Nucleophilicity towards a Vinylic Carbon Atom: Rate Constants for the Addition of Amines to the 1-Methyl-4-vinylpyridinium Cation in Aqueous Solution

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Second-order rate constants (k_{Nu}) have been measured for the addition of 44 primary amines (including five α-effect amines), 28 secondary amines, 19 tertiary amines, ammonia and hydroxide ion to the vinyl group of the 1-methyl-4-vinylpyridinium cation (**1**) in aqueous solution at 25 °C (ionic strength 0.1 mol dm^{-3}). Nucleophilic attack is shown to be rate-determining for primary and secondary amines, with secondary amines being generally more reactive than primary amines of the same basicity. After classification of these species in terms of structure, they describe a number of Brønsted-type correlations having β_{nuc} in the range 0.35–0.54 for six structural classes of primary amine, $\beta_{nuc} = 0.48$ for α-effect amines, and β_{nuc} in the range 0.23–0.34 for four structural classes of secondary amine. Substitution upon the α-carbon atom reduces amine nucleophilicity of both primary and secondary amines. The presence of an unsaturated carbon atom (either sp^2- or sp-hybridized) as the β-carbon atom leads to an enhanced reactivity relative to the corresponding β-sp^3 species in all cases. Tertiary amines are in general less reactive than other amines of the same basicity. Brønsted-type plots for tertiary amines present the appearance of random scatter which is not readily decipherable in terms of structure. β-Hydroxy and β-amino tertiary amines are unusually reactive relative to their basicity. All of these phenomena suggest that protonation of the carbanionic intermediate by a molecule of water is the rate-determining step for the addition of tertiary amines to **1**.

Rate constants for the attack of primary and secondary amines on **1** are shown to correlate with literature data for a variety of other reactions involving rate-determining nucleophilic attack of amines upon electrophilic carbon. These k_{Nu} for primary and secondary amines reacting with **1** are also shown to correlate with Ritchie's N_+ parameters for nucleophilic attack at electrophilic sp^2-carbon. N_+ parameters for amine nucleophiles have not been widely available previously; the parameters that have been available for selected amines are known to be sensitive to the nature of the defining electrophile. The minimal steric hindrance at the electrophilic centre in nucleophilic attack upon **1** suggests that this species is an appropriate electrophile for the definition of N_+ parameters for amine nucleophiles; these parameters are evaluated for 70 primary and secondary amines and ammonia and are suggested to provide an appropriate data base for future investigations of the reactivity and selectivity of amine attack upon sp^2-carbon electrophiles in aqueous solution.

Ritchie defined and evaluated the N_+ parameter to describe the reactivity of a wide range of nucleophiles with sp^2-hybridized carbon electrophiles.[1-5] Although N_+ was originally defined[1] for reactions of carbocations with nucleophiles, it has also been used for the analysis of rates of nucleophilic attack upon neutral aromatic ring systems (nucleophilic aromatic substitution)[6] and acyl derivatives (nucleophilic acyl substitution)[7] and also upon electrophilic nitrogen in diazonium cations.[1] In contrast with other linear free energy relationships, correlations of nucleophilic reactivity in terms of eqn. (1) are unique in

$$\log k_{Nu} = N_+ + \log k_{H_2O} \quad (1)$$

displaying constant unit slope which indicates that the selectivity for various nucleophiles is independent of the reactivity of the electrophile that is under investigation (k_{Nu} is the second-order rate constant for reaction of a nucleophile with an electrophile and k_{H_2O} is the first-order rate constant for the reaction of water with that same electrophile in aqueous solution).

Some particular strengths of the N_+ parameter lie in its ability to combine data for both neutral and anionic nucleophiles, data for nitrogen, oxygen, sulfur and carbon nucleophilic atoms, and also data for reactivities in different solvents, into single correlation relationships. A number of recent reports[4,8,9] of the inapplicability of eqn. (1) in reactions where it might reasonably be expected to have been useful, are still overshadowed by the large body of correlations, mainly from Ritchie's laboratory,[1-4] which dramatically demonstrate its impressive range of utility. In a review[5] of the N_+ concept, Ritchie pointed out the continuing lack of a sound theoretical basis for the existence of eqn. (1), as well as some complications which arise in some of the applications that had been previously considered. Rappoport[10] has reviewed the whole area of nucleophilic attack upon vinylic carbon, and has demonstrated the enigmas which continue to complicate attempts to develop systematic quantitative treatments for these reactions.

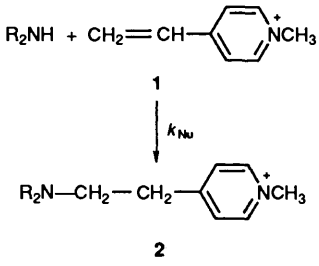
In protic solvents, the desolvation of the hydrogen-bonded nucleophilic atom must occur as an initial step upon the reaction coordinate. Such desolvation is generally believed to lie at the root of the poor correlations that are observed between nucleophilicity and basicity, especially in comparisons of anionic and electrically neutral nucleophiles. Ritchie originally suggested[2,11,12] that a major reason for the success of the N_+ approach might lie in the possibility that desolvation of the nucleophile may be at least partly rate-determining in many nucleophile–electrophile combination reactions. A direct demonstration that such desolvation can have a significant influence in nucleophilic reactions has been provided[13-15] by inverse relationships between nucleophilicity and basicity (*i.e.*,

negative β_{nuc} parameters) in several reactions in aqueous solution.

Steric interactions between the nucleophile and electrophile as well as the polarizability of the electron density on the nucleophilic atom are also significant determinants of the experimentally observed nucleophilicity of any particular reagent. The nucleophilicities of primary, secondary and tertiary amines would be expected to be particularly sensitive to steric effects. However, it is not unusual to observe higher reactivities for secondary and tertiary amine nucleophiles than for less hindered primary amine nucleophiles of the same basicity. The only obvious rationalization of such observations lies in a resort to implicating profound differences in solvation phenomena for these different classes of amine nucleophile.

The first N_+ parameters for amines were defined by Ritchie and Virtanen [16] for 12 primary amines (including several α-effect amines) reacting with the bis(4-dimethylaminophenyl)phenylmethyl cation in aqueous solution. These values were shown to correlate the rate constants for the aminolysis reactions of several activated acetate esters (*e.g.*, 2,4-dinitrophenyl acetate). This list was then extended [7] to include N_+ values for 26 amines in aqueous solution in a multiple regression analysis of the reactivities of amines towards a series of carbocations, diazonium cations and acetylated species. However, subsequent examination [5] of the data for the reactivities of amines with ring-substituted triphenylmethyl cations, the pyronin-Y cation and aryltropylium cations indicated variations in N_+ for individual amines by over 1 unit in several cases (*i.e.*, greater than a tenfold variation in rate constant) depending upon which series of electrophiles was used as the basis for the definition of N_+. At least some of these variations can probably be traced to the fact that steric differences are considerable at the electrophilic centres of these various carbocations, although it is curious that the triphenylmethyl cations, which are presumably most highly hindered of these electrophiles, do not usually generate the smallest N_+ value for any given amine.[5] Ritchie [4] discussed the potential role of steric hindrance at the electrophilic centre in these reactions, but reached no definite conclusion on this matter.

In principle, the best basis for the evaluation of N_+ would be a reaction which involves rate-determining nucleophilic attack at an electrophilic carbon atom for which there is minimal steric hindrance. For an sp^2-hybridized electrophilic carbon atom, this implies a species in which a vinyl methylene group is the electrophilic site. Such an unhindered electrophilic carbon atom is present in the 1-methyl-4-vinylpyridinium cation (**1**), which we have found to react readily with a wide range of amine nucleophiles in basic aqueous solutions in a Michael-type addition reaction to give the corresponding 1-methyl-4-(2-aminoethyl)pyridinium cations (**2**) for primary and secondary amines, or their 4-(2-ammonioethyl)pyridinium dication derivatives (**3**) for tertiary amine nucleophiles. We have been able to demonstrate that nucleophilic attack is rate-determining in these reactions for most primary and secondary amines, and have taken advantage of the relative ease of measurement of second-order rate constants in most of these reactions to survey the reactivity of 91 amine nucleophiles for the reactions of eqns. (2) and (3) in aqueous solution.



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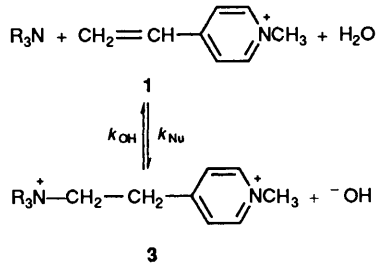


(3)

This broad data base allows us to demonstrate a number of discrete linear free energy relationships between nucleophilic reactivity and Brønsted basicity for primary and secondary amines in addition reactions according to eqn. (2). Tertiary amines do not give simple linear Brønsted-type plots for their addition reactions according to eqn. (3). This is consistent with protonation of the carbanionic intermediate by a water molecule being the rate-determinining step for tertiary amines, in contrast with the rate-determining nucleophilic attack that occurs for most primary and secondary amines.

