Kinetics and Equilibria of Keto-Enol Conversion in Aqueous Solution. Rate and Equilibrium Constants Determined from a Single Experiment

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The zero-order bromination of 2-carbethoxycyclohexanone in aqueous solution, followed spectrophotometrically at 267 nm, transforms near the end of the reaction quite suddenly into an opposing first-order process, representing a restoration of the perturbed keto-enol equilibrium. This is partly due to a (coincidental) overlap of the spectra for bromine and the substrate (enol) in the range 250–280 nm. Rate constants and the equilibrium constant for the keto-enol conversion can be determined (in principle) from a single kinetic experiment.
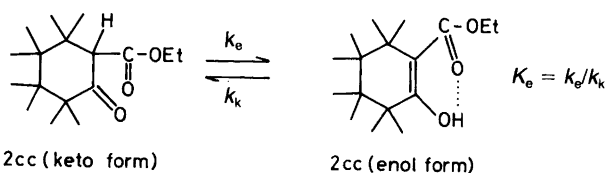
The keto-enol conversion studied here is catalyzed only by bases, although a small component of catalysis by the hydronium ion is also found. Catalytic data for twelve bases, including water and the hydroxide ion, are correlated with pK_A in a Brønsted plot. Carboxylates form a linear correlation with a Brønsted slope of $\beta = 0.67$, in accordance with earlier observations. Phosphates exhibit moderately negative deviations, presumably due to electrostatic effects. Stronger bases show large negative deviations, undoubtedly relating to strong solvation of these ions.

Kinetic experiments by stopped-flow in aqueous hydroxide provide a basis for determining the acidity constants for the substrate.

Rate-limiting proton abstraction from carbon, as exemplified by the enolization of carbonyl compounds, is an important type of reaction in organic chemistry and biochemistry.[1]

The enol content at equilibrium of most simple carbonyl compounds in the pure state or in aqueous solution is usually difficult to quantify, since it is in the ppm or ppb region. Some compounds, however, have enol contents large enough to be detectable by UV spectrophotometry. Classical examples are the esters of 2-carboxycycloalkanones, where the enol form is stabilized by intramolecular hydrogen bonds. Scheme 1 shows the keto-enol equilibrium for 2-carbethoxycyclohexanone (2cc).

We report here a technique whereby the rate constants k_e and k_k in Scheme 1, and therefore also the equilibrium constant K_e, can be derived (in principle) from a *single* kinetic experiment.

2cc (keto form)   2cc (enol form)

$K_e = k_e/k_k$

Scheme 1.

Studies by Bell *et al.* of the zero-order halogenation of 2cc in aqueous solution have questioned whether the correct rate constants for enolization are best obtained by using iodine or bromine.[2]

In a preliminary approach to this question we studied the bromination of 2cc spectrophotometrically at a wavelength of 267 nm, the tribromide ion (Br_3^-) absorbing strongly here. Somewhat to our surprise we observed a kinetic curve as shown in Fig. 1: the zero-order straight line (C) for bromination was succeeded by a sudden break and a first-order increase in absorption (D), which finally levelled off at a constant (infinity) value.

We interpret the observations summarized in Fig. 1 as follows: (1) C represents the well-known zero-order enolization reaction in which the enol is trapped efficiently by bromine, and from which k_e can be determined, (2) D represents a first-order regeneration of enol corresponding to the content at equilibrium in the solution, the rate constant for which is equal to (k_e+k_k) according to Scheme 1. The fact that both processes are observable successively in the same solution is partly due to a (coincidental) overlap of the UV absorption band for 2cc at 255 nm and that for the tribromide ion at 267 nm (Fig. 2).

The first-order section of the curve in Fig. 1 provides an excellent basis for studying acid-base catalysis of the keto-enol conversion over a large range of reaction rates by conventional as well as stopped-flow spectrophotometry.

