General-base-catalysed Proton Exchange in 1,3-Dimethyl-2-iminoimidazolidin-4-one Hydriodide

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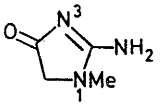
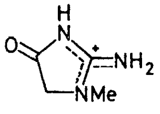
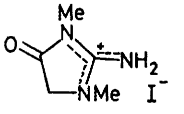
The general-base-catalysed exchange of the methylene protons of the title compound in D_2O has been studied using n.m.r. techniques with 70 bases that include aliphatic monocarboxylates and dicarboxylates, *o*-, *m*-, and *p*-substituted benzoates, 2-, 3-, and 4-substituted pyridines, creatinine, and D_2O. Aliphatic monocarboxylates, *m*- and *p*-substituted benzoates, the pyridines, and D_2O conform to a single Brønsted relationship (β 0.79 ± 0.05). However, *o*-substituted benzoates exhibit enhanced catalytic activity while the aliphatic dicarboxylates and creatinine show reduced catalytic activity. The possible causes for such deviations are discussed.

We have previously examined the mechanism of exchange of the methylene protons in creatinine (I), catalysed by general acids and general bases.[1] It was not possible to make accurate measurements of the general-acid-catalysed exchange rates by acids weaker than creatininium ion (II) (pK_{SH^+} 4.83)[2] and of the general-base-catalysed exchange rates by bases weaker than creatinine, because of substrate self-catalysis that took place under such experimental conditions. As a consequence, the Brønsted coefficients could not be obtained. Compound (III) (pK_{SH^+} 8.07),[3] the methyl quaternary salt of creatinine, being a much weaker acid than (I), permits general-base-catalysed exchange rates to be determined using catalysts whose base strengths vary over a considerably wider range. The Brønsted coefficient for the general-acid-catalysed exchange of creatinine can then be obtained from the values of the general-base-catalysed rates for (III). The underlying assumption in this approach is that (III) provides a satisfactory model for (II) and the validity of this assumption has been established previously.[4]


(I)


(II)


(III)

We report herein studies of general-base-catalysed exchange of methylene protons of (III) using n.m.r. to follow the reaction. A variety of carboxylate and substituted pyridine buffers were used and the Brønsted coefficient for the reaction is deduced and commented upon.

EXPERIMENTAL

Solvents and Reagents.—The deuteriated solvents D_2O (99.7 atom % D), MeOD, and aqueous solutions of DCl and NaOD were purchased from Merck, Sharp and Dohme. Prior to use D_2O was heated to boiling and allowed to cool with a slow stream of nitrogen bubbling through it. The remaining deuteriated solvents were used as supplied.

The carboxylic acids and substituted pyridines were obtained from commercial sources and purified by crystallisation or distillation. *o*-t-Butylbenzoic acid and *o*-isopropylbenzoic acid were obtained from laboratory stock.[5]

Hydrogen methyl fumarate was prepared as described previously,[6] crystallised thrice from acetonitrile–methanol, m.p. 142—144° (lit.,[6] 142—144°), and titrated against standard NaOH (alkalimetry assay 100.8%). The strengths of solutions of bromoacetic and formic acids were also determined by titration.

Substituted benzoic acids, dichloroacetic, and cyanoacetic acids were converted to their sodium salts by reaction with sodium hydrogen carbonate and these used for the preparation of the buffer solutions.

1-Methyl-2-amino-2-imidazolin-4-one (creatinine) (I) was purchased from Matheson, Coleman and Bell and purified by crystallisation from aqueous ethanol. It could not be used directly as a base in exchange experiments since its methylene signal overlaps with that of compound (III). Accordingly, *NN*,5,5-tetradeuteriocreatinine was prepared as follows. A solution of creatinine in D_2O (*ca*. 2.5M) was refluxed for 12 h and allowed to cool. The crystals that separated on cooling were removed by filtration and the process of refluxing in D_2O, cooling, and filtration of the separated solid repeated. The n.m.r. spectrum of the resulting solid showed no detectable peak due to methylene protons.

