Acta Chemica Scandinavica A 38 (1984) 309–326

Extended Brønsted Plots and Solvent Isotope Effects for the Base Catalyzed Mutarotation of Glucopyranoses in Water

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Kinetic data obtained by conventional polarimetry for the base catalyzed mutarotation of glucose and some derivatives have been extended by a stopped-flow polarimetric technique. Thus a Brønsted plot for glucose covering a pK range of 17 units could be constructed. Kinetic primary deuterium isotope effects were also measured for some of the catalysts.

The most pertinent feature of the results is the observation of a tendency for convex curvature in the Brønsted plot for glucose or, alternatively, a linear plot of slightly higher slope than observed before.

If the apparent change in Brønsted β is real it corresponds to a direct correlation (an anti-Hammond effect). This may be rationalized by suggesting a class n mechanism for catalysis by weaker bases which gradually changes into a stepwise reaction for stronger bases. Such a transition involves a decrease in coupling between C–O bond breaking and proton transfer in the transition state, and this is consistent with an accompanying decrease in observed kinetic deuterium isotope effects. However, a more complicated mechanism involving bi- or polyfunctional proton transfer cannot be excluded.

In a previous paper we have reported results from a stopped-flow polarimetric study of the hydroxide ion catalyzed mutarotation of a series of glucopyranoses, preferentially glucose.[1] In the present contribution stopped-flow as well as conventional polarimetry are applied to extend this work, *i.e.* to investigate the general base catalyzed mutarotation of some sugars over a much larger pK range than looked at systematically before. We also present primary kinetic isotope effects (solvent isotope effects) for a selection of bases.[2]

For a century the mechanism of addition of nucleophiles to carbonyl compounds, *e.g.* the hydration of simple aldehydes, has been of interest to chemists[3] and still is,[4] although recent advances [5,6] have thrown much light upon the reaction. Studies of structure reactivity relationships and extensive use of so-called More O'Ferrall-Jencks-square diagrams for visualization and rationalization of experimental data have been very helpful here.[7,8]

However, a number of questions still remain to be answered. We decided to concentrate on the intriguing fact that Brønsted plots for base as well as acid catalysis of carbonyl addition reactions "always" appear to be linear. This behaviour is unlikely according to *e.g.* Marcus' theory for a rate determining proton transfer, although a large intrinsic barrier tends to straighten the plots.[9] Absence of expected curvature in a plot is usually explained by suggesting coupling between proton transfer and heavy atom motion, *e.g.* C–O bond breaking. This explanation is qualitatively acceptable, but it seems unlikely that the tendency for curvature according to Marcus theory should be exactly counterbalanced by a coupling effect to give a straight line in all cases. Therefore, the apparent linearity might simply reflect the fact that Brønsted plots are almost always based on measurements over only a few pK units and studies over a much larger range might well demonstrate curvature (convex or

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0302-4377/83 $2.50

concave). A manifestation of this is given by Bell who has collected a large set of structure-reactivity data for proton transfer from various substrates (carbon acids) to a variety of bases covering a very wide pK range.[9] However, such studies do present difficulties due to variations in charge type, molecular structure, molar transparences etc., of the different "families" of base catalysts that necessarily have to be applied to cover the extended pK range referred to above.

We think we have been able to overcome these problems in the present studies to an extent that allows us to supplement in a constructive way the large amount of information already available about the mechanisms of acid-base catalyzed carbonyl addition reactions.

EXPERIMENTAL

Materials. All the sugars investigated were characterized in an earlier paper.[1] Trichloroacetic acid (Fluka, *purum*), dichloroacetic acid (Fluka, *puriss.*), pyridine (BDH Chemicals, lab. reag.), 3-methylpyridine (Fluka, *pract.*), 4-methylpyridine (Merck, *zur Syntese*), di- and triethylamine (Fluka, *purum*) and piperidine (Fluka, *puriss.*) were all distilled before use and boiling points checked. 2,4-Dinitrophenol (Merck, *zur Syntese*), 3- and 4-chlorophenol (Fluka, *purum*), phenol (Org. Inst., DTH) and 4-methylphenol (Merck, *puriss.*) were purified by sublimation. 3- and 4-Nitrophenol were recrystallized from water before use. Sodium acetate (Riedel-de Haën, *für Analyse*) and Sodium monochloroacetate (Org. Inst., DTH) and all other chemicals were of *Analar* grade and used without further purification. Purified water (millipore from a Milli-Q2 System) and deuterated water (Stohler Isotope Chemicals, 99,8 % deuterium content) were used as solvents.

Kinetic measurements. Rates of mutarotation were followed by conventional or stopped-flow polarimetry as also described earlier.[1] Solutions of the various catalyst buffers were prepared from the appropriate catalysts and stock solutions of standard sodium hydroxide or hydrochloric acid. Ionic strengths (I) were adjusted to 0.20 by either aqueous or solid sodium chloride. For the weaker bases where large catalyst concentrations were needed, the ionic strength was 0.5 whereas it was only 0.1 in the case where catalysis by the sugar anion was investigated, which served to improve the reliability of calculated activity coefficients that are of importance in the theoretical treatment of the experimental data in this case. The effect of varying the buffer *ratio* was investigated systematically only in a few cases, *e.g.* for acetate where both acid and base catalytic constants were determined. According to these results and to the general observations by Brønsted and Guggenheim in 1927[10] the acid catalysis of the mutarotation is negligible except for relatively strong acid catalysts. Base to acid buffer ratios (r) were therefore kept at relatively high values for the stronger acid catalysts (75–90 % basic form) leading to simplification in the derivation of base catalytic constants. Buffer ratios were currently checked by, and in some cases directly calculated from pH-measurements (Radiometer pH-meter 28) applying activity coefficients according to Kielland.[11]

In most experiments sugar concentrations were kept in the range 0.012 M (at 365 nm) to 0.025 M (at 578 nm). The higher wavelength was convenient when the strong UV-absorbing phenols were used as catalysts and polarimetry here clearly proves advantageous to UV-spectrophotometry.

For the investigation of rates in D_2O, compounds were not deuterated prior to use. Relatively concentrated stock solutions of HCl and NaOH in D_2O and reasonably low concentrations of buffer and sugar reduced the contamination of the reaction mixture with protium to a minimum (<1 %).

All experiments were carried out at 25.0±0.2 °C.

RESULTS

As pointed out in the introduction and discussion of this paper the question whether Brønsted plots for the processes studied here, and in general, are linear or curved (convex or concave) is not a trivial one. However, a slight curvature over a large ΔpK-range might be difficult to detect due to experimental uncertainties and to the fact that several "families" of catalysts necessarily have to be applied. One must therefore be careful not to draw too categoric conclusions from a relatively limited stock of experimental results.

We think we have detected a weak convex curvature in the Brønsted plot for the base catalyzed mutarotation of glucose. This statement is based upon a substantial set of measured catalytic constants over a large pK range. Because of the precautions described above we report and discuss our expertimental data slightly more detailed than might otherwise be justified.

Kinetics. As described earlier[1] the catalyzed as

well as the uncatalyzed mutarotation of the investigated sugars exhibit excellent first order behaviour under very different protolytic conditions, conforming to the simple reaction scheme

$$\alpha\text{-sugar} \underset{k_\beta}{\overset{k_\alpha}{\rightleftharpoons}} \beta\text{-sugar}$$

although the reaction is a relatively complex one. This may be taken as an indication that the ring opening of the sugar molecule *i.e.* the decomposition of an intramolecular hemiacetal, as described by

$$\alpha\text{-sugar} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \gamma\text{-sugar} \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} \beta\text{-sugar}$$

is always rate-determining. Here γ denotes the aldehydic chain form. This is in line with the observations that in aqueous solutions of most sugars the equilibrium concentration of aldehyde is extremely small,[13c] and it means that observed values of k_α or k_β are likely to be directly proportional to k_{12} and k_{32}, respectively.[12]

Apart from the electrochemical methods applied by various authors[13] trapping of the intermediate γ-form of glucose by chemical reagents has been attempted,[14] but results are so far inconclusive. Interesting results on trapping of the intermediate thiol group in the mutarotation of thiosugars has been published by Cleland *et. al.*[15] In some cases the authors found that mutarotation proceeds much faster than trapping and Cleland explained this by assuming mutarotation to take place *via* an "induced dipole intermediate" which cannot be trapped by the scavenger. This intermediate corresponds roughtly to the "pseudoacyclic" form of a sugar proposed earlier by Isbell *et al.*[16] It would be of considerable interest to compare results from trapping of sugar thiol intermediates with data from electrochemical (polarographic)[13] studies of the same compounds, if such experiments are possible.