We have also sought correlations of the nucleophilicities in the current amine attacks upon a vinylic carbon atom with reactivities that have been previously reported for these same amine nucleophiles in a variety of other reactions in aqueous solution. We feel that the current data make a significant contribution to the understanding of nucleophilicity towards a vinylic carbon atom. Comparison of the current rate data with the analogous rate constants for aminolysis of methyl 4-nitrobenzenesulfonate that are reported in the accompanying paper [17] gives insight into the relationship between the *n* (Swan–Scott) [18] and N_+ (Ritchie) parameters for amine nucleophiles. These sets of data now provide a large data basis for nucleophilic reactivity of amines, and should form the basis of all future correlations of amine nucleophilicity in aqueous solution.

Results

Reaction of the 1-*Methyl*-4-*vinylpyridinium Cation with Hydroxide Ion.*—The electronic absorption spectrum of the 1-methyl-4-vinylpyridinium cation (**1**) is time-dependent in basic aqueous solutions. This time-dependence is conveniently observed in the region pH 12–13 at 25 °C. The initial spectrum due to **1** (λ_{max} = 265 nm, ε = 15 000 dm^3 mol^{-1} cm^{-1}) undergoes a decrease in the intensity of absorption and also a shift in absorption maximum to shorter wavelength. These spectral changes ultimately produce the spectrum of a stable product (λ_{max} = 255 nm, ε = 4300 dm^3 mol^{-1} cm^{-1}). These spectral changes in aqueous KOH solution, which are quite similar to those indicated for an analogous amine addition to **1** in Fig. 1, are consistent with the conversion of **1** into a species having a chromophore similar to that of a simple 4-alkylpyridinium cation. The final spectrum is identical with that of an authentic sample of the 4-(2-hydroxyethyl)-1-methylpyridinium cation (**4**) in aqueous solution.

The identity of the product of the reaction of **1** in aqueous base of pH 13 as the hydrated derivative, **4**, was confirmed by ^1H NMR spectral observations of the reaction of **1** in 0.1 mol dm^{-3} NaOD in D_2O. These observations are somewhat complicated by the tendency of **1** to undergo polymerization in these basic solutions; such polymerization is indicated by the development of broad signals in the regions δ 1.7–2.5 and 7.5–8.2. However, in experiments at low concentrations of **1** (10 mmol dm^{-3}) the polymerization is sufficiently slowed that

Table 1 ^{1}H NMR spectral data for adducts (**2**-D_2) from the reaction of selected amines with **1**

Amine	^{1}H NMR spectrum of **2**-D_2 (δ in D_2O)
CH_3NH_2	2.38 (s, 3 H), 2.92 (s, 2 H), 4.31 (s, 3 H), 7.90 (d, 2 H), 8.64 (d, 2 H)
$(CH_3)_2CHNH_2$	1.15 (d, 6 H), 2.88 (m, 1 H), 2.95 (s, 2 H), 4.30 (s, 3 H), 7.90 (d, 2 H), 8.65 (d, 2 H)
$(CH_3)_3CNH_2$	1.13 (s, 9 H), 2.90 (s, 2 H), 4.31 (s, 3 H), 7.90 (d, 2 H), 8.65 (d, 2 H)
$^-O_2CCH_2NH_2$	2.97 (s, 2 H), 3.15 (s, 2 H), 4.37 (s, 3 H), 7.93 (d, 2 H), 8.65 (d, 2 H)
H_2NNH_2	3.20 (s, 2 H), 4.40 (s, 3 H), 7.98 (d, 2 H), 8.70 (d, 2 H)
$(CH_3)_2NH$	2.28 (s, 6 H), 2.75 (s, 2 H), 4.35 (s, 3 H), 7.95 (d, 2 H), 8.65 (d, 2 H)
$(CH_3CH_2)_2NH$	0.96 (t, 6 H), 2.60 (q, 4 H), 2.89 (s, 2 H), 4.28 (s, 3 H), 7.90 (d, 2 H), 8.60 (d, 2 H)
Morpholine	2.60 (t, 4 H), 2.95 (s, 2 H), 3.75 (t, 4 H), 4.30 (s, 3 H), 7.90 (d, 2 H), 8.65 (d, 2 H)

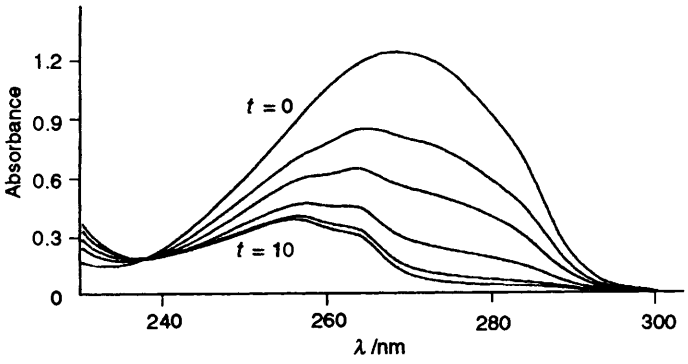
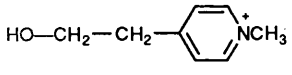


Fig. 1 Time-dependence of the electronic absorption spectrum of an aqueous solution of 1-methyl-4-vinylpyridinium iodide (0.07 mmol dm^{-3}) in the presence of ethanolamine (0.2 mol dm^{-3}) at pH 11.98 and 25 °C. Curves 1–6 are recorded at 0, 1, 2, 4, 7 and 10 min, respectively.

the disappearance of the vinylic proton signals [δ 5.95 (d), 6.45 (d) and 6.95 (dd)], and their replacement by a 2 H singlet at δ 3.93, is clearly apparent. This spectral change is consistent with the formation of **4**-D_2. The spectrum of an authentic sample of **4**-I^- in D_2O displays δ 3.12 (t, 2 H), 3.93 (t, 2 H), 4.30 (s, 3 H), 7.89 (d, 2 H) and 8.60 (d, 2 H). Upon addition of sodium carbonate (0.1 mol dm^{-3}) to this solution, the triplet at δ 3.12 disappears and the triplet at 3.93 becomes a two-proton singlet over a period of 24 h; the other signals in this spectrum remain unchanged. This experiment demonstrates the conversion of **4** into **4**-D_2 in basic D_2O. One of the deuterium atoms in **4**-D_2 is



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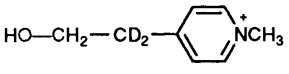
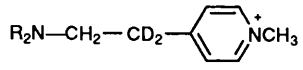


4-D_2

a direct result of the hydration of **1** in D_2O; the other deuterium atom is presumably introduced in the base-catalysed exchange of hydrogen for deuterium in the CHD group of this initial product.

The time-dependence of the electronic absorption spectrum described above was found to be kinetically first order in **1**, with pseudo-first-order rate constants that are linear in hydroxide ion concentration. The second-order rate constant for nucleophilic attack upon **1** by hydroxide ion is 2.6 (± 0.2) × 10^{-3} dm^3 mol^{-1} s^{-1} at 25 °C and ionic strength 0.1 mol dm^{-3}.

Reactions of the 1-*Methyl*-4-*vinylpyridinium Cation with Amines.*—Similar time-dependent electron absorption spectra to those discussed above were observed for the reactions of a wide range of non-chromophoric amines with **1** in aqueous base. A typical example is shown in Fig. 1. These data are consistent with the addition of these amines to **1** to give the Michael-type adducts, **2**. The formation of a number of these adducts was confirmed by ^{1}H NMR spectral observations upon mixtures of **1** and individual amines in D_2O solution. The formation of the characteristic 2 H singlet at $\delta \approx 2.9$ for the methylene group adjacent to the exocyclic nitrogen atom in **2**-D_2 (*cf.*, **4**-D_2 above) is clear in all cases. ^{1}H NMR spectral data are collected in Table 1 for the formation of **2**-D_2 from the reactions of **1** with a number of amines.



2-D_2

Pseudo-first-order rate constants (k_{obs}) for the disappearance of **1** in the presence of primary and secondary amines are linear in amine concentration at constant pH. These k_{obs} represent the competitive formation of the hydrate (**4**) and the amine adduct (**2**) from **1** in basic solution [eqn. (4) where Nu represents the free amine and HNu^+ is its ammonium ion conjugate acid].

$$k_{obs} = k_f([Nu + [HNu^+]) + 0.0026[^-OH] \quad (4)$$

Pseudo-first-order rate constants for amine addition were obtained by correcting k_{obs} for hydration using the second-order rate constant for hydroxide attack that is reported above. Such corrections were always quite small and usually amounted to less than 10% of k_{obs}. Second-order rate constants (k_{Nu}) for nucleophilic attack of a variety of primary and secondary amines were evaluated from eqn. (5) and are listed in Table 2. In

$$k_{obs} - 0.0026[^-OH] = k_{Nu}[Nu] = k_f(1 + [H^+]/K_a)[Nu] \quad (5)$$

general, such second-order rate constants were pH-independent to within experimental error, although in several cases a weak pH-dependence for k_{Nu} was observed. The largest effect of this type was found for glycine (k_{Nu} = 0.117 dm^3 mol^{-1} s^{-1} at pH 10.8; k_{Nu} = 0.151 dm^3 mol^{-1} s^{-1} at pH 12.0) and several other amino acid derivatives. We were unable to deduce the source of this effect; studies in the presence of a variety of background salts (including sodium acetate) and at several different ionic strengths did not produce significant variations in k_{Nu}. Since this effect was observed with anionic amines (although not all anionic amines displayed the effect) we assume that it arises from some type of specific ionic interaction between the anionic amine and the cationic substrate (**1**). For consistency, in Table 2 we have reported k_{Nu} for those anionic amines which displayed this effect from calculations at a common pH (pH 12.0).

