View Online
Dynamic Article Links

Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6685

www.rsc.org/obc

PAPER

Nucleophilicity parameters for amines, amino acids and peptides in water. Variations in selectivities for quinone methides

T. William Bentley*

Received 6th May 2011, Accepted 21st June 2011
DOI: 10.1039/c1ob05715d

Downloaded by John Rylands University Library on 25 September 2011
Published on 02 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB05715D

Second order rate constants for reactions of 4,4′-dimethylaminobenzhydrylium cations with amines and other nucleophiles in water define a scale of nucleophilicity ($N_+'' = \log k + 2.63$). The N_+'' scale can be extended by linking directly to an established N_+ scale based on reactions of methyl vinyl pyridinium cations with amine nucleophiles. Logarithms of rate constants for other benzhydrylium ions and quinone methides (QMs) are correlated by the equation: $\log k = s_E\, N_+'' +$ constant, having a nucleophilicity parameter (N_+'' defined as in the Ritchie N_+ equation with $N_+'' = 4.75$ for hydroxide ion), and an electrophile's response (selectivity) parameter (s_E, as in the Swain-Scott equation). Correlations for other benzhydrylium cations require only one slope and one intercept per cation, and fit data for up to 54 amines, amino acids and peptide nucleophiles; the slope s_E increases as the reactivity of the cation decreases. Contrary to recent reports, s_E is significantly less than unity for reactions of *o*- and *p*-benzoquinone methides. As the reactivities of QMs decrease, s_E increases and the response of s_E to changes in reactivity is larger for QMs than for cations.

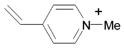
Introduction

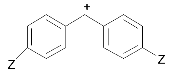
Correlations and predictions of nucleophilic reactivity require plots of log *k* for a nucleophilic reaction *vs.* a suitable parameter. The most readily available parameter is an appropriate pK_a for the nucleophile, giving a slope β_{nuc} of an extended Brønsted equation representing the response of the electrophile to changes in pK_a.[1] Well established alternatives, limited by the availability of suitable parameters are: (a) the Swain-Scott nucleophilicity parameter *n* defined from reactions of methyl substrates with nucleophiles, giving a slope *s* representing the response of the electrophile to changes in *n*;[2] (b) the Ritchie parameter N_+, defined by reactions of triarylmethyl or other cations (*e.g.* **1**, **2**) with nucleophiles, and usually assumed to have a slope of unity.[3,4]

More recently, many reactions of secondary benzhydrylium cations (**2**) with nucleophiles have been correlated using eqn (1);[5] the various parameters are defined below. Cations (**2**) are the reference electrophiles for about half of the *E* scale of electrophilicity, covering ~15 orders of magnitude of reactivity.[5]

$$\log k = s_N\,(E + \mathrm{N}) \qquad (1)$$

k = second order rate constant ($\mathrm{M^{-1}s^{-1}}$)
E = electrophilicity parameter
N = nucleophilicity parameter
s_N is a substituent effect (slope) parameter, referred to[5] as a ‘nucleophile specific’ parameter

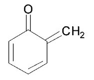

1

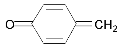

2

Nucleophilicity parameters (*N*) have been obtained from eqn (1) for reactions of cations (**2**) with amines,[6] amino acids,[7] and peptides[7] in water by plotting log *k vs. E*; the extrapolated intercept ($s_N N$) is divided by the slope s_N to obtain *N*. These nucleophilicity parameters have recently been applied[6b,8] to quinone methides (QMs, **3** and **4**) by plotting $\log k/s_N$ *vs.* *N* (eqn (2)), where s_E is referred to as an ‘electrophile specific’ parameter.

$$(\log k)/s_N = s_E(E + \mathrm{N}) \qquad (2)$$

Alternatively, $\log k = s_E s_N(E + \mathrm{N})$


3


4

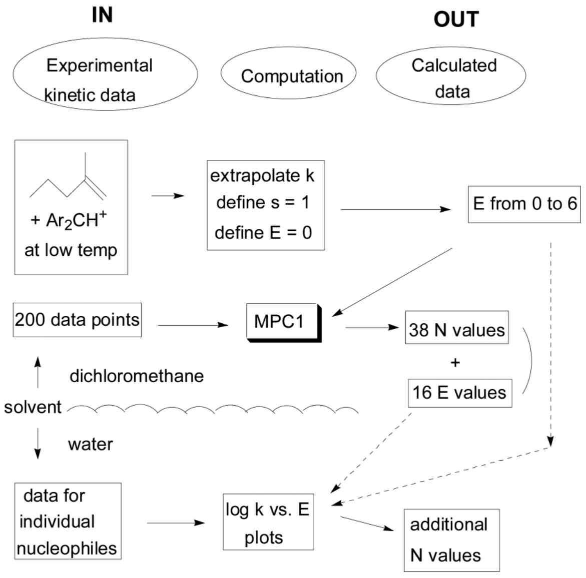
QMs are alkylating and cross linking agents involved in a large number of chemical and biological processes,[9] and QMs are of particular interest here as a test of eqn (2). Also, QMs are the reference electrophiles covering the lower half of the *E* scale,[8,10] and they are used to extend greatly the *N* scale to more reactive nucleophiles (*e.g.* carbanions in DMSO).[10]

