Water-catalysed Mutarotation of Glucose and Tetramethylglucose in Dioxan, Acetonitrile, and Dimethyl Sulphoxide

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We have studied the mutarotation of glucose and 2,3,4,6-tetra-*O*-methylglucose in mixtures of water and the organic solvents 1,4-dioxan, acetonitrile, and dimethyl sulphoxide at 303.2 K. At high water concentration the reaction orders with respect to water are about two for all the solvents. For low ($\lesssim$11 M) water concentration this reaction order decreases to about one for dioxan and acetonitrile, whereas it increases to about 3.7 for dimethyl sulphoxide. This behaviour parallels a decrease and an increase, respectively, in both the activation energy and the activation entropy for the two groups of solvents. On the basis of information about the properties of the mixed solvents and predictions of modern quantum theories of proton transfer reactions in polar media the data are shown to be compatible with concerted proton transfer *via* the water catalyst molecules.

A SUBSTANTIAL amount of evidence suggests that co-operative elementary proton transfer reactions constitute the key steps in a variety of different processes. This relates to electrical and spectroscopic properties of hydrogen-bonded materials,[1] the action of hydrolytic enzymes such as α-chymotrypsin,[2] introduction of coding errors during DNA replication,[3] and to many hydration, isomerization, polymerization, and hydrolysis reactions

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undergoing tautomeric catalysis.[4] Conclusions about the concerted or stepwise nature of the coupled elementary proton transfer reactions in tautomerically catalysed processes are usually based on (a) the role of the acidity or basicity of the catalyst and (b) a comparative analysis of activation parameters in tautomeric and in general acid–base catalysis. It has recently been possible to supplement such an analysis with deductions based on new theories of multiphonon radiationless transitions adapted to electron and proton transfer reactions.[5] Along such lines studies of the water-assisted keto–enol conversion reactions [5] in aprotic solvents have given reasonably unambiguous conclusions as to the nature of the elementary proton transfer steps, and similar conclusions can be drawn for carbonyl hydration reactions.

TABLE 1

Solvent mixture (sugar)		Concentration range		Number of different concentrations	T/K	Ref.
Water–methanol	(G)	100—0	wt% H_2O	11	298.2	17
Water–methanol	(G)	100—0.5	wt % H_2O	22		
	(TMG)	100—0.9		9		
Water–methanol	(G)	100—50.2	wt % H_2O	11	293.2	18
	(TMG)	100—0		9		
Water–pyridine	(G)	100—0	wt % H_2O	12	293.2	19
	(TMG)	100—0		14		
Water–ethanol	(G)	100—0	wt % H_2O	7	298.2	20
Water–dioxan	(G)	95.3—0	wt % dioxan	9	298.2	21, 23*a*
Water–methanol	(G)	75.2—0	wt % MeOH	3	308.2	22
		75.0—0		3	318.2	
Water–dimethylformamide	(G)	54.3—23.1	C_{H_2O} mol dm^{-3}	5	293.2	
		54.2—22.9		5	303.2	23*a*
		54.0—22.7		5	313.2	
Water–DMSO	(G)	0—0.298	X_{DMSO}	2	288.2	24
		0—0.992		8	297.9	
		0—0.992		7	308.3	
		0.298—0.992		5	317.6	

Since hydroxylic solvents which possess both proton donor and acceptor properties also frequently seem to be reactants in proton transfer reactions by providing a low-energy reaction channel for the proton transmission,[5,6] we have found it desirable to extend such investigations to other systems. In this context the mutarotation of glucose and other cyclic sugars has special interest, since there is good evidence for tautomeric catalysis in non-aqueous solvents by various molecular species which are both proton donors and acceptors (bifunctional catalysis).[4,7-12] Moreover, the reaction involves intramolecular hemiacetal formation associated with ring opening and closure which is similar to the carbonyl addition reactions.

Although other mechanisms have been proposed,[13] practically all experimental evidence suggests that the anomerization process proceeds through an intermediate state represented by an acyclic carbonyl compound [14] [reaction (1) where α and β are the two anomeric forms,

$$\alpha \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \gamma \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} \beta \qquad (1)$$

and γ the acyclic intermediate, and where furthermore k_{12}, $k_{32} \ll k_{21}$, k_{23} [15]]. The acyclic intermediate might also exist in several conformational states,[7] but since no direct experimental evidence has been reported that conformational relaxation between such states constitute independent elementary reactions we shall only consider the overall scheme [reaction (1)] in the following.