The reactions of tertiary amines with **1** usually occurred considerably more slowly than the reactions of primary and secondary amines with this electrophile. For tertiary amines, non-zero ordinate intercepts were commonly observed in plots of (k_{obs} − 0.0026 [$^-$OH]) *vs.* [amine]. These observations are consistent with the formation of the equilibrium mixture of eqn. (3), with the ordinate intercepts representing the pseudo-first-order rate constants for the elimination reaction that is

represented by the reverse reaction in eqn. (3). Values of k_{Nu} for tertiary amines and also of the second-order rate constants (k_{OH}) for the hydroxide-ion-catalysed elimination reactions from the ammonium cations (**3**) were evaluated, and are listed in Table 3.

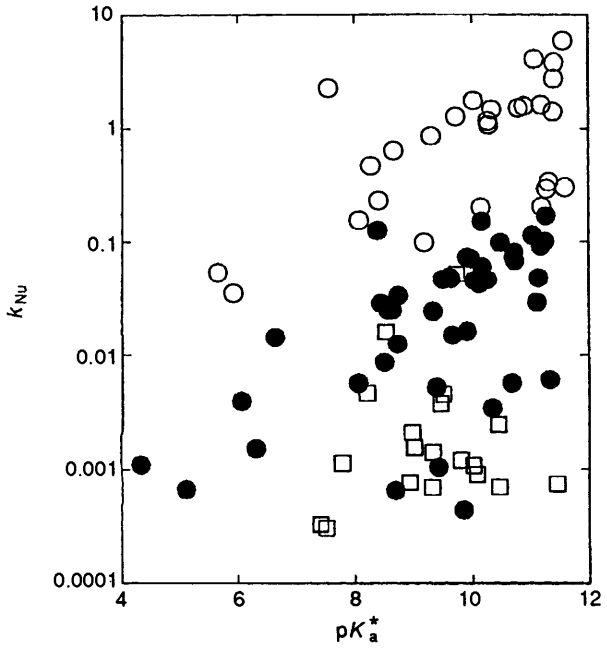


Fig. 2 Brønsted-type plot for the second-order rate constants (k_{Nu}/dm^3 mol^{-1} s^{-1}) for addition of amines to the 1-methyl-4-vinylpyridinium cation in aqueous solution: primary amines (●), secondary amines (○), tertiary amines (□)

Discussion

The relative reactivities of amine nucleophiles towards a common electrophile are usually expressed in the form of a Brønsted-type plot relating log k_{Nu} to the thermodynamic acidity (pK_a) of the ammonium ion conjugate acids. Such a plot for all data collected in the current study is shown in Fig. 2, which includes appropriate statistical corrections for the number of equivalent protons (p) in each ammonium ion, and the number of equivalent basic nitrogen atoms (q) for those amines having more than one basic site. For convenience in the following discussion, we define the statistically corrected pK_a of the ammonium cations as $pK_a^* = pK_a + \log (p/q)$. It is immediately apparent from Fig. 2 that there is no simple general relationship between basicity and nucleophilicity that can be applied to all amines. In many previous studies, different correlation lines have been invoked for primary, secondary and tertiary amines in such Brønsted-type plots. Although the coding of the data points in Fig. 2 does appear to indicate that data points for the subclasses of primary, secondary and tertiary amines do cluster together in the same general regions of this figure, consideration of each of these subclasses individually still produces a generally chaotic scattering of data points. We have therefore sought specific structural features within each of these subclasses which may lead to rational correlations of nucleophilicity with basicity.

Primary Amines.—The data for four series of structurally related primary amines are presented in the form of Brønsted-

Table 2 Second-order rate constants for the addition of primary and secondary amines to **1**[a]

No.[b]	Amine	Class[c]	pK_a[d]	pK_a^*[e]	k_{Nu}/dm^3 mol^{-1} s^{-1}	N_+[f]
1	NH_3		9.24	9.84	0.000 44	3.98
2	CH_3NH_2	1A	10.79	11.27	0.169	6.56
3	$CH_3(CH_2)_3NH_2$	1A	10.77	11.25	0.101	6.34
4	$CH_3CH_2NH_2$	1A	10.70	11.18	0.092	6.30
5	$^-O_2C(CH_2)_3NH_2$	1A	10.56	11.04	0.114	6.39
6	$H_2N(CH_2)_3NH_2$	1A	10.55	10.73	0.068 5[g]	6.17
7	$^-O_2C(CH_2)_2NH_2$	1A	10.24	10.72	0.081	6.24
8	$HO(CH_2)_3NH_2$	1A	10.23	10.71	0.073	6.20
9	$H_2N(CH_2)_2NH_2$	1A	10.08	10.26	0.046 5[g]	6.00
10	$C_6H_5(CH_2)_2NH_2$	1A	10.00	10.48	0.098 6	6.33
11	$HO(CH_2)_2NH_2$	1A	9.64	10.12	0.043	5.97
12	$CH_3O(CH_2)_2NH_2$	1A	9.55	10.03	0.046	6.00
13	$^-O_3S(CH_2)_2NH_2$	1A	9.01	9.49	0.047	6.01
14	$H_3\overset{+}{N}(CH_2)_3NH_2$	1A	8.88	9.66	0.015 0	5.51
15	$H_3\overset{+}{N}(CH_2)_2NH_2$	1A	7.28	8.06	0.005 57	5.08
16	$CF_3CH_2NH_2$	1A	5.84	6.32	0.001 52	4.52
17	Cyclohexylamine	1B	10.66	11.14	0.048	6.02
18	$(CH_3)_2CHNH_2$	1B	10.63	11.11	0.029 4	5.80
19	$HOCH_2CH(CH_3)NH_2$	1B	9.43	9.91	0.016 2	5.54
20	$(HOCH_2)_2CHNH_2$	1B	8.90	9.38	0.005 14	5.05
21	$(CH_3)_3CNH_2$	1C	10.86	11.34	0.006 0	5.11
22	$HOCH_2C(CH_3)_2NH_2$	1C	9.87	10.35	0.003 4	4.87
23	$(HOCH_2)_2C(CH_3)NH_2$	1C	8.93	9.41	0.001 05	4.36
24	$(HOCH_2)_3CNH_2$	1C	8.20	8.68	0.000 657	4.15
25	$^-O_2CCH_2NH_2$	1D	9.68	10.16	0.151	6.51
26	$CH_2{=}CHCH_2NH_2$	1D	9.49	9.97	0.071	6.19
27	$C_6H_5CH_2NH_2$	1D	9.43	9.91	0.073	6.20
28	Gly–Gly	1D	8.25	8.73	0.033 7	5.86
29	$HC{\equiv}CHCH_2NH_2$	1D	8.15	8.63	0.025 0	5.73
30	$H_2NCOCH_2NH_2$	1D	8.07	8.55	0.025 3	5.74
31	Gly–Gly–Gly	1D	7.96	8.44	0.028 8	5.79
32	$N{\equiv}CCH_2NH_2$	1D	5.59	6.07	0.003 89	4.92
33	Alanine	1E	9.69	10.17	0.060 0	6.11
34	Serine	1E	9.15	9.63	0.047 6	6.01
35	Glutamine	1E	9.13	9.61	0.049	6.03
36	Asparagine	1E	8.84	9.32	0.024 4	5.72

(*contd.*)

Table 2 (*continued*)

No.[b]	Amine	Class[c]	pK_a[d]	pK_a^*[e]	k_{Nu}/dm^3 mol^{-1} s^{-1}	N_+[f]
37	Ala–Gly	1E	8.24	8.72	0.012 5	5.43
38	$H_2NCOCH(CH_3)NH_2$	1E	8.02	8.50	0.008 6	5.27
39	$^-O_2CC(CH_3)_2NH_2$	1F	10.20	10.68	0.005 6	5.08
40	H_2NNH_2	1G	8.20	8.38	0.127[g]	6.44
41	$HONH_2$	1G	6.17	6.65	0.014 4	5.49
42	CH_3ONH_2	1G	4.62	5.10	0.000 67	4.16
43	$H_2NCONHNH_2$	1G	3.86	4.34	0.001 1	4.38
44	$CH_3CONHNH_2$	1G	3.24	3.72	0.001 24	4.43
45	$(CH_3)_2NH$	2A	10.78	11.08	4.1	7.95
46	$CH_3(CH_2)_3NHCH_3$	2A	10.90	11.20	1.63	7.55
47	$CH_3NH(CH_2)_3NHCH_3$	2A	10.80	10.80	1.52[g]	7.52
48	$CH_3NH(CH_2)_2NHCH_3$	2A	10.29	10.29	1.08[g]	7.37
49	$HO(CH_2)_2NHCH_3$	2A	9.98	10.28	1.17	7.40
50	$N{\equiv}C(CH_2)_2NHCH_3$	2A	8.10	8.40	0.23	6.70
51	$CH_3\overset{+}{N}H_2(CH_2)_2NHCH_3$	2A	7.47	8.07	0.155	6.53
52	$(CH_3)_2CHNHCH_3$	2B	10.90	11.20	0.202	6.64
53	$^-O_2CCH_2NHCH_3$	2D	10.05	10.35	1.48	7.51
54	$C_6H_5CH_2NHCH_3$	2D	9.73	10.03	1.77	7.58
55	$N{\equiv}CCH_2NHCH_3$	2D	5.35	5.65	0.054	6.07
56	$CH_3NHNHCH_3$	2G	7.56	7.56	2.3[g]	7.70
57	$(CH_3CH_2)_2NH$	2H	11.02	11.32	0.334	6.86
58	$(CH_3CH_2CH_2)_2NH$	2H	11.00	11.30	0.300	6.81
59	$HO(CH_2)_2NHCH_2CH_3$	2H	9.85	10.15	0.200	6.64
60	$(HOCH_2CH_2)_2NH$	2H	8.88	9.18	0.102	6.34
61	Pyrrolidine		11.27	11.57	5.9	8.11
62	Piperidine	2J	11.12	11.42	3.83	7.92
63	Perhydroazepine		11.11	11.41	2.75	7.77
64	Perhydroazocine		11.10	11.40	1.42	7.49
65	Piperazine	2J	9.72	9.72	1.28[g]	7.44
66	Thiamorpholine	2J	9.00	9.30	0.864	7.27
67	Morpholine	2J	8.36	8.66	0.642	7.14
68	4-Formylpiperidine	2J	7.97	8.27	0.467	7.00
69	Piperazinium cation	2J	5.33	5.93	0.035 4	
70	2-Methylpiperidine	2K	10.98	11.28	0.292	6.80
71	2-Hydroxymethylpiperidine	2K	9.90	10.20	2.31	7.70
72	Proline		10.60	10.90	1.58	7.53