1,3-Dimethyl-2-iminoimidazolidin-4-one hydriodide (III) was synthesised by methylating creatinine with iodomethane,[3] and crystallised from acetonitrile, m.p. 213—215° (decomp.) [lit.,[3] 213—215.5° (decomp.)]. The amino-protons in (III) were replaced by deuterium atoms by dissolving (III) in MeOD and evaporating the solvent under reduced pressure. The resulting solid, also referred to as (III) throughout this paper, was used in the rate measurements.

Acidity Measurements and Determination of the Concentration of Buffer Base.—Acidity measurements were made on buffer solutions using a Radiometer model 26 pH instrument with an aqueous glass–calomel assembly, calibrated with standard aqueous buffers; the pD values were obtained from the relationship, pD = 'pH reading' + 0.40.[7]

In a typical experiment a solution of the acid or base in D_2O was prepared. Sufficient sodium chloride was then added so that the resulting buffer solution had an ionic

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[1] R. Srinivasan and R. Stewart, *Canad. J. Chem.*, 1975, **53**, 224.

[2] A. K. Grzybowski and S. P. Datta, *J. Chem. Soc.*, 1964, 187.

[3] G. L. Kenyon and G. L. Rowley, *J. Amer. Chem. Soc.*, 1971, **93**, 5552.

[4] R. Stewart and R. Srinivasan, *Canad. J. Chem.*, 1975, **53**, 2906.

[5] R. Stewart and M. R. Granger, *Canad. J. Chem.*, 1961, **39**, 2508.

[6] S. M. Spatz and H. Stone, *J. Org. Chem.*, 1958, **23**, 1559.

[7] (*a*) P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188; (*b*) E. Mikkelsen and S. O. Nielsen, *ibid.*, p. 632; (*c*) P. Salomaa, L. Schaleger, and F. A. Long, *J. Amer. Chem. Soc.*, 1964, **86**, 1.

strength of 1.2 and the acidity of the medium adjusted with NaOD or DCl. The substrate, (III), was added (*ca.* 0.3M) just before making exchange measurements. The pD value of the solution was determined after exchange and this value was used to calculate the concentration of buffer base. When the exchange reaction had a half-life exceeding 4 h the pD measurements of the buffer solutions were made before and after exchange. From such measurements it was concluded that the acidity of the medium did not change during the course of the reaction.

Since the pK^{25}_{DA} values (D_2O, 25°) are not available for all the carboxylic acids studied they have been calculated from the reported pK^{25}_{HA} values [8,9] (water, 25°) using equation (1).[10] The pK^{25}_{HA} values determined by Kurz and Farrar [11] are used for dichloro- and difluoro-acetic acids, while for sorbic acid the ionisation constant is that reported by Yanovskaya *et al.*[12] The dissociation constants for salicylic, maleic, and glycolic acids in D_2O were obtained from

$$pK^{25}_{DA} = 0.41 + 1.02\, pK^{25}_{HA} \qquad (1)$$

the literature.[10] The pK^{25}_{DA} values for malonic acids were reported by Glasoe and Hutchison.[13] In view of the insensitivity of dissociation constants of carboxylic acids to changes in temperature [14] the concentration of the buffer anion was simply calculated from pK^{25}_{DA} and pD (room temperature) values.