No deviation from the simple behavior mentioned above was observed for any of the systems investigated in this paper. The catalyzed mutarotation of the sugars obey the well-known catalytic equation

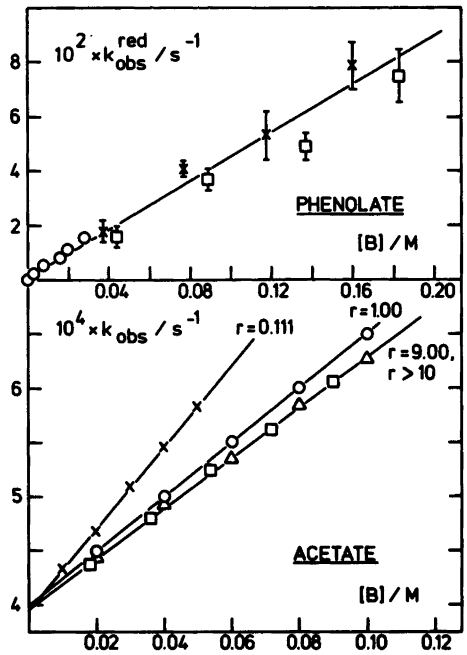


Fig. 1. Observed kinetic data for the mutarotation of glucose catalyzed by phenolate and acetate buffers (taken From Tables 1 and 2). Acetate: × r=0.111, ○ r=1.00, □ r=9.00, △ r>10. Phenolate: × Glucose(1), □ Glucose(2), ○ Glucose(3).

$$k_{obs} = k_o + k_H[H^+] + k_{HO}[HO^-] + k_{HB}[HB] + k_B[B] \quad (1)$$

with substantial values for the various catalytic constants in most cases, and this may serve as a further justification for the assumptions above since this equation is also valid for carbonyl group addition reactions in general, *e.g.* hydration.[3] We can conclude that although being of more complex nature, the mutarotation reaction obviously models a carbonyl group reaction very closely *i.e.* it reflects the decomposition of an intramolecular hemiacetal.

Results from the mutarotation of seven glucopyranoses catalyzed by carboxylic buffers and by water are given in Table 1 where the method for evaluation of the various catalytic constants is also explained. The data for acetate are plotted in Fig. 1 and it is obvious from this plot that catalysis by acetic acid as well as by the acetate ion contributes to the overall rate. However, at

Table 1. Kinetic data for the mutarotation of seven glycopyranoses catalyzed by various acetate buffers and by water. Conventional polarimetry (PE 141), λ=365 nm, I=0.20 (NaCl), t=25.0±0.2 °C. Each k_{obs} is an average from at least 4 single runs; k_{obs} at zero buffer concentration [k_o in eqn. (1)] is either determined by extrapolation (values given in parentheses) or taken from Ref. 1.

Acetate (K_A=1.78×10^{-5}, p=1, q=2)[a,b]

Glucose (1) r=0.111[c], pH=3.70,[e] (r=0.122)

10^2[B]/M[d]	0	1.0	2.0	3.0	4.0	5.0
10^4 k_{obs}/s^{-1}	(3.98(2))	4.33(2)	4.67(3)	5.08(3)	5.45(4)	5.83(4)

Glucose (2) r=1.00, pH=4.65[e] (r=1.08)

10^2[B]/M	0	2.0	4.0	6.0	8.0	10.0
10^4 k_{obs}/s^{-1}	(3.98(2))	4.50(2)	5.00(1)	5.50(2)	6.01(2)	6.49(2)

Glucose (3) r=9.00, pH=5.60[e] (r=9.69)

10^2[B]/M	0	1.8	3.6	5.4	7.2	9.0
10^4 k_{obs}/s^{-1}	(3.99(4))	4.37(1)	4.83(2)	5.25(2)	5.62(3)	6.05(3)

Glucose (4) r>10, pH=6.22[h] (r=40.4)

10^2[B]/M	0	2.0	3.9	5.9	7.8	9.8
10^4 k_{obs}/s^{-1}	(3.99(3))	4.43(2)	4.93(2)	5.35(1)	5.84(1)	6.27(3)

Eqn. (1) is now rewritten to give k_{obs}=const.+[(1/r) k_{HB}+k_B][B] and the equations combined as indicated by the figures in parentheses to give the following catalytic constants:

	(1)+(2)	(1)+(3)	(2)+(3)	(4)	Mean
10^3k_{HB}/M^{-1}s^{-1}	0.21(3)	0.19(2)	0.15(3)	—	0.18(3)
10^3k_B/M^{-1}s^{-1}	2.25(4)	2.28(4)	2.29(3)	2.36(2)	2.30(5)

3-*O*-Methylglucose r>10 pH=6.22[h] (r=40.4)

10^2[B]/M	0	4.9	9.8	
10^4 k_{obs}/s^{-1}	3.53(3)	4.47(5)	5.40(4)	k_B=1.91(4)×10^{-3}M^{-1}s^{-1}

2-*O*-Methylglucose r>10 pH=6.22[h] (r=40.4)

10^2[B]/M	0	4.9	9.8	
10^4 k_{obs}/s^{-1}	5.02(2)	6.57(3)	8.11(6)	k_B=3.16(6)×10^{-3}M^{-1}s^{-1}

N-Acetylglucosamine r>10 pH=6.22[h] (r=40.4)

10^2[B]/M	0	4.9	9.8	
10^4 k_{obs}/s^{-1}	5.17(3)	6.15(3)	7.12(7)	k_B=2.00(4)×10^{-3}M^{-1}s^{-1}

N-Benzoylglucosamine r>10 pH=6.22[h] (r=40.4)

10^2[B]/M	0	4.9	9.8	
10^4k_{obs}/s^{-1}	5.08(5)	5.96(3)	6.83(5)	k_B=1.79(4)×10^{-3}M^{-1}s^{-1}

Glucosamine hydrochloride r>10 pH=6.22[h] (r=40.4)

10^2[B]/M	0	4.9	9.8	
10^4k_{obs}/s^{-1}	5.12(4)	6.77(6)	8.41(7)	k_B=3.37(4)×10^{-3}M^{-1}s^{-1}

TMG[f] r>10 pH=6.22[h] (r=40.4)

10^2[B]/M	0	4.9	9.8	
10^4k_{obs}/s^{-1}	3.68(8)	4.82(5)	5.96(6)	k_B=2.95(6)×10^{-3}M^{-1}s^{-1}

Monochloroacetate ($K_A=1.41\times10^{-3}$, $p=1$, $q=2$)[a,b] pH=6.28[h]

10^2[B]/M[g]	0	10	20	
	$10^4k_{obs}/s^{-1}$			$10^4k_B/M^{-1}s^{-1}$
Glucose	4.00(3)	4.49(4)	5.00(4)	4.90(7)
3-*O*-Methylglucose	3.53(3)	3.92(3)	4.33(5)	4.00(6)
2-*O*-Methylglucose	5.02(2)	5.60(6)	6.17(5)	5.77(7)
N-Acetylglucosamine	5.17(3)	5.67(4)	6.17(5)	5.00(6)
N-Benzoylglucosamine	5.08(5)	5.53(6)	6.00(8)	4.60(8)
Glucosamine, HCl	5.12(4)	5.75(3)	6.37(6)	6.30(7)
TMG[f]	3.68(8)	4.18(7)	4.70(7)	5.03(8)

Dichloroacetate ($K_A=5.5\times10^{-2}$, $p=1$, $q=2$)[a,b] pH=6.35[h], $I=0.40$

10^2[B]/M[g]	0	20	40	
	$10^4k_{obs}/s^{-1}$			$10^4k_B/M^{-1}s^{-1}$
Glucose	4.00(3)	4.12(3)	3(1)	0.7(1)
3-*O*-Methylglucose	3.53(3)	3.51(7)	3.54(6)	—
2-*O*-Methylglucose	5.02(2)	5.35(5)	5.70(8)	1.70(9)
N-Acetylglucosamine	5.17(3)	5.45(3)	5.75(7)	1.40(8)
N-Benzoylglucosamine	5.08(5)	5.09(5)	5.06(8)	—
Glucosamine, HCl	5.12(4)	5.45(7)	5.80(8)	1.70(9)
TMG[f]	3.68(8)	3.70(6)	3.68(9)	—