We report here the results of experimental studies of the water-catalysed mutarotation of glucose (G) and

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2,3,4,6-tetra-*O*-methylglucose (TMG) in the aprotic solvents dioxan (DO), acetonitrile (AN), and dimethyl sulphoxide (DMSO). These studies relate to the following aspects of tautomeric catalysis. (a) Water and oligomeric water aggregates are potential bifunctional catalyst groups for coupled proton transfer reactions and seem to be generally representative of hydroxylic solvents in this respect.[6] (b) Several previous investigations of the mutarotation of G or TMG in water-containing organic solvents have been reported (Table 1). However, generally only qualitative conclusions can be drawn from these reports. This is because (1) in a number of cases both solvent components are bifunctional catalysts, and their effects on the reaction impossible to separate (water–methanol and water–ethanol mixtures); (2) a reaction order with respect to water is not reported, except in two studies of the reaction in water–dimethylformamide (DMF) [23] and water–DMSO [24] mixtures; (3) generally, no data for the activation parameters are reported. (c) We have measured both reaction orders with respect to water and activation parameters for the mutarotation of G in three different ' inert ' solvents of widely different dielectric properties (DO, ε 2.21; AN, 37.5; DMSO, 48.9, where ε is the static dielectric permittivity). (d) The experimental data have been analysed on the basis of recent adaptions of the quantum theory of multiphonon radiationless electronic transitions to reactions involving step-wise and coupled proton transfer reactions.[25,26]

EXPERIMENTAL

Materials.—Dioxan (technical; BASF) was purified and stored according to procedures described earlier.[16] DMSO (purum; Fluka) was distilled *in vacuo* from calcium hydride shortly before use, and the middle fraction collected. AN (uvasol; Merck) was used without further purification. Doubly distilled water, free of carbon dioxide, was used throughout.

α-D-Glucose (AnalaR; B.D.H., with equilibrium specific optical rotation in water, $\alpha_D^{20} = +52.5$—$53.0°$) and β-D-glucose (Sigma) were used without further purification. TMG was synthesized by the procedure described by West and Holden.[27] The equilibrium optical rotation of the product in water was +79.4° compared with +81.3° reported by these authors. A subsequent sublimation *in vacuo* gave a product for which $\alpha_D^{20} = +79.8°$. A kinetic experiment showed that the crystalline form of this product was almost totally equilibrated. To increase the amount of the α-form the substance was treated in a Soxhlet apparatus with light petroleum (Petri; b.p. <50 °C, distilled from a spinning band column). The resulting product now contained 78% of the α-form (see below) which allowed a sufficiently accurate determination of the rate of anomerization. The melting temperature range was 73—84 °C, and the C and H content was found to be 50.75 and 8.55%, respectively (calc. for $C_{10}H_{20}O_6$: C, 50.85; H, 8.45%). The product was stored *in vacuo* over silica gel.

Equilibrium Constants.—The equilibrium constants of the overall process, K_α, are given by equation (2) where $|\alpha|_\alpha$ and

$$K_\alpha = (|\alpha|_\alpha - |\alpha|_\infty)/(|\alpha|_\infty - |\alpha|_\beta) \qquad (2)$$

$|\alpha|_\beta$ are the specific rotations of the pure α- and β-form, respectively, under the appropriate conditions, and $|\alpha|_\infty$ the specific rotation of the equilibrium mixture. For glucose $|\alpha|_\alpha$ and $|\alpha|_\beta$ could be obtained by short back extrapolations of the kinetic curves to zero time (see below). For aqueous solutions α_D^{30} was found to be +111.6 and +19.1° for the α- and β-form, respectively, in good agreement with literature values [28] (+112.2 and 18.7°, respectively and a negligible temperature dependence). No specific rotation data for the pure α- and β-forms of TMG were available. For this compound K_α was therefore estimated by n.m.r. measurements [29] (Varian A-60 D; 60 MHz) integrating the 1-OH (τ 3.58—3.73 and 3.21—3.30 for the α- and β-form, respectively) or the 1-H peak (τ 4.87 and 5.62). TMG (5%) was dissolved in D_2O (Stohler; isotope chemical; 99.8%) and in mixtures of D_2O and DO or DMSO (D_2O concentration c_w 5.56M) and the n.m.r. spectra recorded immediately after dissolution and again after equilibration which took several days for the solutions of low D_2O content.

