Table IV. Use of Eq 4 and 5 to Estimate Tautomer Ratio of 4-Substituted Imidazole Derivatives

Compound	K_π/K_τ	Eq 4		Eq 5	
		$k = 0.537$	$k = 1$	$k = 0.537$	$k = 1$
4-Nitroimidazole	501	353	189	−3.42	−1.61
Histamine	4.37	4.50	1.95	3.86	−3.09
Histidine	4.07	4.37	1.88	3.14	−3.42
Boc-histidine	1.58	1.34	0.26	2.09	−4.86
TRF	2.88	2.63	0.95	3.86	−3.09

greatly improves the use of eq 4 or 5 to calculate tautomer ratio, when the dissociation constants of the appropriate methyl derivatives are not available. It also shows that eq 4 is better than eq 5 for the estimation of tautomer ratios.

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References and Notes

(1) Y. Nozaki, F. R. N. Gurd, R. F. Chen, and J. T. Edsall, *J. Am. Chem. Soc.*, **79**, 2123–2129 (1957).
(2) N. C. Li, J. M. White, and E. Doody, *J. Am. Chem. Soc.*, **76**, 6219–6223 (1954).
(3) A. Grimison, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1352–1356 (1960).
(4) M. J. Collis and G. R. Edwards, *Chem. Ind.*, 1097–1098 (1971).
(5) See (a) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1–80 (1973). $\bar{\sigma} = \sigma_I + (\rho_R/\rho_I)\sigma_{R(A)}$, where σ_I values were taken from (b) M. Charton, *J. Org. Chem.*, **29**, 1222–1227 (1970); $\sigma^-_{R(A)}$ values were taken from (a), except for compound 3, obtained from (c) T. Birchall and W. L. Jolly, *J. Am. Chem. Soc.*, **88**, 5439–5443 (1966), and compound 4, from (d) A. Fischer, G. L. Leavy, R. D. Topsom, and J. Vaugham, *J. Chem. Soc. B*, 846–851 (1967). Values for $\rho_R = 7.273$ and $\rho_I = 2.323$ were found by a least-squares multiple linear regression fitting of the data according to the equation: $\log (K/K_0) = \rho_I\sigma_I + \rho_R\sigma^-_{R(A)}$.
(6) J. Elguero, E. Gonzalez, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 5009–5017 (1968).
(7) J. Elguero, E. Gonzalez, J. L. Imbach, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 5017–5019 (1968).
(8) S. F. Mason, *J. Chem. Soc.*, 674–685 (1958).
(9) G. G. Gallo, C. R. Pasqualucci, P. Radaelli, and G. C. Lancini, *J. Org. Chem.*, **29**, 862–865 (1964).
(10) C. R. Ganellin, *J. Pharm. Pharmacol.*, **25**, 787–792 (1973).
(11) The imidazole nitrogens in histidine and its derivatives have been named according to the recommendations of the IUPAC–IUB Commission on Biochemical Nomenclature, cf. *Biochemistry*, **11**, 1726–1732 (1972).
(12) B. O. Handford, T. A. Hylton, K.-T. Wang, and B. Weinstein, *J. Org. Chem.*, **33**, 4251–4255 (1968).
(13) J. Rivier, W. Vale, M. Monahan, N. Ling, and R. Burgus, *J. Med. Chem.*, **15**, 479–482 (1972).
(14) T. B. Paiva, A. C. M. Paiva, and H. A. Scheraga, *Biochemistry*, **2**, 1327–1334 (1963).
(15) L. Juliano and A. C. M. Paiva, *Biochemistry*, **13**, 2445–2450 (1974).
(16) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965, p 191.
(17) S. P. Datta and A. K. Grzybowski, *J. Chem. Soc. B*, 136–140 (1966).
(18) L. G. Hepler, *J. Am. Chem. Soc.*, **85**, 3089–3092 (1963); P. D. Bolton and L. G. Hepler, *Q. Rev. Chem. Soc.*, **25**, 521–532 (1971).
(19) D. J. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 649–676 (1965).
(20) P. D. Bolton and F. M. Hall, *J. Chem. Soc. B*, 259–263 (1969); C. L. Liotta, E. M. Perdue, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **96**, 7308–7311 (1974).
(21) R. F. Brown and H. C. Newson, *J. Org. Chem.*, **27**, 3010–3015 (1962); R. F. Brown, *J. Org. Chem.*, **27**, 3015–3026 (1962); L. G. Hepler, *Can. J. Chem.*, **49**, 2803–2807 (1971).
(22) E. M. Arnett, F. M. Jones III, M. Taagepera, W. G. Henderson, J. L. Beauchamp, D. Holtz, and R. W. Taft, *J. Am. Chem. Soc.*, **94**, 4724–4726 (1972); D. H. Aue, H. M. Webb, and M. T. Bowers, *J. Am. Chem. Soc.*, **94**, 4726–4728 (1972); R. W. Taft, M. Taagepera, K. D. Summerhays, and J. Mitsky, *J. Am. Chem. Soc.*, **95**, 3811–3812 (1973); F. M. Jones III and E. M. Arnett, *Prog. Phys. Org. Chem.*, **11**, 263–322 (1974).
(23) T. B. Paiva, M. Tominaga, and A. C. M. Paiva, *J. Med. Chem.*, **13**, 689–692 (1970).
(24) A. Deutsch and P. Eggleton, *Biochem. J.*, **32**, 209–211 (1938).
(25) F. Schneider and W. Schaeg, *Hoppe-Seyler's Z. Physiol. Chem.*, **327**, 74–85 (1962).
(26) D. E. Hultquist, R. W. Moyer, and B. D. Boyer, *Biochemistry*, **5**, 322–331 (1966).
(27) G. Grant, N. Ling, J. Rivier, and W. Vale, *Biochemistry*, **11**, 3070–3073 (1972).
(28) W. F. Reynolds, I. R. Peat, M. H. Freedman, and J. R. Lyerla, Jr., *J. Am. Chem. Soc.*, **95**, 328–331 (1973).

