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Bifunctional Acid-base Catalysis of the Mutarotation of Glucose in Mixed Aqueous Solvents*

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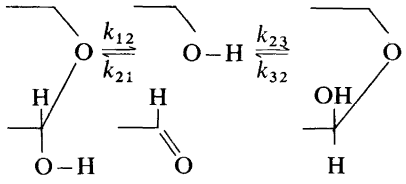
We have investigated the catalysis of the mutarotation of glucose by 2- and 4-hydroxypyridine, pyrazole, formic acid and the formate ion in mixed aqueous solutions of dimethyl sulfoxide and dioxane in the water concentration range 10–55 mol dm^{-3}. The dependence of the catalytic rate constants on the solvent composition is understandable on the basis of the solvation of the reactants and the bulk medium structure. Although being a weaker base, 2-hydroxypyridine is a more effective catalyst in water-dioxane than 4-hydroxypyridine, which is most likely due to bifunctional acid-base catalysis. The formate anion exhibits a similar effect. In view of the monofunctional nature of this ion this is, however, probably caused by a partial desolvation prior to its interaction with the glucose molecule.

The kinetic deuterium isotope effect decreases with increasing water content of the solutions in line with expectations from the mechanism suggested.

Hydrolytic enzyme catalysis is commonly believed to involve cooperative multiple proton transfer,[2,3] at enzyme-substrate binding sites located in regions partly or totally screened from the external aqueous medium.[4,5] Several recent investigations of acid-base catalysed chemical processes involving small mobile reactants have shown that water itself is an effective but rather unselective catalyst,[6–11] and at least in some cases it seems to operate as a bifunctional catalyst with "simultaneous" proton transfer occurring at different parts of both substrate and catalyst molecules.[10] These results suggest that in addition to the formation of specific enzyme-substrate complexes an important function of the enzyme is to screen the reaction centre from the external and abundantly present unselective water catalyst.

In order to elucidate further the competition between the catalytic effects of the medium and the effects of more specific catalysts we have – as a continuation of previous studies of the water-catalysed process[10] – investigated the mutarotation of α-D-glucose in mixed aqueous dioxane (DO) and dimethyl sulfoxide (DMSO) solutions and in the presence of various mono- and bifunctional catalysts. This kind of process is generally well suited for the study of both general acid-base[12] and bifunctional catalysis.[6,9,13] Phenomenologically it is described as an equilibrium between the optically active α- and β-forms, $\alpha \rightleftarrows \beta$. However, at least one open-chain unstable intermediate is also involved as follows:[14]



(1)

α-form intermediate chain form β-form

The rate of interconversion of the α- and β-form is mainly determined by the ring-opening of the intramolecular hemiacetal, and the reaction is thus a typical carbonyl group reaction. At least two proton transfer steps are furthermore involved, and the process also seems to undergo bifunctional (tautomeric) acid-base catalysis in the presence of

* See Ref. 1.

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2-hydroxypyridine (2-pyridone), pyrazole and other potential bifunctional catalysts in nonaqueous solvents.[6,12] No such phenomena have been detected for these catalysts when the reaction proceeds in pure water.[12]

EXPERIMENTAL

Solvents. Dioxane (BASF, technical) was purified and stored as described earlier.[10] Dimethyl sulfoxide (Fluka, *purum*) was distilled *in vacuo* from calcium hydride shortly before use, and the middle fraction collected. Doubly distilled water, free of carbon dioxide, was used throughout.

Reagents. α-D-Glucose (BDH, AnalaR) with equilibrium specific optical rotation in water, $|\alpha|_D^{20} = +52.5$ to $+53.0$ degrees, was used without further purification. 2-Hydroxypyridine (Merck, "zur Synthese") was recrystallized from ether, dried and vacuum sublimed; m.p. 104.5 – 105 °C. 4-Hydroxypyridine (EGA, technical) was dissolved in ethyl alcohol and repeatedly treated with charcoal until all coloured impurities had disappeared. After evaporation and crystallization the colourless crystals were sublimed *in vacuo* and subsequently stored over conc. H_2SO_4; m.p. 148 °C. Pyrazole (EGA, *ca.* 99 %) was vacuum sublimed and kept over silica gel; m.p. 68.5 °C. Formate buffers were made up by neutralizing formic acid (Fluka, *puriss. p.a.*) with sodium hydroxide (Merck, Titrisol). Ionic strengths were adjusted by sodium chloride (BDH, AnalaR). Deuterium oxide was a Stohler isotope chemical (99.8 % D_2O).