Kinetic Experiments.—Rates of mutarotation were measured by a Perkin-Elmer 141 polarimeter using a thermostatted 10 cm reaction cell. A mercury lamp (546 nm) was used as light source, and the change in optical rotation recorded on a Servograph Rec. 51 (Radiometer). In a typical experiment 10.00 cm³ of reaction solution was prepared by transferring a weighed amount of the sugar to a standard flask, adding a calculated amount of water and filling the flask with the inert solvent. When the sugar had dissolved, part of the solution was quickly transferred to the reaction cell. For determination of the equilibrium optical rotation *ca.* 10 mm³ of concentrated ammonia solution was added to the remaining solution to obtain rapid mutarotation. This solution was stored at the same temperature as the one followed kinetically. The sugar concentration was usually *ca.* 0.2M, but due to reduced solubility lower concentrations were required in the experiments at very low concentrations of water in AN and DO. The kinetic experiments with TMG were carried out as described above, but the concentrations were usually only *ca.* 0.05M, and smaller volumes were used to reduce the consumption of this compound.

RESULTS

Equilibrium Constants.—K_α Values for glucose in the different solvent mixtures investigated are given in Table 2. Table 4 gives the enthalpy and entropy of reaction calculated as the differences of the corresponding activation parameters for k_α and k_β [see equation (4)]. The n.m.r. data based on the 1-OH peaks for TMG in DMSO solution showed that our TMG sample contained 78% of the α-form (as compared with the value 74.5% obtained by Casu *et al.*[29]). For TMG in pure D_2O, D_2O–DO, and D_2O–DMSO the content of the α-form immediately after dissolution was 77, 77, and

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TABLE 2

Rate and equilibrium data for the mutarotation of glucose and tetramethylglucose in various solvent mixtures at 303.2 K. c_w in mol dm^{-3}; k_{obs}, k_α, and k_β in s^{-1}

Solvent	Water concentration, c_w	$10^5 \times k_{obs}$	K_α	$10^5 \times k_\alpha$	$10^5 \times k_\beta$
		Glucose			
H_2O in dioxan	55.5 *	63.7 †	1.71 ‡	40.2	23.5
	44.4	37.9	1.60	23.3	14.6
	33.3	20.5	1.50	12.3	8.21
	27.8	16.3	1.45	9.63	6.68
	22.2	11.1	1.40	6.49	4.64
	16.7	7.83	1.36	4.53	3.32
	13.3	5.99	1.33	3.42	2.57
	11.1	4.45	1.32	2.53	1.92
	5.56	1.90	1.27	1.07	0.844
H_2O in dimethyl sulphoxide	44.4	39.2	1.70	24.7	14.5
	33.3	16.7	1.69	10.5	6.22
	27.8	7.83	1.68	4.91	2.92
	22.2	3.49	1.69	2.20	1.30
	16.7	1.22	1.68	0.764	0.453
	11.1	0.296	1.68	0.186	0.111
	5.56	0.064 1	1.67	0.039 9	0.024 0
H_2O in acetonitrile	44.4	39.5	1.63	24.5	15.0
	33.3	25.1	1.57	15.4	9.79
	27.8	20.7	1.54	12.6	8.18
	22.2	17.5	1.51	10.5	6.95
	16.7	13.4	1.49	7.98	5.37
	11.1	8.02	1.47	4.80	3.25
	5.56	2.30	1.44	1.36	0.944
		Tetramethylglucose			
H_2O in dioxan	55.5	47.2	$\simeq 0.92$	$\simeq 23.0$	$\simeq 24.2$
	44.4	29.9			
	33.3	14.4			
	27.8	11.5			
	22.2	8.02			
	16.7	4.26			
	11.1	2.38			
	5.56	1.04	$\simeq 0.76$	$\simeq 0.46$	$\simeq 0.58$
H_2O in dimethyl sulphoxide	44.4	29.9			
	33.3	16.0			
	27.8	8.71			
	22.2	4.07			
	16.7	1.50			
	11.1	0.449			
	5.56	0.107	$\simeq 0.82$	$\simeq 0.50$	$\simeq 0.58$

* Pure water. † 66.4, 64.1, and 64.5 × 10^{-5} s^{-1} reported in ref. 33, 34, and 30, respectively. ‡ 1.73 reported in ref. 30 but incorrectly quoted as K_α^{-1}.