Deuterium Isotope Effects in the General Base Catalyzed Deprotonation of Methylcreatininium Ion

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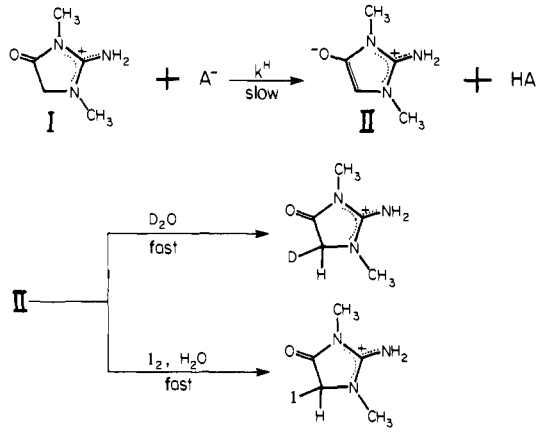
Abstract: The general base catalyzed deprotonation of methylcreatininium ion (I) has been measured with 39 bases that include aliphatic carboxylates, ortho-, meta-, and para-substituted benzoates and substituted pyridines, and the salt effect, solvent isotope effect, and the temperature effect on the catalytic rate constants determined. Except for the ortho-substituted benzoates the variation in isotope effect, k_H/k_D, for **I**-d_2 (I containing deuterium at the methylene site) is normal for proton abstraction from carbon—the lower the equilibrium basicity of the reagent, the smaller the catalytic constant and the smaller the isotope effect. Ortho-substituted benzoates exhibit increased catalytic activity and lower isotope effects, the reasons for which are unclear. Proton tunneling does not appear to be significant in the reaction. An estimate of 17 is made for the pK of the methylene group in creatinine, based on its kinetic acidity and that of I.

The kinetics of the general base catalyzed exchange of the methylene protons in I, the quaternary methyl derivative of creatinine, have previously been studied in D_2O using NMR (Scheme I).[1,2] We now report the result of an iodination study of the reaction of I and I-d_2 with 39 general bases in H_2O. (I-d_2 is deuterated at the methylene position.)

The present results, which are consistent with Scheme I, allow us to compare the two methods, but more importantly we are now able to examine the relation between deuterium isotope effect and reaction rate over a wide range of reactivities, and with a large number of bases. The extent to which isotope effects and Bronsted coefficients can be used to probe transition-state structure is a matter of considerable current interest,[3] and we believe the present work is pertinent in this regard.