Trichloroacetate ($K_A=2.3\times10^{-1}$, $p=1$, $q=2$)[a,b] pH=6.50[h], $I=0.50$

10^2[B]/M[g]	0	25	50	
	$10^4k_{obs}/s^{-1}$			$10^5k_B/M^{-1}s^{-1}$
Glucose	4.00(3)	4.20(6)	4.40(7)	8.00(9)
3-*O*-Methylglucose	3.53(3)	3.51(7)	3.51(9)	—
2-*O*-Methylglucose	5.02(2)	4.98(6)	4.97(9)	—
N-Acetylglucosamine	5.17(3)	5.38(8)	5.66(9)	9.60(9)
N-Benzoylglucosamine	5.08(5)	5.01(6)	5.0(1)	—
Glucosamine, HCl	5.12(4)	5.09(9)	5.10(1)	—
TMG[f]	3.68(8)	3.7(1)	3.7(1)	—

[a] Acidity constants taken from Ref. 18. [b] Statistical factors chosen according to Ref. 9 p. 198 and Ref. 19. [c] r denotes the base to acid buffer ratio [B]/[HB], where $[B]+[HB]=C_{total}^{buffer}$; r is either obtained directly from the known buffer composition or calculated (values given in parentheses) from $(1/f_-)$ antilg $(pH-pK_A)$, where f_- is the activity coefficient for the involved anionic species, taken as $f_-=0.731$ for carboxylic acids at $I=0.20$.[11] [d] Calculated from $[r/(1+r)]\ C_{total}^{buffer}$. [e] Measured average value for the series. [f] 2,3,4,6-Tetra-*O*-methylglucose. [g] $[B]=C_{total}^{buffer}$ $(r\gg1)$. [h] Adjusted.

$r>\sim9$ the anion dominates completely. Most catalytic constants in Table 1 have not been reported before, but in the case of *e.g.* acetic acid values of $k_{HB}=2.4\times10^{-4}$ $M^{-1}s^{-1}$ and $k_B=2.31\times10^{-3}$ $M^{-1}s^{-1}$ (25 °C) found by Morgan and Neuberger[17] are in fair agreement with ours.

Table 2 presents data for catalysis by phenolates. The systematic variation of r for catalysis of the mutarotation of glucose by unsubstituted phenolate in top (see Fig. 1 for plots) might at first sight indicate a (small) catalytic contribution from undissociation phenol (*cf.* data for acetic acid/acetate). However, the experiment at pH=5.82 ([phenol]=0.4 M) disproves this and the small trend in the data (Fig. 1) is doubtful and may be due to experimental uncertainty. Thus a mean value is taken as represented by the slope of the line in Fig. 1. It is appropriate here to

Table 2. Catalysis of the mutarotation of some glucopyranoses (mainly glucose) by a series of phenolates. Conventional (PE 141) or stopped-flow polarimetry, λ=546.1 nm, I =0.20 (NaCl), t=25.0±0.2 °C. Each k_{obs} is an average from at least 4 single runs.

pH[c]	$10^4\times[HO^-]$[d]/ M	r[e]	$10^3\times C^{buffer}_{total}$/ M	$10^3\times[B]$[f]/ M	$10^2\times k_{obs}$/ s^{-1}	$10^2\times k^o_{obs}$[g]/ s^{-1}	$10^2\times k^{red}_{obs}$[h]/ s^{-1}
Phenolate (K_A=1.00×10^{-10}, p=1, q=1)[a,b]							
Glucose (1) (stopped-flow)							
10.35	3.16	2.95	50	37	4.7(4)	2.9(1)	1.8(4)
10.40	3.54	3.31	100	77	7.3(2)	3.2(2)	4.1(3)
10.45	3.98	3.72	150	118	8.9(9)	3.6(2)	5.3(9)
10.50	4.46	4.17	200	161	11.9(9)	4.0(2)	7.9(9)
					k_B=0.47(4) $M^{-1}s^{-1}$		
Glucose (2) (stopped-flow)							
10.75	7.93	7.42	50	44	8.7(1)	7.1(4)	1.6(4)
10.80	8.90	8.32	100	89	11.6(2)	7.9(4)	3.7(4)
10.90	11.20	10.48	150	137	14.7(2)	9.8(5)	4.9(5)
10.90	11.20	10.48	200	183	17.3(9)	9.8(5)	7.5(10)
					k_B=0.41(4) $M^{-1}s^{-1}$		
Glucose (3) (PE 141)							
9.43	0.380	0.355	10	2.62	0.58(3)	0.35(3)	0.23(4)
9.46	0.407	0.380	30	8.26	0.91(1)	0.37(3)	0.54(3)
9.55	0.500	0.468	50	15.94	1.31(1)	0.46(4)	0.85(4)
9.47	0.416	0.389	70	18.60	1.49(3)	0.38(4)	1.11(5)
9.47	0.416	0.389	100	28.00	1.92(9)	0.38(4)	1.54(10)
					k_B=0.51(4) $M^{-1}s^{-1}$		
Glucose (4) (PE 141)							
5.82	9.32 ×10^{-5}	~0	400	~0	4.03(8) ×10^{-2}	~0	4.03(8)[i] ×10^{-2}
3-*O*-Methylglucose (stopped-flow)							
10.70	7.07	6.62	50	43	8.6(1)	6.4(3)	2.2(3)
10.80	8.90	8.32	100	89	11.4(2)	7.9(4)	3.5(4)
10.85	9.99	9.34	150	136	13.5(1)	8.9(4)	4.6(4)
10.85	9.99	9.34	200	181	15(1)	8.9(4)	6.1(4)
					k_B=0.33(3) $M^{-1}s^{-1}$		
2-*O*-Methylglucose (stopped-flow)							
10.65	6.30	5.89	50	43	8(1)	5.7(3)	2(1)
10.70	7.07	6.62	100	87	11.5(5)	6.4(3)	5.1(6)
10.80	8.90	8.32	150	134	14(3)	7.9(4)	6(3)
10.80	8.90	8.32	200	179	18(4)	7.9(4)	10(4)
					k_B=0.5(1) $M^{-1}s^{-1}$		

N-Acetylglucosamine (stopped-flow)

10.65	6.30	5.89	50	43	9(1)	5.7(3)	3(1)
10.70	7.07	6.62	100	87	11.3(4)	6.4(3)	4.9(5)
10.80	8.90	8.32	150	134	14(1)	7.9(4)	6(1)
10.80	8.90	8.32	200	179	15.6(4)	7.9(4)	7.7(6)

k_B=0.4(1) $M^{-1}s^{-1}$

Glucosamine, HCl (stopped-flow)

8.90	0.112	0.105	50	4.7	1.1(2)	0.10(1)	1.0(2)
9.90	1.12	1.05	100	51	3.8(3)	1.0(1)	2.8(3)
10.20	2.24	2.09	150	101	6.7(5)	2.0(1)	4.7(5)
10.60	5.62	5.25	200	168	10.2(8)	5.1(3)	5.1(9)

k_B=0.35(5) $M^{-1}s^{-1}$

4-Methylphenolate ($K_A=5.50\times10^{-11}$, $p=1$, $q=1$)[a,b]

Glucose (1) (PE 141)[j]

9.80	0.830	0.347	2	0.5	0.54(1)	0.76(4)	−0.22(4)[k]
9.80	0.830	0.347	5	1.3	0.75(2)	0.76(4)	−0.01(4)[k]
9.80	0.830	0.347	10	2.6	1.13(3)	0.76(4)	0.37(5)

Glucose (2) (stopped-flow)

10.60	5.62	2.89	50	37	9.(1)	5.1(3)	4(1)
10.68	6.75	3.47	100	78	13.4(7)	6.1(3)	7.3(8)
10.72	7.40	3.80	150	119	17(2)	6.6(3)	10(2)

k_B=0.9(1) $M^{-1}s^{-1}$ [(1)+(2)]

4-Chlorophenolate ($K_A=3.80\times10^{-10}$, $p=1$, $q=1$)[a,b]

Glucose (1) (stopped-flow)

10.10	1.78	6.31	50	43	3.7(3)	1.6(1)	2.1(3)
10.15	1.99	7.08	100	88	6.0(7)	1.8(1)	4.2(7)
10.20	2.24	7.95	150	133	8(1)	2.0(1)	6(1)
10.25	2.51	8.92	200	180	9(1)	2.3(1)	7(1)