TABLE 3

Apparent reaction orders with respect to water, $n(c_w)$, for mutarotation of glucose and tetramethylglucose in various solvent mixtures. c_w in mol dm^{-3}

Solvent mixture (sugar)		T/K	$n(c_w)$ (concentration range)		Ref.
Water–dioxan	(G)	298.2	2.4 (42—55)	2.0 (22—42)	21, 23*a*
	(G)	303.2	2.3 (28—55)	1.3 (6—28)	This work
	(TMG)	303.2	2.1 (28—55)	1.3 (6—28)	This work
Water–acetonitrile	(G)	303.2	2.3 (40—55)	1.0 (11—40) →1.8 (<11)	This work
Water–methanol	(G)	293.2	2.0 (44—55)	1.2 (25—44)	18, 23*a*
Water–dimethylformamide	(G)	293.2			
		303.2	2.4 (23—55)		23*a*
		313.2			
Water–dimethyl sulphoxide	(G)	298.2	3.3 (>19M)		24
		308.2	3.3 (>19M)		24
		303.2	2.3 (38—55)	3.7 (11—38) →2.2 (<11)	This work This work
	(TMG)	303.2	2.0 (38—55)	3.3 (11—38) →2.1 (<11)	This work This work

69%, respectively. After equilibration the values were 52, 55, and 57%, respectively, which corresponds to the figures for K_α given in Table 2. These values, which should be considered as preliminary, are based on integration of the 1-H peak, since the 1-OH peak here vanishes due to rapid proton exchange with D_2O in the solvent. We have ignored solvent equilibrium isotope effects, since in our formulation of the overall equilibrium c_w does not enter the expression for K_α [equation (3)].

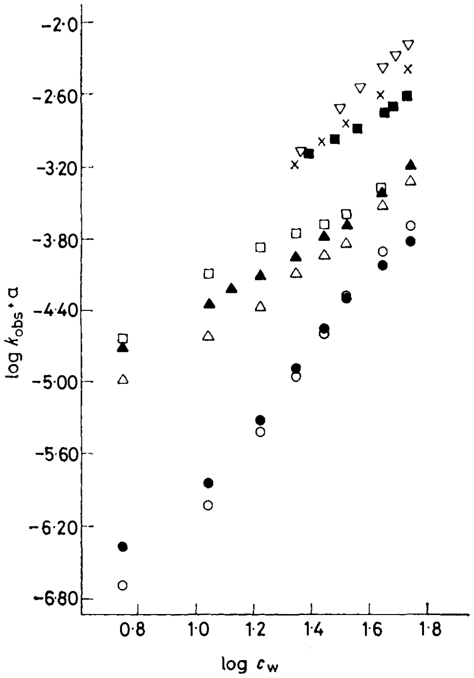
$$nH_2O + \alpha \underset{k_\beta}{\overset{k_\alpha}{\rightleftharpoons}} nH_2O + \beta \qquad (3)$$

TABLE 4

Activation and thermodynamic parameters for the conversion of α-D- into β-D-glucose in different solvent mixtures. c_w in mol dm^{-3}, E_A, ΔH°, and $\Delta H^\ddagger$ in kJ mol^{-1}; ΔS° and $\Delta S^\ddagger$ in J K^{-1} mol^{-1}

Water concentration, c_w	E_A	$\Delta H^\ddagger$	$\Delta S^\ddagger$	$\Delta G^\ddagger$	ΔH°	ΔS°
			H_2O in dioxan			
55.5 [a]	71.0	69.0	−75	92	0	−4
33.3	72 ± 2	70 ± 2	−90 ± 5	97 ± 3	−3 ± 3	−13 ± 8
16.7	69 ± 2	67 ± 2	−111 ± 6	100 ± 3	0 ± 3	−2 ± 8
5.56	68 ± 3	66 ± 3	−124 ± 10	103 ± 4	0 ± 4	−4 ± 12
			H_2O in dimethyl sulphoxide			
33.3	73 ± 2	71 ± 2	−90 ± 6	98 ± 3	0 ± 3	−2 ± 8
22.2	81 ± 3	79 ± 3	−76 ± 8	102 ± 3	0 ± 4	−4 ± 11
11.1	88 ± 3	86 ± 3	−73 ± 11	108 ± 4	0 ± 4	−4 ± 16
			H_2O in acetonitrile			
33.3	66 ± 1	64 ± 1	−109 ± 2	98 ± 1	1 ± 1	0 ± 3
16.7	59 ± 2	57 ± 2	−139 ± 5	98 ± 2	0 ± 3	0 ± 7

[a] Data taken or calculated from results in ref. 30.



log k_{obs} plotted against log c_w for the mutarotation of glucose (G) and tetramethylglucose (TMG) in various solvent mixtures. G: □ water–acetonitrile (a 0), ▲ water–dioxan (a 0), ○ water–dimethyl sulphoxide (a −0.5), ◩ water–methanol (a 1.0),[18,23a] × water–dioxan (a 1.0),[21,23a] ▽ water–dimethyl formamide (a 1.0).[23a] TMG: ● water–dimethyl sulphoxide (a −0.5), △ water–dioxan (a 0)