[a] In aqueous solution, ionic strength 0.1 mol dm^{-3}, at 25 °C. [b] Numbering of amines is common to this work and the accompanying study[17] of the aminolysis of methyl 4-nitrobenzenesulfonate. [c] Assigned in terms of structure as discussed in the text and Table 4. [d] From ref. 19. [e] $pK_a^* = pK_a + \log(p/q)$ where p is the number of equivalent protons in the ammonium ion, and q is the number of equivalent basic sites in the amine. [f] Calculated from eqn. (12). [g] Corrected for two equivalent nucleophilic sites; N_+ for this amine is also based upon this statistically corrected value.

Table 3 Second-order rate constants for the equilibration of **1** and **3** for tertiary amines[a]

No.[b]	Amine	pK_a[c]	pK_a^*[d]	k_{Nu}/dm^3 mol^{-1} s^{-1}	k_{OH}/dm^3 mol^{-1} s^{-1}
74	$(CH_3)_2N(CH_2)_3N(CH_3)_2$	9.80	9.50	0.004 45[e]	0.010
75	$HO(CH_2)_2N(CH_3)_2$	9.31	9.31	0.001 4	0.030
76	$HO(CH_2)_3N(CH_3)_2$	9.30	9.30	0.000 69	0.013
77	$(CH_3)_2N(CH_2)_2N(CH_3)_2$	9.26	8.96	0.002 1[e]	0.026
85	$(HOCH_2CH_2)_2NCH_3$	8.52	8.52	0.016	*f*
87	$HOCH_2CH_2N(CH_2CH_3)_2$	9.80	9.80	0.001 2	0.030
88	$(HOCH_2CH_2)_2NCH_2CH_3$	8.92	8.92	0.000 77	0.060
89	$(HOCH_2CH_2)_3N$	7.78	7.78	0.001 13	0.10
90	*N*-Methylpyrrolidine	10.46	10.46	0.000 70	0.004 0
91	*N*-Methylpiperidine	10.08	10.08	0.000 90	*f*
92	*N*,*N*′-Dimethylpiperazine	8.50	8.20	0.004 55[e]	*f*
93	*N*-Methylmorpholine	7.41	7.41	0.000 332	*f*
95	*N*-Methyl-3-hydroxypiperidine	9.00	9.00	0.001 55	0.016
96	*N*-Ethylpiperidine	10.45	10.45	0.002 43	0.011
97	*N*-(2-Hydroxyethyl)piperidine	9.45	9.45	0.003 7	*f*
100	Quinuclidine	11.45	11.45	0.000 74	*f*
101	3-Hydroxyquinuclidine	10.02	10.02	0.001 08	0.002 0
104	4-Dimethylaminopyridine[g]	9.73	9.73	0.052	0.56
105	Imidazole	7.21	7.51	0.000 308	*f*

[a] In aqueous solution at 25 °C, ionic strength 0.1 mol dm^{-3}. [b,c,d] See Table 2. [e] Statistically corrected. [f] Indistinguishable from zero in the current experiments. [g] Data from ref. 24.

type plots in Fig. 3. Class 1A represents primary amines of general structure, $XCH_2CH_2NH_2$ (and also CH_3NH_2), class 1B represents primary amines bearing a second alkyl substituent on the α-carbon atom, $(XCH_2)_2CHNH_2$, and class 1C represents α,α,α-trisubstituted primary amines, $(XCH_2)_3CNH_2$. Each of these classes defines a statistically acceptable correlation line with reactivity decreasing with increasing steric hindrance at the α-carbon atom. The appropriate Brønsted

Table 4 Parameters for Brønsted-type correlations for addition of amines to **1**

Amine type	Class	β_{nuc}	log k_o	r	n	$k_{Nu,10}$[a]	$k^{rel}_{Nu,10}$
$XCH_2CH_2NH_2$	1A	0.40 (±0.03)	−5.35 (±0.14)	0.969	15	0.045	(1)
$(XCH_2)_2CHNH_2$	1B	0.45 (±0.10)	−6.4 (±0.2)	0.944	4	0.013	0.27
$(XCH_2)_3CNH_2$	1C	0.38 (±0.04)	−6.50 (±0.08)	0.988	4	0.0020	0.044
$(sp^2/sp)C-CH_2NH_2$	1D	0.35 (±0.03)	−4.57 (±0.09)	0.983	8	0.085	1.9
$(sp^2)C-CH(CH_2X)NH_2$	1E	0.54 (±0.06)	−6.65 (±0.09)	0.971	6	0.062	1.4
$(sp_2)C-C(CH_3)_2NH_2$	1F				1	(0.003)[b]	0.07
α-Effect amines	1G	0.48 (±0.11)	−5.1 (±0.4)	0.934	5	0.55	12
$XCH_2CH_2NHCH_3$	2A	0.34 (±0.02)	−3.52 (±0.07)	0.990	6	0.76	17
$(sp^2/sp)C-CH_2NHCH_3$	2D	0.32 (±0.03)	−3.1 (±0.1)	0.994	3	1.3	29
$(XCH_2CH_2)_2NH$	2H	0.23 (±0.03)	−3.06 (±0.05)	0.985	4	0.17	3.8
$X(CH_2CH_2)_2NH$	2J	0.29 (±0.01)	−2.71 (±0.02)	0.998	5	1.5	33

[a] From interpolation on the Brønsted-type plot at $pK_a^* = 10.0$; units: $dm^3\ mol^{-1}\ s^{-1}$. [b] Calculated from k_{Nu} for amine No. 39 in Table 2, by assuming $\beta_{nuc} = 0.40$ for class 1F amines.

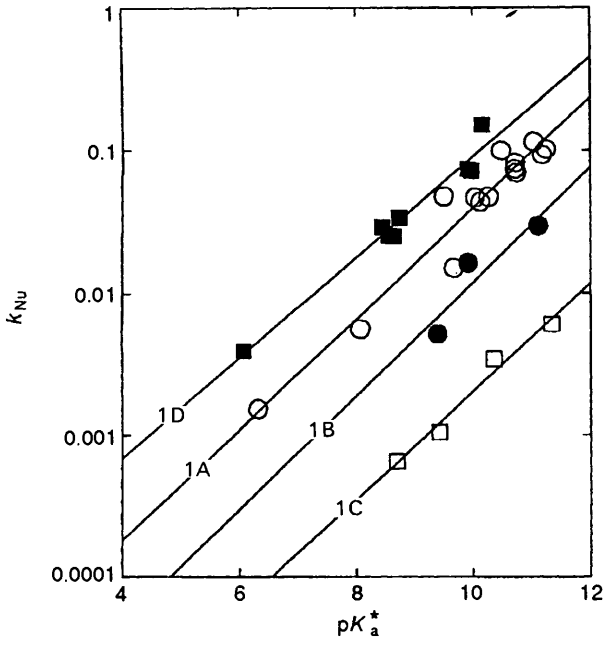


Fig. 3 Brønsted-type plots for the addition of primary amines [classes 1A (○), 1B (●), 1C (□) and 1D (■)] to the 1-methyl-4-vinylpyridinium cation. Correlation equations are from Table 4.

slopes (β_{nuc}) are collected in Table 4, along with the interpolated second-order rate constants ($k_{Nu,10}$) in each category for an amine having $pK_a^* = 10$. These latter data are also presented as relative reactivities ($k^{rel}_{Nu,10}$) and indicate that primary amines bearing a single methyl substituent on the α-carbon atom (class 1B) are 3.7 times less reactive than those having an α-CH_2 group (class 1A), while α,α-disubstituted primary amines of class 1C are 23 times less reactive than the α-unsubstituted series in class 1A. These relative reactivities are conveniently rationalized in terms of the expected increasing non-bonded interactions in the transition state species for nucleophilic attack by members of the 1A, 1B and 1C series of amines. In passing, we note that the relative reactivities 1:0.27:0.044 found for classes 1A, 1B and 1C are similar to the relative reactivities that are usually quoted[20] for increasing methyl substitution at the β-carbon atom of the electrophilic substrate in an S_N2 reaction; *i.e.*, $CH_3CH_2L:CH_3CH_2CH_2L:(CH_3)_2CHCH_2L$ = 1:0.4:0.03 (where L is a constant nucleofuge). While this relationship to S_N2 reactions is interesting, the *quantitative* similarity in relative reactivities in these two reaction series is probably fortuitous, since the steric phenomena in the two reaction series are related, but not identical. In particular, the geometric changes required at the α-carbon atom in the S_N2 transition state in the latter series are considerably more dramatic than the much smaller changes in geometry implicated at the nitrogen atom in the transition states for nucleophilic attack by an amine nitrogen atom.