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Fig. 1. Absorbance-time plot (at 267 nm) observed for the reaction between 2-carbethoxycyclo-hexanone and bromine (Br_3^-). A. Reference reading. B. Absorbance of 2cc before reaction. C. Observed zero-order plot after addition of a small excess of bromine (with respect to enol content). D. First-order section following the disappearance of bromine, indicating a regeneration of the enol content in the solution.
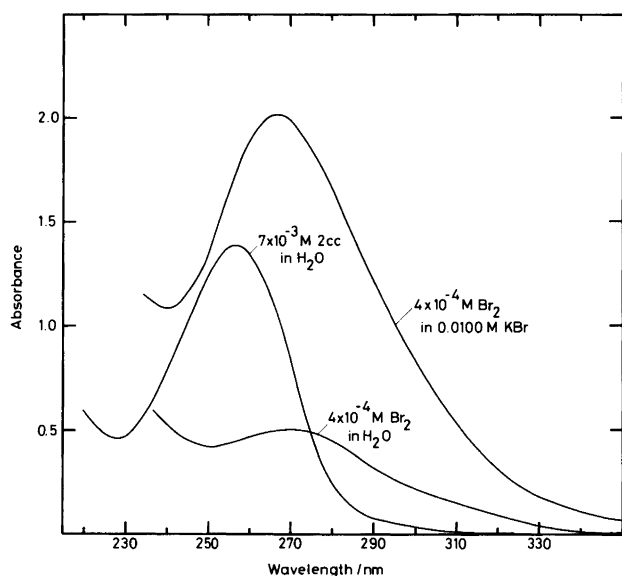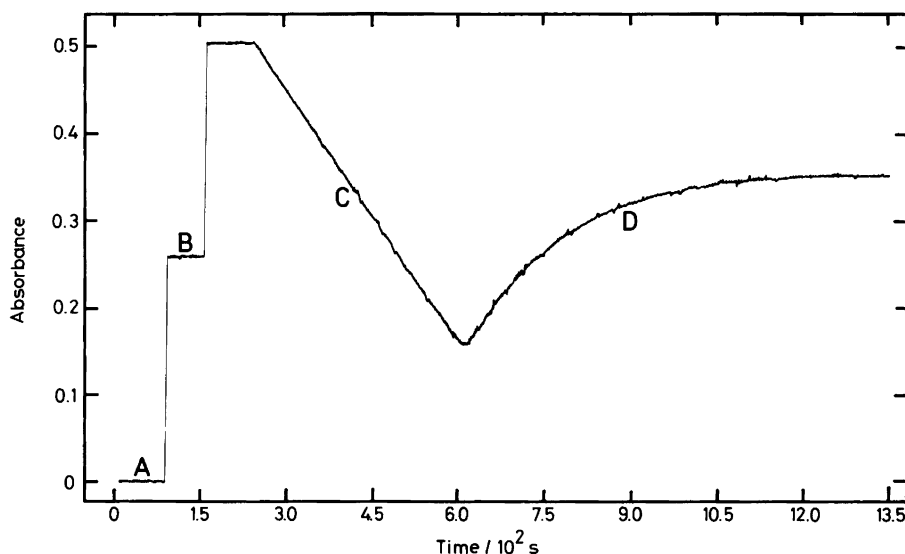

Fig. 2. Absorption spectra, showing the overlap between the spectra of 2cc and tribromide ion in the range 250–280 nm.

Experimental

Materials. A commercial sample of 2-carbethoxycyclohexa-none (2cc) was distilled from a spinning-band column; the middle fraction boiling at 103°C (1.20 kPa) was collected and kept in a sealed tube at 4°C.

Methylphosphonic and trichloromethylphosphonic acid were synthesized and handled according to Kresge and Tang.[3] All other substances were commercially available and of high purity. Filtered water from a Milli-Q apparatus was used as solvent throughout.

Kinetic measurements. All kinetic data for the evaluation of catalytic constants for the various buffers and of the keto-enol equilibrium constant in water were obtained by con-

ventional UV spectrophotometry at a wavelength of 267 nm in 1 cm quartz cells. Zero-order rates were read directly from recordings of absorbance-time plots on graph paper, whereas all first-order kinetic data were collected and treated by a microcomputer. Reactions were initiated by injecting 1–5 μl of a saturated bromine solution (2×10^{-2} M) into the reaction cell containing 2cc (10^{-3} M), potassium bromide (0.0100 M), a variable amount of buffer, and sodium chloride to an ionic strength of 0.10 M.

