Proton Activating Factors in General Acid and General Base Catalysis

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Many organic reactions are catalyzed by acids or bases and the mechanisms of most of these processes are fairly well understood, the usual first step being either protonation or deprotonation of the substrate.[1] The activation that results from addition or removal of a proton is easily explained in qualitative terms; our concern has been to relate degree of activation to structural factors in the organic compound and to provide a rationale for the enormous variations in effect that can be found within the reactions of organic chemistry.

Consider a compound Z reacting with a base or nucleophile A^-. Protonation of Z will promote attack

$$\begin{array}{l} ZH^+ + A^- \xrightarrow{k_{ZH^+ + A^-}} \\ H^+\downarrow \qquad\qquad\qquad \searrow \text{products} \\ Z + A^- \xrightarrow{k_{Z+A^-}} \end{array}$$

$$\text{paf} = k_{ZH^+ + A^-}/k_{Z+A^-}$$

by A^-, causing acid catalysis to be observable, and the question arises: how large is the *proton activating factor* (paf)? In some cases the reactive entity ZH^+ is present in minute or uncertain concentration and the quantity $k_{ZH^+ + A}$ must be obtained indirectly.

There are two general methods for determining paf. The first makes use of the appropriate catalytic coefficients obtained by means of a kinetic analysis of the reaction of Z in aqueous buffers. (For $A^- = HO^-$ simple pH–rate profiles can be used.) The basicity of Z, i.e., pK_{ZH^+}, must be known for this method to be used. The second approach uses alkylated salts ZR^+ as surrogates for the protonated substrate ZH^+,[2] and since the concentration of ZR^+ is invariant an approximate value for $k_{ZH^+ + A^-}$ can be very easily obtained. This second method can only be used if the appropriate salt can be synthesized and, of course, it assumes that hydrogen and alkyl have the same effect on cation reactivity.

This Account deals only with acid–base, or prototropic, reactions, those in which A^- removes a proton from Z and from its conjugate acid ZH^+. Such a reaction is the rate-controlling step of a number of important organic processes, including many racemizations, oxidations, condensations, halogenations, and isotope exchanges. Reactions in which A^- behaves as a nucleophile are, in principle, amenable to similar treatment.

Ross Stewart is Professor of Chemistry at the University of British Columbia. He was born in Vancouver and received B.A. and M.A. degrees from U.B.C. He was on the staff of the Canadian Services College, Royal Roads, for 6 years and, after completing Ph.D. work with K. B. Wiberg at the University of Washington, returned to U.B.C. in 1955. His research interests are in oxidation mechanisms, strongly basic systems, substituent effects, and catalysis.

R. Srinivasan was born in Madras, India, in 1944. He studied at the University of Madras for his B.Sc. and M.Sc. degrees, and then went to the University of Saskatchewan, where he received his Ph.D. under the supervision of D. G. Lee. He is visiting assistant professor at Simon Fraser University.

Catalysis by General Acids and Bases (Method 1)

Prototropic reactions that are catalyzed by both general acids and general bases respond to changes in the strength of the buffer acid in the manner shown in Figure 1, assuming that the Brønsted relation is obeyed. Each buffer acid HA and its anion A^- contribute to the observed rate; the greater the strength of HA, the larger its contribution, and the weaker, the larger the contribution of A^-. What is the significance of the crossover point in Figure 1?

It turns out that the pK_{HA} of the particular buffer acid that appears at this point on the plot is given by eq 1, where K_{ZH^+} is the acidity constant of the conjugate

$$K_{HA} = K_{ZH^+}/\text{paf} \qquad (1)$$

acid of the substrate Z. This follows from eq 2 which

$$\text{paf} = \frac{k_{ZH^+ + A^-}}{k_{Z+A^-}} = \frac{k_{HA}K_{ZH^+}}{k_{A^-}K_{HA}} \qquad (2)$$

expresses paf in terms of the respective catalytic coefficients and equilibrium constants.[3,4] Although the catalytic coefficient k_{A^-}, which is a product of standard kinetic analysis, is identical with the term k_{Z+A^-} in eq 2, the corresponding term k_{HA} is complex, being equal to $k_{ZH^+ + A^-}$ (K_{HA}/K_{ZH^+}). It can be shown that paf is independent of the identity of the buffer acid HA provided the sum of the Brønsted coefficients α and β is unity.[4] In the subsequent discussion this will be assumed to be so, although only modest variations in paf could be attributed to this effect in any case.