A serious flaw in the complex procedure (Scheme 1) is the tacit assumption that values of *E* for cations (**2**) obtained[5] from kinetic data in dichloromethane are applicable to reactions in protic media.[12] A much more direct alternative procedure is described below. Nucleophilicity parameters for amine nucleophiles will be defined as in the Ritchie N_+ equation, but will be obtained directly from the extensive kinetic data already available for reactions of

---

Chemistry Unit, Grove Building, School of Medicine, Swansea University, Swansea, Wales, UK SA2 8PP. E-mail: t.w.bentley@swansea.ac.uk; Fax: +44 1792 295554; Tel: +44 1792 295262

Downloaded by John Rylands University Library on 25 September 2011
Published on 02 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB05715D



Scheme 1 Determination of E for benzhydrylium cations (**2**) from eqn (1) and the multi-parameter correlation (MPC1),[5] and extrapolate log k *vs.* E plots, leading to N values for nucleophiles in water.[6,7,12]

2, Z = NMe_2.[6,7,11] Using these nucleophilicity parameters, rate constants for QMs fit an equation requiring a selectivity parameter, dependent on the electrophile as in of the Swain-Scott equation. The results cast further doubt[12] on the validity of eqn (2) and show limitations of eqn (1).

Results

The nucleophilicity parameter (N'') is defined directly from experimental data by eqn (3) and second order rate constants (log k) for reaction of 4,4′-dimethylamino benzhydrylium cations (**2**, Z = NMe_2) with nucleophiles.[13] Values of N'' are given in Tables 1 and 2 for amines,[6] amino acids,[7] peptides,[7] pyridines[11a] and azoles.[11b] Conversion to an N_+ logarithmic scale of relative rates (termed N_+'') is carried out as shown in eqns (4–6); as for other N_+ scales, hydroxide ion ($N_+ = N_+'' = 4.75$) is the anchor point[3] (not water[2a]).

$$\log k \text{ for } \mathbf{2}, \mathrm{Z} = \mathrm{NMe_2} \text{ at } 20\ ^\circ\mathrm{C} = N'' \text{ (for any nucleophile in any solvent)}^{13} \quad (3)$$

$$N'' \text{ (for hydroxide as nucleophile in water at } 20\ ^\circ\mathrm{C})^{6a} = 2.12 \quad (4)$$

$$N_+'' = 4.75 \text{ (for hydroxide in water, by definition)}^{3} \quad (5)$$

$$N_+'' = N'' + 2.63 \text{ (for any nucleophile in a given solvent)} \quad (6)$$

Nucleophilicity parameters (N_+) based on second order rate constants for additions to methyl vinyl pyridinium iodide (**1**) are available for 70 primary and secondary amines, and a few amino acids and peptides.[14] These were designed for nucleophilic substitutions at vinylic carbon, but were also shown to be applicable more generally (*e.g.* they are less susceptible to steric effects than N_+ parameters based on triarylmethyl cations).[14]

Published values[14] of N_+ for amines in water based on reactions of **1** at 25 °C are compared with N_+'' obtained from eqn (6) in Table 1. Although the data refer mainly to primary and secondary amines, imidazole and DMAP are also included. Only 4 values deviate by more than 0.4 log units (NH_2OH, pyrrolidine, piperidine and proline), and the largest deviation is due to proline ($\Delta = 0.61$). Values of N'' and N_+'' based on **2**, Z = NMe_2 are shown in Table 2 for other amines, for which data based on **1** are not available. It is assumed that the additional 37 values of N_+ based on **1**, previously listed[14] for other primary and secondary amines, can be used when values of N_+'' are not available (*e.g.* hydrazine and trifluoroethylamine, Table 3).

Table 1 Values of N'' (eqn (3)) and comparisons of N_+'' (eqn (6)) with published values of N_+ for amines in water

Amine	N''	N_+''	N_+[a]
NH_3[b]	1.28	3.91	3.98
NH_2OH[c]	2.40	5.03[d]	5.49
Semicarbazide[c]	2.08	4.71[e]	4.38
$MeNH_2$[b]	3.63	6.26	6.56
$EtNH_2$[b]	3.38	6.01	6.30
i-$PrNH_2$[b]	2.83	5.46	5.80
t-$BuNH_2$[b]	2.20	4.83	5.11
$CHCHCH_2NH_2$[b]	3.08	5.71	5.73
$CH_2CHCH_2NH_2$[b]	3.37	6.00	6.19
$PhCH_2NH_2$[b]	3.48	6.11	6.20
$NCCH_2NH_2$[b]	2.34	4.97	4.92
$NH_2(CH_2)_2NH_2$[b]	3.62	6.25	6.00
$NH_2(CH_2)_3NH_2$[b]	3.76	6.39	6.17
$HO(CH_2)_2NH_2$[b]	3.21	5.84	5.97
$^{-}O_2CCH_2NH_2$[f]	3.75	6.38	6.51
$NH_2COCH_2NH_2$[b]	3.02	5.65	5.74
$^{-}O_2C(CH_2)_2NH_2$[f]	3.56	6.19	6.24
$^{-}O_2C(CH_2)_3NH_2$[f]	3.67	6.30	6.39
glygly[f]	3.43	6.06	5.86
glyglygly[f]	3.28	5.91	5.79
Alanine[f]	3.41	6.04	6.11
Serine[f]	3.40	6.03	6.01
Glutamine[f]	3.49	6.12	6.03
Asparagine[f]	3.26	5.89	5.72
Proline[f]	5.51	8.14	7.53
Me_2NH[b]	5.02	7.65	7.95
$NCCH_2NHMe$[b]	3.81	6.44	6.07
Et_2NH[b]	4.05	6.68	6.86
$(HOC_2H_4)_2NH$[b]	3.69	6.32	6.34
Pyrrolidine[b]	5.03	7.66	8.11
Piperidine[b]	4.78	7.41	7.92
Perhydroazepine[b]	5.20	7.83	7.77
Piperazine[b]	5.10	7.73	7.44
Morpholine[b]	4.66	7.29	7.14
Imidazole[g]	1.51	4.14	3.82
DMAP[h]	3.42	6.05	6.05

