvent. Thus for catalysis by benzoate, the catalytic constant in DMSO is approximately equal to that in water (allowing for the small temperature difference), and that in DMF is *ca.* eight times larger. This is in sharp contrast with the results of earlier studies involving anionic bases or nucleophiles in dipolar aprotic solvents, where for anions such as Cl^-, Br^-, and N_3^- rate increases of *ca.* 10^6 fold (*i.e.* decreases in $\Delta G^\ddagger$ of *ca.* 8 kcal mol^{-1}) have been commonly observed,[2] particularly with DMF as solvent. Similar kinetic studies involving transfer to pure aprotic solvents have not been reported for reactions involving acetate or benzoate ions, but thermodynamic studies on sparingly soluble acetate and benzoate salts [23] have shown that the free energy change (ΔG_{tr}) on transfer of benzoate from water to DMSO or DMF is the same as that for chloride ions, and that of acetate is considerably higher (*e.g.* 4.5 kcal mol^{-1} more positive for transfer to DMF). In addition, results obtained in DMSO-H_2O [24] show considerable rate enhancements for the deprotonation of carbon acids by acetate in DMSO-rich mixtures, *e.g. ca.* 10^4 fold in 95 vol % DMSO for the reaction between acetate and 2-nitropropane. Such results suggest that for these reactions substantial desolvation of the base is required on forming the transition state in aqueous solution.



Brönsted plots for the mutarotation of glucose in dimethyl sulphoxide (●) and dimethylformamide (+). The points, from the left, correspond to the following bases: DMSO–*p*-nitrobenzoate, 3,4-dichlorobenzoate, *m*-bromobenzoate, benzoate, 3,4-dimethylbenzoate; DMF–3,5-dinitrobenzoate, 4-chloro-3-nitrobenzoate, *p*-nitrobenzoate, *m*-bromobenzoate, benzoate, 3,4-dimethylbenzoate

In view of all this, our results may seem surprising, but they can, however, be understood in terms of current ideas concerning the addition of water and alcohols to carbonyl compounds. A reasonable mechanism for the conversion of α- or β-glucose into the open-chain form, involving two successive proton transfers, is shown in the Scheme. However, it was pointed out by Eigen [25] that the observed rates in some related systems imply

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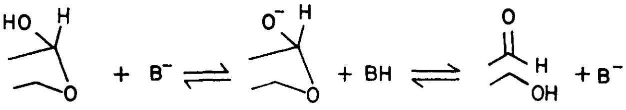
[23] I. M. Kolthoff and M. K. Chantooni, *J. Phys. Chem.*, 1972, **76**, 2024.

[24] B. G. Cox and A. Gibson, *J.C.S. Perkin II*, 1977, in the press.

[25] M. Eigen, *Discuss. Faraday Soc.*, 1965, **39**, 7.

individual rate constants in excess of the diffusion-controlled limit. He proposed a ' one-encounter ' mechanism for such reactions, in which the two proton transfers take place within a single encounter, presumably assisted by H-bonded water molecules. The high reaction orders with respect to water and methanol for addition to aldehydes in inert solvents found by Bell and his co-workers [12,13,26] indicate a strong involvement of these molecules in the reaction, and support this view. If the required proton transfers occurring during the mutarotation in aqueous solution can take place *via* H-bonded water molecules, there need be no substantial desolvation of the base on forming the transition state, in contrast to reactions involving nucleophilic substitution by anions or proton transfer from carbon acids. Thus, in dipolar aprotic solvents, while the reactivity of the base should be much higher than in aqueous solution, there is no possibility of assistance in the proton transfers by H-bonded water molecules (or other H-bond donors), and this could account for the lack of any significant increase in the overall rate.



SCHEME

A more quantitative indication of the extent of the stabilization of the transition state in aqueous solution, resulting from interaction with water molecules, may be obtained from a consideration of the free energy changes (ΔG_{tr}) accompanying the transfer of the various species to DMSO or DMF. The transfer of glucose should involve little change in free energy. Results for the transfer of a variety of non-electrolytes from water to DMSO [3,27] show ΔG_{tr} values ranging from *ca.* 3 kcal mol^{-1} for solutes such as trimethyl phosphate which interact strongly with water, to *ca.* 0 to -1 kcal mol^{-1} for polar solutes such as acetone, and -4 kcal mol^{-1} for benzene. Glucose, which can interact quite favourably with DMSO, DMF, and H_2O *via* H-bonding, should fall within this range. The change in free energy for the transition state should then be of the same order as that for the benzoate ions. The application of reasonable extrathermodynamic assumptions [3] to the free energies of transfer of electrolytes from aqueous to dipolar aprotic solvents suggests that ΔG_{tr} (benzoate) values for transfer to DMSO and DMF are *ca.* 9 and 10.5 kcal mol^{-1}, respectively. Thus the transition state for the mutarotation in dipolar aprotic solvents has a substantially higher energy than that in aqueous solution. The present results then provide evidence of a strong involvement of water molecules with the transition state in aqueous media. This, of course, need not necessarily be *via* a ' one-encounter ' H-bonded transition state; indeed our results show that the reaction occurs quite readily in anhydrous DMF and DMSO, where such a transition state is not possible.

Recently Bell and Sørensen [10] have suggested, on the basis of substituent effects and enthalpy data, that addition of hydroxide ions to benzaldehyde requires very little solvent reorganization on forming the transition state. Extrapolation of our results suggests that the transfer of the reaction to aprotic solvents should lead to only small increases in the rate of addition of hydroxide, despite the known very high activity of hydroxide in such solvents.

The Figure shows that the catalytic constants in DMF and DMSO correlate very well with the pK_a values of the respective benzoic acids. The only exception is *m*-bromobenzoate in DMSO, which deviates substantially from the line joining the points for the other four bases. There is no obvious reason for this, and it may be that the deviation is a result of an error in either the determination of the pK_a or the catalytic constant. The observed slopes correspond to β values of 0.61 in DMSO and 0.59 in DMF, which may be compared with a value of 0.40 for the reaction in water.[19] The catalytic constants for acetate and chloroacetate in 80 vol % DMSO–H_2O correspond to $\beta = 0.51$.

We have earlier argued [7] that solvation effects can play an important role in determining Brönsted coefficients, because charges are, in general, considerably more dispersed in the transition state than in the reactants (for reactions of the charge type considered here). Similar considerations apply to the relationship between H-bonding and proton-transfer equilibria, as discussed recently by Arnett and his co-workers.[28] In particular, Bronsted coefficients will be considerably reduced, and may even be less than zero, for reactions in which there are considerably stronger specific interactions between the solvent and *reactants*, than between the solvent and transition state, *e.g.* proton transfer from a carbon acid to a series of carboxylate anions in water. The transfer of such reactions from water to dipolar aprotic solvents has, as expected, resulted in a considerable increase in the observed β values.[7] The relatively small increase in β observed here on transfer to DMSO and DMF could be interpreted along similar lines, but the undoubtedly strong interactions between the transition state and the solvent make any detailed interpretation difficult.

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[7/729 *Received, 2nd May,* 1977]

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[26] R. P. Bell and D. G. Horne, *J.C.S. Perkin II*, 1972, 1371.

[27] B. G. Cox, *J. Chem. Soc.*, 1973, 607.

[28] E. M. Arnett, E. J. Mitchell, and T. S. S. R. Murty, *J. Amer. Chem. Soc.*, 1974, **96**, 3875.