Glucose (2) (PE 141)[j]

8.90	0.105	0.377	10	2.7	0.249	0.096(5)	0.153(5)
8.90	0.105	0.377	20	5.5	0.340(4)	0.096(5)	0.244(6)
8.90	0.105	0.377	30	8.2	0.416(8)	0.096(5)	0.320(9)

k_B=0.48(5) $M^{-1}s^{-1}$ [(1)+(2)]

3-Chlorophenolate ($K_A=8.32\times10^{-10}$, $p=1$, $q=1$)[a,b]

Glucose (1) (stopped-flow)

9.90	1.12	8.72	50	45	1.47(7)	1.02(5)	0.45(9)
9.92	1.17	9.13	100	90	2.6(1)	1.06(5)	1.5(1)
9.94	1.23	9.56	150	136	3.9(9)	1.12(6)	2.8(9)
9.95	1.26	9.78	200	181	4.8(3)	1.15(6)	3.6(3)

Glucose (2) (PE 141)[j]

8.50	4.16×10^{-2}	0.329	20	4.9	0.173	0.038(2)	0.135(2)
8.50	4.16×10^{-2}	0.329	60	15	0.418(1)	0.038(2)	0.380(2)
8.50	4.16×10^{-2}	0.329	100	25	0.59(1)	0.038(2)	0.55(1)

k_B=0.20(3) $M^{-1}s^{-1}$ [(1)+(2)]

3-Nitrophenolate ($K_A=3.98\times10^{-9}$, $p=1$, $q=1$)[a,b]

Glucose (PE 141)

7.90[j]	1.05×10^{-2}	0.395	20	5.7	0.116(2)	0.010(1)	0.106(2)
7.90[j]	1.05×10^{-2}	0.395	60	17	0.233(5)	0.010(1)	0.223(5)
7.90[j]	1.05×10^{-2}	0.395	100	28	0.312(6)	0.010(1)	0.302(6)
8.70	7.07×10^{-2}	2.63	8	5.8	0.154(4)	0.064(3)	0.090(5)
8.70	7.07×10^{-2}	2.63	20	15	0.251(3)	0.064(3)	0.187(4)
8.70	7.07×10^{-2}	2.63	40	29	0.348(6)	0.064(3)	0.284(7)
8.72	7.40×10^{-2}	2.76	8	5.9	0.169(2)	0.067(3)	0.102(4)
8.72	7.40×10^{-2}	2.76	20	15	0.25(1)	0.067(3)	0.18(1)
8.72	7.40×10^{-2}	2.76	40	29	0.325(8)	0.067(3)	0.258(9)
8.90[j]	0.105	3.95	20	16	0.333(4)	0.096(5)	0.237(6)
8.90[j]	0.105	3.95	30	24	0.394(6)	0.096(5)	0.298(8)
8.90[j]	0.105	3.95	40	32	0.44(3)	0.096(5)	0.34(3)

k_B=0.095(5) $M^{-1}s^{-1}$

4-Nitrophenolate ($K_A=7.08\times10^{-8}$, $p=1$, $q=1$)[a,b]

Glucose (PE 141)

6.65[j]	5.88×10^{-4}	0.395	20	5.7	0.0528(3)	0.00054(3)	0.0523(3)
6.65[j]	5.88×10^{-4}	0.395	60	17	0.0765(1)	0.00054(3)	0.0760(1)
6.65[j]	5.88×10^{-4}	0.395	100	28	0.106(2)	0.00054(3)	0.105(2)
7.75[j]	7.40×10^{-3}	4.98	20	17	0.0882(3)	0.0067(3)	0.0815(4)
7.75[j]	7.40×10^{-3}	4.98	60	50	0.151(2)	0.0067(3)	0.144(2)
7.75[j]	7.40×10^{-3}	4.98	100	83	0.220(2)	0.0067(3)	0.213(2)
8.50	4.46×10^{-2}	29.53	10	9.7	0.084(2)	0.041(2)	0.043(3)
8.50	4.46×10^{-2}	29.53	80	77	0.227(7)	0.041(2)	0.186(7)
8.50	4.46×10^{-2}	29.53	100	97	0.268(3)	0.041(2)	0.227(4)

k_B=0.019 (1) $M^{-1}s^{-1}$

2,4-Dinitrophenolate ($K_A=8.13\times10^{-5}$, $p=1$, $q=1$)-[a,b]

Glucose (PE 141)

6.80	8.90×10^{-4}	677	8	8	0.0412(2)	0.00081(4)	0.0404(2)
6.80	8.90×10^{-4}	677	20	20	0.0415(3)	0.00081(4)	0.0407(3)
6.80	8.90×10^{-4}	677	40	40	0.044(1)	0.00081(4)	0.043(1)

$k_B=7.4(5)\times10^{-4}$ $M^{-1}s^{-1}$

[a, b] See Table 1. [c] PE 141: pH of the reaction solution measured directly; stopped-flow: pH of either the reaction solution collected from the apparatus or of an *ad hoc* manually prepared equivalent solution. There was always good agreement between pH values obtained by the two procedures. [d] Calculated from $(1/f_-)$ antilg (pH−14.00), where f_- is taken as 0.709 at I=0.20.[11] [e] r defined in Table 1, f_- for phenolates taken as 0.758 at I=0.20.[11] [f] Calculated from $[r/(1+r)]\times C_{total}^{buffer}$. [g] Calculated from eqn. (3) in Ref. 1 or simply from $91\times[HO^-]$ s^{-1} (at lower pH).[1] [h] $k_{obs}^{red}=k_{obs}-k_{obs}^{o}$. [i] The rate constant for pure water catalysis is $4.00(3)\times10^{-4}s^{-1}$.[1] [j] I=0.10, f_-=0.80 and 0.76 for the phenolate and hydroxide ion, respectively.[11] [k] The negative rate constants indicate that the standard deviations of k_{obs}^{o} may be underestimated or are due to minor uncertainties in [B] and/or the measured pH.

Table 3. Catalysis of the mutarotation of glucose by a series of nitrogen bases. Conventional (PE 141) or stopped-flow polarimetry, λ=546.1 nm, I=0.20 (NaCl), t=25.0±0.2 °C. Each k_{obs} is an average from at least 4 single runs.

pH[c]	$10^4\times[HO^-]^{d}$/ M	r^e	$10^3\times C_{total}^{buffer}$/ M	$10^3\times[B]^f$/ M	$10^2\times k_{obs}$/ s^{-1}	$10^2\times k_{obs}^{o}{}^g$/ s^{-1}	$10^2\times k_{obs}^{red}{}^h$/ s^{-1}
Piperidine ($K_A=7.59\times10^{-12}$, p=2, q=1)[a,b]							
Glucose (stopped-flow)							
10.25	2.51	0.102	50	4.6	2.9(2)	2.3(1)	0.6(2)
10.25	2.51	0.102	100	9.3	3.7(3)	2.3(1)	1.4(3)
10.25	2.51	0.102	150	14	4.7(1)	2.3(1)	2.4(1)
10.25	2.51	0.102	200	19	5.6(4)	2.3(1)	3.3(4)
11.15	19.9	0.812	50	23	26(2)	17.0(8)	9(2)[10]
11.30	28.1	1.15	125	67	39(2)	23(1)	16(2)[18]
11.31	28.8	1.17	194	105	44(2)	24(1)	20(2)[23]
11.55	50.0	2.04	50	33	41(1)	39(2)	2(2)[3]
11.60	56.2	2.29	100	70	61(3)	43(3)	18(4)[23]
11.65	63.0	2.57	150	108	73(2)	47(3)	26(4)[34]
11.70	70.7	2.88	200	149	82(3)	52(3)	30(4)[41]
				k_B=2.8(5) $M^{-1}s^{-1}$			
Diethylamine ($K_A=1.00\times10^{-11}$, p=2, q=1)[a,b]							
Glucose (stopped-flow)							
10.25	2.51	0.130	50	5.8	3.0(3)	2.3(1)	0.7(3)
10.25	2.51	0.130	100	12	3.5(4)	2.3(1)	1.2(4)
10.25	2.51	0.130	150	17	4.0(1)	2.3(1)	1.7(1)
11.55	50.0	2.59	50	36	38(1)	39(2)	−1(2)
11.60	56.2	2.91	100	74	53(2)	43(3)	10(4)[13]
11.65	63.0	3.27	150	115	60(2)	47(3)	13(4)[17]
11.70	70.7	3.66	200	157	67(1)	52(3)	15(4)[20]
				k_B=1.5(5) $M^{-1}s^{-1}$			
Triethylamine ($K_A=1.86\times10^{-11}$, p=1, q=1)[a,b]							
Glucose (stopped-flow)							
11.40	35.4	3.46	50	38	26.8(3)	29(1)	−2(1)
11.40	35.4	3.46	150	116	38.6(7)	29(1)	10(1)[12]
11.45	39.8	3.88	200	159	43(2)	32(2)	11(3)[13]
				k_B=0.9(2) $M^{-1}s^{-1}$			
Pyridine ($K_A=6.03\times10^{-6}$, p=1, q=1)[a,b]							
Glucose (PE 141)							
6.02[i]	1.05×10^{-4}	4.79	20	17	0.0511(8)	0.0001	0.0510(8)
6.02[i]	1.05×10^{-4}	4.79	60	50	0.0726(6)	0.0001	0.0725(6)
6.02	1.05×10^{-4}	4.79	100	83	0.0923(9)	0.0001	0.0922(9)
				$k_B=6.4(2)\times10^{-3}M^{-1}s^{-1}$[j]			