[a] Ref. 14 at 25 °C. [b] Ref. 6b. [c] Ref. 6a. [d] Also 5.16, eqn (7), ref. 6a. [e] Also 4.83, eqn (7), ref. 6a. [f] Ref. 7 [g] Ref. 11b. [h] Ref. 11a.

Table 3 shows values of N_+'' for other miscellaneous nucleophiles, required to extend the correlations for QMs (see below). Values of N_+'' are compared with those previously obtained[6a] from a series (typically 3–5) of benzhydrylium cations (**1**) using the Ritchie N_+ eqn (7),[3] where log k_0 is an optimised parameter characteristic of individual cations (1).[6a] The same value of log k_0 was used subsequently to evaluate N_+ for carbanion nucleophiles in water,[16] and a few of these are also shown in Table 3. Eqn (7) was 'derived' from eqn (1) by setting $s_N = 0.6$ for 'most *n*-nucleophiles'.[17]

$$\log k = N_+ + \log k_0 \quad (7)$$

Kinetic data for QMs (**3–5**) from the literature are assembled in Table 4. Rates of hydration of *o*-naphthoquinone methides are closely similar to those of the parent (**3**).[9b]

View Online

Downloaded by John Rylands University Library on 25 September 2011
Published on 02 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB05715D

Table 2 Values of N'' (eqn (3)) and N_+'' (eqn (6)) for amines and amino acids in water

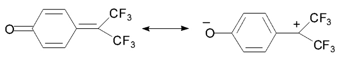
Amine	N''	N_+''
n-PrNH$_2$[a]	3.49	6.12
Aniline[b]	4.23	6.86
p-Toluidine[b]	4.60	7.23
p-Anisidine[b]	4.82	7.45
Pyridine[c]	2.95	5.58
4-Methylpyridine[c]	3.06	5.69
4-Methoxypyridine[c]	2.98	5.61
4-Aminopyridine[c]	3.35	5.98
4-pyrrolidinopyridine[c]	3.56	6.19
N-Methyl imidazole[d]	1.65	4.28
2-Methyl imidazole[d]	1.34	3.97
Glycine methyl ester[d]	3.08	5.71
Valine[e]	3.76	6.39
Leucine[e]	3.64	6.27
Phenylalanine[e]	3.79	6.42
Threonine[e]	3.36	5.99
Arginine[e]	3.42	6.05
Histidine[e]	3.63	6.26
Aspartic acid[e]	3.58	6.21
Glutamic acid[e]	3.76	6.39
Methionine[e]	3.49	6.12
Cysteine[e]	6.9[f]	9.5

[a] Ref. 6a; solvent contained 0.4% acetonitrile. [b] Ref. 6b. [c] Ref. 11a. [d] Ref. 11b. [e] Ref. 7. [f] Estimated from eqn (1).

Table 3 Values of N'' (eqn (3)) and N_+'' (eqn (6)) from a single reference electrophile (**2**, Z = NMe$_2$) and N_+ from a series of electrophiles (eqn (7)) for nucleophiles in water

Nucleophile[a]	N''	N_+''	N_+
Water	–1.59[b]	1.04[b]	
Hydroxide ion	2.12	4.75[c]	4.75[c]
Hydroperoxide ion	4.63	7.26	7.35
Trifluoroethoxide ion	3.33	5.96	5.99
Sulphite, SO_3^{2-}	5.56[d]	8.2	8.26
–SCH$_2$CO$_2$–	6.75[d]	9.4	9.72
Chloride ion[e]	~2[f]	~4.6[g]	
Bromide ion[e]	~3[f]	~5.6[g]	
–CH(CN)$_2$[h]	6.83	9.46	9.54
–CH(COCH$_3$)$_2$[h,i]	4.33	6.96	6.87
–CH$_2$NO$_2$[i,j]	2.71	5.34	5.41
CF$_3$CH$_2$NH$_2$		(4.52)[k]	
Hydrazine		(6.44)[k]	

[a] Solvent contained 0.4% acetonitrile, ref. 6a. [b] Based on first order rate constants. [c] By definition. [d] Calculated by a short extrapolation of a correlation with kinetic data for hydroxide ion. [e] Ref. 15 [f] Estimated by a long extrapolation. [g] Highly approximate value – uncertainty at least ± 0.5. [h] Ref. 16a. [i] Data for similar carbanions are available from the reference cited. [j] Ref. 16b. [k] N_+ value based on **1** from ref. 14.