A few experiments in hydroxide solution (pH ≳ 11) were carried out by stopped-flow, syringes 1 and 2 containing 2cc in neutral solution and sodium hydroxide, respectively. A large increase is observed in absorbance upon mixing the two solutions, due to a dramatic increase in the content of enolate ion under such conditions (Scheme 2). Again, excellent first-order behaviour was observed.

All experiments were carried out at 25.0(1)°C.

Molar absorptivities. A drawback in determining rate constants from zero-order kinetics is the necessity for absolute values of concentrations (absorbances) of the reactants. The molar absorptivity of bromine (tribromide, Br_3^-) at 267 nm was obtained as the slope of a Beer plot based upon absorbances in adequate buffer solutions after successive additions of known amounts of bromine, but without 2cc.

Since bromine evaporates quite readily from aqueous solutions, concentrations were verified continuously by titration. This was done by the standard iodide/thiosulphate method.

The concentration of an equilibrated solution of 2cc in water (or buffer) can also be measured conveniently by spectrophotometry at 267 nm, since this is near the strong absorption peak of the enol form at 255 nm (Fig. 2). A stock solution of 2cc was prepared by transferring an accurately weighed sample (ca. 0.1 g) to a 1 l standard flask and diluting with water to the mark. Since 2cc is not very (or quickly) soluble in water, the solution was stirred over-

night. This procedure was repeated with a slightly different amount of 2cc to check for consistency between the spectrophotometric measurements resulting from dilution of both stock solutions.

Results and discussion

Molar absorptivities for bromine (tribromide). The distribution of bromine between the species Br_2, Br_3^-, HBrO and BrO^- in aqueous solution is shown as a function of pH in Fig. 3 ([Br^-] fixed at 0.0100 M).[4] The presence of species such as Br^+, H_2OBr^+ and Br_5^- can be neglected for all practical purposes.[4]

Since sodium chloride is present in the buffers in varying concentrations, the formation of the ion Br_2Cl^- could represent a disturbing factor in the curves in Fig. 3 (K) = [Br_2Cl^-]/[Br_2][Cl^-] = 1.14).[5] However, this was shown not to be the case: Table 1 lists determinations of ε_{267} (Br_3^-) at different concentrations of chloride, and no systematic variation is observed within experimental error. A mean value for ε_{267} (Br_3^-) of $5.4(2)\times10^3$ M^{-1} cm^{-1} is found. This value is not expected to vary much with hydrogen ion concentration for pH < 5, and has been used in all subsequent determinations of k_e for enolization of 2cc.

Molar absorptivities for 2cc. Although the peak for UV absorption of this substance is shifted slightly towards a lower wavelength compared with tribromide (Fig. 2), it is convenient for kinetic purposes to determine ε_{267} also for 2cc. A mean value for ε_{267}(2cc) equal to $1.97(4)\times10^2$ M^{-1} s^{-1} was determined from two separate Beer plots.

Kinetics and equilibria. With the molar absorptivities of 2cc and bromine at hand, k_e in Scheme 1 can now be derived from the zero-order slope in Fig. 1 (C), i.e. from
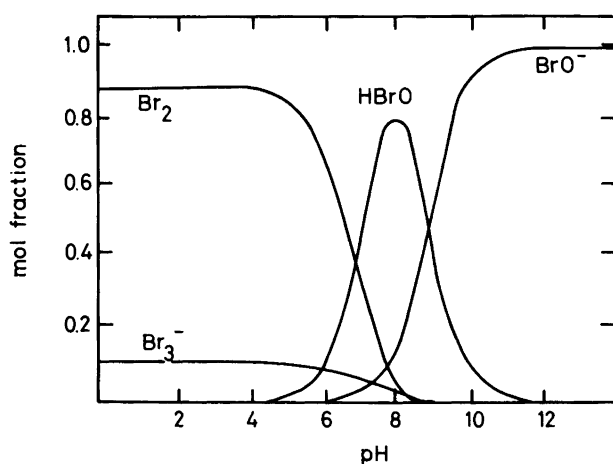

Fig. 3. Plot showing the distribution of bromine between the species Br_2, Br_3^-, HBrO and BrO^- in aqueous solution as a function of pH.