Kinetic experiments. The rates of mutarotation were measured by a Perkin-Elmer 141 polarimeter using a thermostatted 10 cm reaction cell.[10] The wave length was 546 or 365 nm, and kinetic curves were recorded on a Servograph Rec. 51 (Radiometer). All experiments were carried out at 30.0 °C. Glucose solutions with well defined concentrations of water and catalyst were made up in 10 cm^3 standard flasks and handled as described earlier.[10] At high water concentrations, *e.g.* "pure" water, the influence of sugar and catalyst on the water concentration is important, since the catalytic effects of many tautomeric catalysts are very small here and high concentrations for the detection of appreciable catalytic effects needed. In these water concentration ranges the amount of water was weighed and the total volume of the solution measured very carefully.

RESULTS

Catalytic constants. The mutarotation process was first order in both glucose and catalyst concentration for all the investigated solvent mixtures and catalysts, and rate constants were generally determined either by the Guggenheim method or by plotting $\ln|\alpha_t - \alpha_\infty|$ against time. In some instances, especially when the reactions were very slow, an exponential function was fitted numerically to the observed kinetic curves by the method of least squares. In such cases only one or two half-lives of the reaction were needed to provide accurate estimates of the rate constants. Catalytic constants, k_{cat}, for the catalysis by 2-hydroxypyridine, 4-hydroxypyridine and pyrazole in water – DO and water – DMSO mixtures were calculated from the relation $k_{obs} = k^\circ_{obs} + k_{cat}[cat]$, where k°_{obs} refers to the catalysis by the pure solvents. We have omitted terms accounting for catalysis by H^+ or HO^- which might be generated in the solution by adding the catalyst. This is well justified since the three amphoteric catalysts have extremely weak acidic and basic properties and also verified by the very small pH change on dissolution of the catalysts. The pH of the solutions (relative to aqueous standard buffers) were always well inside the rather broad pH-interval (*ca.* 2.5 to *ca.* 7.0) in which no catalysis of the mutarotation of glucose by H^+ or HO^- is expected.

A selection of typical kinetic results for catalysis by 2-hydroxypyridine is given in Table 1. Specific optical rotations for pure α-D-glucose ($|\alpha_o|$) and for the fully equilibrated sugar ($|\alpha_\infty|$) under various conditions are also shown. The constancy of these values for different catalyst concentrations shows that the mutarotation equilibrium is unaffected by the catalyst, at least in the concentration range investigated here. Formation of double hydrogen-bonded substrate-catalyst complexes (see later) which could alter the equilibrium position and which would most likely occur in the less polar DO-solvents could not be detected here. The possibility of this effect in the polar solvent DMSO was not investigated.

We have plotted all the kinetic results obtained for 2-hydroxypyridine catalysis in Fig. 1. For each solvent composition the linear dependency of k_{obs} on [cat] is obvious and values of k_{cat} obtained from the slopes are collected in Table 2 together with the results for 4-hydroxypyridine and pyrazole. The data for the latter two compounds were shown to conform to the same catalytic law as 2-hydroxypyridine (Fig. 1). Finally, log k_{cat} for the three catalysts are plotted against log C_w in Fig. 3.

The study of mutarotation in formate buffers of

Table 1. Selection of primary kinetic data for the determination of k_{cat} for 2-hydroxypyridine under various conditions. Some relevant specific optical rotations are also given.