5

Table 4 Logarithms of second order rate constants for reactions of quinone methides (**3**, **4** and **5**) with nucleophiles

Nucleophile	log k (**3**)[a]	log k (**4**)[b]	log k (**5**)[c]
Water[d]	2.41[e]	0.52[f]	–3.19
Chloride		3.04[f]	–0.80
Hydroxide	4.48[e]		
Bu^{t}NH$_2$[g]	5.04	3.63	
Bromide		4.3[f]	0.15
Pr^{n}NH$_2$[g]	5.74	4.38	
Glycine[g]	5.84		
Morpholine[g]	6.36	5.34	
Piperidine[g]	6.11	5.26	
Pyrrolidine[g]		5.38	
Cysteine[h]	8.11	7.53	

[a] Data in water at 25 °C from ref. 18 [b] Data in water at 25 °C from ref. 9a. [c] Data in water at 25 °C for **5** from ref. 19; additional data: nucleophile, log k for **5** at 25 °C; hydroxylamine, 2.52; glygly, 2.63; EtNH$_2$, 3.61; CF$_3$CH$_2$NH$_2$, 0.94; hydroperoxide ion, 5.46; sulphite dianion, 5.0. [d] Values of log k for water as nucleophile are calculated from pseudo-first order rate constants in s^{-1}. [e] Reference 20a. [f] Reference 20b. [g] At pH 12.0. [h] pH = 12.2.

Table 5 Correlations based on eqn (8) for reactions of benzhydrylium cations with amines

Cation[a]	Slope s_E	Intercept	r	n[b]
(mor)$_2$CH$^+$	0.88 ± 0.02	–0.93 ± 0.09	0.997	23
(dma)$_2$CH$^+$	1.00[c]	–2.63[c]		
(pyr)$_2$CH$^+$	1.00 ± 0.01	–3.02 ± 0.07	0.997	54
(thq)$_2$CH$^+$	1.03 ± 0.01	–3.47 ± 0.07	0.997	46
(ind)$_2$CH$^+$	1.03 ± 0.01	–3.80 ± 0.08	0.997	32
(jul)$_2$CH$^+$	1.07 ± 0.02	–4.37 ± 0.13	0.994	36
(lil)$_2$CH$^+$[d]	1.06 ± 0.01	–4.59 ± 0.07	0.998	37

[a] All of the cations are 4,4′-nitrogen substituted; (dma)$_2$CH$^+$ is **2**, Z = NMe$_2$, and structures of the other cations are shown in ref. 5. [b] Number of nucleophiles in the correlation. [c] By definition in eqn (6). [d] The correlation is shown in Fig. 1 of ref. 12; data for azoles are now included, where previously[12] data for imidazole was predicted.

Discussion

Cations

All of the previously published data[6,7,11] for reactions of amino-benzhydrylium cations with nucleophiles in water has been used to obtain parameters (N and s_N in eqn (1) or log k_0 and N_+ in eqn (7)). It is assumed[6] inexactly (see below) that s_E = 1.00 for an extensive series of cations. In contrast to parameters obtained from a series of cations, N'' and N_+'' are based on a formula setting s_E = 1.00 for the single electrophile (**1**, Z = NMe$_2$). Using this standard procedure for many reactivity scales,[2] definitions are clear and new experimental data to correct or to extend the available results can be readily incorporated. In practice, values of N_+ based on a single electrophile agree satisfactorily with those based on a series (Table 3).

An approach based on a single reference electrophile has the following major advantage. Instead of using all of the data to define the parameters (eqn (1) requires a value of N and s_N obtained from plots of log k *vs.* E for each of 58 amine nucleophiles), improved precision and/or additional insights are provided by correlations based on eqn (8). The results for all available data for amines in water (up to 54, including amino acids, peptides and azoles, Table 5) show that slopes (s_E) increase as the intercepts (relative reactivities for reaction with a hypothetical nucleophile having N_+'' = 0) of the electrophiles decrease. The standard errors in log k are in the range 0.05 to 0.11, showing that the correlations for these very similar substrates are relatively precise.

$$\log k = s_E\, N_+'' \text{ (or } s_E\, N''\text{)} + \text{intercept} \qquad (8)$$

Downloaded by John Rylands University Library on 25 September 2011
Published on 02 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB05715D

Table 6 Comparisons of values of the s_E parameter from eqn (1), 2 and 8 for cations and quinone methides (QM) in water

Substrate	eqn (1)	eqn (2)	eqn (8)
1	1.0[a]	0.77 ± 0.04[b]	1.03 ± 0.04[b]
2[c]	1.0[a]	1.003 ± 0.007[b]	1.00[d]
QM(**3**)	1.0[a]	0.89 ± 0.02[e]	0.65 ± 0.04[f]
QM(**4**)	1.0[a]	0.92 ± 0.03[g]	0.79 ± 0.04[f]
QM(**5**)	1.0[a]	1.15 ± 0.13[g,h]	1.23 ± 0.12[i]
Ph_3C^+[j]	1.0[a]	0.70 ± 0.05[k]	0.36 ± 0.04[l]

[a] Enforced by the application of eqn (1) – see ref. 8 [b] Reference 12. [c] With Z = NMe_2. [d] By definition in eqn (6). [e] A value of 0.909 was quoted in ref. 6b. [f] Fig. 2. [g] From data in Table 4, excluding data for halides. [h] Standard error in log k/s_N = 1.20. [i] Fig. 3; std error in log k = 0.69. [j] In 2 : 1 water-acetonitrile; data from ref. 29a, nucleophilicity parameters are uncorrected for the difference in solvent. [k] Standard error in log k/s_N = 0.82. [l] Intercept = 4.87 ± 0.24, r = 0.923, n = 16, std error in log k = 0.30.