The data for primary amines in which the β-carbon atom is either sp^2- or sp-hybridized do not fall on the same correlation line as those for class 1A amines which have sp^3-hybridization at the β-carbon atom. This result is clear from Fig. 3 which shows that such β-unsaturated primary amines (class 1D) are more reactive than predicted by the correlation line for class 1A by a factor of 1.9 at $pK_a^* = 10$. The Brønsted $\beta_{nuc} = 0.35$ for class 1D is slightly smaller than β_{nuc} reported in Table 4 for the other classes of primary amines that are discussed above.

This observation of a specific effect upon nucleophile reactivity in amines having an unsaturated β-carbon atom is unprecedented to the best of our knowledge. Note that: (*i*) neutral and anionic amines coexist on the same class 1D correlation line; (*ii*) amines having sp- and sp^2-hybridized β-carbon atoms appear to fall on this same correlation line; (*iii*) the electronegativity of the atom attached to this β-carbon atom is unimportant since carbonyl, nitrile, vinyl and ethynyl species fall in the same amine class; and (*iv*) benzylamine appears to be a member of this general category of β-unsaturated amines. The only common feature to the structures of all of the amines in class 1D is the presence of π-electron density on the β-carbon atom.

Comparison of $k^{rel}_{Nu,10}$ for class 1D, 1E and 1F amines indicates that substitution on the α-carbon atom of class 1D amines leads to lower reactivities similar to those observed for class 1A, 1B and 1C amines. Furthermore, $k^{rel}_{Nu,10}$ indicates that the specific effect noted above for an enhancement in reactivity when there is π-electron density on a β-carbon atom is a constant phenomenon (*i.e.*, relative reactivities are 1D > 1A, 1E > 1B and 1F > 1C). The class 1E amines for which $\beta_{nuc} = 0.54$ have the largest Brønsted slope of any of the amine classes identified in the current study.

The well known α-effect amines (derivatives of hydrazine and hydroxylamine) show the usual enhanced nucleophilicities of this amine class. For these α-effect amines $k_{Nu,10}$ is 12 times greater than for class 1A primary amines.

Secondary Amines.—*N*-Methyl secondary amines can be classified according to structure and reactivity in similar terms to the classifications discussed above for primary amines, although we have not examined as broad a range of structures in the case of secondary amines. Parameters for Brønsted-type correlations for four series of secondary amines are included in Table 4. We note that dimethylamine (k_{Nu} = 4.1 $dm^3\ mol^{-1}\ s^{-1}$) appears to be more reactive than predicted (k_{Nu} = 1.8 $dm^3\ mol^{-1}\ s^{-1}$) for a class 2A amine of $pK_a^* = 11.08$. This is

presumably a reflection of a smaller steric effect for dimethylamine than for class 2A amines in general.

A class 2A secondary amine ($XCH_2CH_2NHCH_3$) of $pK_a^* = 10$ reacts 17 times faster than the corresponding class 1A primary amine. Class 2D amines (*N*-methylglycine, *N*-methylbenzylamine and methylaminoacetonitrile) have $k_{Nu,1O}$ 1.7 times larger than for class 2A amines; this again suggests that an unsaturated β-carbon atom leads to an enhanced reactivity for these class 2D amines analogous to that discussed above for class 1D unsaturated species which are 1.9 times more reactive than class 1A amines. For both class 2A and 2D secondary amines, β_{nuc} appears to be smaller than for the corresponding class 1A and 1D primary amines (Table 4).

The importance of steric phenomena upon nucleophilicity within the class of secondary amines, is clear from the much lower reactivities of *N*,*N*-diethylamine and structurally related species (designated class 2H secondary amines) relative to *N*-methyl secondary amines (class 2A) which, as noted above, are in turn, less reactive than dimethylamine when compared at the same basicity. The four examples of the class 2H amines in Fig. 4 have $k_{Nu,1O}$ which is 4.5 times smaller than for the class 2A amines. The $\beta_{nuc} = 0.22$ for class 2H amines is also significantly smaller than $\beta_{nuc} = 0.34$ for their less sterically hindered *N*-methyl class 2A analogues.

Secondary amines in which the nucleophilic nitrogen atom is part of a saturated ring show reactivities which are quite sensitive to the size of the ring. This phenomenon is apparent in Table 2 for methylene imines containing five- to eight-membered rings. Such species vary little in basicity, and yet their relative nucleophilicities decrease over fourfold with increasing ring size from a five-membered ring (pyrrolidine) to an eight-membered ring (perhydroazocine). The latter cyclic amine is still over four times more reactive than *N*,*N*-diethylamine and *N*,*N*-dipropylamine which show similar reactivities to one another. The almost 20-fold variation in reactivity for these six amines (pyrrolidine, piperidine, perhydroazepine, perhydroazocine, diethylamine and dipropylamine), which vary less than twofold in basicity (pK_a in the range 11.00–11.27), leads to an apparent $\beta_{nuc} \approx 5$! This result dramatically demonstrates the importance of classifying such nucleophiles by structural class before attempting to evaluate meaningful β_{nuc} parameters.

Fig. 4 also demonstrates that piperidine and related six-membered ring endocyclic secondary amines form a class of nucleophile that are 1.9 times more reactive than *N*-methyl secondary amines (class 2A) and 8.7 times more reactive than *N*-ethyl secondary amines (class 2 H). Such six-membered ring cyclic amines have $\beta_{nuc} = 0.29$. We have evaluated β_{nuc} for this series ignoring the rate constant for the weakly basic piperazinium monocation ($pK_a = 5.33$) since this species appears to be far less reactive than expected on the basis of the other six members of this series. As discussed below, one expects that nucleophilic attack will not be rate-determining for weakly basic nucleophiles, and we suspect that the negative deviation observed for this weak base may arise from a change in rate-determining step between pK_a 5.33 and 7.97. As expected, 2-methylpiperidine ($k_{Nu} = 0.292$ dm^3 mol^{-1} s^{-1}) is much less reactive than piperidine ($k_{Nu} = 3.83$ dm^3 mol^{-1} s^{-1}), although 2-hydroxymethylpiperidine ($k_{Nu} = 2.31$ dm^3 mol^{-1} s^{-1}) is only slightly less reactive than piperidine. This latter similarity in reactivity is remarkable in view of the greater than ten-fold difference in basicity of these two species, and strongly suggests an important role for the hydroxy substituent in the solvation phenomena of this amine, its conjugate acid and/or the transition state for nucleophilic attack (see the discussion of related tertiary amines below).

The only α-effect secondary amine that we have examined is *N*,*N*′-dimethylhydrazine. This species is 20 times more reactive than a simple *N*-methyl secondary amine (class 2A), and 68 times more reactive than an α-effect primary amine of the same basicity.

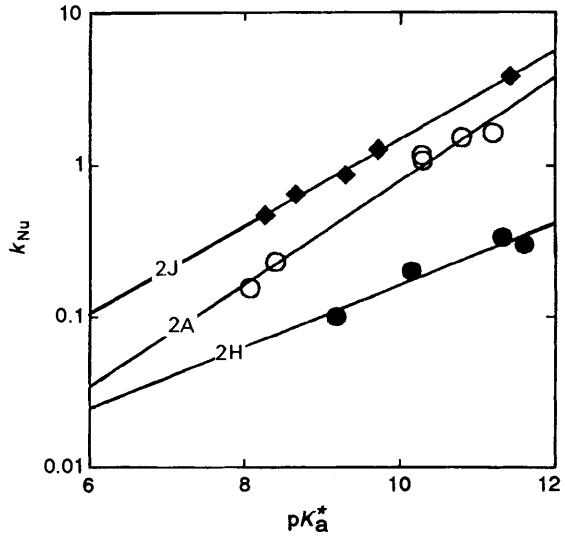


Fig. 4 Brønsted-type plots for the addition of secondary amines [classes 2A (○), 2H (●) and 2J (◆)] to the 1-methyl-4-vinylpyridinium cation. Correlation equations are from Table 4.

Tertiary Amines.—The scatter in the Brønsted-type plot for the addition of tertiary amines to the 1-methyl-4-vinylpyridinium cation is apparent in Fig. 2. In general, tertiary amines are less reactive than primary or secondary amines of the same basicity. No simple structural correlations are observable within the chaotic scatter for tertiary amines that is apparent in Fig. 2. We were unable to observe any reaction of trimethylamine with this vinylic electrophile, even at concentrations of trimethylamine up to 0.5 mol dm^{-3}. This is presumably attributable to an unfavourable equilibrium position according to eqn. (3) for this amine under all conditions examined. Other simple *N*,*N*-dimethyl amines [$XCH_2CH_2N(CH_3)_2$] did react provided X is an oxygen- or nitrogen-containing substituent, however, such species do not appear to describe a simple correlation of nucleophilicity upon basicity.