3-Methylpyridine ($K_A=2.34\times10^{-6}$, $p=1$, $q=1$)[a,b]

Glucose (PE 141)

6.50[i]	4.46×10^{-4}	5.61	20	17	0.0596(5)	0.0004	0.0592(5)
6.50[i]	4.46×10^{-4}	5.61	60	51	0.0963(4)	0.0004	0.0959(4)
6.50[i]	4.46×10^{-4}	5.61	100	85	0.130(1)	0.0004	0.130(1)

$k_B=1.10(3)\times10^{-2}M^{-1}s^{-1}$

4-Methylpyridine ($K_A=9.33\times10^{-7}$, $p=1$, $q=1$)[a,b]

Glucose (PE 141)

6.83[i]	9.54×10^{-4}	4.78	20	17	0.0673(8)	0.0009	0.0664(8)
6.83[i]	9.54×10^{-4}	4.78	60	50	0.1165(5)	0.0009	0.1156(5)
6.83[i]	9.54×10^{-4}	4.78	100	83	0.163(1)	0.0009	0.162(1)

$k_B=1.48(2)\times10^{-2}M^{-1}s^{-1}$ [k]

[a,b] See Table 1. [c,d] See Table 2. [e] r is determined from f_+ antilg (pH−pK_A), where f_+ is taken as 0.758 for piperidine and pyridines and equal to 0.731 and 0.740 for di- and triethylamine, respectively.[11] [f] Calculated from $[r/(1+r)]\times C_{total}^{buffer}$. [g] See table 2. [h] See Table 2. Figures in square brackets are equal to $(1+50\times[HO^{-1}])\times k_{obs}^{red}$ (see text). [i] Adjusted. [j] Values of $k_B=5.98\times10^{-3}$ (Capon and Walker),[21] 7.48×10^{-3} (Worley and Andrews),[22] 5.09×10^{-3} (Morgan and Neuberger)[17] have been reported for this constant. [k] Capon and Walker found $k_B=1.42\times10^{-2}$ for this compound.[21]

notice that for the strongly basic catalysts r cannot be kept constant in a series of experiments where the total buffer concentration is varied systematically, at least not when the sugar concentration is kept constant. This is of course due to the fact that the acidities of catalyst and sugar are now relatively similar and a minor "neutralization" takes place. This appears as a slight change in pH throughout a series of runs and complicates the derivation of catalytic constants. A k_B (phenolate) for glucose mutarotation has been reported before by Smith and Smith[20] as equal to 0.38 $M^{-1}s^{-1}$ and 25 °C (extrapolated from data at 0–15 °C). This value is slightly smaller than ours.

Table 3 presents data for the catalysis of glucose mutarotation by six nitrogen bases. The procedure of data treatment is similar here to that for the phenolates, but one further complication arises: the pH of the reacting solutions is now so high that corrections for conversion of the substrate sugar into its anion are needed. Although the glucosate anion is not completely insensitive to catalysis by the hydroxide ion[1] we will assume here that this is so for bases weaker than hydroxide. It is easily shown that the observed, uncorrected, individual rate constants for determination of the catalytic constants should be multiplied by a factor of $(1+[HO^-]\times K_A(\text{glucose})/K_{H_2O})\approx(1+50[HO^-])$ to give the correct values indicated in square brackets in Table 3.[9]

In an earlier, preliminary presentation of this work (see Ref. 2) the necessity for this correction was not realized by us and an Eigen type

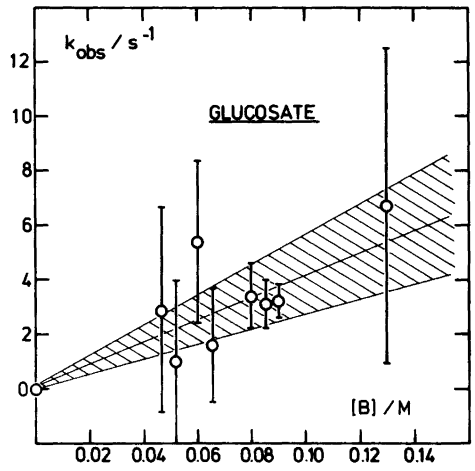


Fig. 2. Data from Table 4 for the catalysis of glucose mutarotation by the glucosate anion.

Table 4. The autocatalytic effect in the mutarotation of glucose. Rates measured by stopped-flow at different sugar concentrations, λ=546,1 nm, I=0.10 (NaCl), t=25.0±0.2 °C. Each k_{obs} is an average from at least 4 single runs.

pH[c]	$10^4\times[HO^-]$[d]/ M	$10^3\times C^{sugar}_{total}$/ M	$10^3\times[B]$[e]/ M	k_{obs}/ s^{-1}	k^o_{obs}[f]/ s^{-1}	k^{red}_{obs}[g]/ s^{-1}	k^{red}_{obs}(corr.)[h]/ s^{-1}
Glucosate (K_A (mean)=5.01×10^{-13}, p=1, q=1)[a,b]							
12.61	536.0	60	46.4	2.08(3)	2.0(1)	0.08(10)	0.29(38)
12.56	477.7	70	52.2	1.94(1)	1.91(9)	0.03(9)	0.10(30)
12.48	401.2	80	59.9	1.89(4)	1.71(9)	0.18(10)	0.54(30)
12.42	346.1	100	65.4	1.63(2)	1.57(8)	0.06(8)	0.16(21)
12.39	322.3	120	67.8	1.58(4)	1.50(8)	0.08(9)	0.21(23)
12.18	201.0	160	79.9	1.28(1)	1.11(6)	0.17(6)	0.34(12)
12.05	146.6	200	85.3	1.09(1)	0.91(5)	0.18(5)	0.31(9)
12.69[i]	690.9	200	131	2.45(8)	2.3(1)	0.15(13)	0.67(58)
11.90	104.5	250	89.5	0.953(8)	0.74(4)	0.21(4)	0.32(6)
			k_B=4±2 M^{-1} s^{-1}				

[a] K_A(mean) taken from Ref. 1. [b] Statistical factors: see Table 1. [c] See Table 2. [d] Calculated from (1/f_-) antilg (pH−14.00), where f_- is taken as 0.76 at I=0.10.[11] [e] Equal to $[HO^-]_{initial}-[HO^-]_{calculated}$ ($[HO^-]_{initial}$=0.10 M apart from the experiment at pH=12.69, where it was 0.20 M). [f] Calculated from eqn. (3) in Ref. 1. [g] $k^{red}_{obs}=k_{obs}-k^o_{obs}$. [h] $k^{red}_{obs}(corr.)=1+50\times[HO^-])\times k^{red}_{obs}$ (see text). [i] I=0.2, f_-=0.709 for hydroxide.[1] Literature values for k_B (glucosate): 7.47 and 5.70 for α- and β-form, respectively (Los and Simpson),[23] 1.0 (Schmid and Bauer),[24] 1.73 (Isbell and Wade) (20 °C),[25] 5.91 (Euler and Ölander) (20 °C).[26]

curvature in this region was erroneously suggested.

There is no immediately obvious reason why the glucosate anion should not be functioning as a catalyst for mutarotation analogously to the other bases of similar strength in this region. However, it might be difficult to quantify the effect because of complications arising from the relatively strong basic conditions that are needed to generate a considerable concentration of the catalyst.