Correlations using eqn (8) can accommodate a much wider range of nucleophiles than Brønsted plots *vs.* pK_a.[21] Consequently, Brønsted plots are often restricted to 'families' of nucleophiles (*e.g.* primary amines), from which more detailed mechanistic insights can often be obtained.[25,26] Rate constants for reactions of 4 primary amines in 33% acetonitrile-water with triarylmethyl cations (varying in reactivity by a factor of at least 10^6) show a 'clear trend', indicating that β_{nuc} decreases with increasing cation reactivity.[25] Rates decrease 10–100-fold from acetonitrile to water, and the effect is more pronounced for basic amines. Paralleling what is well established for anionic nucleophiles,[25a] the results are explained by equilibrium desolvation of a hydrogen-bonded amine prior to reaction of the free amine with the cation.[25b] General base catalysed hydrolysis was excluded in this[25b] and other[27] cases, although it was observed for more sterically hindered reactions.[27]

The trend[25b] in β_{nuc} is consistent with the trends in s_E (Table 5), and an independent study of six primary amines with a wide range of electrophiles led to the same conclusion.[28] Plots of log k for the parent triphenylmethyl[29a] and 9-arylxanthylium[29b] cations correlate with N_+ only if slopes (0.33[29a] and 0.65[29b]) are varied.

The correlation[29a] for triphenylmethyl cation was extended to include the approximate N_+'' values for halides (Table 3), and the solvent; eqn (8) fits all of the data satisfactorily with $s_E = 0.36 \pm 0.04$ (Table 6, footnote l), in agreement with the published value (0.33[29a]). The plot is very similar to the published plot (Fig. 4 of ref. 29a); significantly, the slope is unchanged by omission of the leverage point for solvent as nucleophile. In contrast, calculations using eqn (1) for chloride or bromide yield rate constants 6 or 20 fold too high.[15]

Adherence to a constant selectivity relationship depends on the stability of the cation,[4,30] as illustrated by variations in the selectivity of azide ion with cation lifetime (Figure 8 of ref. 30b). The most stable cations (*e.g.* triarymethyl cations containing electron donating groups) are in a region where large changes in reactivity lead to small or negligible changes in selectivity.

Amino-substituted benzhydryl cations (**2**) are relatively unreactive,[31] and **1** is even less reactive (more stable) than **2**, Z = NMe_2.[12] Values of log k for **1** in water at 25 °C correlate well with N_+ scales for amine nucleophiles based on **2** (*vs.* N_+'', slope 1.03 ± 0.04),[12] aryltropylium cations (slope: 1.15 ± 0.08),[14] the pyronin Y cation (slope: 0.97 ± 0.14),[14] or triarylmethyl cations (slope: 1.02 ± 0.16)[14] as electrophiles; the slopes of correlations are all approximately unity, but the errors are larger and the intercepts vary significantly.[14]

From the approximately unit slopes, a reasonable alternative viewpoint is that the results (*e.g.* for **1** noted above, and for **2** in Table 5) illustrate that the Ritchie eqn (7) is 'adequately obeyed',[28] and it was recently stated[6a] that 'most *n*-nucleophiles approximately follow the Ritchie's constant selectivity relationship'. The different value of s_N (eqn (1)) for water (0.89) was 'recognised'[6a] as the main reason for deviations from eqn (7).

In summary, the decision[3] to change from water to hydroxide as the anchor point for N_+ in eqn (7) facilitated the omission of water as nucleophile from N_+ correlations, and helped to prolong the acceptability of unit slopes (eqn (7)). Nevertheless, by 1995 there was wide agreement[14,30,32,33] that a slope parameter was required (S_+ was proposed initially[32]). Eqn (8) allows for variations in s_E (or S_+), but includes s_E = 1. However, eqn (1) was introduced around 1994,[34] and since then the assumption of unit slopes (s_E = 1) has again become dominant.[5–8,11,15–17] The two approaches (eqn (1) and 8) are compared below.

Quinone methides (QMs)

QMs can be drawn in a dipolar resonance form as highly resonance-stabilised cations (*e.g.* **5**),[19] and so were chosen to extend the E scale (eqn (1)) to less reactive electrophiles.[10] QMs (**3** and **4**) are more reactive than **2**, Z = NMe_2 in water, but **5** is less reactive (first entries in Tables 3 and 4). How will selectivities be affected? A plot (Fig. 1) of log k for (**4**) *vs.* log k for (**3**) gives a very good correlation with three noteworthy features: (a) the slope of 1.24 ± 0.04 is significantly greater than unity; (b) excluding the data point for water gave the same slope (within errors quoted); (c) values of s_N of the attacking nucleophiles vary significantly from 0.42 for cysteine to 0.89 for water, and only 3 of the 6 values are within 10% of the value of s_N ~ 0.6, suggested[17] as typical of N_+ correlations.

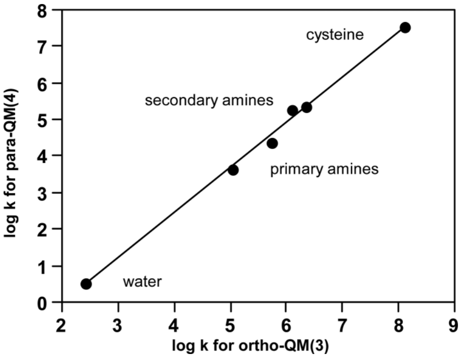


Fig. 1 Logarithms of rate constants for *p*-benzoquinone methide (**4**) *vs.* *o*-benzoquinone methide (**3**) in water at 25 °C; slope: 1.24 ± 0.04; intercept: −2.51 ± 0.22; r = 0.998, n = 6; excluding the leverage point for water: slope 1.28 ± 0.08; data from Table 4.