One curious feature of the data for tertiary amines lies in the observation of enhanced reactivities for *N*-(β-hydroxyethyl) tertiary amines relative to the corresponding *N*-ethyl tertiary amines, despite the fact that the latter are the stronger bases. This phenomenon is demonstrated in Table 2, and is observable for both acyclic and cyclic tertiary amines, and extends to 1-methyl-3-hydroxypiperidine which is 1.7 times more reactive than 1-methylpiperidine despite the tenfold greater basicity of the latter species, and 3-hydroxyquinuclidine which is 1.5 times as reactive as the much more basic quinuclidine. The only exception to this general enhanced effect of a β-hydroxy group upon nucleophilicity is found in the lower reactivity of *N*-ethyldiethanolamine than for *N*,*N*-diethylethanolamine, although the effect is again observed in the 1.5-fold greater reactivity of triethanolamine than for *N*-ethyldiethanolamine. In fact triethanolamine shows the same reactivity as *N*,*N*-diethylethanolamine despite the 100-fold greater basicity of the latter amine. The most reactive tertiary amine in the current study is *N*-methyldiethanolamine which is one of the least basic tertiary amines that we have investigated.

A further inversion of expected nucleophilicities is found in the tenfold greater reactivity of *N*,*N*′-dimethylpiperazine than for the much more basic *N*-methylpiperidine. No similar enhancement of reactivity is found for piperazine relative to piperidine which we showed above to define a clean Brønsted-type plot with other six-membered ring endocyclic secondary

amines, although of particular interest in this context is the enhanced reactivity of 2-hydroxymethylpiperidine which was noted above. There is no evidence for an enhanced reactivity of β-hydroxyethyl or β-aminoethyl derivatives in the primary and secondary amine series (with the exception of 2-hydroxymethylpiperidine as discussed above); ethanolamine, ethylenediamine, *N*-methylethanolamine and *N*,*N*′-dimethylethylenediamine appear to be quite normal members of the class 1A and class 2A series of primary and secondary amines.

As discussed below, we attribute the disorder in Brønsted-type plots for the reaction of tertiary amines with **1** to rate-determining protonation of the carbanionic atom in the intermediate (**6**) by a molecule of water rather than the rate-determining nucleophilic attack by the amine. However, a further contributing factor is the enhanced nucleophilicity for a tertiary amine in the presence of a neighbouring hydroxy or amino group which has previously been demonstrated[21,22] for the reactions of amino alcohols and diamines with various activated esters and amides.

Ammonia and Hydroxide Ion.—Ammonia is less reactive than any of the primary or secondary amines in Table 2. In fact of the 91 amines listed in Tables 2 and 3, only *N*-methylmorpholine and imidazole are less reactive than ammonia. The relative reactivities of ammonia, methylamine and dimethylamine are 1:380:9300. However, since the latter two amines are both considerably more basic than ammonia, a more reasonable estimate of the reactivity of ammonia with respect to primary and secondary amines can be obtained by interpolation in the linear free energy relationships established (Table 4) for each of these series of amines at $pK_a^* = 9.84$. Thus the relative reactivities of ammonia, class 1A primary amines and class 2A secondary amines of the same basicity are 1:90:1500.

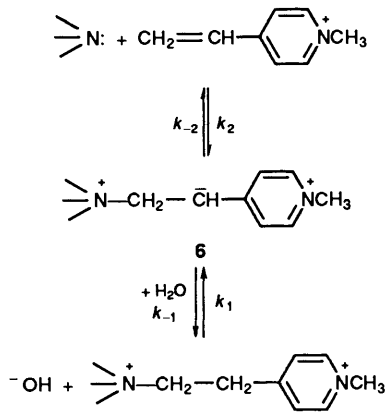
Hydroxide ion ($k_{Nu} = 2.6 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}) is less reactive than most of the primary and secondary amines listed in Table 2. As discussed below, this result is consistent with the well established smaller N_+ value for hydroxide ion than for most primary and secondary amines.

Reaction Mechanisms and Rate-determining Steps.—The reactions of eqns. (2) and (3) are typical Michael-type nucleophilic additions to an activated alkene. Such reactions involve a carbanionic intermediate and may be summarized by Scheme 1 for the case of tertiary amines. This scheme indicates nucleophilic attack upon **1** to form the intermediate, **6** (which is actually a net cation, although it bears a formal carbanionic atom), followed by the protonation of **6** by a water molecule. For primary and secondary amine nucleophiles, Scheme 1 must be expanded to Scheme 2 which involves an additional acid–base equilibrium (**6** $\rightleftharpoons$ **7** + H^+) for the deprotonation of the ammonium ion of the formal carbanionic intermediate. In this latter case, two routes for the protonation of the carbanionic centre are available. In fact, the route to **2** *via* protonation of **7** is probably faster than the route *via* protonation of **6** since: (*i*) the equilibration of **6** with **7** is expected to be fast and to lie in favour of **7** in aqueous base; and (*ii*) protonation of **7** by a water molecule should be faster than protonation of **6**. (Rate constants in Schemes 1 and 2 are assigned so as to be consistent with the definitions in our earlier studies).[23,24]

In terms of Scheme 1, the second-order rate constant (k_{Nu}) for amine addition is given by eqn. (6). Rate-determining

$$k_{Nu} = k_2k_{-1}/(k_{-2} + k_{-1}) \quad (6)$$

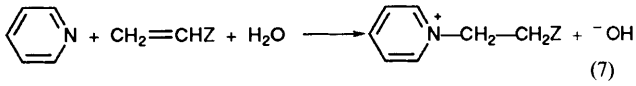
nucleophilic attack upon **1** requires that $k_{-2} \ll k_{-1}$; *i.e.*, that **6** undergoes protonation by water more rapidly than it reverts to **1** by loss of the amine. Scheme 2 for primary and secondary amines predicts an even more complex definition for k_{Nu}. The



Scheme 1

clean Brønsted-type plots observed for the various structural classes of primary and secondary amines are only readily reconciled with k_2 being rate-determining in these cases. The lack of any systematic relationship for k_{Nu} for tertiary amines then suggests that k_2 is no longer rate-determining in these cases. If k_{-1} and k_{-2} are of similar magnitude, then eqn. (6) predicts that k_{Nu} may have a complex dependence upon pK_a since each of k_2, k_{-2} and k_{-1} would be expected also to be dependent upon pK_a. As noted above, there is precedent[21,22] for neighbouring hydroxy and amino substituents having an unusual influence upon the rate of nucleophilic attack by amines. It would not be surprising then if the presence of β-hydroxy or β-dialkylamino substituents in tertiary amines might also influence each of the rate constants in eqn. (6) and lead to the pronounced effects upon k_{Nu} for tertiary amines.

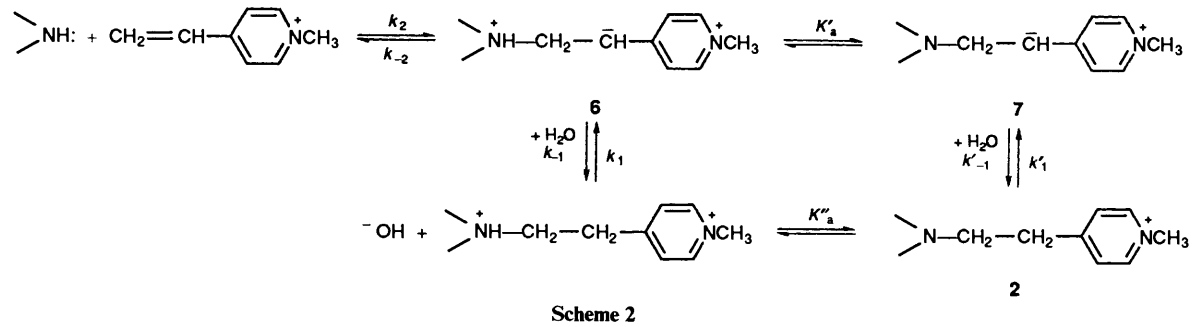
We have demonstrated[23,24] a change in rate-determining step for the nucleophilic addition of ring-substituted pyridines to a variety of electrophilic alkenes [eqn. (7) with Z = CHO,



(7)

$COCH_3$, SO_3CH_3, CN, $CONH_2$]. In these reactions, nucleophilic attack (equivalent to k_2 in Scheme 1) is rate-determining for the more basic pyridines with β_{nuc} for k_2 in the range 0.15–0.31 for various Z. Protonation of the carbanionic intermediate becomes rate-determining for substituted pyridines of lower basicity, with $k_{Nu} = k_{-1}K_2$ in terms of Scheme 1. In this latter case, β_{nuc} is larger than in the former case, and is as large as 0.83 for Z = CN. The reactivity of **1** with 4-dimethylaminopyridine is intermediate in the scale of reactivities of the above range of activated alkenes with this nucleophile.[24] The β_{nuc} values reported in Table 4 for primary and secondary amines are similar to those found for rate-determining nucleophilic attack by pyridines upon these activated alkenes. We also note that the piperazinium cation reacts much more slowly than predicted by the correlation line for more basic class 2J amines; this observation is consistent with a change in rate-determining step to protonation of the carbanionic intermediate for this weakly basic secondary amine.

Comparisons with Other Reactions.—The requirement for different correlation lines for primary, secondary and tertiary amine nucleophiles in Brønsted-type plots has been noted many times in the past. However, we have not located any studies in which a sufficiently comprehensive range of amine nucleophiles has been investigated to allow the demonstration of the subsets of amines which have been identified in the current study within each of these classes of amines.