Table 5. Catalysis of the mutarotation of glucose by different bases in deuterium oxide. Conventional or stopped-flow polarimetry, I=0.20 (NaCl), t=25.0±0.2 °C. Each k_{obs} is an average of at least 4 single runs. k_{obs} values at zero buffer concentration (k_o in eqn. (1)) are determined by extrapolation (values given in parentheses).

Acetate ($K_A(D_2O)$=5.25×10^{-6}, p=1, q=2),[a,b] pD=6.19[e], r=9.00[c]					
$10^3\times$[B]/M[d]	0	54	108		k_B=1.04(4)×10^{-3} $M^{-1}s^{-1}$
$10^4\times k_{obs}/s^{-1}$	(1.06(3))	1.62(3)	2.18(2)		
2,4-Dinitrophenolate ($K_A(D_2O)$=2.57×10^{-5}, p=1, q=1),[a,b] pD=5.71[e], r=12.46[c]					
$10^3\times$[B]/M[d]	0	13	40		k_B=2.6(8)×10^{-4} $M^{-1}s^{-1}$
$10^4\times k_{obs}/s^{-1}$	(1.05(3))	1.11(1)	1.18(7)		
4-Nitrophenolate ($K_A(D_2O)$=1.95×10^{-8}, p=1, q=1),[a,b] pD=8.41[e], r=9.00[c]					
$10^3\times$[B]/M[d]	0	18	54	90	
$10^4\times k_{obs}/s^{-1}$	(0.6(1))	2.3(1)	5.8(1)	9.4(2)	k_B=9.9(2)×10^{-3} $M^{-1}s^{-1}$
3-Nitrophenolate ($K_A(D_2O)$=1.05×10^{-9}, p=1, q=1),[a,b] pD=9.29[e], r=3.00[c]					
$10^3\times$[B]/M[d]	0	6	15	30	
$10^4\times k_{obs}/s^{-1}$	(4.5(2))	6.8(2)	11.1(1)	16.9(6)	k_B=4.2(1)×10^{-2} $M^{-1}s^{71}$

Phenolate ($K_A(D_2O)=2.40\times10^{-11}$, $p=1$, $q=1$),[a, b]

pD[e]	$10^4\times[DO^-]^f$/ M	r^g	$10^3\times C^{buffer}_{total}$/ M	$10^3[B]^d$/ M	$10^2\times k_{obs}$/ s^{-1}
—	(1.75)[j]	—	0	0	(2.5(5))
10.99	1.86	3.09	50	38	3.1(5)
11.03	2.04	3.39	100	77	4.0(5)
11.01	1.95	3.24	150	115	4.3(7)
11.07	2.24	3.72	200	158	5.5(6)

$k_B=0.19(2)$ $M^{-1}s^{-1}$, k_B (corr)$=0.16(2)$ $M^{-1}s^{-1}$ (k_B-15 %)[i]
$k_{DO^-}=143\pm30$ $M^{-1}s^{-1}$ [k]

4-Methylphenolate ($K_A(D_2O)=1.32\times10^{-11}$, $p=1$, $q=1$)[a, b]

—	(2.7)[j]	—	0	0	(2.75(5))
11.21	3.09	2.82	50	38	4.7(3)
11.29	3.71	3.39	100	77	7(1)
11.31	3.89	3.55	150	117	8.7(7)
11.35	4.26	3.89	200	159	11(4)

$k_B=0.53(6)$ $M^{-1}s^{-1}$, k_B (corr)$=0.44(5)$ $M^{-1}s^{-1}$ (k_B-17 %)[i]
$k_{DO^-}=100\pm20$ $M^{-1}s^{-1}$ [k]

Piperidine ($K_A(D_2O)=1.9\times10^{-12}$, $p=2$, $q=1$)[a, b]

—	(10.6)[j]	—	0	0	(10(3))[11][h]
11.83	12.87	0.974	50	25	15.0(5)[16]
11.91	15.47	1.17	100	54	25(1)[27]
11.96	17.35	1.31	150	85	26(2)[28]

$k_B=2.5(3)$ $M^{-1}s^{-1}$, k_B (corr)$=1.8(2)$ $M^{-1}s^{-1}$ (k_B-28 %)[i]
$k_{DO^-}=104\pm30$ $M^{-1}s^{-1}$ [k]

[a] Acidity constants for acetic acid and phenols in D_2O are either taken directly or interpolated from data in Ref. 29. The value for piperidine is taken as $pK_A(H_2O)$ +0.6. [b] Statistical factors, see Table 1. [c] r=[B]/[HB] obtained from known buffer composition. [d] Calculated from $[r/(1+r)]C^{buffer}_{total}$. [e] Obtained by adding 0.41 to the value measured by normal glass and calomel electrodes[27] (see text). [f] Calculated from ($1/f_-$) antilg (pD–14.87), where the f_- values are given in previous tables, $pK_{D_2O}=14.87$ is reported by Salomaa on the basis of a critical comparison of various experimental results.[30] [g] Values of r are here obtained from ($1/f_-$) antilg (pD$-pK_A(D_2O)$) where f_- values are given in previous tables. [h] Figures in square brackets are equal to $(1+50\times[DO^-])\times k_{obs}$ (see text). [i] k_B has been corrected by the given percentages for contributions from deuteroxide ion catalysis according to considerations elsewhere (see text). [j] Obtained by simple linear extrapolation. [k] k_{DO^-} obtained from extrapolated values in the first row.

Nevertheless, a number of determinations of this constant have been reported in the literature, some of which are given in Table 4 (bottom). The scatter is obvious and our value determined from Table 4 is no better (see Fig. 2 for plot). Presumably, the most accurate value for this catalytic constant is the one determined by Los and Simpson by electrometric measurements.[23] These authors could even distinguish between k_B for α- and β-glucosate.

Isotope Effects. Kinetic, primary isotope (solvent isotope) effects were also determined for some of the catalysts. Kinetic data from experiments carried out in deuterated water are given in Table 5, where treatment of the data is also explained. Of course, pK_A (D_2O), pD, and pK_{D_2O} must now be known. K_{D_2O} and K_A for the various catalysts could be obtained form various sources as explained in Table 5, or they could be estimated. Measurements of pD were accom-

Table 6. Observed primary kinetic isotope effects for the mutarotation of glucose catalyzed by various bases.

Catalyst	K_A[a]	$k_B^H/M^{-1}s^{-1}$	$k_B^D/M^{-1}s^{-1}$	k_B^H/k_B^D
Water	5.55×10^{1}	$4.00(4)\times10^{-4}$	$1.06(3)\times10^{-4}$	3.77(11)[b]
Acetate	1.78×10^{-5}	$2.30(5)\times10^{-3}$	$1.04(4)\times10^{-3}$	2.21(9)[c]
2,4-Dinitrophenolate	8.33×10^{-5}	$7.4(5)\times10^{-4}$	$2.6(8)\times10^{-4}$	2.86(90)
4-Nitrophenolate	7.08×10^{-8}	$1.9(1)\times10^{-2}$	$9.9(2)\times10^{-3}$	1.92(11)
3-Nitrophenolate	3.98×10^{-9}	$9.5(5)\times10^{-2}$	$4.2(1)\times10^{-2}$	2.26(13)
Phenolate	1.00×10^{-10}	$4.7(4)\times10^{-1}$	$1.6(2)\times10^{-1}$	2.94(44)
4-Methylphenolate	5.50×10^{-11}	$9(1)\times10^{-1}$	$4.4(5)\times10^{-1}$	2.05(32)
Piperidine	7.59×10^{-12}	2.8(5)	1.8(2)	1.56(33)
Hydroxide ion	1.82×10^{-16}	$9(1)\times10^{1}$	$1.0(2)\times10^{1}$	0.90(19)[d]