It is curious that the wealth of quantitative data on general acid catalysis that has accumulated over a period of half a century has so seldom been analyzed in terms of individual steps; that is, in terms of mechanism. As far as we are aware the first analysis of the sort we are concerned with was done by Lienhard and Anderson[5] in 1967. They examined the enolization of acetone catalyzed by buffer acids and concluded that

(1) R. P. Bell, "The Proton in Chemistry", 2nd ed., Cornell University Press, Ithaca, N.Y., 1973, Chapter 9; M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley-Interscience, New York, N.Y., 1971, Chapter 4; J. Toullec and J. E. Dubois, *J. Am. Chem. Soc.*, **96**, 3524 (1974).

(2) (a) R. Stewart and R. Srinivasan, *Can. J. Chem.*, **53**, 2906 (1975); (b) R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, **26**, 685 (1970); (c) R. A. Olofson and J. M. Landesberg, *J. Am. Chem. Soc.*, **88**, 4263 (1966); (d) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *ibid.*, **88**, 4265 (1966); (e) B. G. Cox, *ibid.*, **96**, 6823 (1974); (f) A. R. Katritzky and C. D. Johnson, *Angew. Chem., Int. Ed. Engl.*, **6**, 608 (1967); (g) A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. B*, 2365 (1971).

(3) R. Srinivasan and R. Stewart, *Can. J. Chem.*, **53**, 224 (1975).

(4) R. Stewart and J. M. McAndless, *J. Chem. Soc., Perkin Trans. 2*, 376 (1972).

(5) G. E. Lienhard and F. H. Anderson, *J. Org. Chem.*, **32**, 2229 (1967); see also ref 28 and 37a.

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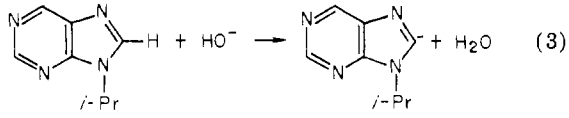
$$CH_3-\overset{+OH}{\overset{\|}{C}}-CH_3 + AcO^- \rightarrow CH_3-\overset{OH}{\overset{|}{C}}=CH_2 + AcOH$$

$$CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + AcO^- \rightarrow CH_3-\overset{O^-}{\overset{|}{C}}=CH_2 + AcOH$$

acetate ion removes one of the methyl protons from protonated acetone 3×10^{11} times as fast as from acetone itself. (The value we give in Table I for this quantity is considerably lower because we use a more recent estimate of the basicity of acetone.)

In 1972 Stewart and McAndless[4] derived the general expression for proton activation, eq 2, and subsequently Stewart and Srinivasan introduced the term paf.[3]

Table I lists paf values for all reactions for which we have been able to locate firm data on k_{HA}, k_{A^-}, and K_{ZH^+} (see ref 2–22). The paf values for compounds **12** to **20** were determined from pH–rate profiles. For example, the isotopic exchange[21] of the proton in the 8-position in 9-isopropylpurine **14** varies with acidity at 85 °C in the manner shown in Figure 2. The two paths that dominate the pH region are Z + HO^- (eq 3), which is



(3)

14

the principal path in basic solution, and $ZH^+ + HO^-$, which is the principal path in neutral and acidic solution. At the acidity at which they make equal contributions $k_{Z+HO^-}[Z][HO^-] = k_{ZH^+ + HO^-}[ZH^+][HO^-]$, and therefore at this particular acidity eq 4 holds. In the

$$\text{paf} = \frac{k_{ZH^+ + HO^-}}{k_{Z+HO^-}} = \frac{[Z]}{[ZH^+]} = \frac{K_{ZH^+}}{[H^+]} \qquad (4)$$

case of **14**, paf = 10^8 since K_{ZH^+} for this compound[21,23] is 3×10^{-3} and the H^+ molarity at which the two routes make equal contributions is 3×10^{-11} (the acidity for which the logarithm of the overall rate is 0.3 unit above the plateau). The change in slope near pH 3 in Figure 2 corresponds to protonation of Z, and paf can also be obtained by simply taking the horizontal distance between the points shown in Figure 2.

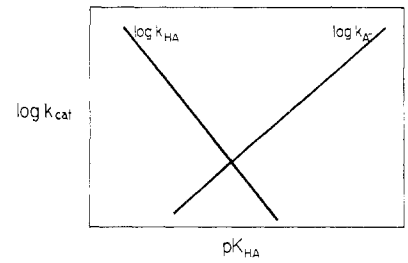


Figure 1. Catalytic coefficients of the buffer components HA and A^- for a reaction catalyzed by a series of general acids and bases, as a function of the pK_{HA} of the acids.

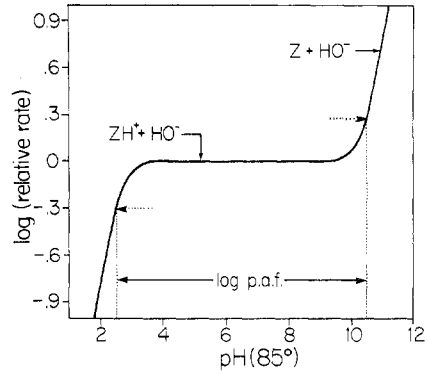


Figure 2. Rate–pH profile for the exchange of the 8-hydrogen in 9-isopropylpurine (**14**).