[Glucose]/ mol dm^{-3}	$\lvert\alpha_0\rvert^{30\,°C}_{546\,nm}$ degr.	$\lvert\alpha_\infty\rvert^{30\,°C}_{546\,nm}$ degr.	[cat]/ mol dm^{-3}	$10^5 k_{obs}$/ s^{-1}	$10^4 k_{cat}$/ dm^3 mol^{-1} s^{-1}
Pure water					
–	131.1	62.0	0	63.7	
0.247	129.5	63.0	0.105	65.3	
0.223	130.6	62.8	0.208	66.9	1.47[a]
0.248	127.1	61.2	0.299	68.0	
–	–	–	0.408	69.7	
11.10 M water in DO					
–	131.7	71.2	0	4.45	
0.123	–	71.3	0.102	11.4	
0.115	135.7	–	0.221	20.9	6.0
0.119	135.4	69.8	0.322	24.9	
0.151	130.7	67.7	0.423	31.1	
0.208	133.7	69.7	0.533	36.3	
11.10 M water in DMSO					
–	–	–	0	0.296	
–	–	–	0.100	1.54	
–	–	–	0.205	2.97	
–	–	–	0.264	3.60	1.26
–	–		0.394	4.99	
–	–	–	0.437	6.03	

[a] Uncorrected for changes in C_w of "pure" water.

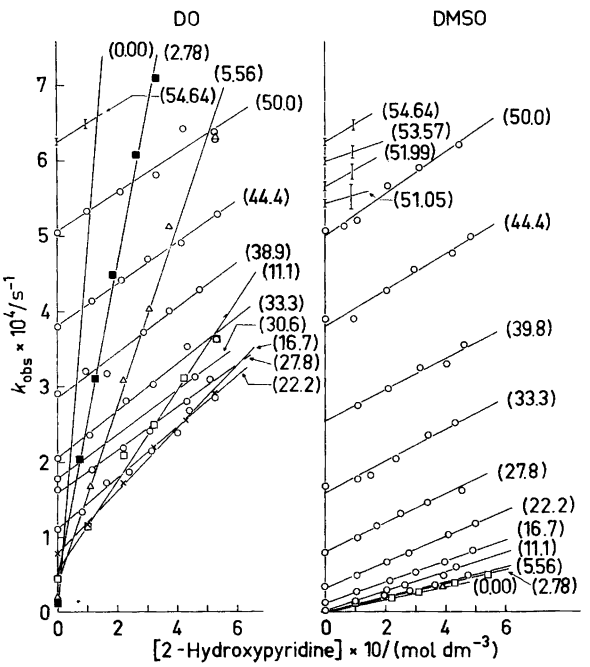


Fig. 1. Kinetic results from the 2-hydroxypyridine-catalysed mutarotation of glucose in water–DO and water–DMSO mixtures at 303 K. The figures in parentheses refer to water concentrations in mol dm^{-3}.

Table 2. Some catalytic constants found at various concentrations of water in DO and DMSO.

C_{water}/ mol dm^{-3}	2-Hydroxypyridine $10^4 k_{cat}$/dm^3 mol^{-1} s^{-1}		4-Hydroxypyridine $10^4 k_{cat}$/dm^3 mol^{-1} s^{-1}		Pyrazole $10^4 k_{cat}$/dm^3 mol^{-1} s^{-1}	
	DO	DMSO	DO	DMSO	DO	DMSO
54.98(1)	–	–	27(6)	27(6)	–	–
54.74(1)	–	–	–	–	7.4(7)	7.4(7)
54.64(3)	2.4(10)	2.4(10)	–	19(3)	–	–
53.67(2)	–	–	–	–	–	7.8(9)
53.57(2)	–	2.2(11)	–	–	–	–
53.36(2)	–	–	–	23(9)	–	–
52.65(2)	–	–	–	–	–	7.7(11)
51.99(3)	–	1.3(9)	–	–	–	–
51.63(1)	–	–	–	–	–	–
51.36(1)	–	–	–	–	–	–
51.05(3)	–	1.0(18)	–	–	–	–
50.00(2)	2.6(3)	2.8(2)	–	–	–	–
44.39(1)	2.8(1)	2.4(2)	12.3(4)	10.8(3)	5.5(2)	4.1(9)
38.90(2)	3.0(3)	2.1(2)	11.3(3)	–	–	–
33.29(1)	3.1(2)	2.1(2)	10.0(3)	6.8(2)	3.5(1)	2.5(5)
30.60(1)	3.0(3)	–	–	–	–	–
27.75(1)	2.9(1)	1.92(5)	8.0(3)	5.7(3)	2.0(1)	1.5(2)
22.20(1)	3.4(1)	1.70(4)	8.1(3)	3.3(1)	1.8(2)	0.73(10)
16.67(1)	4.1(1)	1.41(3)	8.1(3)	2.3(1)	1.1(3)	0.37(17)
11.10(1)	6.0(3)	1.26(5)	10.9(3)	1.36(4)	1.3(1)	0.14(3)
5.56(1)	11.8(6)	0.99(4)	14.3(4)	0.77(2)	1.2(1)	0.041(3)
2.78(1)	21.2(8)	0.94(4)	14.5(4)	0.69(2)	–	–
≈0	48(5)	0.88(5)	–	0.57(2)	–	–