Correlations were also carried out using eqn (8). Slopes (Fig. 2) are 0.65 for **3** and 0.79 for **4**, so the ratio of 0.79/0.65 = 1.22 agrees well with the slope of Fig. 1 (based on a slightly different selection of nucleophiles). By definition, an eqn (8) plot for **2**, Z = NMe_2 has a unit slope, so there are substantial variations in slopes (s_E) for **2**, **3** and **4** (Table 6). Because of uncertainties in N_+'' values

This journal is © The Royal Society of Chemistry 2011

View Online

Downloaded by John Rylands University Library on 25 September 2011
Published on 02 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB05715D

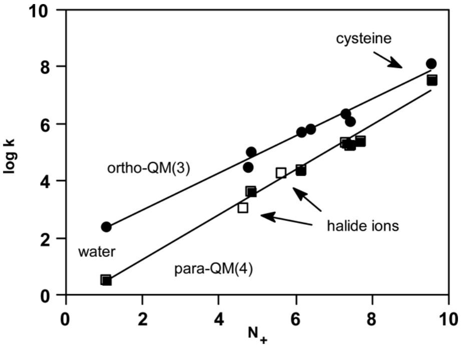


Fig. 2 Logarithms of rate constants for *o*-benzoquinone methide (**3**) and *p*-benzoquinone methide (**4**) in water at 25 °C *vs.* N_+''; slopes: 0.65 ± 0.04 and 0.79 ± 0.04; intercepts: −1.66 ± 0.23 and −0.36 ± 0.26; r >0.99; standard error in log *k*, 0.24 and 0.26; data points for halide ions (open squares) excluded from the correlation; data from Table 4.

for chloride and bromide (Table 3), they were omitted from the correlation for **4**, but they fit satisfactorily (Fig. 2).

Correlations (eqn (8)) for the least reactive QM (**5**) include a more diverse range of nucleophiles (Table 4, footnote c); the slope is 1.23 ± 0.12, if water is included (Fig. 3), and 1.14 ± 0.24 if excluded; calculated rate constants for halides are over 100-fold faster than observed. The published plot[19b] for **5** *vs.* N_+ (from Ar_3C^+)[4] has a slope of 0.92 ± 0.10 (n = 8, solid circles in Fig. 5a of ref. 19b), and the standard error in log *k* is 0.53 (*cf*. 0.69 for Fig. 3). Extrapolation[19b] gave values of N_+ for chloride (1.2) and bromide (2.2) over 3 log units lower than the approximate values of N_+'' values estimated in Table 3. Since the N_+'' values fit the data for QM (**4**) in Fig. 2 and for Ph_3C^+ (Table 6, footnote l), the N_+ values for halide based on QM (**5**)[19b] appear to be anomalous, perhaps because of the close proximity to the reaction site of a two polar trifluoromethyl groups.

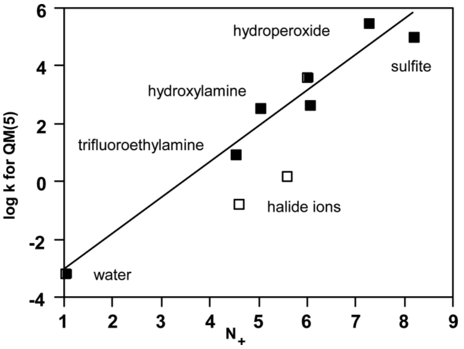


Fig. 3 Logarithms of rate constants for quinone methide (**5**) in water at 25 °C *vs.* N_+''; slope: 1.23 ± 0.12; intercept: −4.29 ± 0.71, r = 0.977; data points for halide ions (open squares) excluded from the correlation; data from Table 4.

In contrast to reactions of **3** and **4**, the relatively unreactive QMs used as reference electrophiles for eqn (1) in the lower half of the *E* scale in DMSO have higher values of s_E than benzhydrylium cations (Table 4 of ref. 35), and less reactive QMs (including **5**) have the higher s_E values. QMs are approximately twice as sensitive as cations to an increase in s_E as reactivity decreases, but the effect is hidden when all of the data are forced to fit eqn (1).

Limitations of equations 1, 2 and 8

Eqn (8) operates as a plot of log *k* *vs.* N_+'' for a single electrophile, and gives *the order of responses* to changes in nucleophilicity (s_E), summarised in Table 6. Slopes *vs.* other N_+ scales would be similar,[12,14] but exact values will depend on which cation is chosen as the reference (Table 5). A more reactive electrophile, such as **2**, Z = OMe would give higher values of s_E; a link to eqn (1) can be made in this case, because $E = 0$,[5] and so $\log k = s_N \times N$.

In contrast, eqn (1) is usually operated as a plot of log *k* *vs.* *E* (slope s_N) for various electrophiles and a single nucleophile. Under these conditions, the parameter s_E cannot be determined, so the assumption[17] that $s_E = 1$ implies 'not known' or enforced. The slopes (Table 6) of an eqn (2) plot of $\log k/s_N$ *vs.* *N* for QMs **3–5** are approximately 1, as required by eqn (1). However, the parameter s_E is included in eqn (2), which should at least give the correct order of values; the results in Table 6 show substantial discrepancies between values of s_E from eqn (2) and eqn (8), consistent with the recent proposal[12] that eqn (2) is incorrect.