Quaternary Salts as Surrogates for ZH^+ (Method 2)

The paf values for compounds **21** to **28** (Table II) were determined by comparing the rates of proton loss from the parent compounds with those from the cations alkylated at the positions designated. For several systems, e.g., **9** and **23a**, it can be shown that the cations ZR^+ and ZH^+ react at roughly the same rate,[2a–c] and we shall assume that the paf values determined by this method are as reliable as those determined using neutral substrates and aqueous buffers.

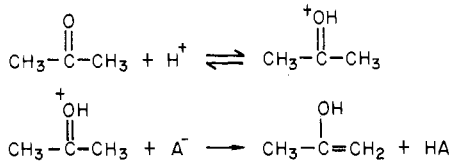
Variations in paf

Enormous variations in paf covering 11 orders of magnitude or more can be found in Tables I and II (compare number **9** and **10** with **22** and **26b**) (see ref 2–22, 24). It is of interest to determine the structural factors in the substrate that are responsible. We have divided the compounds into two types. In type I, the site of protonation in the general-acid-catalyzed route is conjugated with the developing negative charge, while in type II there is no such conjugation; that is, a mesoionic intermediate is formed. An example of a type I reaction is the enolization of acetone, and of type II, proton loss from the C-2 position of thiazole. All of the compounds in Table II and compounds **9**–**20** in Table I belong to type II.

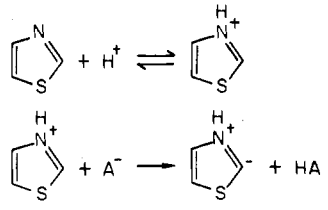
In type I, the paf values with acetate as the base vary from 10^7 for acetone (**1**) to 200 for 6,7,8-trimethyllumazine (**8**). We have used recently determined values for ketone basicities which reveal these compounds to be much more basic[25] than had previously been be-

(6) R. A. McClelland and W. F. Reynolds, *Can. J. Chem.*, **54**, 718 (1976).
(7) R. A. Cox and J. Warkentin, *Can. J. Chem.*, **50**, 3242 (1972).
(8) R. P. Bell and O. M. Lidwell, *Proc. R. Soc. London, Ser. A*, **176**, 88 (1940).
(9) J. T. Edward and S. C. Wong, *J. Am. Chem. Soc.*, **99**, 4229 (1977).
(10) D. W. Earls and J. R. Jones, *J. Chem. Soc., Faraday Trans. 1*, 2186 (1975).
(11) R. P. Bell and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1681 (1973).
(12) M. M. Mhala and K. J. Singh, *J. Ind. Chem. Soc.*, **L11**, 1092 (1975).
(13) R. Stewart and R. Srinivasan, unpublished results.
(14) D. J. Brown, "The Pyrimidines—Supplement I", Wiley-Interscience, New York, N.Y., 1970, p 378.
(15) T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc. B*, 171 (1967).
(16) D. J. Brown and T. C. Lee, *Aust. J. Chem.*, **21**, 243 (1968).
(17) The p*K* is corrected according to the method of I. R. Bellabono and E. Diani, *J. Chem. Soc., Perkin Trans. 2*, 1707 (1972).
(18) W. Pfleiderer, J. W. Bunting, D. D. Perrin, and G. Nübel, *Chem. Ber.*, **99**, 3503 (1966).
(19) M. Tomasz, J. Olson, and C. M. Mercado, *Biochemistry*, **11**, 1235 (1972).
(20) (a) R. V. Wolfenden, *J. Mol. Biol.*, **40**, 307 (1969); (b) J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J. Chem. Soc., Perkin Trans. 2*, 2138 (1973).
(21) J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J. Chem. Soc., Perkin Trans. 2*, 1889 (1973).
(22) J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans and H. C. Sheppard, *J. Chem. Soc., Perkin Trans. 2*, 174 (1974).
(23) There is uncertainty regarding the structure of the cation, and it appears that N-1, N-3, and N-7 may be protonated to comparable extents.[29b]
(24) P. Beak and R. N. Watson, *Tetrahedron*, **27**, 953 (1971).