Scheme I



Experimental Section

Acidity measurements were made on buffer solutions as described previously.[1,2]

The carboxylic acids and substituted pyridines were obtained from commercial sources and purified by crystallization or distillation. *o-tert*-Butylbenzoic acid was synthesized from *o-tert*-butylbromobenzene,[4] mp 67–68 °C (lit.[4] mp 68.5 °C).

1,3-Dimethyl-2-iminoimidazolin-4-one hydriodide (the iodide salt of I) was synthesized as previously described,[5] mp 213–215 °C dec (lit.[5] mp 213–215.5 °C dec).

The amino and methylene hydrogens in I were replaced by deuterium atoms by repeatedly refluxing the salt of I in D_2O for 3 h. The NMR spectrum showed no detectable absorption due to methylene protons. Dissolving this salt in H_2O produced I-d_2, which was used in the rate studies.

Iodine was purified by sublimation; the inorganic salts were of analar grade and were used without further purification.

Rate Measurements. Rates of iodine loss were observed at 353 nm with a Cary 16 spectrophotometer equipped with a thermostated cell compartment. The concentration of I was varied from 8×10^{-4} to 8×10^{-3} M while the initial concentration of iodine was kept constant at 7.83×10^{-5} M. All reactions were carried out in the presence of 0.01 M sodium iodide at an ionic strength of 0.34, maintained by the addition of $NaClO_4$ or NaCl.

In all cases the reactions gave excellent zero-order plots with respect to iodine, for at least 60% of reaction. Absorbance readings were converted to concentrations using an effective extinction coefficient of 2.30×10^4 at 353 nm for iodine in the presence of 0.01 M iodide ion.[6] Rates of iodination of I in salicylate buffer were measured at 380 nm because of significant absorption due to salicylate buffer at 353 nm under the experimental conditions. A value of 1.55×10^4 was used for the extinction coefficient of I_2/I_3^- solutions at 380 nm.[6] The catalytic constants calculated from rate measurements at 353 and 380 nm in acetate buffer were identical. The pH values of buffer solutions before and after rate measurements were unchanged.

Rates of iodine loss were measured in a series of buffer solutions of constant buffer ratio and ionic strength but varying total buffer concentrations. The pseudo-first-order rate constants, obtained by dividing the zero-order rate constants by the substrate molarity, were then plotted against the concentration of the basic component of the buffer, and the second-order catalytic constant for the base calculated from the slope of the resulting straight line. The catalytic constant for water-catalyzed iodination of I was obtained in 1.00, 0.10, and 0.01 M HCl solutions, where the iodination rates were found to be identical.

Results and Discussion

The catalytic constants, k^H and k^D, for the reaction of I and I-d_2 with various bases as determined by iodination are listed in Table I. Iodination rates were found to be insensitive to the concentration of the acid component of the buffer, indicating an absence of any general acid catalyzed route.

Comparison between Iodination and Proton Exchange Results. A number of reaction parameters have been determined in the present study that were unobtainable, or not readily obtainable, in the earlier work[2]—salt effect, activation parameters, and solvent isotope effect. All are consistent with the mechanism of Scheme I.

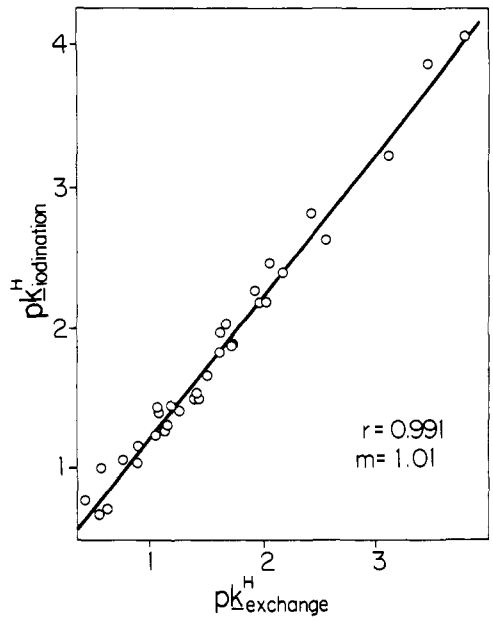


Figure 1. Comparison of iodination rates and proton exchange rates of I in buffer solutions.