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Table 1. Molar absorptivities ($\varepsilon_{267}(Br_3^-)$) for bromine (tribromide) in varying concentrations of 1:1 acetate buffer (pH=4.7) and chloride ion {25°C, [Br^-] = 0.0100 M, I = 0.10 M (NaCl)}.

$10^2\times$[Total buffer]/M	$10^2\times$[Cl^-]/M	$\varepsilon_{267}/M^{-1}cm^{-1}$
4.00	5.00	5240
3.00	6.00	5061
2.00	7.00	5341
1.00	8.00	5773
1.00	8.00	5584
0.40	8.60	5367
		mean:
		$5.4(2)\times10^3$ $M^{-1}cm^{-1}$

$$k_e = \frac{-d[Br_3^-]/dt}{[2cc]} = \frac{-dA/dt}{[2cc]\times\varepsilon_{267}(Br_3^-)\times l}$$

$$= \frac{-slope\times\varepsilon_{267}(2cc)\times l}{A_{init}(2cc)\times\varepsilon_{267}(Br_3^-)\times l} = 3.65\times10^{-2}\times\frac{-slope}{A_{init}(2cc)} \qquad (1)$$

where l is the light path in the reaction cell and A_{init}(2cc) is the absorption by 2cc before bromine is added (B in Fig. 1).

The first-order curve D in Fig. 1 provides us with a value for (k_e+k_k), this rate constant being obtained by plotting $\ln(A-A_\infty)$ vs. time or by the Swinbourne-Kezdy procedure.

Results for three buffers are shown in Table 2 where K_e = k_e/k_k is seen to be independent of buffer, an average of K_e = $2.31(17)\times10^{-2}$ was found. This value may be compared with K_e = 2.04×10^{-2} found earlier by titration of the enol with bromine.[6]

Table 3 lists catalytic data for nine bases investigated. These results are based on determinations of (k_e+k_k) only, thus avoiding the uncertainties associated with zero-order bromination kinetics. We were unable to detect general acid catalysis for any of the conjugate acids of the base catalysts, in agreement with earlier observations by Bell and Goldsmith.[7] These authors have also shown that no hydronium ion catalysis can be detected for pH above 3. However, we have noticed that catalysis by H_3O^+ corresponding to a value of k_H = $7.2(2)\times10^{-3}$ $M^{-1}s^{-1}$ is observed in more acidic solution ([H^+] → 0.1 M, Fig. 4), and this represents a new discovery since β-dicarbonyl compounds are usually too acidic to exhibit acid catalysis.

Kinetic data for catalysis by borate and hydroxide ions are presented separately in Table 4. The catalytic constants for these two species can be evaluated by fitting eqn. (2).

$$k_{obs} = k_{HO}\times a_{HO} + k_{borate}\times[borate] \qquad (2)$$

to the observed rate constants, and are also given in the Table. Although the hydroxide ion is a much better catalyst than borate, the experimental conditions are such that the two terms in the equation are of comparable magnitude, leading to catalytic constants of reasonable accuracy for both catalysts.

Table 2. Catalytic data and the equilibrium constant K_e for the enolization of 2-carbethoxycyclohexanone.