known composition gives information about the catalytic effect of the two buffer constituents. Thus,

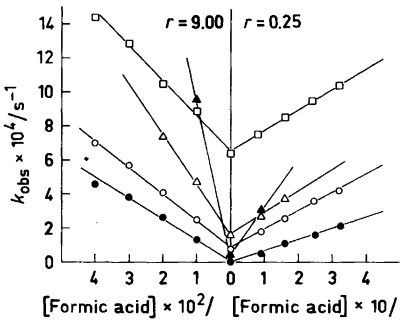


Fig. 2. Some kinetic results for the formate buffer catalysed mutarotation of glucose in mixed aqueous solvents at 303 K. The buffer ratio is indicated as r and the solvent composition as follows: □, pure water; ○, water in DMSO (27.8 mol dm^{-3}); ●, water in DMSO (11.1 mol dm^{-3}); △ water in DO (27.8 mol dm^{-3}); ▲, water in DO (11.1 mol dm^{-3}).

if (as before) catalysis by H^+ or HO^- can be ignored, the observed rate constant in a given solvent is expressed as $k_{obs} = k^{\circ}_{obs} + (k_{formic\ acid} + k_{formate\ ion} r) \times$ [formic acid], where r = [formate ion]/[formic acid]. A plot of k_{obs} against the concentration of formic acid should, therefore, give a straight line with a slope depending on r, and the catalytic constants can be found from two sets of experiments at two different values of r (r = 9 and 0.25 throughout in this work).

A selection of such plots is given in Fig. 2. Since all intercepts are in good agreement with mutarotation rate constants in the pure solvents,[10] catalysis by H^+ which might be expected when r = 0.25 (I = 0.1, pH = 3.15 in water), is clearly negligible. All final results, *i.e.* catalytic constants for formic acid and formate ions, are presented in Table 3, and the logarithm of these constants plotted against log C_w in Fig. 3.

Isotope effects. From measurements of catalytic constants for 2-OD-pyridine in mixtures of deuterium oxide in DO and DMSO, respectively, the kinetic isotope effects given in Table 4 were found.

Table 3. Catalytic constants for formate buffer constituents under various conditions.