Kinetic Measurements.—The usual and most simple representation of the overall water-catalysed anomerization process is (3) [7] (see further below for resolution of k_α and k_β). Since H_2O was always present in large excess, the overall rate constant, $k_{obs} = k_\alpha + k_\beta$, and provided that the equilibrium constant, $K_\alpha = k_\alpha/k_\beta$, is known, k_{obs} can be separated into k_α and k_β. Plots of $\ln|\alpha_t - \alpha_\infty|$, where α_t is the measured optical rotation at time t, against t always showed good linearity throughout the kinetic runs, and within the experimental accuracy rate constants from kinetic runs using each of the anomers as starting materials were identical (this was only possible to check for glucose). At the lowest water concentrations where the anomerization process is very slow the reactions were only followed over one or two half-lives. The equilibrium was subsequently rapidly achieved by the addition of traces of ammonia which was shown to give the same value of α_∞, as when the reaction went to equilibrium with no ammonia added.

Rate constants at 303.2 ± 0.2 K for different c_w in the various solvent mixtures are collected in Table 2. As for the equilibrium constants, the figures reported are mean values, differing by <2%, of results from at least two experiments. The Figure displays a plot of log k_{obs} against log c_w, from which n [equation (3)] could be calculated. On the figure results of earlier reports are also shown, and the values of n for the different solvent mixtures are collected in Table 3. Table 4 displays the activation parameters calculated from k_α at different temperatures. The Arrhenius plots generally showed good linearity over a 20 K interval, and the standard deviations given are least squares values from these plots.

DISCUSSION

Equilibrium Constants.—K_α Values for glucose in pure water agree well with literature values.[30] The value measured for TMG confirms the assumption of several authors that the rate constants of the forward and reverse reactions for this compound are practially equal.[4,10]

It is noted that K_α for glucose in water–DO mixtures decreases with decreasing c_w. This is in accordance with the 'anomeric' effect arising from the dipole–dipole interaction between the oxygen atoms at the anomeric carbon atom and in the ring.[31] In apolar solvents this interaction stabilizes the axial position of the hydroxy-group (the α-form), whereas the dipoles in polar solvents give a preferential solvation to the equatorial hydroxy-group and therefore stabilize the β-form. This is further supported by the fact that K_α is much less dependent on c_w, when the ' inert ' solvent component is also polar (AN and DMSO). Similar effects are observed for TMG, even though the reported K_α values are here of a preliminary nature.

The enthalpy and entropy of reaction given in Table 4 are very inaccurate, because of their small values. A calorimetrically estimated value of $\Delta H^\circ = -1.162$ kJ mol^{-1} was reported by Sturtevant.[32a] This gives a value of ΔS° approximately equal to zero.[32b]

Rate Constants and Reaction Orders.—k_{obs} Values for glucose in pure water also agree well with literature values.[30,33,34] k_{obs} for TMG in pure water shows a reasonably good agreement with the value of 37.3×10^{-5} s^{-1} at 298.2 K reported by Huang *et al.*[35] whereas the value 48.8×10^{-5} s^{-1} at 293.2 K reported by Richards *et al.*[18] is somewhat higher. Gram *et al.*[23a] observed deviations from first-order kinetics for the mutarotation reaction of glucose in H_2O–DMF mixtures of water mole fractions lower than 0.7. This effect was not observed in our work.

In order to resolve k_α and k_β into rate constants of the ' elementary ' reaction steps of equation (1) we notice that the steady-state expressions for k_{obs} and k_α are given by equation (4).[23a] Very little direct information

$$k_{obs} = (1 + K_\alpha)k_{12}/(k_{12}/k_{32} + K_\alpha) = (1 + K_\alpha)k_{32}/(1 + K_\alpha k_{32}/k_{12}) \quad (4a)$$

$$k_\alpha = k_{12}/(k_{12}/k_{32}K_\alpha + 1) \quad (4b)$$

about k_{12} and k_{32} is available, except that they are apparently somewhat larger than k_α and k_β for a number of different sugars including glucose.[15,36] However, if we make the following three plausible assumptions, then equation (4) provides the necessary basis for further analysis. (A) The ring-opening of the α- and β-forms displays the same reaction order with respect to water [23a] [equation (5)]. This assumption is justified in view of the