The dissociation constants of pyridinium ions are, however, temperature sensitive.[14] Consequently, the pD measurements were made at 35°. The pK^{35}_{BD+} values (D_2O, 35°) were obtained either directly (pK^{35}_{BD+} for pyridine = 5.61) [15] or computed from equations (2) [16] and

$$pK^{35}_{BH+} = pK^{T}_{BH+} - \frac{(pK^{T}_{BH+} - 0.9)}{273 + T}(35 - T) \qquad (2)$$

(3),[17a] from the dissociation constants in water at T° (pK^{T}_{BH+})

$$pK_{BD+} = 0.48 + 1.005\, pK_{BH+} \qquad (3)$$

given in parentheses [(61) pK^{35}_{BH+} 5.83; [18] (62) pK^{35}_{BH+} 5.78; [18] (63) pK^{35}_{BH+} 5.50; [18] (65) pK^{20}_{BH+} 3.33; [19] (66) pK^{35}_{BH+} 3.20; [20] (67) pK^{25}_{BH+} 2.97; [21] (68) pK^{35}_{BH+} 1.19 [17b]]. The reported pK_{BD+} value for creatinine under the experimental conditions (D_2O, 35°, μ 1.2) is 5.40.[1]

Rate Measurements.—The exchange of methylene protons of (III) in D_2O at 34.5° (the probe temperature) was measured by n.m.r. technique at a sweep width of 100 Hz as described previously.[1,4] The exchange was usually followed to 70% completion, the reaction being cleanly first order over this range (Figure 1). The exchange goes to completion as shown by the absence of a methylene signal after the lapse of many half-lives. The observed first-order exchange constant, k_{obs}, was obtained by plotting the data according to equation (4) (Figure 1);

$$\ln R_t/S_t = k_{obs}t \qquad (4)$$

R_t = average area of *N*-methyl peaks and S_t = average area of methylene peak both at time t. R_t Was arbitrarily assigned a constant value when rate measurements were made without removing the n.m.r. tube from the probe and keeping all the conditions constant during the course of the reaction.[4] The reproducibility was better than ±10%.

Because of the insolubility of cinnamic acid in D_2O the exchange rates in cinnamate buffer were measured in 20% MeOD. From a study of the exchange rates of (III) in benzoate in 20% MeOD and in D_2O it was concluded that the exchange rates are similar in the two solvent systems.

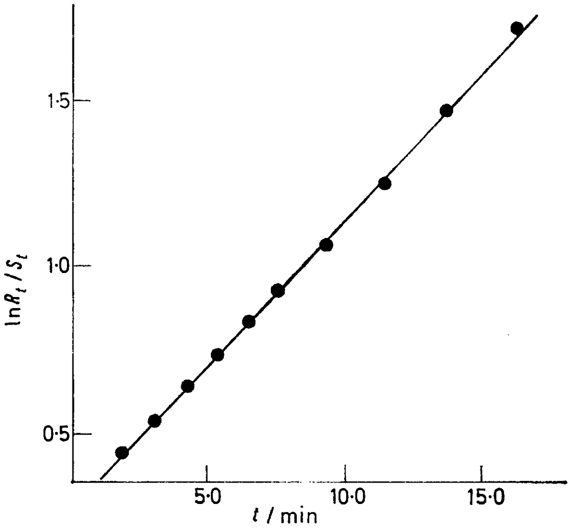

FIGURE 1 Exchange kinetics for (III) in 0.40M malonic acid buffer in D_2O: μ = 1.2, T = 34.5°, pD = 6.48

RESULTS

The second-order constant, k_2, for the abstraction of methylene protons by a base, B, is obtained using equation (5). In most cases the pD values of buffer solutions were kept

$$k_{obs} = k_2[B] \qquad (5)$$

1.5 units or more above the p*K* values of the buffer acids; all rate measurements, in any case, were made at pD $\leqslant$6.7. The observed first-order exchange constant at pD 6.7 in the absence of buffers was found to be small, becoming smaller still in more acidic solutions (Table 1). Comparison of k_{obs} values found in the presence and absence of buffer reveals that the basic component of the buffer is responsible for almost all the observed exchange. This conclusion is supported by the observation that varying the concentration of base produces essentially no change in the second-order rate constant (Table 2). The catalytic

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[8] G. Kortüm, W. Vogel, and K. Andrussow, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961.

[9] H. C. Brown, D. H. McDaniel, and O. Häfliger, in ' Determination of Organic Structures by Physical Methods,' eds. E. A. Braude and F. C. Nachod, Academic Press, New York, 1955, vol. I, p. 567.