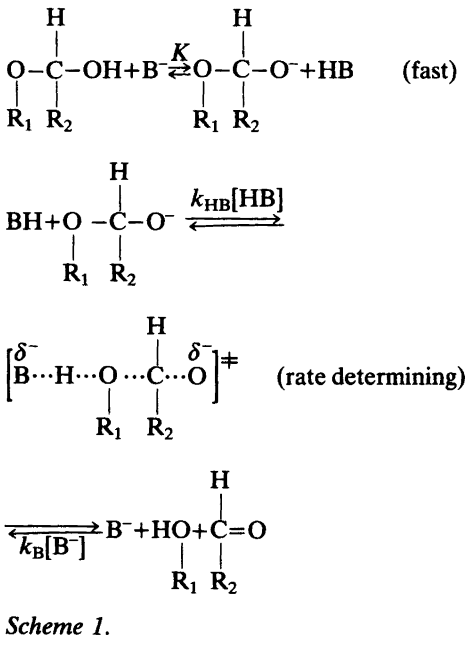
[a] Acidity constant for corresponding acid in water at 25 °C. [b] A number of literature values ranging from 3.16 to 3.85 are found for this constant, although most results tend to lie around 3.80. [c] Values of 2.38 (Challis *et al.*)[31], 2.60 (Schowen)[28] and 2.38 (Huang *et al.*)[32] were found in the literature. [d] Schowen reports a value of ~1 for the hydroxide ion.[28]

plished by the ordinary glass electrode standardizes as usual in H_2O and by adding 0.41 to the reading according to Covington *et al.*[27]

Since Ref. 1 does not contain figures for DO^- catalysis of the mutarotation of glucose we were not able to make direct corrections for this contribution where necessary in Table 5. However, the kinetic primary isotope effect for hydroxide ion catalysis is hardly distinguishable from unity (see later) and we have therefore applied a percentual correction to the final k_B-values (% given in parentheses) for phenolate, 4-methylphenolate and piperidine, taken from the *corresponding* pH intervals for HO^- catalysis.[1] This is probably a good approximation because the absence of an isotope effect means that the two rate-pH(D)-profiles for $H(D)O^-$ catalysis are directly comparable. As shown in Table 5 three values for k_{DO^-} can be deduced from the data. If the two coinciding values at the higher deuteroxide concentrations (k_{DO^-} ~100 $M^{-1}s^{-1}$) are considered to be most accurate it becomes immediately clear that the kinetic isotope effect (k_{HO^-}/k_{DO^-}) is indistinguishable from or slightly less than unity (k_{HO^-} ~90 $M^{-1}s^{-1}$).[1] This result is in line with k_{HO^-}/k_{DO^-} ~1 reported by Schowen.[28] All the kinetic isotope effects are collected in Table 6 and also plotted in Fig. 3 as a function of pK_A. Furthermore, Table 6 as well as Fig. 3 contain isotope effects for various catalysts determined by other workers.

DISCUSSION

General base catalysis. The generally accepted mechanisms for simple carbonyl addition reactions such as hydration and hemiacetal formation are a class *e* scheme[33] for general acid and class *n*[33] for general base catalysis.[4,5,6] Scheme 1 illustrates a class *n* reaction appropriate to the catalytic data in the present paper.



Scheme 1.

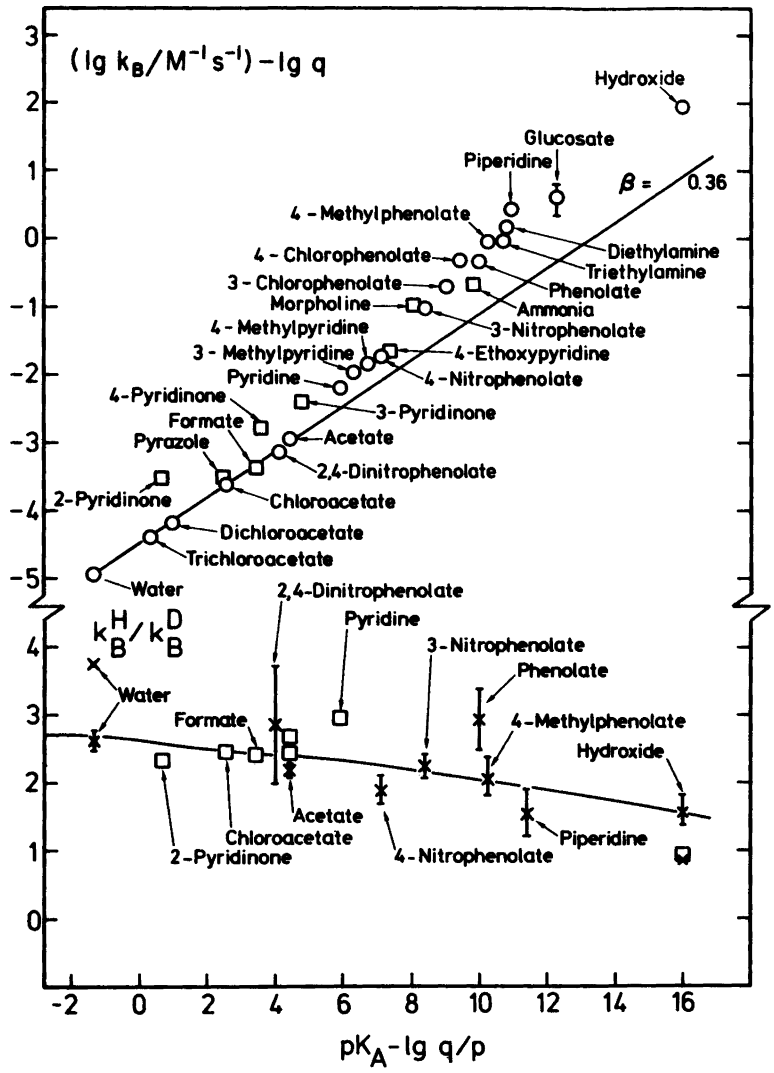
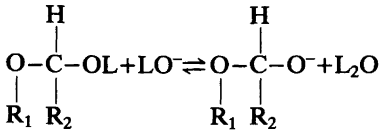
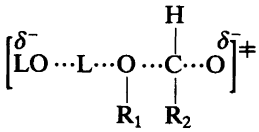


Fig. 3. Observed catalytic data for the mutarotation of glucose arranged in a Brønsted plot (for details see Tables 1–4 and text). The figure also contains primary kinetic isotope effects (solvent isotope effects) from Tables 5 and 6 for selected catalysts. ○, × Data from this work, □ Other sources as follows: Ammonia (Ref. 41), morpholine (Ref. 21), 4-ethoxypyridine (Ref. 21), 3-pyridine (Ref. 17), 4-pyridinone (Ref. 43), formate (Ref. 24), pyrazole (Ref. 43), 2-pyridinone (Refs. 43 and 28), chloroacetate (Ref. 28), acetate (Ref. 31), pyridine (Ref. 45), hydroxide (Ref. 28). It should be noted that pK values for several of the nitrogen bases have been corrected according to text. Experimentally observed isotope effects for hydroxide and water have been corrected due to secondary isotope effects. The secondary effect appears because catalyst water and hydroxide contain extra exchangeable protons in contrast to the other catalysts applied, although for hydroxide stretching of bonds to solvating molecules is probably also a contributing factor. For hydroxide catalysis Scheme 1 becomes

Fig. 3. Continued.





where only the transition state for the second (rate-determining) step is shown. The observed isotope effect k_H/k_D is now equal to $\phi_h/[\phi_1^{\neq} \cdot (\phi_h)^{1-\beta}]$, where ϕ_h denotes the fractionation factor for the hydroxide proton and $\phi_1^{\neq}$ the fractionation factor for the proton "in flight". If ϕ_h is taken as 0.4 and β as 0.44 $(\phi_1^{\neq})^{-1}$, which is the corrected isotope effect, will be equal to 1.5.

Similar considerations for water catalysis lead to a corrected value for k_H/k_D of $(k_H/k_D)_{obs} \cdot (l^{1-\beta})^2$. If l (the fractionation factor for protons in H_3^+O) is taken as 0.7 and β as 0.36 $(k_H/k_D)_{corr.}$ becomes 2.4.[46]

The relevance of Scheme 1 in general base catalysis was first suggested by Bell and co-workers,[19,34] and later studies of structure-reactivity parameters have further supported this mechanism. Brønsted and co-workers[10,35] restricted their investigations to substitution in the acid and base catalysts, but structure-reactivity studies are now being used more broadly. The effect of substitution on the shape of a two- or many-dimensional energy surface for a reacting system can conveniently be visualized and rationalized by the aid of square diagrams. Such diagrams were applied by More O'Ferrall[7] to describe possible mechanisms in β-elimination reactions, and Jencks and co-workers have emphasized and demonstrated the importance and usefulness of square diagrams in a number of cases where a mathematical description of the energy surface (saddle-point area) and its response to substitution has also been given.[5,8,36]

The experimentally observed change of Brønsted β on substitution in either the leaving group (nucleophile)[5] or the carbonyl substrate (electrophile)[6] can be rationalized only by class *n* and *not* by class *e*. In a class *e* mechanism the rate determining C–O bond breaking coupled with proton transfer takes place in the top line of Scheme 1 and the bottom line becomes a very fast proton equilibration reaction.