C_{water}/ mol dm^{-3}	$10^4 \times$ slope ($r=9$)/ dm^3 mol^{-1} s^{-1}		$10^4 \times$ slope ($r=0.25$)/ dm^3 mol^{-1} s^{-1}		Formic acid $10^4 \times k_{cat}$/ dm^3 mol^{-1} s^{-1}		Formate ion $10^4 \times k_{cat}$/ dm^3 mol^{-1} s^{-1}	
	DO	DMSO	DO	DMSO	DO	DMSO	DO	DMSO
≈55[a]	200(9)	200(9)	11.8(2)	11.8(2)	6.4(3)	6.4(93)	22(1)	22(1)
50.00	206(14)	–	12(1)	–	6.5(15)	–	22(2)	–
44.39	221(10)	190(5)	16(1)	12.2(4)	10.1(11)	7.2(4)	23.4(11)	20.3(6)
38.90	193(7)	–	12.8(5)	–	7.7(6)	–	20.6(8)	–
33.29	300(7)	168(4)	14(1)	11.4(5)	5.8(10)	6.9(5)	32.7(8)	17.9(5)
27.75	289(13)	157(4)	12.9(2)	10.9(5)	5.0(4)	6.7(5)	31.6(15)	16.7(5)
22.20	357(5)	140(9)	15.1(5)	9.4(5)	5.3(5)	5.7(6)	39.1(6)	15(1)
16.67	486(16)	131(4)	18.2(7)	7.8(3)	4.8(5)	4.3(3)	54(2)	14.1(5)
13.30	680(35)	–	25(1)	–	6.3(14)	–	75(4)	–
11.10	910(50)	117(6)	32(2)	6.6(1)	6.9(25)	3.2(2)	100(6)	12.6(7)

[a] "Pure" water.

DISCUSSION

The effect of the aqueous medium of variable composition on carbonyl hydration and related reactions such as the mutarotation of glucose is essentially two-fold:

(A) Water participates as a reactant. This is reflected as a certain reaction order $n(c_w) \equiv n$ with respect to water in the mixed solvents, given by the slopes of the curves shown in Fig. 3 and representing the difference in the number of solvating water molecules in the "collision complex" and the initial state.[7-11,14] The value of n is close to 2 for mutarotation in pure water[10] but decreases when other potential catalysts are present. This implies that water molecules are replaced by the catalyst molecules, but in most cases n is still positive, *i.e.* water is required also for the catalytic paths. The values of n in water-DMSO mixtures are generally larger than for water-DO mixtures. This is expected in view of the larger solvation of the initial-state reactants by the more polar DMSO.[10]

Table 4. Some kinetic isotope effects for the 2-hydroxypyridine-catalysed mutarotation of glucose in aqueous mixtures of DO and DMSO.

C_{D_2O}/ mol dm^{-3}	k_H/k_D DO	DMSO
44.39	2.54	2.53
22.20	2.73	2.91

(B) The rate of the process also depends on the solvent reorganization energy. This quantity is determined by the absorption spectrum of the medium in the microwave and infrared regions[15] (frequency dispersion) and by the short-range structure close to the reaction centre[15] (space dispersion). This effect is commonly characterized by "the effect of water structure",[9,16,17] but we should note that this notation is only adequate if the appropriate structure refers to the dynamic rather than the static medium structure.[15] For our present purpose it is sufficient to note that the more extensive the local solvent structure (the "ordering" of the solvent), the smaller is the solvent reorganization energy.

When DMSO is added to pure water in mol fractions, X_{DMSO}, up to about 0.2, thermodynamic[18] and neutron inelastic scattering data[19] indicate that the local "order of the medium structure" is increased. Neutron diffraction,[19] IR,[20] Raman[21] and NMR[22] data suggest that further addition of DMSO causes labile compound formation *via* hydrogen bonding between H_2O and DMSO but also a disruption of the bulk water structure. Since increasing water concentrations in the region of low values of the latter also cause an increasing long-range disorder and compound formation[19,20] the solvent reorganization energy is likely to pass through a broad minimum over the range $0 < X_{DMSO} < 1$.

^1H chemical shifts, self-diffusion coefficients, spinlattice relaxation times[23] and X-ray diffraction data[24] show that water-DO mixtures exhibit