| $10^5 \times [\text{base}]/\text{M}$	$-10^3 \times \text{d}A/\text{d}t/\text{s}^{-1}$	$A_{init}(2cc)$	$10^4 \times k_e/\text{s}^{-1}$	$10^2(k_e+k_k)/\text{s}^{-1}$	$10^2 \times K_e$
Chloroacetate					
485	0.166	0.237	0.256	0.114	2.30
789	0.174	0.237	0.268	0.122	2.25
990	0.183	0.237	0.282	0.126	2.29
1295	0.191	0.237	0.292	0.132	2.28
1494	0.193	0.237	0.297	0.136	2.23
1799	0.205	0.237	0.316	0.138	2.34
1999	0.213	0.237	0.328	0.144	2,33
Acetate					
~0	1.48	2.17	0.249	0.118	2.16
334	2.60	2.02	0.470	0.201	2.39
781	0.51	0.249	0.730	0.318	2.35
954	3.20	1.306	0.894	0.345	2.66
1336	4.13	1.489	1.01	0.446	2.32
1387	0.66	0.249	0.970	0.448	2.21
1947	3.77	0.965	1.43	0.574	2.55
1982	0.86	0.249	1.26	0.662	1.94
2388	1.02	0.249	1.50	0.743	2.06
2804	8.90	1.391	2.33	–	–
2987	1.25	0.249	1.83	0.849	2.20
3588	1.46	0.249	2.14	1.005	2.18
3988	1.59	0.249	2.33	1.069	2.23
Propionate					
378	–	–	–	0.217	–
579	–	–	–	0.281	–
778	–	–	–	0.345	–
970	6.36	2.43	0.955	0.446	2.19
978	–	–	–	0.410	–
1177	–	–	–	0.465	–
1379	–	–	–	0.528	–
1576	–	–	–	0.597	–
1976	–	–	–	0.757	–
1980	8.17	1.637	1.82	0.726	2.57
2980	14.40	1.960	2.68	1.05	2.62
3980	20.10	2.18	3.37	1.39	2.48
					mean: 2.31(17)
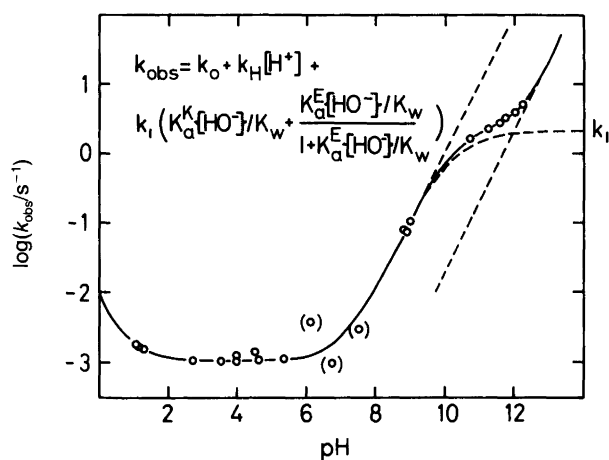
Fig. 4. A pH-profile for the buffer-independent keto-enol conversion of 2cc in aqueous solution, data taken from Tables 3 and 4. The expression shown for k_{obs} is discussed in the text; [HO⁻] taken as 10^{pH-14}.

Rate constants obtained in pure hydroxide solution and measured by stopped-flow are also reported in Table 4. The expression for k_{obs} in eqn. (2) is not expected to apply here since appreciable ionization of both enol and ketone will take place.

Following Kresge et al.,[8] the keto-enol conversion under such conditions is described by Scheme 2,
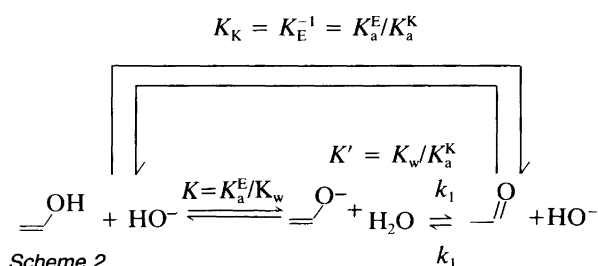
$$K_K = K_E^{-1} = K_a^E/K_a^K$$

$$K' = K_w/K_a^K$$

Scheme 2.

Table 3. Catalytic constants for the base-catalyzed keto-enol conversion of 2-carbethoxycyclohexanone.

Catalyst	Fraction acid	pH	p,q	$k_{cat}/M^{-1}s^{-1}$	$10^3 \times k_c/s^{-1}$	$k_B/M^{-1}s^{-1}$
Chloroacetate (pK_A=2.86)[b]	0.500[a]	–	1,2	–	1.05(5)	0.019(1)
	0.500	2.75		0.0093(6)	1.07(5)	0.018(1)
	0.833	3.54		0.0125(7)	1.01(5)	0.015(1) mean: 0.017(2)
3-Chloropropionate (pK_A=4.00)[b]	0.500	3.99	1,2	0.052(3)	1.20(5)	0.104(6)
Acetate (pK_A=4.76)[b]	0.167	3.95	1,2	0.0375(3)	1.06(5)	0.225(2)
	0.500[a]	–		–	1.10(5)	0.245(8)
	0.500	4.67		0.118(7)	1.06(5)	0.24(1)
	0.833	5.40		0.207(8)	1.10(5)	0.25(1) mean: 0.24(1)
Propionate (pK_A=4.87)[b]	0.500[a]	–	1,2	–	0.95(5)	0.323(5)
Trichloromethylphosphonate (pK_A=4.93)[c]	0.500	4.56	1,2	0.044(5)	1.38(5)	0.09(1)
Cacodylate (pK_A=6.27)[b]	0.500	6.13	1,2	3.25(7)	(3.8)[e]	6.5(1)
Phosphate (pK_A=7.21)[d]	0.500	6.73	2,3	1.18(3)	(1.0)[e]	2.36(6)
Methylphosphonate (pK_A=8.00)[c]	0.500	7.52	1,3	2.16(8)	(3.0)[e]	4.3(2)
Ammonia (pK_A=9.24)[d]	0.250	7.78	4,1	2.8(3)	–	11(1)