Capon and Walker[21] have argued that a class *n* mechanism is also most likely in base catalyzed mutarotation reactions since introduction of more electron-withdrawing substituents at C_6 in the hexoses under consideration led to an expected increase in Brønsted β.[5]

All base catalytic constants obtained in the present work for mutarotation of glucose are collected in the Brønsted plot given in Fig. 3, where observed kinetic isotope effects are also shown. Before being plotted some of the data have been corrected as follows. There is much evidence to show that relative catalytic powers of tertiary and secondary amines are not correctly expressed by the difference in their pK values in water. This is due to the different degrees of solvation of the cations (operating to a smaller extend in the transition state).[37] Thus in the decomposition of nitramide in anisole[38] the points for secondary and tertiary amines are brought on to the same Brønsted plot if 1.0 unit is subtracted from the pK values of the secondary amines in water. For nitramide in water[39] the difference between tertiary and *primary* amines (there are no data for secondary amines) is less than in anisole: it therefore seems reasonable for the glucose mutarotation to subtract 0.5 from pK (secondary) to make them comparable with tertiary ones. This correction has been applied to

diethylamine and piperidine in Fig. 3 (no statistical factors have been included since the secondary/tertiary differences have been inferred from observed kinetic behaviour). The results for nitramide in anisole[38] showed also that it was necessary to *add* 1.4 units to the pK values of pyridine bases to bring them on to the same Brønsted line as the other tertiary bases. If we apply half of this correction (*i.e.* add 0.7) to the pyridine pK's in the glucose mutarotation we obtain points, which are now close to the curve in Fig. 3, thus suggesting that it is reasonable to use the evidence from nitramide decomposition to "correct" the data for glucose. Kreevoy *et al.*[40] had to exclude four nitrophenols from a Brønsted plot in their work on the catalyzed hydrolysis of diphenyldiazomethane. We did not observe any anomaly for such compounds, in agreement with the results by Bell and Higginson[19] on the catalyzed dehydration of acetaldehyde hydrate.

If a line is drawn through the points for water and acetates (the solid line in Fig. 3) a Brønsted β value of 0.36 is obtained in agreement with β=0.34 (at 18 °C) reported by Brønsted and Guggenheim.[10] Brønsted β values for the remaining six substituted glucoses (Table 1) are reported in Table 7. Within experimental error these figures are probably indistinguishable and no judgements concerning the mechanism of base catalyzed mutarotation can be made (class *e* or class *n*). McClelland and Coe[6] observed for base catalyzed hydration/dehydration of a series of substituted benzaldehydes a slight but distinct increase in β with decreasing electron withdrawal in the substituent, consistent with a class *n* mechanism.

Table 7. Observed Brønsted β values for mutarotation of seven glucoses catalyzed by bases in the pK range: −1.74 to +4.75.[a] Data taken from Table 1.

Sugar	β
Glucose	0.36
3-*O*-Methylglucose	0.35
2-*O*-Methylglucose	0.37
N-Acetylglucosamine	0.34
N-Benzoylglucosamine	0.34
Glucosamine · HCl	0.37
TMG	0.34

[a] It is worthwhile noticing that the points for phenolate fall above the Brønsted plots in all cases (see Fig. 3 for glucose).

If we include all points in Fig. 3 (except the three pyridinones) in one Brønsted plot, a line of slope 0.42 results (not shown in Fig. 3). However, we think there is good indication of a slight convex curvature in the plot, *i.e.* an increase in β from 0.36 to 0.44 on increasing catalyst basic strength. This corresponds to an anti-Hammond effect which is a new but perhaps not surprising observation pointing towards coupling phenomena as mentioned earlier. The data for most of the nitrogen bases are less certain and do not provide much support for this general conclusion, especially in view of the somewhat arbitrary corrections made for the pK values, but it seems quite definite that there is a clear difference in β for acetates and for phenolates. If a class *n* mechanism is in operation this change in β is only apparent and reflects a real change in Brønsted α from 0.64 (1−0.36) to 0.56 (1−0.44). These α values correspond to the proton transfer in the second (rate-determining) step of Scheme 1. The points for pyridinones in Fig. 3 have been omitted in the considerations above as they exhibit rather distinct positive deviations from the plot. For 2-pyridinone this has been ascribed to catalytic properties of bifunctional nature.[42] However, such an effect is probably small if existing at all in water[43] which is also seen from the fact that 3- and 4-pyridinone show the same tendency for positive deviation although their geometrical structures are unfavourable for bifunctional catalysis. Since the three catalysts are modified *pyridines* the deviations might have a similar origin as that responsible for the observed deviation of the other (ordinary) pyridines in the plot.

It has been known for a long time that hydroxide exhibits distinct positive deviation from the Brønsted line for base-catalyzed mutarotation[10] and for similar reactions involving the carbonyl group.[5] The data in the present paper tend to show that this deviation is an apparent one which may appear only when the point for hydroxide is compared with points for relatively weakly basic catalysts, *e.g.* carboxylate anions. This (apparent) deviation is usually referred to as being due to a different mechanism for hydroxide. Observed structure-reactivity parameters (ρ for substitution in the electrophile,[1,6] and β_{nuc} for substitution in the nucleophile[5]) seem to support

such an assumption, *i.e.* for the adduct decomposition expulsion of the nucleophile takes place with little or no proton transfer from the conjugate acid of the basic catalysts in the transition state (Scheme 1).[5] Such a mechanism involves little coupling between proton transfer and C–O bond cleavage and the small amount of proton transfer in the transition state should lead to small kinetic isotope effects, in agreement with our observations (Fig. 3). For weak basic catalysts, however, there seems to be a considerable amount of coupling and proton transfer in the transition state consistent with the fact that we observed higher isotope effects here.

What our Brønsted plot then may show is a gradual change of mechanism from a more or less concerted to a totally uncoupled reaction when the basic strength is changed over a considerable range, *i.e.* a "merging" of two discrete mechanisms with no abrupt changes in Brønsted coefficient or in isotope effects. The observed anti-Hammond effect (a direct correlation)[36] is not out of place in this context: the strong coupling between proton transfer and C–O bond breaking for the reaction catalyzed by weak bases is governed by a sensitivity to variation in basic strength which is higher perpendicular to the reaction coordinate than in the parallel direction. This eventually leads to a complete decoupling when the bases become very strong, *e.g.* for hydroxide. It is interesting that recently McClelland and Coe may have observed an anti-Hammond effect also for general acid catalysis in their studies of hydration/dehydration of benzaldehydes.[6]

However, although most experimental evidence thus may be rationalized by the mechanism described above, there are still certain features which cannot be immediately explained. Thus a totally decoupled mechanism for hydroxide catalysis should imply a β value of unity (α=0). This is not observed as β approaches a value of only 0.44 for the strongest bases, including hydroxide. We can imagine several possible reasons for this "anomaly": (1) The suggested change of mechanism is correct but β (α) is not a *simple* measure of the degree of proton transfer in the transition state. (2) The suggested change of mechanism is wrong and the observed change in β in this paper is not real but may reflect different β values for different sets (families) of basic catalysts or some other effect that we have not been aware of. (3) The mechanism suggested is incomplete. A mechanism where *both* protons are coupled with C–O bond breaking is not *a priori* unlikely and it is difficult to predict values of β (α) in such a (bifunctional) case. However, various considerations and calculations for the decomposition of formaldehyde hydrate and hemiacetals have shown that such a mechanism is not very plausible in aqueous solution.[5] Thus, even for the weakest base water there seems to be no reason for introducing a doubly concerted mechanism to explain experimental data. However, the calculations are based on certain assumptions and do not necessarily *disprove* the existence of a more complicated mechanism.

We think the results in the present paper may have added some new information to our knowledge of the mutarotation mechanism and of carbonyl addition reactions in general. Some new questions have at least been raised, and more work is clearly needed before these can be answered more specifically.

Acknowledgements. We would like to thank R.P. Bell and M.G. Ettlinger for comments and for their kind interest in this work. Valuable suggestions from J. Ulstrup, W. P. Jencks, A. J. Kresge, J. L. Jensen, and M. M. Kreevoy are also appreciated.

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Received July 22, 1983.