Type I

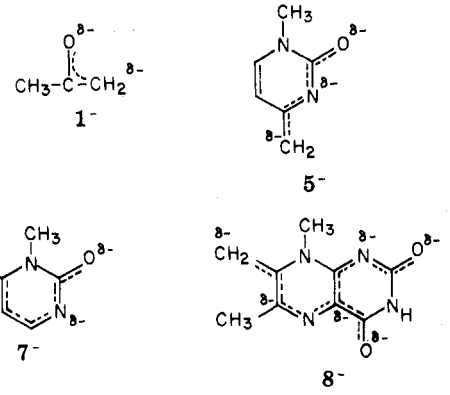


Type II



lieved.[26,27] (The earlier values of K_{BH^+} make the paf values for 1–4 larger by factors of 10^2 to 10^5. We believe, however, that the older values for acetone[26a] and acetophenone,[26b] for example, underestimate these compounds' basicities, despite indirect evidence of the former's reasonableness that can be adduced from other work.[28])

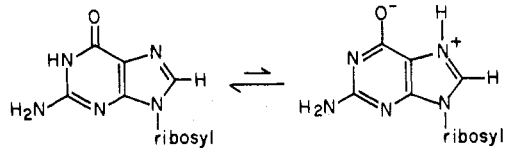
The variability of paf for type I compounds is due chiefly to the sensitivity of the term k_{Z+A^-} to changes in the structure of Z, and particularly to changes in the extent of conjugation. When simple ketones, for example 1–4, lose a proton they produce anions in which



the charge is dispersed between one oxygen and one carbon atom. As the degree of delocalization of anionic charge increases (compounds **5**, **7**, **8**, anions 5^-, 7^-, 8^-) the value of k_{Z+A^-} for a given base increases, as would be expected. (In 5^- there are three atoms bearing formal charge, in 7^- four, and in 8^- there are six.) The effect of conjugation on the other term that makes up paf, $k_{ZH^+ + A^-}$, is small and shows no clear trend—again a reasonable result since conjugation stabilizes both the conjugate acid ZH^+ and the neutral enol formed by proton loss. The net result of these effects is that the greater the degree of conjugation with the site of proton loss, the smaller is paf.

With type II compounds a very much wider range of paf values is found. Here the anionic charge cannot be dispersed by resonance even though the molecule may contain a conjugated system of double bonds. In these compounds the inductive effect of nitrogen and sulfur, particularly the latter, raises the value of the term k_{Z+A^-}, with the effect dropping off with distance, as would be expected. (In the case of the 2- and 4-azaacetophenones, **10** and **11**, the nitrogen atom has virtually no activating effect.[2e]) The effect of protonated nitrogen also tends to decrease with increasing distance between the sites of protonation and deprotonation, as can be seen by comparing the paf values for two different sites of exchange in **23**, **26**, and **27**. When the proximity effect of protonated nitrogen is compared in different compounds the results are not as clear-cut since paf values of 10^7 to 10^{14} can be found for systems in which the positive charge is on the adjacent atom(s); compare **18** and **26b**. It may be that delocalization of the one unit of charge to the pair of adjacent atoms, as in **18**, contributes to the reduction in effect. In support of this notion the lowest paf reported, 17, is for a compound (**9**) with considerable dispersion of the cationic charge in the conjugate acid. Note, however, that **22**, in which the cationic charge can also be dispersed, has a very high value of paf.

Alternatively, the relatively modest paf for **16–20** may be due to the neutral compound reacting through the betaine, as can be illustrated by the case of guanosine (**18**).[19] There is some evidence to indicate that the



removal of the C-8 proton takes place from the minor betaine form **18′**, which places a positive charge at the nitrogen atom adjacent to the exchanging proton. If this be so, the paf values for **16–20** will be larger than those given in the table.

A further source of ambiguity arises with **13–15**, which are believed to be predominantly protonated in the six-membered ring, the N-7 protonated form being a minor component.[29] The latter is probably responsible for exchange, however, meaning that the tabulated paf may be considered the lower limit for the effect of protonating the adjacent nitrogen atom in each of these compounds.

In type I compounds we saw that structural changes that increase the value of k_{Z+A^-} reduce paf. This is not so with type II compounds. For example, inserting an additional nitrogen atom in **23a** would give **28a**, which has a much larger value of k_{Z+A^-}. The paf is essentially unchanged, however, and similarly with **23b** and **28b**. It is evident that activating units tend to act independently in type II systems, unlike the situation with type I compounds, in which conjugative effects are dominant.