Scheme 2

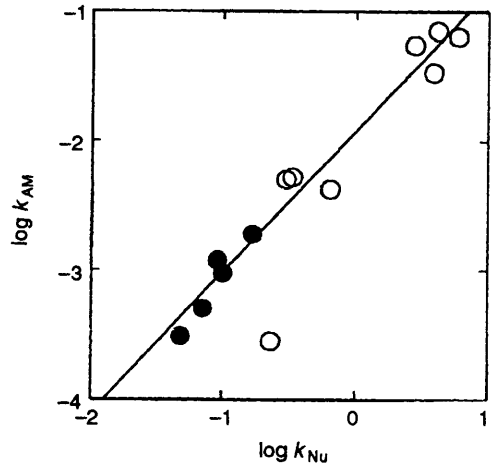


Fig. 5 Relationship between the second-order rate constants (k_{AM}/dm^3 mol^{-1} s^{-1}) for amine addition to acrylamide[25] in aqueous solution at 25 °C and the second-order rate constants (k_{Nu}/dm^3 mol^{-1} s^{-1}) for amine addition to the 1-methyl-4-vinylpyridinium cation: primary amines (●) and secondary amines (○); log k_{AM} = 1.09 (±0.07) log k_{Nu} − 1.9 (±0.2) (r = 0.982, n = 12) ignoring the data point for $NC(CH_2)_2NHCH_3$ which shows a major deviation

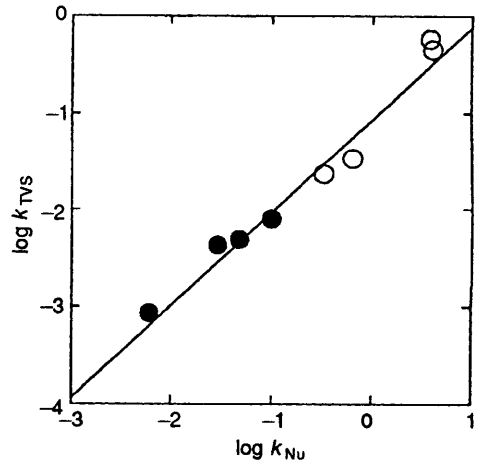


Fig. 6 Relationship between the second-order rate constants (k_{TVS}/dm^3 mol^{-1} s^{-1}) for amine addition to 4-tolyl vinyl sulfone[26] in ethanol solution at 25 °C and the second-order rate constants (k_{Nu}/dm^3 mol^{-1} s^{-1}) for amine addition to the 1-methyl-4-vinylpyridinium cation in aqueous solution: primary amines (●) and secondary amines (○); log k_{TVS} = 0.96 (±0.07) log k_{Nu} − 1.1 (±0.2) (r = 0.974, n = 9)

The current reaction involves nucleophilic attack at a vinylic methylene group. We have located two other reactions in which the reactivities of a reasonable range of amine nucleophiles towards a vinylic methylene group have been reported: (*i*) the addition of amines to acrylamide (and also an analogous study with acrylanilide) in aqueous solution,[25] and (*ii*) the addition of amines to 4-tolyl vinyl sulfone in ethanol.[26] For each of these reactions, secondary amines were reported to be much more reactive than primary amines of the same basicity. Figs. 5 and 6 compare amine reactivities in each of these two reactions with the reactivities of the same amines with the 1-methyl-4-vinylpyridinium cation in the current study. In each case, these comparisons appear to indicate that a single correlation line accommodates the data for both primary and secondary amines. The near unit slopes of these correlation lines indicate the similarity in the β_{nuc} values for these reactions and those of the amine addition to the 1-methyl-4-vinylpyridinium cation.

Friedman and Wall[27] have reported β_{nuc} = 0.43 for the addition of various amino acid derivatives to acrylonitrile and a variety of other acrylic acid derivatives; this value is smaller than we find for class 1E α-amino acid derivatives (β_{nuc} = 0.54), but similar to many of the other β_{nuc} values for primary amines in Table 4. Friedman and Wall did not distinguish between members of our class 1A amines (β-alanine and 6-aminohexanoic acid) and class 1D amines (glycine, glycylglycine and glycylglycylglycine), but they did find that glycine is in general twice as reactive as a class 1E amine of the same basicity and that α-aminoisobutyrate anion is 20 times less reactive than a class 1E amine of the same basicity. The corresponding values from our current investigation of additions to **1** are 2.9 times more reactive for glycine and 16 times less reactive for 2-amino-2-methylpropanoate when compared with class 1E amines.

Correlations with N_+.—In his most recent review of the N_+ parameter, Ritchie[5] indicated three different sets of N_+ parameters for amine nucleophiles depending upon whether they were defined in terms of aryltropylium cations, the pyronin-Y cation, or triarylmethyl cations as the electrophilic species. The correlations of our current data with the available N_+ parameters[5] in each of these series of electrophiles (Atr = aryltropylium cations; pY = pyronin-Y cation; Tam = triarylmethyl cations) are summarized in eqns. (8)–(10). In each case

$$\log k_{Nu}(\mathbf{1}) = 1.15\,(\pm 0.18)\,N_+(\text{Tam}) - 7.4\,(\pm 0.5) \quad (r = 0.888;\ n = 13) \quad (8)$$

$$\log k_{Nu}(\mathbf{1}) = 0.97\,(\pm 0.14)\,N_+(\text{pY}) - 6.8\,(\pm 0.4) \quad (r = 0.942;\ n = 8) \quad (9)$$

$$\log k_{Nu}(\mathbf{1}) = 1.02\,(\pm 0.16)\,N_+(\text{Atr}) - 6.2\,(\pm 0.5) \quad (r = 0.900;\ n = 12) \quad (10)$$

the slope is near unity to within experimental error as expected by the general form of Ritchie's N_+ correlation equation.

The correlations with N_+ defined for pyronin-Y [eqn. (9)]

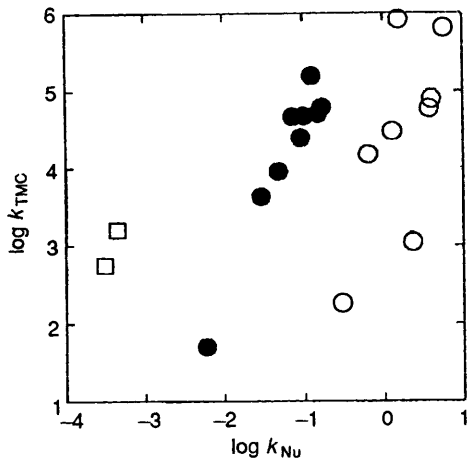


Fig. 7 Relationship between the second-order rate constants (k_{TMC}/dm^3 mol^{-1} s^{-1}) for amine addition to the tris(*p*-methoxyphenyl)-methyl cation[28] in aqueous solution at 25 °C and the second-order rate constants (k_{Nu}/dm^3 mol^{-1} s^{-1}) for amine addition to the 1-methyl-4-vinylpyridinium cation: primary amines (●), secondary amines (○) and ammonia and imidazole (□)

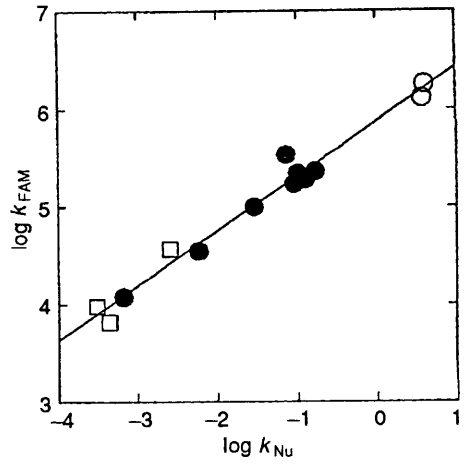


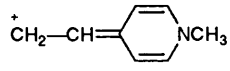
Fig. 8 Relationship between the second-order rate constants (k_{FAM}/dm^3 mol^{-1} s^{-1}) for amine addition to the ferrocenyl(*p*-methoxyphenyl)methyl cation[29] in aqueous solution at 25 °C and the second-order rate constants (k_{Nu}/dm^3 mol^{-1} s^{-1}) for amine addition to the 1-methyl-4-vinylpyridinium cation: primary amines (●), secondary amines (○), ammonia, imidazole and hydroxide ion (□); the correlation line is eqn. (11). (The second-order rate constant for morpholine addition to FAM in ref. 29 appears to be a typographical error, since this value is identical with that given for dimethylamine, and also requires that morpholine should be more reactive than piperidine.)

and aryltropylium cations [eqn. (10)] appear to be somewhat superior statistically to that with N_+ defined for triarylmethyl cations in which steric hindrance at the electrophilic centre would be expected to be greatest. The likely importance of steric hindrance at the electrophilic carbon atom towards an attacking amine nucleophile is best demonstrated by Fig. 7 which compares the rate constants reported by Bunton and Huang[28] for nucleophilic attack by an extensive series of structurally diverse amines upon the tris(*p*-methoxyphenyl)-methyl cation and our own data for these same amine nucleophiles reacting with **1**. This figure leaves little doubt that any attempt to correlate rate data with N_+ for attack at sp^2-hybridized carbon atoms having different steric hindrance will be unsuccessful unless allowance is also made for such steric phenomena.