The reaction conditions for the iodination and proton exchange studies differ with respect to temperature, ionic strength, and solvent (H_2O vs. D_2O). Nonetheless, a very good correlation is obtained between the series of rate constants obtained in the two studies (Figure 1). Furthermore, the iodination of I in nicotinamide and acetate buffers under the same reaction conditions as for proton exchange (D_2O, $\mu = 1.2$, $T = 34.5$ °C) gives catalytic constants in agreement within 3 and 11%, respectively, with those obtained in the proton exchange studies.[2] The Bronsted equation (eq 1) governing the catalytic effects of bases **1** to **26, 36,** and **37** is also in fairly good agreement with that obtained earlier.[2]

$$\log\left(\frac{k^H}{q}\right) = 0.73 \log\left(\frac{p}{qK}\right) - 4.57 \qquad (1)$$

In eq 1, K represents the ionization constant of the conjugate acid of the catalyst, while p and q represent the number of equivalent protons in the conjugate acid of the catalyst and the number of equivalent basic sites in the catalyst, respectively.

When the relative values of log k^H for acetate and nicotinamide catalysis are plotted against the Debye-Hückel parameter, $\sqrt{\mu}$, curved plots result (Figure 2). The slopes of the curves at $\mu = 0$ are near zero (0.04) for nicotinamide and near unity (−1.08) for acetate. The limiting values of the slopes are those expected,[7] since iodination of I in nicotinamide buffer involves reaction between a monocation and a neutral molecule, and in acetate buffer, between a monocation and a monoanion.

The enthalpy of activation, $\Delta H^{\ddagger}$, was found to be 18.9, 16.0, and 20.7 kcal/mol for acetate-, nicotinamide-, and water-catalyzed iodination of I, while the entropy of activation, $\Delta S^{\ddagger}$, for these reactions was −8.1, −22.8, and −26.2 eu, respectively. The less negative $\Delta S^{\ddagger}$ for the reaction of acetate ion than for nicotinamide or water doubtless reflects the decrease in total charge that accompanies the reaction of the former. The difference in $\Delta H^{\ddagger}$ for acetate and nicotinamide is as expected, being smaller, but of the same sign, as the difference in the thermodynamic values for protonation of carboxylate and pyridine bases.[8]

Table I. Specific Catalytic Constants[a] and Isotope Effects[b] for the General Base Catalyzed Iodination of I (k^H) and I-d_2 (k^D); T = 25.0 ± 0.1 °C; μ = 0.34