Type I and II compounds also respond differently to changes in the identity of the attacking base. Type I compounds seem to have "normal" values of the Brønsted coefficient β ranging from 0.88 for **1**[8] to 0.50

(25) See ref 6 and 9 and also A. R. Butler, *J. Chem. Soc., Perkin Trans. 2*, 959 (1976).
(26) (a) H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109 (1960); (b) R. Stewart and K. Yates, *J. Am. Chem. Soc.*, **80**, 6355 (1958).
(27) E. M. Arnett, *Prog. Phys. Org. Chem.*, **1**, 223 (1963).
(28) R. P. Bell and J. E. Crooks, *Proc. R. Soc. London, Ser. A*, **286**, 285 (1965).
(29) (a) R. Wagner and W. von Phillipsborn, *Helv. Chim. Acta*, **54**, 1543 (1971); (b) J. H. Read and J. H. Goldstein, *J. Am. Chem. Soc.*, **87**, 3440 (1965); (c) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles", Academic Press, New York, N.Y., 1976, pp 505, 515. (d) D. Lichtenberg and F. Bergmann, *J. Chem. Soc., Perkin Trans. 1*, 789 (1973).

Table I
Rate and paf Data for Prototropic Reactions Catalyzed by General Acids and Bases[a,b]

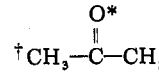
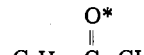
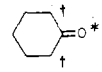
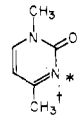
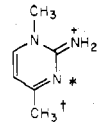
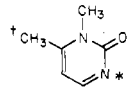
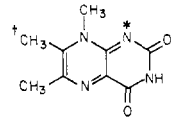
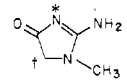
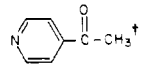
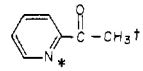
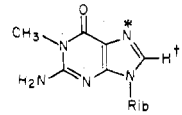
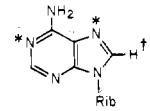
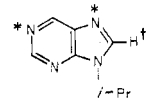
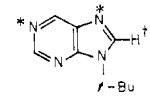
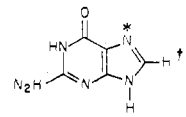
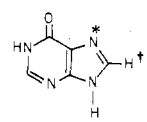
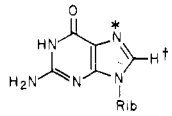
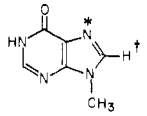
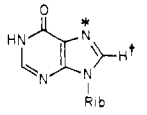
No.	Ref	Substrate, Z[c]	pK_{ZH^+}	Base, A^-	$k_{ZH^+ + A^-}$,[d] M^{-1} s^{-1}	$k_{Z + A^-}$, M^{-1} s^{-1}	paf
1	6-8		−2.72	H_2O	2.6×10^{-4}	8.3×10^{-12}	3.1×10^{7}
				AcO^-	3.1	2.4×10^{-7}	1.3×10^{7}
				AcO^-[f]		8.0×10^{-7}	
2	9, 10		−4.32	H_2O[e]	1.6×10^{-3}	3.6×10^{-11}	4.4×10^{7}
3	6, 11		−2.76	AcO^-	11	5.9×10^{-7}	1.9×10^{7}
4	6, 11, 12		−2.59	H_2O	1.4×10^{-2}	6.0×10^{-8}	2.3×10^{5}
				AcO^-	4.1	7.5×10^{-7}	5.5×10^{6}
5	13, 14		3.21	AcO^-	6.2×10^{-2}	1.0×10^{-5}	6.2×10^{3}
				DO^-[f,g]		1.3×10^{-3}	
				DMG	0.44	3.3×10^{-5}	1.3×10^{4}
6	13, 15		<−1	Nic	$>10^{-1}$	4.7×10^{-7}	$>10^{5}$
				AcO^-[f]		8.4×10^{-6}	
7	13, 16, 17		3.88	AcO^-[f,g]	0.12	1.3×10^{-4}	9.2×10^{2}
				DO^-[f,g]		3.1×10^{-2}	
8	4, 18		0.9	AcO^-[f,g]	2.9	1.4×10^{-2}	210
9	3		5.40	AcO^-[f,g]	1.2×10^{-3}	7.3×10^{-5}	17
10	2e		3.43	AcO^-	7.1×10^{-4}	3.4×10^{-5}	21
11	2e		2.64	AcO^-	1.5×10^{-3}	7.3×10^{-6}	206
12	19		2.3	HO^-[h]			$>10^{9}$
13	20		3.0	HO^-[i]	2.2×10^{5}	1.9×10^{-2}	1.1×10^{7}[j]
14	21		2.5	HO^-[i]	1.5×10^{6}	1.1×10^{-2}	1.3×10^{8}[j]
15	21		2.8	HO^-[i]	2.9×10^{5}	2.5×10^{-3}	1.2×10^{8}[j]
16	22		2.6	HO^-[i]	3.1×10^{5}	0.18[k]	1.7×10^{6}
17	22		1.9	HO^-[i]	$\sim 1.2 \times 10^{6}$	1.3[k]	10^{6}

Table I (*Continued*)