[a]Results from Table 2. [b]Ref. 14. [c]Ref. 3. [d]Ref. 15. [e]Uncertain due to large extrapolation.

Table 4. Catalysis by borate and hydroxide ions of the keto-enol conversion of 2-carbethoxycyclohexanone.

$10^3 \times$[Borate]/M[a]	pH	$10^6 \times a_{HO}$	$10^2 \times k_{obs}/s^{-1}$	$10^2 \times k_{obs}$(calc)/s^{-1} [b]	
7.51	8.813	6.50	11.7(7)	10.6	k_{HO}=1.0(2)×10^4 M^{-1}s^{-1}
8.08	8.855	7.23	11.9(3)	11.6	
8.35	8.880	7.59	12.5(3)	12.1	
8.39	8.883	7.64	12.4(3)	12.2	(pK_A=15.74; p,q=2,1)
8.64	8.903	8.00	11.6(3)	16.3	
9.39	8.959	9.16	12.8(5)	14.2	
10.40	9.045	11.10	13.7(5)	16.8	k_{borate}×5.4(5) M^{-1}s^{-1}
14.10	9.009	10.20	18.0(5)	17.8	
14.30	9.017	10.40	17.6(5)	18.1	(pK_A=9.18; p,q=3,4)
14.50	9.030	10.70	18.1(6)	18.5	
0	10.73	537	158(4)	154	
0	11.27	1862	232(2)	218	
0 [d]	11.60	3981	291(2)	276	[e]
0	11.72	5248	319(5)	306	
0	12.02	10471	392(2)	427	
0	12.25	17783	510(2)	594	

[a]Calculated from [borate] = $(1+10^{9.18-pH})^{-1} \times$ total borate buffer concentration. [b]Calculated from k_{obs} (calc) = $k_{HO} \times a_{HO}$ + $k_{borate} \times$ [borate]; k_{HO} and k_{borate} given in the table. [d]Experimental results from stopped-flow investigations. [e]Based on eqn. (3) and the following constants: k_1 = 1.95(5) s^{-1}, K_a^E = 5.0(5)×10^{-11} M, K_a^K = 1.2×10^{-12} M.

in which K_a^E and K_a^K are acidity constants for the enol and keto forms of 2cc, respectively, and where k_1 and k_{-1} are individual rate constants for the rate-limiting step.

A relaxation of the reaction in Scheme 2 is characterized by an observed rate constant, as given in eqn. (3):

$$\tau^{-1} = k_{obs}$$
$$= k_1 \left(K_a^K \{HO^-\}/K_w + \frac{K_a^E \{HO^-\}/K_w}{1 + K_a^E \{HO^-\}/K_w} \right) \qquad (3)$$

assuming a constant and relatively high concentration of hydroxide ions during the reaction. The value of k_1 is related to k_{HO} in Table 4 through $k_1 = k_{HO} \times K_w/(K_a^K + K_a^E)$. The calculated values of k_{obs} in Table 4 are obtained from eqn. (3) by inserting k_1, K_a^K and K_a^E, also listed in Table 4. These parameters are obtained by fitting a pH-profile, shown in Fig. 4 and covering the whole range of acidities investigated, to the experimental data for catalysis by the solvent and solvent-derived species (H_3O^+ and HO^-).

Our value of $K_a^E = 5.0(5) \times 10^{-11}$ M is three times higher than the value $K_a^E = 1.7 \times 10^{-11}$ M determined earlier at the same ionic strength by simple titration.[6] The discrepancy seems to be outside experimental error and is probably due to slight differences in interpretation of the experimental data.