[10] A. O. McDougall and F. A. Long, *J. Phys. Chem.*, 1962, **66**, 429.

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[14] A. Albert and E. P. Serjeant, ' Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

[15] I. R. Bellobono and P. Beltrame, *J. Chem. Soc.* (*B*), 1969, 620.

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[18] H. H. Perkampus and G. Prescher, *Ber. Bunsengesellschaft Phys. Chem.*, 1968, **72**, 429.

[19] A. V. Willi, *Helv. Chim. Acta*, 1954, **37**, 602.

[20] S. Cabani and G. Conti, *Gazzetta*, 1965, **95**, 533.

[21] H. C. Brown and D. H. McDaniel, *J. Amer. Chem. Soc.*, 1955, **77**, 3752.

constants for most of the bases studied are subject to an estimated uncertainty of ±10%. However, the exchange rates of the weaker bases, dichloroacetate, difluoroacetate, and 2,6-dinitrobenzoate are extremely slow and had to be corrected for water catalysis. Consequently, their rate constants are subject to a larger uncertainty, possibly as much as ±25%.

TABLE 1

Rate data for the exchange of (III) in the absence of added buffer. $T = 34.5°$, $\mu = 1.2$, $[(III)] = 0.3$M

pD [a]	$10^5 k_{obs}$ [b]/min^{-1}
6.7	60
4.0	6.7
2.0	4.0
1.0	3.2
0.5	3.1

[a] DCl used to adjust the acidity. [b] Subject to an estimated error of ±20%.

TABLE 2

Rate data for the exchange of (III) in acetate buffer. $T = 34.5°$, $\mu = 1.2$, $[(III)] = 0.3$M

pD	[Total buffer]/ M	$10^2 k_{obs}$/ min^{-1}	[Acetate]/ M	$10^2 k_2$/ l mol^{-1} min^{-1}
4.83	0.60	2.41	0.149	16.2
4.83	0.40	1.81	0.100	18.1
4.83	0.20	0.89	0.050	17.8
4.43	0.85	1.75	0.099	17.7
4.43	0.60	1.36	0.070	19.4

The ionisation constants of buffer acids along with the catalytic constants k_2 of their conjugate bases are collected in Table 3.

TABLE 3

Specific catalytic constants for the exchange of (III) in buffer solutions. $T = 34.5°$, $\mu = 1.2$, $[(III)] = 0.3$M