No.	Ref	Substrate, Z[c]	pK_{ZH^+}	Base, A^-	$k_{ZH^+ + A^-}$,[d] $M^{-1}\ s^{-1}$	k_{Z+A^-}, $M^{-1}\ s^{-1}$	paf
18	22		1.7	HO^-[i]	8.3×10^6	0.95[k]	8.7×10^6
19	22		1.9	HO^-[i]	2.3×10^6	4.5[k]	5.1×10^6
20	22		1.4	HO^-[i]	9.6×10^6	8.4[k]	1.1×10^6

[a] In water at 25 °C unless otherwise indicated. [b] Abbreviations used: DMG, 3,3-dimethylglutarate; Nic, nicotinamide; Rib, β-D-ribofuranosyl. [c] Position of protonation indicated by *; reactive hydrogen atom(s) indicated by †. [d] Calculated using pK_{ZH^+} values and catalytic coefficients given in references. [e] 50 °C. [f] 35 °C. [g] In D_2O. [h] 37 °C. [i] 85 °C. [j] Protonation is believed to take place predominantly in the six-membered ring (see text). [k] Reactive form may be the betaine (see text). Protonation occurs predominantly as shown.[7d]

for 6.[13] Many type II reactions, on the other hand, must have β values of unity (or greater) since they reveal only the effect of HO^- when they are conducted in buffer solution. The reverse reaction, protonation of the mesoionic intermediate, is presumably diffusion controlled in these cases.[1,30]

Deprotonating Factor (dpf)

Activation of prototropic processes can be achieved either by protonating the substrate Z, as in the cases discussed up to this point, or by removing a proton from the reagent base. Thus HO^- is a more effective kinetic base than H_2O, the magnitude of the difference depending on the Brønsted β value for the particular reaction. Almost all the information available on dpf deals with the H_2O–HO^- pair, where dpf = k_{HO^-}/k_{H_2O}, with k_{H_2O} being the bimolecular rate constant. The values range from 10^8 for 2,4-pentanedione[31] and 2-methylbutanal[32] to $\sim 10^{15}$ for thiazole.[2b] For acetone[8] the value is 3×10^{10}, significantly larger than the value of 3×10^7 for paf. (Other carbonyl compounds are similar.[8,31,33]) Creatinine (**9**) has a dpf(HO^-/H_2O) of 3×10^9.[3,34] Likewise, with other compounds for which both paf and dpf(HO^-/H_2O) are known the latter are larger, reflecting the greater effect of removing a proton from the atom in the base that is immediately involved in the bond-breaking process than of adding a proton to an atom in the substrate that is merely adjacent to that suffering the proton loss. Removing a distant proton in the base has only a slight effect, as would be expected. For example, the dianion of succinic acid is but 4.7 times more effective than the monoanion in removing a proton from the quaternary salt of creatinine (**9**).[34,35]

(30) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 3; A. J. Kresge, *Chem. Soc. Rev.*, **2**, 475 (1973).
(31) M. L. Ahrens, M. Eigen, W. Kruse, and G. Maass, *Ber. Bunsen. Phys. Chem.*, **74**, 380 (1970).
(32) J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *J. Am. Chem. Soc.*, **87**, 5050 (1965).
(33) R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc. B*, 827 (1967).
(34) R. Srinivasan and R. Stewart, *J. Chem. Soc., Perkin Trans. 2*, 674 (1976).

Relevance of paf and dpf to the Areas of Mechanism and Synthesis

Consider two reactions (eq 5 and 6) that follow ki-

$$Z + H_2O \rightarrow P \quad (5)$$

$$ZH^+ + HO^- \rightarrow P \quad (6)$$

netically equivalent, pH-independent, routes to products or reactive intermediates (P). Addition of hydroxide ion to each system will cause, at some point, a linear increase in rate to be observed as the route given by eq 7 becomes important. For reactions that

$$Z + HO^- \rightarrow P \quad (7)$$

follow eq 5 and 7 the routes make equal contributions when

$$[H^+] = K_w(\text{dpf})/[H_2O]$$

or, since $K_w = 10^{14}$ and $[H_2O] = 55.5$, when

$$[H^+] = 1.8 \times 10^{-16}(\text{dpf}) \quad (8)$$

For reactions that follow eq 6 and 7 we have seen (eq 4 and Figure 2) that hydroxylic catalysis becomes manifest when

$$[H^+] = K_{ZH^+}/\text{paf} \quad (9)$$

If the right hand side of eq 9 is smaller than that of eq 8, then eq 6 describes the pH-independent path, and vice versa for eq 5 to apply.