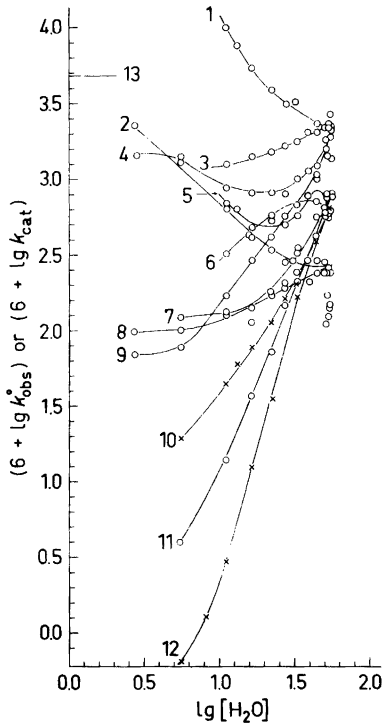


Fig. 3. Dependence of mutation rate constants on solvent composition at 303 K. The purely solvent catalysed reaction rate constants (k°_{obs}) are expressed in s^{-1} and k_{cat} in $dm^3\ mol^{-1}\ s^{-1}$. Water concentrations are in mol dm^{-3}. The following code identifies the nonaqueous solvent component and catalyst belonging to each curve: 1 DO + formate ion; 2 DO + 2-hydroxypyridine; 3 DMSO + formate ion; 4 DO + 4-hydroxypyridine; 5 DO + formic acid; 6 DMSO + formic acid; 7 DO + pyrazole; 8 DMSO + 2-hydroxypyridine; 9 DMSO + 4-hydroxypyridine; 10 DO + water (taken from Ref. 15); 11 DMSO + pyrazole; 12 DMSO + water (taken from Ref. 15); 13 Upper limit for curve 2, *i.e.* the 2-hydroxypyridine catalysed mutarotation in pure DO.

qualitatively essentially similar effects. With reference to this we then notice the following about Fig. 3:

(a) The medium effect is much smaller for the catalyzed reactions than for the reaction with water. This shows that direct water participation is more important than medium structural effects.

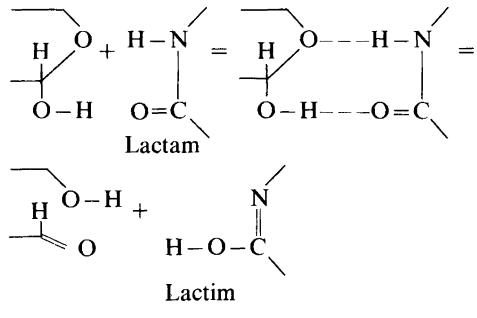
(b) In water – DMSO mixtures n is approximately constant over very wide concentration ranges. However, the decrease of the rate constant at the low water concentrations is slower than expected from extrapolation from higher water concentrations. This would be compatible with the increased solvent order in the highly dipole- and compound-associated solutions of large DMSO content.

(c) The medium effects on the catalysed reaction paths in water – DO mixtures are also smaller than the effects for the water-assisted process. This is, however, better correlated with the specific solvation effects discussed below than with the changes of the medium structure.

We then proceed to a consideration of the individual catalyst molecules.

2-Hydroxypyridine. There is much evidence that this compound is a very effective bifunctional catalyst for mutarotation and related processes in organic nonpolar solvents,[6,13] and it is commonly believed that the two protons are transferred in a concerted fashion. Fig. 1 and Table 2 clearly display its strong catalytic effect. The effect is smaller the higher the water content of the solutions, because the catalyst molecule has to compete with the large amount of water molecules. This is also reflected in the apparently negative reaction order with respect to water in water – DO mixtures, which suggests that 2-hydroxypyridine, preferentially solvated by water, is partly desolvated before being incorporated in the "collision complex".

Some evidence from the lactam-lactim tautomerisation rate of 2-hydroxypyridine in mixed solvents supports this.[25,26] In aprotic solvents this process proceeds *via* the formation of a hydrogen-bonded dimer. The dimer concentration decreases drastically even when traces of water are added, most likely because a new, less effective proton transfer pathway *via* a water chain is opened. In line with this and with the suggestion of Swain and Brown[13] the reaction scheme (4) for the mutarotation of glucose in non-polar media is therefore compatible with the experimental evidence available.