	Base	pK	k^H, M^{-1} min^{-1}	k^D, M^{-1} min^{-1}	k^H/k^D
1	3,3-Dimethylglutarate	6.34	1.20	0.271	4.43
2	Succinate	5.48	0.210	5.13×10^{-2}	4.09
3	Glutarate	5.42	0.189	4.18×10^{-2}	4.52
4	Pivalate	5.05	0.165	3.59×10^{-2}	4.60
5	Propionate	4.88	9.84×10^{-2}	2.14×10^{-2}	4.59
6	Acetate	4.76	8.40×10^{-2}	1.85×10^{-2}	4.54
7	Methoxyacetate	3.57	1.48×10^{-2}	3.72×10^{-3}	3.98
8	Phenylacetate	4.31	4.04×10^{-2}	9.81×10^{-3}	4.12
9	Oxalate	4.29	4.15×10^{-2}	1.10×10^{-2}	3.78
10	Mandelate	3.41	5.38×10^{-3}	1.73×10^{-3}	3.11
11	2-Furoate	3.17	6.58×10^{-3}	1.93×10^{-3}	3.41
12	Bromoacetate	2.90	3.45×10^{-3}	1.22×10^{-3}	2.83
13	Chloroacetate	2.87	4.04×10^{-3}	1.26×10^{-3}	3.21
14	Cyanoacetate	2.47	2.40×10^{-3}	7.59×10^{-4}	3.16
15	Dichloroacetate	1.36	5.94×10^{-4}	2.01×10^{-4}	2.95
16	Difluoroacetate	1.34	8.78×10^{-5}	4.01×10^{-5}	2.19
17	Trimesate	4.70	0.140	4.24×10^{-2}	3.30
18	*p*-Methoxybenzoate	4.47	9.03×10^{-2}	2.24×10^{-2}	4.04
19	*m*-Toluate	4.27	5.90×10^{-2}	1.51×10^{-2}	3.90
20	Benzoate	4.20	5.21×10^{-2}	1.43×10^{-2}	3.64
21	*p*-Fluorobenzoate	4.14	4.91×10^{-2}	1.35×10^{-2}	3.64
22	*m*-Methoxybenzoate	4.08	3.87×10^{-2}	1.06×10^{-2}	3.64
23	*m*-Fluorobenzoate	3.86	3.15×10^{-2}	8.97×10^{-3}	3.51
24	*m*-Chlorobenzoate	3.83	2.86×10^{-2}	8.10×10^{-3}	3.53
25	*m*-Trifluoromethylbenzoate	3.77	3.07×10^{-2}	8.98×10^{-3}	3.42
26	*m*-Cyanobenzoate	3.64	2.16×10^{-2}	6.71×10^{-3}	3.22
27	*o*-Phthalate	5.41	0.840	0.237	3.55
28	*o*-Methylbenzoate	3.91	3.63×10^{-2}	1.17×10^{-2}	3.09
29	*o*-*tert*-Butylbenzoate	3.54	6.78×10^{-2}	2.82×10^{-2}	2.40
30	*o*-Fluorobenzoate	3.27	1.09×10^{-2}	3.76×10^{-3}	2.90
31	2,6-Dimethylbenzoate	3.25	3.59×10^{-2}	1.83×10^{-2}	1.96
32	*o*-Chlorobenzoate	2.92	1.30×10^{-2}	4.83×10^{-3}	2.69
33	*o*-Bromobenzoate	2.85	1.36×10^{-2}	4.49×10^{-3}	3.03
34	*o*-Iodobenzoate	2.85	9.28×10^{-3}	3.35×10^{-3}	2.77
35	Salicylate	2.99	1.54×10^{-3}	6.70×10^{-4}	2.30
36	Nicotinamide	3.33	6.61×10^{-3}[c]	1.98×10^{-3}	3.34
37	3-Cyanopyridine	1.13	1.37×10^{-4}	5.57×10^{-5}	2.46
38	Fluoride	3.23	1.80×10^{-3}	6.55×10^{-4}	2.75
39	Water	−1.74	4.77×10^{-7}	1.57×10^{-7}	3.04

[a] Subject to estimated errors of ±3% for **1-16** and **36-39**, and ±8% for **17-35**. [b] Includes secondary isotope effect. [c] $k^H_{D_2O} = 6.66 \times 10^{-3}$ M^{-1} min^{-1}.

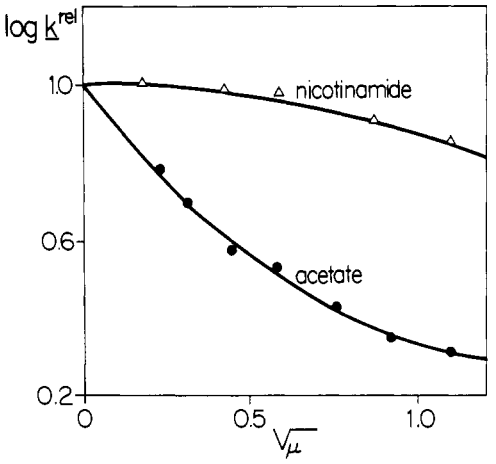


Figure 2. Effect of ionic strength on the general base catalyzed iodination rate of I. (The experimental results in acetate buffer (circles) and in nicotinamide buffer (triangles) were each fitted to a second-order equation and the best fit curve drawn. The log k value at μ = 0, obtained from extrapolation of the curve, is taken to be unity for acetate and nicotinamide buffer.)

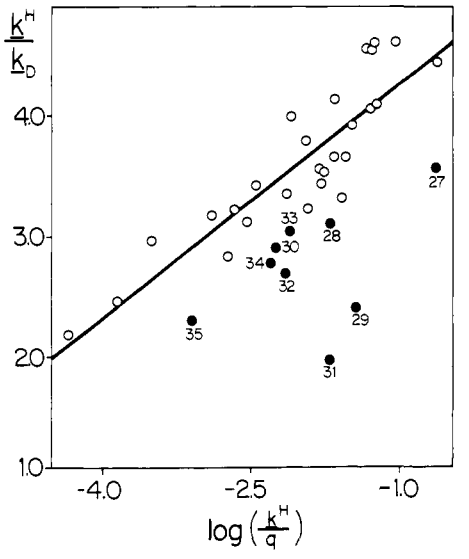


Figure 3. Correlation of isotope effects for the iodination of I with log (k^H/q). (The numbering corresponds to that in Table I.)