Base	pK *	$10^2 k_2$/l mol^{-1} min^{-1}
(1) Pivalate	5.54	38
(2) Propionate	5.39	27
(3) Acetate	5.26	18
(4) Crotonate	5.20	17
(5) Sorbate	5.12	14
(6) Cinnamate	4.94	11
(7) *p*-Methoxyphenylacetate	4.86	9.8
(8) Phenylacetate	4.82	8.4
(9) *m*-Methoxyphenylacetate	4.76	8.6
(10) *p*-Chlorophenylacetate	4.68	8.1
(11) *p*-Bromophenylacetate	4.68	9.3
(12) Hydrogen succinate	4.68	12
(13) *m*-Chlorophenylacetate	4.63	8.3
(14) *o*-Nitrophenylacetate	4.49	7.6
(15) Glycolate	4.37	2.2
(16) *p*-Nitrophenylacetate	4.34	5.2
(17) Formate	4.20	2.4
(18) Methoxyacetate	4.05	2.5
(19) Mandelate	3.90	1.2
(20) Fumarate monomethyl ester	3.85	2.5
(21) Iodoacetate	3.65	0.84
(22) 2-Furoate	3.64	0.96
(23) Bromoacetate	3.41	0.90
(24) Hydrogen malonate	3.37	1.1
(25) Chloroacetate	3.34	0.68
(26) Cyanoacetate	2.91	0.29
(27) Dichloroacetate	1.80	0.080
(28) Difluoroacetate	1.78	0.017
(29) *p*-Methoxybenzoate	4.97	13
(30) *m*-Methylbenzoate	4.77	9.1
(31) Benzoate	4.71	7.3
(32) *p*-Fluorobenzoate	4.63	7.0
(33) *m*-Methoxybenzoate	4.59	5.5
(34) *m*-Fluorobenzoate	4.35	3.7
(35) *m*-Chlorobenzoate	4.32	3.9
(36) *m*-(Trifluoromethyl)-benzoate	4.26	3.8
(37) *m*-Cyanobenzoate	4.08	3.1
(38) *m*-Nitrobenzoate	3.97	2.8
(39) *o*-Methoxybenzoate	4.58	11
(40) *o*-Methylbenzoate	4.40	8.7
(41) *o*-Ethylbenzoate	4.28	11
(42) *o*-Isopropylbenzoate	4.12	9.2
(43) *o*-t-Butylbenzoate	4.02	13
(44) *o*-Fluorobenzoate	3.75	2.4
(45) *o*-Chlorobenzoate	3.39	1.9
(46) *o*-Bromobenzoate	3.32	1.9
(47) *o*-Iodobenzoate	3.33	2.2
(48) *o*-Nitrobenzoate	2.67	0.53
(49) 2,6-Dimethylbenzoate	3.73	6.6
(50) 2,6-Dichlorobenzoate	2.03	0.25
(51) 2,6-Dinitrobenzoate	1.57	0.025
(52) Salicylate	3.69	0.39
(53) Maleate	6.71	36
(54) α-Isopropylmalonate	6.36	54
(55) α-Ethylmalonate	6.28	51
(56) Malonate	6.12	32
(57) Succinate	6.00	56
(58) Glutarate	5.92	48
(59) Sebacate	5.92	62
(60) Fumarate	4.47	6.1
(61) 4-Methylpyridine	6.34	150
(62) 2-Methylpyridine	6.29	132
(63) 3-Methylpyridine	6.01	95
(64) Pyridine	5.61	49
(65) 3-Carbamoylpyridine	3.71	1.1
(66) 3-Acetylpyridine	3.70	0.83
(67) 3-Fluoropyridine	3.39	0.57
(68) 3-Cyanopyridine	1.68	0.038
(69) Creatinine	5.40	8.6
(70) D_2O	-1.74	0.000 06 †

* K refers to the appropriate acid dissociation constant of the catalyst acid-base pair (See Experimental section).

† $k^{\circ}_{obs}/55.2$.

DISCUSSION

The exchange of methylene protons in (III) proceeds by rate-limiting abstraction of proton by general base. The catalytic effectiveness of a base for this process is related to its base strength by the Brønsted equation (6) [22,23] where K is the appropriate acid dissociation

$$\frac{k_2}{q} = G_B\left(\frac{p}{qK}\right)^{\beta} \qquad (6)$$

constant of the catalyst acid–base pair, p the number of equivalent protons in the conjugate acid of the catalyst, q the number of equivalent basic sites in the catalyst and G_B the proportionality constant. For catalysis by monocarboxylates, dicarboxylates, and substituted pyridines p and q are assigned values of 1 and 2, 1 and 4, and 1 and 1 respectively. For catalysis by hydrogen malonate and hydrogen succinate, p and q have the values 2 and 2.

Figure 2 represents a plot of $\log k_2/q$ *versus* $\log p/qK$ for the exchange of (III) with all bases listed in Table 3, except water. Aliphatic monocarboxylates * (1)—(28), *m*- and *p*-substituted benzoates (29)—(38), and substituted pyridines (61)—(68) obey quite well a single

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* 2-Furoate has been included in this category.

[22] D. M. Bishop and K. J. Laidler *J. Chem. Phys.*, 1965, **42**, 1688.

[23] R. P. Bell and P. G. Evans, *Proc. Roy. Soc.*, 1966, *A*,**291**, 297.