For most compounds of type II (those giving mesoionic intermediates),

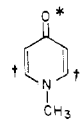
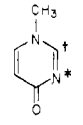
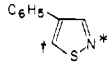
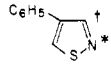
$$K_{ZH^+}/\text{paf} < 1.8 \times 10^{-16}(\text{dpf}) \quad (10)$$

and hence eq 6 applies. For thiazole,[2b-d] for example, $K_{ZH^+} = 3 \times 10^{-3}$, paf = 2×10^{10}, dpf $\approx 10^{15}$, thus making the right-hand side of eq 10 greater than the left by a factor of $\sim 10^{12}$ and ensuring that the path $ZH^+ + HO^-$ completely dominates its kinetically equivalent rival $Z + H_2O$ under all conditions.

If the right-hand sides of eq 8 and 9 are equal there will be an acidity at which the three routes given by eq

(35) R. Srinivasan and R. Stewart, *J. Am. Chem. Soc.*, **98**, 7648, (1976).

Table II
Rate and paf Data for Prototropic Reactions Determined Using Quaternary Salts

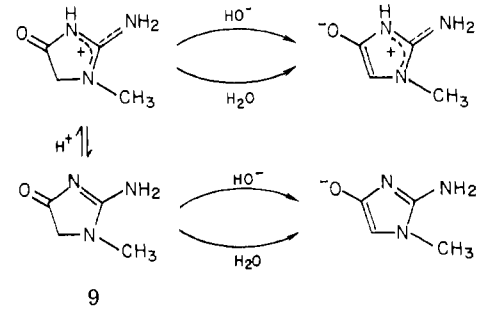
No.	Ref	Substrate, Z[a]	Medium (T)	Base, YO^-	$k_{ZR^+ + YO^-}$	$k_{Z + YO^-}$	paf[b]
21	24		D_2O (70 °C)	DO^-			5×10^3
22	24		D_2O (70 °C)	DO^-	$\sim 9 \times 10^6$	$\sim 10^{-7}$	$\sim 10^{12}$
23a	2c,d		D_2O (31 °C)	DO^-	9.8×10^5	5.8×10^{-5}	1.7×10^{10}
23b	2c,d		D_2O (31 °C)	DO^-	$\sim 10^2$	4.3×10^{-5}	$\sim 10^7$
24	2c,d 13		CH_3OD (31 °C) D_2O (31 °C) CH_3OD/D_2O (35 °C)	CH_3O^- DO^- CH_3O^-/DO^-	 7.3×10^2	3.9×10^{-4} 4.6×10^{-4}	 $\sim 1.6 \times 10^6$
25	2c,d 13		CH_3OD (31 °C) D_2O (31 °C) CH_3OD/D_2O (35 °C)	CH_3O^- DO^- CH_3O^-/DO^-	 3×10^2	9.7×10^{-5} 8.5×10^{-5}	 $\sim 4 \times 10^6$
26a	2c,d		CH_3OD (31 °C) D_2O (31 °C)	CH_3O^- DO^-	 6.5×10^3	5.9×10^{-4} 	$\sim 10^7$[c]
26b	2c,d		CH_3OD (31 °C) D_2O (31 °C)	CH_3O^- DO^-	 2.1×10^2	$<10^{-12}$ 	$>10^{14}$[c]
27a	2c,d		D_2O (31 °C)	DO^-	4.6×10^5	1.8	2.6×10^5
27b	2c,d		D_2O (31 °C)	DO^-	4.2×10^3	$<6 \times 10^7$	$>10^{10}$
28a	2c,d		D_2O (31 °C)	DO^-	$\sim 10^9$	0.18	$\sim 10^{10}$
28b	2c,d		D_2O (31 °C)	DO^-	1.8×10^5	0.18	1.0×10^6

[a] Position of alkylation indicated by *; reactive hydrogen atom indicated by †. [b] Calculated assuming effects of alkylation and protonation are identical. [c] Calculated assuming reactivities of DO^- and CH_3O^- are identical (see compounds 24 and 25).

5, 6, and 7 make essentially equal contributions to the rate of reaction. It so happens that this condition is approximately met for exchange at C-5 of creatinine **9** in the region pH 6 to 7. Furthermore, if β be not very different for the reactions of Z and ZH^+, a fourth route ($ZH^+ + H_2O$) will make a comparable contribution. The four routes to exchanging intermediates shown in Scheme I will thus all be expected to make significant contributions to the overall rate near neutrality.[2a,3,34,36]

What are the conditions that determine how a neutral solution of a reactive substrate responds to addition of H^+ or HO^-? For most simple ketones and other type I compounds, 1.8×10^{-16} (dpf) $>10^{-7}$ and, therefore, addition of HO^- will speed up the reaction and addition of H^+ (up to a point) will slow it down; for most type II compounds the pH–rate profile resembles that shown in Figure 2 for 9-isopropylpurine. Thus most of the condensation, racemization, oxidation, and other reactions that proceed via proton abstraction processes

Scheme I



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are activated more effectively by addition of base than by addition of acid. We suspect that organic chemists have long held this view, and the present work can be regarded as placing it within a quantitative framework.