$$k_{12} = k_{12}{}^0 c_w{}^n; \quad k_{32} = k_{32}{}^0 c_w{}^n \quad (5)$$

chemical similarity of the two anomers and the very weak dependence of K_α on c_w. The dependence of k_{obs} on c_w is therefore identical to the corresponding dependence of k_{12} and k_{32}. Furthermore, equation (4) shows that k_{obs} is quite insensitive to minor changes in K_α. For these reasons the values of $n(c_w)$ reported in Table 3 are not corrected for variations in K_α. (B) The temperature dependence of K_α can be ignored compared with the temperature dependence of k_{12} and k_{32}. This is justified by the values of the activation parameters and the enthalpy and entropy of reaction. (C) The temperature dependence of the ratio k_{12}/k_{32} can be ignored compared to the dependence of k_{12} and k_{32} separately. Both rate constants refer to a ring-opening step, and the appropriate free energies of activation are determined by the solvent and intramolecular reorganization energies and by the free energies of reaction for the individual steps. The former must be practically identical for k_{12} and k_{32}. It follows from application of equation (8) to k_{12} and k_{32} that when $\Delta G^\circ \ll E_s$, then $k_{12}/k_{32} = \exp(-\Delta G^\circ/2\,\boldsymbol{k}_B T) = K_\alpha{}^{\frac{1}{2}}$, where ΔG° is the difference in the free energies of formation of the acyclic intermediate from the β- and α-form, $\boldsymbol{k}_B$ Boltzman's constant, and T the absolute temperature. Since the measured activation energy is always much larger than $\boldsymbol{k}_B T \ln K_\alpha{}^{\frac{1}{2}}$, assumption (C) is well justified.

Table 3 shows that for $c_w \geqslant 28$M, the apparent reaction order is *ca.* 2, independent of the organic component. This is strong evidence for the participation of several water molecules in the collision complex, possibly in a cyclic configuration, such as suggested earlier for the hydration and dehydration reactions of carbonyl compounds.[16]

However, the absolute value of $n(c_w)$ is of course not necessarily identical with the actual number of water molecules in the collision complex. First, the apparent reaction order only determines the difference in the number of water molecules in the activated and the initial states, and since the latter is likely to be strongly solvates the number of water molecules in the activated state is also likely to be larger than revealed by the apparent reaction order. Secondly, the fact that it is not an integer suggests that oligomeric water aggregates may also be incorporated into the reaction complex. This would give a lower apparent reaction order than that corresponding to the actual number of water molecules.[16d] Finally, when the water concentration is varied over such large ranges, the water activity coefficient is expected to change. Although there is evidence that this effect is cancelled by corresponding changes of the activity coefficient of the collision complex in the carbonyl hydration reaction in dioxan and acetonitrile,[16] it cannot in principle be distinguished from possible changes in the collision complex structure.

For low water concentrations Table 3 and the Figure show that the apparent reaction order depends on the nature of the organic component. The features to be noted in Table 3 are that (a) in DO, AN, and methanol the apparent reaction order is lower by approximately one compared with the reaction order of higher water concentrations; (b) in DMSO the apparent reaction order

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at first increases with decreasing c_w and then returns to approximately the same value as for higher water concentrations.

The effect in DO and AN is understandable if one or more solvate water molecules also contribute to the proton transmission. In the presence of large amounts of the less polar solvent component glucose or TMG would thus be preferentially solvated by water, possibly even to a larger extent than in pure water. On the other hand, there is much experimental evidence, based on i.r.,[37] Raman,[38] and n.m.r. [39] spectroscopy, *X*-ray diffraction,[40] neutron inelastic scattering data,[41] and ultrasonic propagation,[42] that DMSO possesses a much stronger polarity and hydrogen-bonding capability than DO and AN. This could explain the variation in $n(c_w)$ in mixtures of this solvent and water. DMSO is thus likely to contribute to the reactant solvation, and the higher value of n for $11\text{M} \lesssim c_w \lesssim 38\text{M}$ could reflect the necessity of replacing some of the solvate DMSO molecules by water.

The behaviour of the mutarotation of glucose in respect to the apparent reaction order in water may be compared with that of the chloral hydration in mixtures of water and DO or DMSO.[16d] Thus, for high water concentrations $n \simeq 2$ for both reactions. For lower water concentrations $n \simeq 4$ for chloral hydration which is likely to be due to lower preferential solvation of chloral than of glucose by water in the mixed solvents. The same effect is probably also reflected in the apparent intramolecular catalysis of the hydration of glyoxylic acid [43] compared with the hydration of acetaldehyde. The carboxy-group of the former compound is more hydrated than the methyl group of the latter and may therefore provide some of the catalyst molecules. On the other hand, the lower apparent reaction order of the mutarotation reaction with respect to water in water–methanol mixtures of low water content,[18] is more likely to be due to a replacement of water by methanol in the proton transferring chain. This replacement is known to occur in other proton transfer reactions [6] and is due to the close correspondence between the acid and base properties of the two molecules.