(4)

The detailed proton transfer path can be illuminated by noting that the concerted pathway is favoured relative to the step-wise pathway, the smaller the proton transfer distances, the smaller the solvent reorganization energies associated with the proton transfer steps, and the less stable the intermediate state (*i.e.* the larger the pK difference between 2-hydroxypyridine and glucose) in the step-wise process.[10,27] The pK values of glucose ($\approx$12.3) and 2-hydroxypyridine (12.8) in aqueous solution then seem to provide no advantage for a concerted two-proton transfer over a step-wise mechanism, but this situation may be quite different in nonaqueous media, where both the free energy of the proton transfer is less favourable for single proton transfer and the lactam-lactim ratio more favourable for a concerted two-proton transfer.

The increasing catalytic effect of 2-hydroxypyridine with higher DO-content of the solvent might be caused by a shift of the strongly solvent dependent[28] lactam-lactim equilibrium of the catalyst, assuming that the lactim form is the better catalyst. In pure water the equilibrium constant is 10^3 in favour of the lactam form,[29] while the equilibrium is shifted in favour of the lactim form[28] in dioxane or cyclohexane. In the gas phase the equilibrium ratio between lactim and lactam form is 2.5.[30] The large stability of the lactam in water must therefore be due to preferential solvation of this form, which excludes the possibility that the increasing catalytic effect with decreasing solvent polarity is caused by better catalytic properties of the lactim form.

4-Hydroxypyridine. Although possessing tautomeric properties, this compound is not expected to operate as a bifunctional catalyst because of its unfavourable molecular geometry. This is supported by the curves in Fig. 3 which appear qualitatively different from those of 2-hydroxypyridine, and the larger catalytic activity and higher basic strength (pK_B=10.8) compared with 2-hydroxypyridine (pK_B=12.8) most likely reflects general base catalysis.

Pyrazole. Since the catalytic behaviour of this substance is much more similar to 4- than 2-hydroxypyridine, the solvation of the two neighbouring nitrogen atoms is probably too strong and/or the double hydrogen bonding to glucose too weak for tautomeric catalysis to be of importance at the relatively high water concentrations in our experiments. This is in accord with other reports of pyrazole being much less active than 2-hydroxypyridine and carboxylic acids as a bifunctional catalyst in apolar solvents.[6] Comparison of the catalytic constants (Table 2) and pK_B for pyrazole (pK_B=11.5) and the hydroxypyridines rather suggests that in water these substances are general base catalysts.

Formic acid. Carboxylic acids are sometimes regarded as bifunctional catalysts in nonpolar solvents.[6a] This is, however, not unambiguously reflected in our results for formic acid (Fig. 3). On the other hand, the catalytic constant in dioxane clearly tends to increase at the lower water concentrations, but solubility problems prevented further investigations of this.

Formate ion. The rates of bimolecular reactions between anions and uncharged species are usually drastically increased on changing the solvent from water to a dipolar aprotic solvent, *e.g.* DMSO or DMF.[31] This is commonly explained as a destabilization of the anionic reactants due to desolvation. In the present case, however, a slight decrease in rate is observed, when DMSO is added, which might be caused[32] by a simultaneous desolvation of the highly solvated transition state.[10,12,33]

The catalytic constant for formate in dioxane increases somewhat with decreasing water concentration (n is negative as for 2-hydroxypyridine). It is difficult to reconcible this effect with bifunctional catalysis, and we believe that this behaviour is more likely due to preferential solvation of the ion by water and the release of water molecules when it is incorporated in the transition state (*cf.* Ref. 7).

Isotope Effects. We have observed relatively small kinetic deuterium isotope effects which increase with decreasing water content of the solution. In comparison, the isotope effect is 3.5 for the 2-hydroxypyridine-catalysed mutarotation of tetramethylglucose in benzene and 3.6–3.8 for the water-catalysed mutarotation of glucose.[34] These values have previously been taken as evidence against a concerted multiple-proton transfer.[6a,34] However, discussions elsewhere[35,36] have shown that values of the kinetic isotope effects are not very informative with respect to the concerted or stepwise nature of the process for proton transfer between oxygen or nitrogen acceptor atoms, involving small proton transfer distances compared to processes in which carbon acceptor atoms participate. Small proton transfer distances cause small kinetic isotope effects, even if several protons are transferred in a single concerted step.

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