One further point: The ubiquity of general acid catalysis in biological systems raises the question as to the manner in which weakly basic substrates such as carbonyl compounds can be activated at neutral pH, the concentration of protonated forms being so small that

(36) Creatinine itself can act as a general base, and so self-catalysis is also observed in all but very dilute solutions.[3]

an enormous paf would be required to effect simple proton removal. A possible alternative route is the conversion of the carbonyl compound to the protonated Schiff base.

$$R_2C{=}O + RNH_2 + H^+ \rightleftharpoons R_2C{=}\overset{+}{N}HR + H_2O$$

Such species do indeed have reactive methylene groups,[37] and can be present in reasonable concentrations in neutral solution. Further work is needed to determine the importance of this alternative form of activation.

(37) (a) M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966); (b) G. E. Lienhard and T. C. Wang, *ibid.*, **90**, 3781 (1968); (c) M. Roseman, personal communication; (d) J. Hine, *Acc. Chem. Res.*, 11, 1 (1978).

Flow and Stopped-Flow Nuclear Magnetic Resonance Investigations of Intermediates in Chemical Reactions

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The investigation of reaction intermediates has played an important role for many years in the elucidation of the mechanisms of chemical reactions. In the earliest work, investigation of intermediate species depended upon their isolation from the reaction mixture and was thus limited to relatively stable, long-lived species. With the advent of spectroscopic techniques, it became possible to investigate these intermediate species in situ during the reaction.

Various spectroscopic techniques have been used, but UV–visible spectroscopy has become by far the most widely used in these investigations in both flow and stopped-flow experiments.[1] The main advantage of UV–visible spectroscopy is its extreme sensitivity, which permits the use of low concentrations of substrates (10^{-4}–10^{-6} M) which gives relatively ideal solutions and in many instances considerably lowers the rate of reaction. Ultraviolet–visible spectroscopy has, however, the disadvantage of being a relatively nondiagnostic technique so that often accurate kinetic measurements may be made on transient species but little information obtained as to their structures.

High-resolution nuclear magnetic resonance spectroscopy is relatively insensitive and much more concentrated solutions ($\sim 10^{-1}$ M) must be used, but its great diagnostic character has made it the most widely used spectroscopic technique for structure determinations, especially in organic and organometallic systems.[2] NMR has also been used to study very slow chemical reactions ($t_{1/2} \gtrsim 3$–5 min) by measurement of changes in peak areas as the reaction proceeds, and much work has been done in the study of fast exchange reactions in systems at equilibrium by the study of line-shape changes.[3]

Until recently, however, NMR has not been utilized in flow or stopped-flow experiments, possibly due to concern over the relatively long relaxation times commonly found for magnetic nuclei.[4] Recently, techniques and equipment have been developed which make it possible easily and simply to use high-resolution NMR in both flow and stopped-flow experiments. These enable kinetic measurements to be made in the range 50 ms–5 min and thus cover a range of reaction times previously inaccessible to NMR investigation. They also provide an excellent diagnostic tool for the identification of transient intermediate species and in this context usefully complement UV–visible spectroscopy. The techniques to be described all utilize commercial spectrometers available to most chemists. It is hoped that this Account will encourage their wider use.

Flow Nuclear Magnetic Resonance Spectroscopy

The characteristic properties of nuclear magnetic resonance in flowing liquids have been known for some time[5] and are well described.[5,6] The signal amplitude depends on the length of time the sample has been in the magnetic field, and there is broadening of the signals due to a reduction in the effective T_2 of the sample by the flow.[5] There is a corresponding decrease in T_1 which allows more power to be applied before saturation occurs.

The apparatus developed and used in our laboratory for continuous flow NMR measurements is shown in

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(1) C. N. R. Rao, "Ultra-Violet and Visible Spectroscopy: Chemical Applications", 2nd ed, Butterworths, London, 1967.
(2) N. F. Chamberlain, "The Practice of NMR Spectroscopy", Plenum Press, New York, N.Y., 1974.
(3) "Dynamic Nuclear Magnetic Resonance Spectroscopy", L. M. Jackman and F. A. Cotton, Ed., Academic Press, New York, N.Y., 1975.
(4) Characteristically these range from 1 to 30 s.
(5) A. I. Zhernovoi and G. D. Laytshev, "Nuclear Magnetic Resonance in a Flowing Liquid", Consultants Bureau, New York, N.Y., 1965.
(6) D. W. Jones and T. F. Child, *Adv. Magn. Reson.*, 8, 123 (1976).

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