It should finally be noted that substitution of four hydroxy-groups in glucose by methoxide groups apparently does not result in any major changes of the apparent reaction order with respect to water. The solvation around the reaction centre and the mechanism of the proton transfer through water molecules are therefore likely to be the same for glucose and TMG, and only solvation at more remote places of the substrate molecules may differ.

Activation Parameters.—We notice at first that the coefficient of k_{12} in equation (4) is close to unity. With our previous assumptions on the temperature dependence of the various rate and equilibrium constants of equation (4) the activation parameters obtained for k_α therefore closely reflect those of k_{12} or k_{32}. Secondly, there is a considerable spread in previously reported values of the activation parameters of the mutarotation of glucose in pure water.[7] The values given in Table 4 are the ones reported in the work by Kendrew and Moelwyn-Hughes [30] which we consider to be the most extensive and reliable.

Small but significant changes in the activation energy, E_A, when the inert solvent component is changed, are noted. The fact that the changes are small is an indication that the solvent reorganization energy only constitute a certain fraction of the total activation energy. This, and the quite large absolute value of E_A are in line both with the substantial intramolecular chemical conversions associated with the process and with expectations from proton transfer theory (see below). The decrease in E_A with decreasing c_w observed for DO and AN could be due to increasing disruption of the original bulk water structure with increasing amounts of added organic solvent and therefore increasing mobility of the water molecules. The fact that E_A in DMSO shows an opposite effect is then likely to arise from a considerably stronger complex formation between water and DMSO than between water and the other solvents [37] and the necessity of partial decomposition of the water–DMSO complex.

The large negative values of the activation entropy are in line with the substantial loss of translational entropy when several water molecules are incorporated in the collision complex.[16] Thus it was shown earlier that the contribution from proton tunnelling to the activation entropy could only constitute a few entropy units per proton.[5] Large negative activation entropies are also observed in keto–enol tautomerization reactions [5] and in the hydration of dichloroacetone and chloral.[16] In line with expectations from apparent reaction orders with respect to water, the activation entropy for the latter reaction is much more negative (-227 J K^{-1} mol^{-1}) due to the smaller supply of water molecules from the primary hydration shell to the collision complex. It is also noted that the activation entropy for DO and AN decreases with decreasing c_w. This is expected from the increasing ' depolymerization ' of water and the corresponding necessity of incorporating an increasing number of individual water molecules in the collision complex.[16d] On the other hand, an opposite effect is observed for water–DMSO mixtures. From the larger apparent reaction orders with respect to water at lower c_w in DMSO a lowering of the activation entropy might have been expected. However, as noted above, part of these water molecules are likely to be provided by the water–

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DMSO associates. If a desolvation of water precedes its incorporation into the collision complex then this step may well provide an additional positive activation entropy which more than compensates for the negative contributions from the increased apparent reaction order.

Molecular Mechanisms.—It is appropriate to supplement the above discussion with a few considerations on the nature of the detailed proton transfer mechanism, in particular whether the protons are transferred in a stepwise or a concerted fashion. The following experimental results provide strong evidence that both the proton donating and accepting properties of the water catalyst determine its efficiency and therefore suggest that the proton transfers are coupled. (a) The apparent reaction orders and the activation entropy values clearly show that several water molecules are required for proton transmission. (b) Experimental results from studies of solvent isotope effects [35] on the mutarotation of glucose favour a transition complex which contains two or three water molecules. (c) DMSO ($pK \simeq 1$) [45] is a much stronger proton acceptor than water but a much weaker acid. If the reaction proceeded by general base catalysis the rate would be expected to increase with decreasing c_w in water–DMSO solvents. However, the opposite effect is observed, and the reaction does not even seem to proceed in pure DMSO. This effect is analogous to the observation of a very slow mutarotation in pure pyridine.[19]