Calculated values based on eqn (1) or (8) often agree within a factor of two or three in rate constant,[36] and the design of eqn (1) leads to particularly good results for benzhydrylium cations in dichloromethane.[36] Changes of structure and solvent can lead to a rapid deterioration in the reliability of eqn (1), and predictions are regarded as semi-quantitative (reliable to an order of magnitude or two).[15,36] Eqn (1), like the sister equation for solvolytic reactions (the reverse of cation–nucleophile recombinations), does not allow for differences in aromatic ring solvation effects.[12,37–40] Rates of reactions of benzhydrylium cations with protic solvents can be correlated quantitatively with a solvent nucleophilicity parameter (N_T) and an aromatic ring solvation aparameter (*I*).[41]

Since N_+ and N'' are linearly related (eqn (6)), N'' is an alternative scale for eqn (8). If N'' is plotted instead of N_+'' in Fig. 2, the intercepts are due to differences in *E*;[13] assuming $E = -7.02$ for **2**,[5] gives $E = -3.65$ for **3** and −5.3 for **4**, in moderate agreement with 'preliminary determinations' of −3.1 and −5.2 respectively from eqn (1).[8] From eqn (1), log *k* = 9.02 is predicted for reaction of $CH(CN)_2^-$ ($N = 19.5$ and $s_N = 0.55$)[16a] with **3** ($E = -3.1$) in water at 25 °C, whereas extrapolation of Fig. 2 using eqn (8) gives log *k* = 7.86 – a 14-fold discrepancy in *k*,[42] probably due to the different values of s_E.

Conclusions

Despite recent claims[6a,17] to the contrary, there is overwhelming evidence[14,25,28–30,32,33] that in general an electrophile selectivity parameter is required for correlations of nucleophilic reactivity of cations (*e.g.* Table 5) and of quinone methides (Fig. 2).

Instead of complex data processing (Scheme 1),[6a,17] nucleophilicity parameters (N_+'') for amines, amino acids, peptides and other nucleophiles in water can be obtained directly from rate constants for cations **2**, Z = NMe_2. The N_+'' parameters are compatible with those based on **1** (Tables 1 – 3, and ref. 14), and greatly extend the idea[14] of an N_+ scale (based on **1**) less susceptible to steric effects than typical N_+ scales.[3]

Eqn (8), including a Swain-Scott selectivity or response parameter (s_E), is analogous to Brønsted (β_{nuc}) plots and correlates rate constants for more varied nucleophiles; eqn (8) allows for variations in s_E (Table 5), and so is more flexible than the Ritchie eqn (7). A range of values of s_N (including water as nucleophile) are accommodated, implying that there are changes in transition state structure within a single correlation.

Slopes of eqn (2) reflect both random and systematic errors in eqn (1), and are not reliable measures of s_E (Table 6).

Acknowledgements

I thank Professor D. Bethell (University of Liverpool) for many helpful suggestions and exchanges of views on this and related work.

Notes and references

1 (*a*) W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw Hill, New York, 1969; (*b*) A. Williams, *Free Energy Relationships in Organic and Bio-Organic Chemistry*, The Royal Society of Chemistry, Cambridge, 2003, Chapters 2.5 and 2.6.

2 (*a*) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 141–147; (*b*) R. G. Pearson, H. Sobel and J. Songstad, *J. Am. Chem. Soc.*, 1968, **90**, 319–326.

3 C. D. Ritchie, *Can. J. Chem.*, 1986, **64**, 2239–2250.

4 For a broad recent review see: R. A. More O'Ferrall, *Adv. Phys. Org. Chem.*, 2010, **44**, 19–122.

5 H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov and H. Schimmel, *J. Am. Chem. Soc.*, 2001, **123**, 9500–9512.

6 (*a*) S. Minegishi and H. Mayr, *J. Am. Chem. Soc.*, 2003, **125**, 286–295; (*b*) F. Brotzel, Y. C. Chu and H. Mayr, *J. Org. Chem.*, 2007, **72**, 3679–3688.

7 F. Brotzel and H Mayr, *Org. Biomol. Chem.*, 2007, **5**, 3814–3820.

8 D. Richter, N. Hampel, T. Singer, A. R. Ofial and H. Mayr, *Eur. J. Org. Chem.*, 2009, 3203–3211.

9 (*a*) M. Freccero, *Mini-Rev. Org. Chem.*, 2004, **1**, 403–415; (*b*) S. Arumugam and V. V. Popik, *J. Am. Chem. Soc.*, 2009, **131**, 11892–11899.

10 R. Lucius, R. Loos and H. Mayr, *Angew. Chem., Int. Ed.*, 2002, **41**, 91–95.

11 (*a*) F. Brotzel, B. Kempf, T. Singer, H. Zipse and H. Mayr, *Chem.–Eur. J.*, 2007, **13**, 336–345; (*b*) M. Baidya, F. Brotzel and H. Mayr, *Org. Biomol. Chem.*, 2010, **8**, 1929–1935.

12 T. W. Bentley, *Angew. Chem., Int. Ed.*, 2011, **50**, 3608–3611.

13 T. W. Bentley, *J. Phys. Org. Chem.*, 2010, **23**, 836–844.

14 C. K. M. Heo and J. W. Bunting, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2279–2290.

15 S. Minegishi, R. Loos, S. Kobayashi and H. Mayr, *J. Am. Chem. Soc.*, 2005, **127**, 2641–2649.

16 (*a*) T. Bug and H. Mayr, *J. Am. Chem. Soc.*, 2003, **125**, 12980–12986; (*b*) T. Bug, T. Lemek and H. Mayr, *J. Org. Chem.*, 2004, **69**, 7565–7576.