Bunton and co-workers[29] demonstrated that sterically hindered primary amines such as isopropylamine and *tert*-butylamine are much more reactive towards secondary carbocations than they are towards tertiary carbocations when compared on the basis of the relative reactivities of less hindered primary amines towards these two classes of cation. In fact, their data for nucleophilic attack upon the ferrocenyl(*p*-methoxyphenyl)methyl cation (FAM$^+$) correlate extremely well with our data for nucleophilic attack upon **1** [Fig. 8 and eqn. (11)]. Note that isopropylamine and *tert*-butylamine do not deviate in these correlations.

$$\log k_{Nu}(FAM^+) = 0.56\,(\pm 0.03)\log k_{Nu}(\mathbf{1}) + 5.9\,(\pm 0.1) \quad (r = 0.987;\ n = 13) \quad (11)$$

Resonance contributor **1A** (shown below) clearly indicates the electron-deficiency of the β-vinylic carbon atom of the 1-methyl-4-vinylpyridinium cation. As noted above, a species such as **1** (and also related mono-substituted electron-deficient ethylenes) represents the least sterically hindered sp^2-carbon electrophile that is accessible to ready study in aqueous solutions. The current extensive data for primary and secondary amine nucleophiles reacting with **1** therefore represent a suitable *database* for assigning N_+ values unemcumbered by steric hindrance in the electrophilic substrate. We follow Ritchie in assigning $N_+ = 4.75$ for hydroxide ion, and then calculate N_+ for primary and secondary amine nucleophiles relative to this value from eqn. (12). Values of N_+ calculated in this way for all



1A

$$\log k_{Nu} - \log(2.6 \times 10^{-3}) = N_+ - 4.75 \quad (12)$$

primary and secondary amines are included in Table 2. In Table 5, we compare the various N_+ values previously assigned to a more restricted group of amine nucleophiles in reactions with other electrophiles with the values evaluated in the current work for reaction with **1**. Note that N_+ assigned for nucleophilic attack upon **1** is usually larger, and in some cases more than 1 unit larger, than the N_+ values previously assigned for these amine nucleophiles. This is consistent with **1** being subject to considerably less steric hindrance to nucleophilic attack than any of the other electrophiles previously used as a basis for the assignment of N_+.

In addition to the specific reactions discussed above, we have also sought correlations of the current data for amine attack upon **1** with literature data for many other reactions involving amine attack at either sp^2- or sp-hybridized carbon.[9c,16,30-50] While correlations of variable statistical reliability are generally observed, unfortunately most of these earlier studies involve only limited sets of amine nucleophiles (usually less than 10) and/or uncertainty as to whether nucleophilic attack is the rate-controlling step. Ritchie has demonstrated[7] how this latter situation can be handled in the N_+ context for ester aminolysis and related reactions by making reasonable assumptions regarding the relative rates of the forward and reverse reactions from the tetrahedral intermediates. However, the master set of N_+ parameters for amine nucleophiles that was deduced in that earlier work[7] from reactions with a series of 27 electrophiles are no more successful in correlating the data for the reactions of **1** with amines than is eqn. (8) which uses N_+ parameters defined for triarylmethyl cations alone.

The attempt to define a unique set of N_+ parameters for a wide variety of amine nucleophiles is a particularly stringent test of this approach to the quantitative expression of nucleophilicity since no other group of simple nucleophiles are subject to as variable steric phenomena as are these species.

Table 5 Comparison of N_+ parameters for amine nucleophiles in water

Amine	N_+ 1	Tam[a]	p-Y[b]	Atr[c]	27 Electrophiles[d]
Imidazole	3.82[e]				3.66
NH_3	3.98	3.89			
CH_3ONH_2	4.16	4.37		3.16	3.88
$H_2NCONHNH_2$	4.38	3.73		3.42	3.17
$CF_3CH_2NH_2$	4.52	3.54		3.13	2.89
Hydroxide ion	(4.75)	(4.75)	(4.75)	(4.75)	4.75
$H_3\overset{+}{N}(CH_2)_2NH_2$	5.08	4.35		3.84	3.91
$HONH_2$	5.49	5.05		3.82	5.05
Gly–Gly	5.86	4.69		4.63	4.48
$CH_3O(CH_2)_2NH_2$	6.00	5.07	5.57		5.05
$H_2N(CH_2)_2NH_2$	6.00[f]	5.44		5.09	5.37
$CH_3CH_2NH_2$	6.30	5.28	6.11	4.97	5.31
H_2NNH_2	6.44[f]	6.01	4.71	5.00	5.66
Glycine	6.51	5.36	5.79	5.23	5.22
Morpholine	7.14		6.99	5.80	5.25
Piperazine	7.44[f]				5.94
Piperidine	7.92		7.58		6.11

[a] Triarylmethyl cations.[5] [b] Pyronin-Y cation.[5] [c] Aryltropylium cations.[5] [d] Value obtained by numerical analysis of data according to eqn. (1) for amine addition to various subsets of 27 different electrophiles.[7] [e] Calculated from k_{Nu} for imidazole in Table 3, assuming that nucleophilic attack is rate-determining. [f] Based upon the statistically corrected k_{Nu} in Table 2.

Although we conclude that general N_+ correlations for amine nucleophiles are unlikely to be successful without the further allowance for steric effects, this should not be construed as a general dismissal of the usefulness of linear free energy relationships employing N_+. As we noted in the introduction to this paper, the genius of the N_+ approach lies in the ability of these relationships to correlate data for a wide range of nucleophilic species, both neutral and anionic, in a variety of solvents. Such correlations will always be useful in providing a quantitative approach to handling data and making comparisons of reactivities in a wide range of nucleophile–electrophile combination reactions. However, such relationships cannot be used to provide intimate details of transition state structure in the same way that many other linear free energy relationships are rightly or wrongly believed to do.

The simplicity of Ritchie's N_+ relationship [eqn. (1)] makes it very attractive for the correlation of data for all sorts of nucleophile–electrophile combination reactions. However, this very simplicity, which is derived from the lack of any requirement for a selectivity parameter, militates against any significant insight into transition-state structure. In this regard, the correlation demonstrated in Fig. 8 is particularly intriguing. Note that this correlation includes hydroxide ion, ammonia, primary and secondary amines, imidazole and α-effect amines as nucleophiles. However, more importantly, note the slope of 0.56 in eqn. (11). This slope clearly indicates a much smaller selectivity for the reactions of nucleophiles with the very reactive ferrocenyl(*p*-methoxyphenyl)methyl cation ($k_{Nu} = 3.66 \times 10^4$ dm^3 mol^{-1} s^{-1} for hydroxide ion)[29] than for the reactions of these nucleophiles with the much less reactive 1-methyl-4-vinylpyridinium cation ($k_{Nu} = 2.6 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} for hydroxide ion). Similar observations of the onset of reactivity–selectivity relationships with increasing cation reactivity have also recently been noted by other workers.[14,15] Such observations are a tantalizing demonstration that there may indeed be a role for a selectivity parameter in N_+ correlations,[8] and once again raise the question of the appropriate interpretation of the unit slopes that have been commonly observed for correlations according to eqn. (1). We hope that the set of N_+ values that are defined in the present work for an extended series of amine nucleophiles will contribute to the further exploration and analysis of eqn. (1) for the elucidation of transition state species in nucleophile–electrophile combination reactions.

Experimental

1-Methyl-4-vinylpyridinium iodide was prepared and characterized as previously described.[24] 4-(2-Hydroxyethyl)pyridine was prepared by the reduction of ethyl 4-pyridylacetate with excess sodium borohydride in ethanol.[51] This species was methylated by treatment with methyl iodide in ethanol.

All amines were obtained commercially. They were purified by distillation or recrystallization and characterized by ^1H NMR spectroscopy. Buffered amine solutions were prepared by careful addition of standard aqueous hydrochloric acid to achieve the appropriate buffer ratio (usually 1:1) followed by the addition of sufficient KCl to give a total ionic strength of 0.1 mol dm^{-3}. In the case of amino acids, buffered solutions were prepared by the addition of standard potassium hydroxide solution. The addition of hydroxide ion was studied in mixtures of KOH + KCl having ionic strength 0.1 mol dm^{-3}.

All rate data were obtained by monitoring the disappearance of the 1-methyl-4-vinylpyridinium cation (usually 0.06 mmol dm^{-3}) at 270 nm in aqueous solutions of ionic strength 0.1 mol dm^{-3} at 25 °C in a GBC 911 UV–VIS spectrophotometer. Data were collected for at least five amine concentrations covering a fivefold range in amine concentration. Absorbance *vs.* time data were collected for 50–100 data points covering at least 95% of each reaction. Pseudo-first-order rate constants (k_{obs}) were evaluated by fitting the absorbance (A) at time (t) to the first-order rate law of eqn. (13) *via* the Marquardt algorithm (A_0 and

$$A = A_f + (A_0 - A_f) \exp(-k_{obs}t) \qquad (13)$$

A_f are the initial and final absorbances, respectively in any given run, and were treated as parameters to be evaluated in addition to k_{obs}). All reactions were strictly first order for >4 half-times. The pH of the reaction solution was measured at the completion of each run on a Radiometer PHM82 meter fitted with a GK2401B combination electrode and calibrated at 25 °C with BDH Colourkey buffer solutions.

All ^1H NMR spectra were obtained on a Varian Gemini 200 spectrometer in D_2O solution with chemical shifts referenced

to the methyl signals of sodium 4,4-dimethyl-4-silapentanesulfonate at $\delta = 0$.

Acknowledgements

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