The absence of a solvent isotope effect ($k^H_{H_2O}/k^H_{D_2O}$ = 1.00 for the reaction of I with nicotinamide) is consistent with direct proton transfer from I to base, without intervention of solvent molecules.

Isotope Effect. Bulky groups adjacent to the basic site were previously shown to *increase* the catalytic effectiveness of the carboxylate bases used in the proton exchange experiments,[2] and this unusual effect is confirmed in the present work. Since steric effects in proton transfer reactions often give rise to the tunnel effect,[9] we were interested in seeing if the anomalous rate effects we observe are associated with this phenomenon.

Plotted in Figure 3 are the deuterium isotope effects for reaction of I and I-d_2 with carboxylate and pyridine bases as a function of the reaction rate of the protium compound I with the same bases. It is apparent that ortho-substituted benzoates (indicated by filled circles) again give rise to anomalous effects, all their isotope effects being *low*. Proton tunneling, which can only increase the magnitude of an isotope effect,[9] is clearly not important in the present system.

We have used statistically corrected values of log k^H as the basis for comparison in Figure 3, rather than the more customary equilibrium quantity, log K, because it seems appropriate to use energy differences between reactants and transition state, rather than between reactants and products, in such a correlation. [If log (K/q) is used as the abscissa in Figure 3 qualitatively, similar results are obtained, although the degree of divergence of the ortho-substituted bases is somewhat less marked.] A straight line is drawn in the figure for the sake of convenience; clearly, leveling-off would be observed on both sides if the plot could be sufficiently extended.

Since II is a considerably stronger base (with respect to protonation at C-5) than the carboxy and pyridine bases used in this work one might infer that in the transition state the proton is nearer the weaker base, and, therefore, the transition state is product-like in nature.[10] Both the Bronsted exponent (0.73) and the general trend, apparent in Figure 3, for stronger bases to exhibit larger isotope effects is consistent with this view—increasing the equilibrium base strength of the attacking reagent moves the transition state to an earlier point on the reaction coordinate and increases the symmetry of the transition state, giving rise, in turn, to a larger isotope effect.[10b,10c,11] (It is worth noting that the situation depicted in Figure 3 appears to be the general rule for simple proton transfers, i.e., the slower the reaction the smaller the isotope effect.[12,13] Hydrogen transfer accompanying oxidation, on the other hand, often demonstrates an inverse correlation between rate and isotope effect within a structurally related series.[15] The fact that most simple proton transfers that are amenable to study are endergonic while most oxidation processes are exergonic may be pertinent in this regard.)

The effect of ortho substituents is at odds with the conventional picture given above. Although the series of mono-ortho-substituted bases show fair internal consistency in Bronsted and isotope effect plots, the points in both cases are displaced in unexpected directions from the lines that include the meta- and para-substituted bases and, indeed, the aliphatic and pyridine bases as well.[2] There has been growing scepticism in recent years regarding how effective the conventional probes—isotope effects and the Bronsted relation—are in elucidating the detailed structure of the transition states of proton transfer reactions,[3a,3f,14b] and the results reported herein raise further questions in these regards.

Estimation of the Acidities of I and Creatinine. Provided I belongs to the same Bronsted "family" as other carbonyl compounds (ketones, esters, and keto esters), its pK can be estimated to be near 15, since its catalytic rate constant is very near those of 1,1-dichloroacetone[16] and diethyl methylmalonate,[10c] each of which has a pK value[17] of 15. In support of this notion is the fact that Bronsted parameters, β and log G, are similar for I and 1,1-dichloroacetone.[16] A further indication of the normalcy of I as a carbonyl compound is that the isotope effect for the water-catalyzed enolization of I-d_2 and that of diethyl methylmalonate-d[17] are fairly close (after appropriate correction for the secondary isotope effect in the former).[18]

Creatinine, which undergoes proton exchange about 50 times more slowly than I,[19] may be estimated to have a pK of about 17. The value of about 13 recently reported for the pK of this compound[20] would thus appear to correspond to proton loss from the amino group, rather than from the methylene group.