Brønsted relation and these bases, shown as filled circles in Figure 2, were used to determine the regression line. The equation of the line is given by equation (7), with a

$$\log k_2/q = 0.79 \log p/qK - 4.89 \qquad (7)$$

correlation coefficient of 0.991. The linearity in Figure 2 extends over a range of *ca.* 5 pK units and is no doubt due to the velocity of the reverse reaction, protonation of the mesoionic intermediate (IV) to give (III), being much smaller than the diffusion-controlled limit.[23,24] Of all the bases included in the determination of the regression line in Figure 2 the closely related ions dichloroacetate and difluoroacetate exhibit the greatest positive and negative deviations, reacting respectively 2.1 times faster and 2.2 times slower than expected from equation (7).

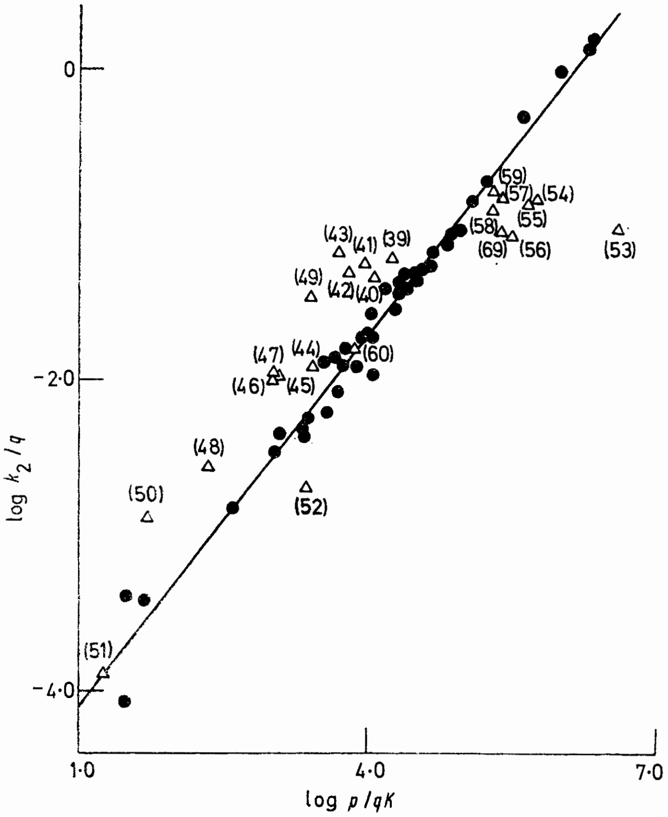

FIGURE 2 Relation between catalytic constant and basicity. [Numbering as in Table 3; filled circles represent bases (1)—(38) and (61)—(69), which were used to determine the regression line shown]

The catalytic constants of m- and p-substituted benzoates correlate, as expected, with their Hammett σ constants giving a ρ value of 0.70 (Figure 3). With these bases ρ and β are, of course, identical. The pyridine series also gives a good Hammett plot with a slightly higher ρ, 0.80. In the pyridine series the single 2-substituted compound that was studied, (62), was included in the determination of ρ since it fell on the Brønsted line in Figure 2. The fact that pyridines, m- and p-substituted benzoates, and aliphatic monocarboxylates fall essentially on the same Brønsted line demonstrates the wide variation in catalyst structure that can be accommodated by such linear free-energy relationships as the Brønsted equation.

It is interesting to note that the catalytic constants of glycolate (2.2×10^{-2} l mol^{-1} min^{-1}) and methoxyacetate (2.5×10^{-2} l mol^{-1} min^{-1}) are comparable, as would be expected from the electronic effect of the substituents OH and OMe, even though glycolic acid is significantly weaker than methoxyacetic acid. The fact that the latter is the better catalyst in rate-controlling protonation reactions[25] suggests that the anomaly may arise from differences in the stabilities of the acid molecules, rather than the conjugate bases.