Most current theoretical discussions on single and coupled proton transfer reactions only consider the classical motion of the transferring proton (possibly with tunnel corrections) and other 'intramolecular' motions,[8,46] whereas very little consideration is given to the solvent. However, in polar media the proton strongly interacts with the surrounding solvent, and the proton transfer may be associated with a considerable medium repolarization. In recent formulations of electron and atom transfer theory this is included by adopting the following scheme.[25,26,44,47] (A) The appropriate chemical reaction is associated with motion along a large number of intramolecular and solvent nuclear modes. The probability, W_ρ, of passing from an initial to a final state potential well *via* an energy barrier, and along a particular mode, is given by an expression of the form (6)

$$W_\rho \propto \sum_v W_\rho(E_v)\exp(-E_v/\boldsymbol{k}_BT) \qquad (6)$$

where $W_\rho\ (E_v)$ is the probability of passage when the system has a particular energy E_v. $\exp(-E_v/\boldsymbol{k}_BT)$ obviously decreases with increasing E_v, whereas $W_\rho(E_v)$ increases towards a limiting value of unity corresponding to passage over the barrier. (B) If $W_\rho(E_v)$ increases more rapidly than $\exp(-E_v/\boldsymbol{k}_BT)$ decreases with increasing E_v, then the system passes from the initial to the final state over the barrier. This classical behaviour is characteristic for nearly all solvent and many intramolecular modes. On the other hand, if $W_\rho(E_v)$ increases less rapidly than $\exp(-E_v/\boldsymbol{k}_BT)$ decreases, then the system passes the barrier by tunnelling from the ground vibrational level through the barrier. Since proton transfer is usually assumed to proceed along a stretching mode for which $\Delta E_v \gg \boldsymbol{k}_BT$, this motion is associated with quantum behaviour.

The general expression for the reaction probability of an elementary proton transfer reaction therefore takes the form (7) which can be interpreted in the following

$$W \propto S\exp(-E_A/\boldsymbol{k}_BT) \qquad (7)$$

way. The classical (solvent) co-ordinates define a potential energy surface for the initial and final states. With a certain probability, given by $\exp(-E_A/\boldsymbol{k}_BT)$ (corresponding to the activation energy E_A) the system reaches the top of the activation barrier with respect to these co-ordinates, and in this region the proton is transferred from its initial to its final equilibrium configuration with a probability given by the tunnelling factor S. After the proton transfer the system relaxes along classical modes to its final state equilibrium configuration. In the formalism of a linear dielectric medium and harmonic intramolecular classical modes expression (7) takes the form (8),[44,47] *i.e.* an approximately quadratic dependence

$$W \propto S\exp[-(E_S + \Delta G^\circ)^2/4E_S\boldsymbol{k}_BT] \qquad (8)$$

between the activation energy and the free energy of reaction is expected. This is borne out by many experimental data.[48,49] (C) If several single proton transfer reactions occur in a concerted or a step-wise fashion the following two mechanisms may operate.[26,50] (a) If the relaxation times, τ_r, of all the classical modes after the transfer of a given proton are small compared with the time, t_d, required for the system to reach the immediately following classical barrier peak, *i.e.* if $\tau_r < t_d$, then the overall reaction consists of a series of step-wise proton transfer reactions. After each proton transfer all the classical modes relax into their equilibrium configurations, and each step proceeds independently of the previous ones and can be described by relations such as (7) or (8). (b) If the inverse inequality is valid, then the classical modes only partially relax after the transfer of a given proton. Such processes have been named quantum dynamical processes,[50] and they also provide an adequate description of concerted proton transfer reactions.

If we assume that the mutarotation reaction is essentially a proton transmission through a chain of water molecules, coupled to the ring opening, then we can apply the previous discussion and expression (8) to this

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system. Thus, if the proton transfers occur in a stepwise fashion, the value of ΔG° to be inserted into expression (8) is at least the difference in the pK values of glucose and water, *i.e.* $\Delta pK \simeq 14$,[51] or $\Delta G^\circ \simeq 79$ kJ mol^{-1}. Since this value is of the same order or even larger than E_A, a step-wise mechanism would have the following implications. (a) $E_s \simeq 0$. Even though E_s is often small for proton transfer between oxygen proton-accepting centres [49] it still amounts to values between 10 and 40 kJ mol^{-1}. (b) Since $E_A \simeq \Delta G^\circ$, the reaction would be barrierless, *i.e.* the Brønsted coefficient should be unity. This disagrees with experimental results.

On the other hand, if the proton transfers are coupled in the way described above, then ΔG° corresponds to the total free energy of reaction when going from the initial state to the acyclic form, *i.e.* $-\Delta G^\circ \simeq k_BT\ln(2.6 \times 10^{-5}) \simeq 26$ kJ mol^{-1}. This gives a value of $E_s \simeq 200$ kJ mol^{-1} which is plausible, since E_s would now include the energy required for the ring opening. We should notice that the conclusion does not depend critically on the exact value for the equilibrium concentration of the acyclic intermediate. Our theoretical considerations therefore support our previous conclusion that the water-assisted mutarotation of glucose in the mixed solvents proceeds by a concerted series of proton transfer reactions with no relaxation of the solvent modes between each individual proton transfer step.

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