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References and Notes

(1) R. Stewart and R. Srinivasan, *Can. J. Chem.*, **53**, 2906 (1975).
(2) R. Srinivasan and R. Stewart, *J. Chem. Soc., Perkin Trans. 2*, 674 (1976).
(3) (a) C. D. Johnson, *Chem. Rev.*, **75**, 755 (1975); (b) A. J. Kresge, *Chem. Soc. Rev.*, **2**, 475 (1973); (c) R. P. Bell, *ibid.*, **3**, 513 (1974); (d) A. J. Kresge in "Proton-Transfer Reactions", E. Caldin and V. Gold, Ed., Chapman and Hall, London, 1975, Chapter 7; (e) R. A. More O'Ferrall, *ibid.*, Chapter 8; (f) D. S. Kemp and M. Casey, *J. Am. Chem. Soc.*, **95**, 6670 (1973).
(4) M. Crawford and F. H. C. Stewart, *J. Chem. Soc.*, 4443 (1952).
(5) G. L. Kenyon and G. L. Rowley, *J. Am. Chem. Soc.*, **93**, 5552 (1971).
(6) B. G. Cox, *J. Am. Chem. Soc.*, **96**, 6823 (1974).
(7) K. J. Laidler, "Chemical Kinetics", 2nd ed, McGraw-Hill, New York, N.Y., 1965, Chapter 5.
(8) J. W. Larson and L. G. Hepler in "Solute-Solvent Interactions", J. E. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 1.
(9) E. S. Lewis in "Proton-Transfer Reactions", E. Caldin and V. Gold, Ed., Chapman and Hall, London, 1975, Chapter 10.
(10) (a) J. R. Murdoch, *J. Am. Chem. Soc.*, **94**, 4410 (1972); (b) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc., Ser. A*, **294**, 273 (1966); (c) R. P. Bell and J. E. Crooks, *ibid.*, **286**, 285 (1965).
(11) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).
(12) For leading references, see R. P. Bell, "The Proton in Chemistry", 2d ed, Cornell University Press, Ithaca, N.Y., 1973, Chapter 12.
(13) Relatively few cases have been observed of the reverse situation, all of them involving nitro compounds whose Bronsted behavior is anomalous.[14]
(14) (a) R. P. Bell and R. L. Tranter, *Proc. Roy. Soc., Ser. A*, **337**, 517 (1974); (b) F. G. Bordwell, W. J. Boyle, J. A. Hautala, and K. C. Yee, *J. Am. Chem. Soc.*, **91**, 4002, (1969); (c) F. G. Bordwell, W. J. Boyle, and K. C. Yee, *ibid.*, **92**, 5926 (1970); (d) F. G. Bordwell and W. J. Boyle, *ibid.*, **93**, 512 (1971); (e) *ibid.*, **94**, 3907 (1972).
(15) R. Stewart and D. G. Lee, *Can. J. Chem.*, **42**, 439 (1964); L. M. McDonough, *Diss. Abstr.*, **21**, 3633 (1961); D. G. Lee and R. Stewart, *J. Org. Chem.*, **32**, 2868 (1967); G. R. Coroar, R. H. Rien, A. MacLachlan, and E. J. Urban, *J. Org. Chem.*, **36**, 2272 (1971); R. Stewart, "Oxidation Mechanisms", W. A. Benjamin, New York, N.Y., 1964, p 69.
(16) R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc., Ser. A*, **176**, 88 (1940).
(17) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).
(18) The secondary isotope effect on the ionization of ketones RCD_2COR is about 15%.[10b,10c] This would reduce the observed primary isotope effect of 3.04 for the water-catalyzed reaction of I to a value of 2.6, in fair agreement with the value of 2.4 found for the water-catalyzed enolization of diethyl methylmalonate.[10c]
(19) R. Srinivasan and R. Stewart, *Can. J. Chem.*, **53**, 224 (1975).
(20) A. R. Butler, *Clin. Chim. Acta.*, **59**, 227 (1975); A. Wollenberger, *Acta Chem. Scand.*, **7**, 445 (1953).