Similarly, although difluoro- and dichloro-acetic acids are reported to have the same acid strength,[11] difluoroacetate is a less effective catalyst (by a factor of 4.7) than dichloroacetate. This order is in keeping with the known inductive effects of the halogens, fluorine being more electronegative than chlorine. Again the kinetic basicities are more in line with expectations than are the equilibrium basicities.

Deviations from the Brønsted Relation.—There are two classes of bases, o-substituted benzoates and multicharged bases, that were not included in the determination of the regression line in Figure 2, both classes deviating significantly from the line for aliphatic monocarboxylates, m- and p-substituted benzoates, and the pyridines. Possible causes for these systematic deviations are discussed below. (The points for these bases are indicated by open triangles in Figure 2.)

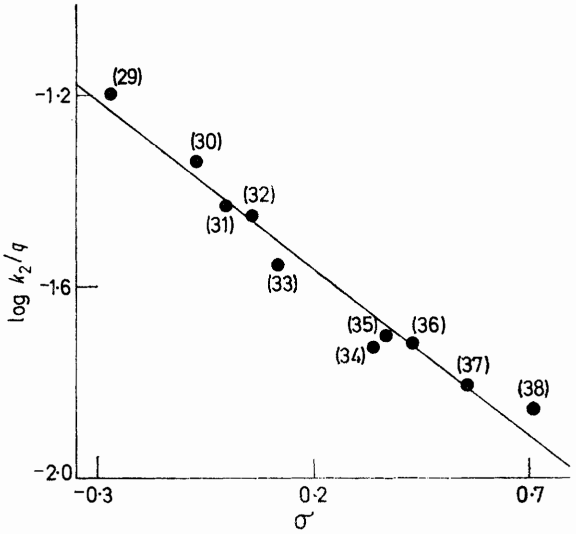

FIGURE 3 Correlation of the catalytic constants with Hammett σ constants for m- and p-substituted benzoates (numbering as in Table 3)

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

[25] A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne, and D. S. Sagatys, *J. Amer. Chem. Soc.*, 1971, **93**, 413.

o-Substituted benzoates. With two exceptions all 14 *o*-substituted benzoates that were examined are significantly *better* base catalysts than their equilibrium basicities would lead one to expect.* The exceptions are 2,6-dinitrobenzoate ion, whose rate is almost exactly that predicted by equation (7), and the internally hydrogen-bonded salicylate ion, whose rate is significantly less than that predicted by equation (7).

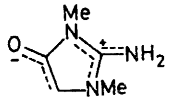
The increased catalytic effectiveness of the other twelve sterically hindered bases (39)—(50) in removing a proton from (III) is perhaps surprising. It indicates that steric effects in the transition state of the proton-abstracting step are less than in the neutral acid molecule that is thereby formed, the *o*-substituted benzoic acid. That the effect increases with the bulk of the group can be seen by comparing the catalytic rates for the ions containing the four alkyl groups, methyl, ethyl, isopropyl, and t-butyl, in Figure 2.

Two explanations have been given for the increase in equilibrium acidity that virtually any *o*-substituent, regardless of its electronic effect, confers on benzoic acid. The generally accepted explanation invokes steric inhibition of resonance between carbonyl group and ring in the neutral acid molecule.[27] The second explanation, which has received little attention, attributes the effect to hindrance to solvation of the neutral molecule, the basis for this view being the virtual disappearance of acidity differences between *o*- and *p*-substituted acids in media of extremely high ionic strength.[28] Since the anion is common both to the equilibrium ionisation and the rate process under consideration here any steric effects therein can be ignored in considering deviations from the Brønsted relation. In any case, benzoate anion stability does not seem to be greatly affected by *o*-substitution, as might be inferred from the efforts, described above, to make the neutral molecule the locus of the steric effect.

