On the Calculation of Tetrahedral Intermediate pK_a Values

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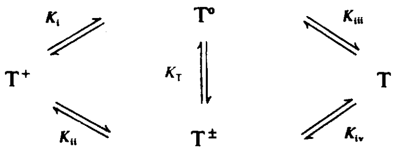
The procedure of Fox and Jencks for calculating tetrahedral intermediate pK_a values, as ΔpK_a = $\rho_I\Sigma\sigma_I$ relative to that of some defined amine or alcohol, is re-examined in the light of more recent estimates for σ_I. Using those of Charton, which are explicitly tuned to aqueous or near-aqueous conditions, we derive a value of ρ_I = −9.1 ± 0.4 for the effect of substituent X on probe Y for a one-carbon separation (X–C–Y). Additionally we derive, for X–C–C–Y, a value of ρ_I = −4.4 ± 0.4.

We also examine the possibility of assigning σ_I values to charged substituents. It is shown that this approach can be made to work under strictly defined conditions, and results in a self-consistent set of $\sigma_I^{\pm}$ values that may be used in the present context.

This subject was first systematised in 1974 by Fox and Jencks,[1] since when it has been further amplified in a number of publications by Jencks[2] and others.[3] Jencks' procedure in outline is to start from some species of general formula $R^1R^2R^3COH$ or $R^1R^2R^3CNR_2$ of known pK_a—the closest match to the tetrahedral intermediate that is available—and then correct this pK_a through the relationship of eqn. (1). The σ_I values are those of Ritchie and Sager[4] and evidence is

$$\Delta pK_a = \rho_I \Sigma \sigma_I \qquad (1)$$

given[1] that the same ρ_I value can be used for amines and for alcohols. This procedure will suffice for the ionisation processes $T^+ \longrightarrow T^o$ (pK_{T^+}) and $T^o \longrightarrow T^-$ (pK_{T^o}). One more microscopic value (Scheme 1) is required, and for this $T^+ \longrightarrow T^{\pm}$ is chosen, starting from pK_a = 9.98 for the ionisation process $MeNH_2{}^+CH_2OH \longrightarrow MeNH_2{}^+CH_2O^-$. This value is corrected, if necessary, for the difference in σ_I value between -NHMe and the amine involved. The fourth microscopic pK_a value (for the process $T^{\pm} \longrightarrow T^-$) then follows by difference. There is impressive evidence, *e.g.* from breaks in Brönsted plots, that many of these estimates are quite accurate.



Scheme 1

We have been forced to reconsider this methodology through having recently encountered an unusually complex area for its application.[5] Some putative intermediates contain extra ionisation processes which may affect the pK_a values of the reaction centre; some may require non-standard ρ_I values; and, since no σ_I value existed for some of our substituent groups at the time of the original work,[1] we have been compelled to look to other sources, or derive our own. Here we address in turn the problems that result.

Standardisation: σ_I *Scales*.—Table 1 collates σ_I values from three sources: the 1964 compilation of Ritchie and Sager[4] (R & S; the set chosen is for compounds XCH_2Y); Charton's 1981 analysis (C);[6] and the recent compendium of Hansch, Leo and Taft (HLT),[7] drawn from a variety of sources. The listing of Table 1 is not comprehensive but includes all of concern to us[5] and, indeed, all or nearly all of those commonly encountered in the present context. Our 'consensus' values are those of Charton in nearly all possible cases, the only exceptions being entries 8, 26, 34, 35 and 37, where minor adjustments have been made in the interests of consistency, plus 45 which has been derived, along with 46, in the present study (see below). Values for 18, 24, 33, 39 and 53 result from obvious interpolation procedures.

Our choice of Charton's set[6] comes about because these values are statistically based; because the resulting analysis is self-consistent; and because they are specifically tuned to aqueous or near-aqueous solution. The last criterion is of special importance for strong proton donors and acceptors which are also highly polarisable; it is not a feature of, for example, the HLT compendium[7] from which we have also drawn some values. Substituent groups most strongly affected include OH and NR_2; the effect of concentrating on aqueous solution, relative to less discriminating scales, is chiefly to reduce σ_I for OH relative to OAlk, and to increase σ_I for all simple amino-groups. Independent evidence exists[8] for the strong effect of solvent on σ_I values.