The Brønsted relation. A Brønsted plot for the general base-catalyzed keto-enol conversion is shown in Fig. 5 (data taken from Table 3). The points do not fall on a single straight line. This is fully consistent with earlier observations and predictions, as reviewed by Kresge.[9] However, the points for the weaker bases (carboxylates), including

water, clearly form a linear correlation represented by a Brønsted coefficient of $\beta = 0.67(4)$. The agreement between our data and those of Bell and Goldsmith[7] (indicated by crosses in Fig. 5 and based on halogenation with *iodine*) is good. This conclusion answers the question mentioned in the introduction of this paper.

The indisputable negative deviations observed for the remaining points in Fig. 5 from the Brønsted plot for weaker bases are due to at least two main sources: (a) electrostatic[9] and (b) solvation effects.[10,11]

An electrostatic effect is clearly demonstrated for the three phosphates in Fig. 5. These catalysts are dinegatively charged, and although one of the charges is partly neutralized in the transition state by the proton transferred from the substrate, the remaining negative charge will interact electrostatically with the developing negative charge on the substrate, and thereby tend to destabilize the transition state.[9] An analogous case concerning the base-catalyzed decomposition of nitramide was discussed long ago.[12] We are not sure whether there is also a significant change in the slope of the plot for phosphates in Fig. 5, but such a change might be induced by a solvation effect (*vide infra*), the stronger bases being relatively more solvated.[10,11]

For borate, ammonia and the hydroxide ion as catalysts, no retarding electrostatic effects compared to the carboxylates would be expected; for ammonia one might in fact expect an accelerating effect. Nevertheless, all three catalysts exhibit a quite large negative deviation. This might be rationalized by drawing a curved Brønsted plot through all the points in Fig. 5, thus indicating a Hammond effect. However, it has been stated by Hupe and Wu[10] that only weak curvature is expected for the relatively small ΔpK range usually studied in "normal" acid-base catalysis investigations. The same authors have shown that a more likely cause of the diminished catalytic activity of the stronger bases is strong solvation of the species. Abstraction of a proton from carbon requires very intimate contact, i.e. a short distance, between the substrate and catalyst. This is because the hydrogen-bonding capability of a carbon acid is small[9] and it is therefore difficult to transfer a proton indirectly via the Grotthuss chain mechanism. Hence, the solvation sphere of the catalyst must be considerably distorted, or solvating molecules may even be removed before reaction can take place, resulting in an increase in the activation energy.

The borate ion seems to be subject to an extra large stabilization by solvation (Fig. 5). This may be understood from the fact that the borate ion probably exists as the tetrahedral species $B(OH)_4^-$ in aqueous solution.[13] Such a structure is expected to fit particularly well into the tetrahedral structural pattern of liquid water.
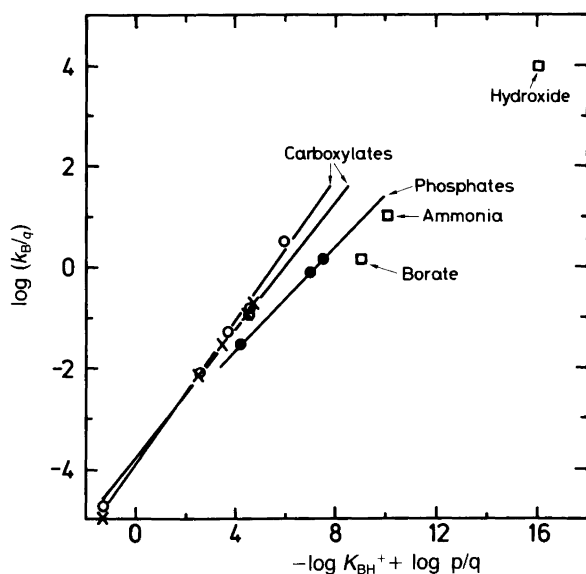

Fig. 5. Brønsted plot for the base-catalyzed keto-enol conversion of 2cc in aqueous solution; data taken from Tables 3 and 4: ○ This work, × Ref. 7, ● phosphates, □ as indicated.

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