The size of the Brønsted coefficient, *ca.* 0.80, and the fact that proton loss from the methylene group of (III) is endergonic suggest that the transition state is well advanced.[29,30] Even so, the incipient acid molecule partly formed in the transition state must be subject to steric hindrance to resonance (or solvation) to a considerably smaller extent than the fully formed acid molecule to account for the increased rates observed here, since any steric compression that occurs in the transition state would serve to *decrease* the rate for bases containing bulky groups near the reaction sites. In support of the view that steric compression in the transition state is not of major importance is the observation that proton tunnelling seems to be absent in these reactions.[31] Curiously enough, the catalytic constants of *o*-alkylbenzoates obey equation (7) satisfactorily if the pK values of the corresponding *p*-alkylbenzoic acids are used.

Doubly charged bases. Bases (53)—(60) are doubly charged and, with the exception of (60), lie in a group in Figure 2. Its location shows that the presence of a nearby negative charge serves to *decrease* the catalytic effectiveness of the attacking basic centre. Of the eight doubly charged bases studied in this work the largest deviation from the Brønsted line is for maleate ion, in which the two units of negative charge are constrained to occupy nearby regions of space. Malonate and its alkyl derivatives show smaller, but still significant effects. However, succinate, glutarate, sebacate, and fumarate ions, in which the second charge is more remote from the first deviate only slightly, if at all. It is of interest that hydrogen malonate falls directly on the regression line in Figure 2. Indeed, being an aliphatic monocarboxylate, it was included in the determination thereof.

It is not clear why an additional unit of negative charge nearby should reduce the effectiveness of a basic site in removing a proton from a cation such as (III). Any interaction between the positive charge of the substrate and the additional negative charge would serve to stabilise the transition state. Possibly the mesoionic character of the formally neutral molecule (IV) formed as the result of proton loss, is responsible, since a partial negative charge develops in the substrate near the reaction site and this would lead to some electrostatic repulsion.



(IV)

Catalysis by Water and by Creatinine.—The first-order rate constant for the exchange of (III), k°_{obs}, is assigned a value of 3.5×10^{-5} min^{-1}—the value obtained in the pD region 0.5—2.0 using DCl as acid (Table 1). [The higher values of the observed exchange constant at pD 4.0 and 6.7 presumably arise from contributions from OD^- and from the conjugate base of (III).] Assigning a value of 55.2M for the concentration of D_2O, —1.74 for $pK_{D_3O^+}$, and 2 and 3 for p and q,[32] it is found

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* Bell and Higginson [26] reported that *o*-substituted benzoic acids are poorer general-acid catalysts in the dehydration of ethane-1,1-diol than *m*- and *p*-substituted benzoic acids of identical acidity. Since the mechanism of dehydration involves rate-limiting general-base-catalysed dehydration of protonated ethane-1,1-diol [26] their results imply reduced catalytic effectiveness for *o*-substituted benzoates, in contrast to the present case.

[26] R. P. Bell and W. C. E. Higginson, *Proc. Roy. Soc.*, 1949, *A*,**197**, 141.

[27] (*a*) L. Eberson, in ' The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Interscience, New York, 1969, ch. 6; (*b*) E. S. Gould, ' Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1959, ch. 7.

[28] J. Steigman and D. Sussman, *J. Amer. Chem. Soc.*, 1967, **89**, 6406.

[29] J. E. Leffler and E. Grunwald, ' Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 158.

[30] R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, *A*,**294**, 273.

[31] R. Stewart and R. Srinivasan, to be published.

[32] (*a*) V. Gold and D. C. A. Waterman, *J. Chem. Soc.* (*B*), 1968, 839; (*b*) R. P. Bell, ' The Proton in Chemistry,' Cornell University Press, Ithaca, 1973, ch. 10.

that the catalysis by water is satisfactorily represented by equation (7). It appears that the rate of the reverse reaction, protonation of (IV) by D_3O^+ to give (III), is well below the diffusion-controlled limit.

The catalytic constant for creatinine is found to be smaller than that for a pyridine of identical basicity by a factor of 3.1; the reduced catalytic power of creatinine has been noted earlier.[1]

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