17 T. B. Phan, M. Breugst and H. Mayr, *Angew. Chem., Int. Ed.*, 2006, **45**, 3869–3874.

18 E. Modica, R. Zaneletti, M. Freccero and M. Mella, *J. Org. Chem.*, 2001, **66**, 41–52.

19 (*a*) J. P. Richard, *J. Am. Chem. Soc.*, 1991, **113**, 4588–4595; (*b*) J. P. Richard, M. M. Toteva and J. Crugeiras, *J. Am. Chem. Soc.*, 2000, **122**, 1664–1674.

20 (*a*) Y. Chiang, A. J. Kresge and Y. Zhu, *J. Am. Chem. Soc.*, 2001, **123**, 8089–8094; (*b*) Y. Chiang, A. J. Kresge and Y. Zhu, *J. Am. Chem. Soc.*, 2002, **124**, 6349–6356.

21 Examples: There is a large amount of scatter in the Brønsted plot for **1** shown in Fig. 2 of ref. 14, even though it is restricted to amines. Nitrosation of amines shows a scattered Brønsted plot, but a satisfactory N_+ correlation.[22] The recent demonstration that liquid ammonia is a suitable solvent for aminolysis of benzyl chloride,[23] is consistent with the low value of N_+'' of ammonia (Table 1). Quantitative data are also important in optimising yields of aminolyses in water.[24].

22 L. García Río, E. Iglesias, J. R. Leis, M. E. Peña and A. Ríos, *J. Chem. Soc., Perkin Trans. 2*, 1993, 29–37.

23 P. Ji, J. A. Atherton and M. I Page, *J. Org. Chem.*, 2011, **76**, 1425–1435.

24 (*a*) J. F. King, M. S. Gill and P. Ciubotaru, *Can. J. Chem.*, 2005, **83**, 1525–1535; (*b*) M. Trmčić and D. R. W. Hodgson, *Beilstein J. Org. Chem.*, 2010, **6**, 732–741.

25 (*a*) E. Buncel and I.-K. Um, *Tetrahedron*, 2004, **60**, 7801–7825 and references there cited; (*b*) R. A. McClelland, V. M. Kanagasabapathy, N. S. Banait and S. Steenken, *J. Am. Chem. Soc.*, 1992, **114**, 1816–1823.

26 (*a*) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7018–7031; (*b*) E. A. Castro, M. Aliaga, P. R. Campodónico, M. Cepeda, R. Contreras and J. G. Santos, *J. Org. Chem.*, 2009, **74**, 9173–9179; (*c*) M. E. Ul Hoque, N. K. Dey, C. K. Kim, B. S. Lee and H. W. Lee, *Org. Biomol. Chem.*, 2007, **5**, 3944–3950.

27 C. A. Bunton and S. K. Huang, *J. Am. Chem. Soc.*, 1974, **96**, 515–522.

28 P. Denton and C. D. Johnson, *J. Chem. Soc., Perkin Trans. 2*, 1995, 477–481.

29 (*a*) R. A. McClelland, N. Banait and S. Steenken, *J. Am. Chem. Soc.*, 1986, **108**, 7023–7027; (*b*) R. A. McClelland, N. Banait and S. Steenken, *J. Am. Chem. Soc.*, 1989, **111**, 2920–2933.

30 (*a*) R. Ta-Shma and Z. Rappoport, *J. Am. Chem. Soc.*, 1983, **105**, 6082–6095; (*b*) J. P. Richard, *Tetrahedron*, 1995, **51**, 1535–1573.

31 S. Minegishi, S. Kobayashi and H. Mayr, *J. Am. Chem. Soc.*, 2004, **126**, 5174–5161.

32 K. Hillier, J. M. W. Scott, D. J. Barnes and F. J. P. Steele, *Can. J. Chem.*, 1976, **54**, 3312–3314.

33 S. Hoz and D. Speizman, *J. Org. Chem.*, 1983, **48**, 2904–2912.

34 H. Mayr and M. Patz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 938–957.

35 T. W. Bentley, *J. Phys. Org. Chem.*, 2011, **24**, 282–291.

36 H. Mayr, *Angew. Chem., Int. Ed.*, 2011, **50**, 3612–3618.

37 K. T. Liu, H. C. Sheu, H. I. Chen, P. F. Chiu and C. R. Hu, *Tetrahedron Lett.*, 1990, **31**, 3611–3614.

38 T. W. Bentley, I. S. Koo and S. J. Norman, *J. Org. Chem.*, 1991, **56**, 1604–1609.

39 D. N. Kevill, N. H. Ismail and M. J. D'Souza, *J. Org. Chem.*, 1994, **59**, 6303–6312.

40 D. N. Kevill and M. J. D'Souza, *Curr. Org. Chem.*, 2010, **14**, 1037–1049.

41 D. N. Kevill and M. J. D'Souza, *J. Chem. Res.*, 2008, 61–66.

42 These are genuine predictions (experimental results are not yet available).

Published on 02 August 2011 on http://pubs.rsc.org | doi:10.1039/C1OB05715D
Downloaded by John Rylands University Library on 25 September 2011