Standardisation: ρ_I *Values*.—Standardisation on a new set of σ_I values necessarily involves re-derivation of the ρ_I values on which eqn. (1) is based. We now present evidence for ρ_I = −9.2 ± 0.4 for amines and −9.0 ± 0.3 for alcohols, leading to a new compromise value of ρ_I = −9.1 ± 0.4 for the relation between $\Delta pK_a(Y)$ and $\Sigma\sigma_I(R)$ in $R^1R^2R^3CY$.

ρ_I *Values for Amines of Type* $R^1R^2NCH_2X$.—The pK_a compilation of Table 2, mostly from Perrin,[9] is the most comprehensive that we have been able to assemble. It has been used to generate eqns. (2)–(10) of Table 4.

The data for primary amines NH_2CH_2X are much the most extensive, as noted by Fox and Jencks,[1] and all data together give ρ_I = −10.0. However, this regression depends heavily on the data points for X = CF_3, CCl_3 and CN; in addition, that for X = CH_2SH is plainly corrupt—the more than one unit pK_a difference reported between compounds **26** and **27** is clearly unacceptable. (Probably ionisation of **26** is complicated by zwitterion formation). Elimination of the latter plus X = CN, or plus X = CF_3 and CCl_3, alters ρ_I in opposite directions, but elimination of all four results in a value for ρ_I not much different from that found when CN is retained. Provisionally we accept the latter value, ρ_I = −9.2. Eqn. (10), with ρ_I = −10.1, is much the better of the two for tertiary amines. Neither equation for secondary amines is of an acceptable standard. Fox and Jencks,[1] using of course a different set of σ_I values, obtained ρ_I values of −8.6 and −9.3 for primary and tertiary amines respectively; Charton[6] obtained −9.16 for the former.

Table 1 σ_I Values for uncharged substituents

		R&S[a]	C[b]	HLT[c]	Other	Consensus
1	H	0.00	0.00	0.03		0.00
2	Me	0.00	−0.01	0.01		−0.01
3	Et		−0.01	0.00		−0.01
4	Pr^i		0.01	0.04		0.01
5	CF_3	0.41	0.40	0.38		0.40
6	CHF_2		0.32	0.29		0.32
7	CH_2F			0.15		0.15
8	CCl_3		0.36	0.38		0.38
9	$CHCl_2$			0.31		0.31
10	CH_2Cl	0.17	0.17	0.13		0.17
11	C≡CH		0.29	0.22		0.29
12	$CH{=}CH_2$	0.05	0.11	0.13		0.11
13	Ph	0.10	0.12	0.12		0.12
14	CH_2Ph		0.03	−0.04		0.03
15	CN	0.56	0.57	0.51		0.57
16	CH_2CN	0.23	0.20	0.17		0.20
17	COMe	0.28	0.30	0.33		0.30
18	CH_2COMe					*d*
19	CO_2Me	0.30	0.32	0.34		0.32
20	CO_2Et	0.30	0.30	0.34		0.30
21	CH_2CO_2Me		0.19			0.19
22	CH_2CO_2Et		0.15			0.15
23	$CONH_2$		0.28	0.26		0.28
24	CONHMe					*e*
25	$CONMe_2$		0.28			0.28
26	CH_2CONH_2		0.06	0.08		0.08
27	OH	0.25	0.24	0.33		0.24
28	CH_2OH	0.11	0.11	0.03		0.11
29	CH_2CH_2OH		0.06			0.06
30	OMe	0.25	0.30	0.30		0.30
31	OEt		0.28	0.26		0.28
32	CH_2OMe		0.11	0.13		0.11
33	CH_2OEt					*f*
34	CH_2CH_2OMe		0.00			0.06[g]
35	OPh	0.38	0.40	0.37		0.38
36	CH_2OPh					*h*
37	OCOMe	0.39	0.38	0.42		0.39
38	CH_2OCOMe		0.15	0.07		0.15
39	CH_2OCOEt					*h*
40	CH_2SH		0.12			0.12
41	CH_2SMe		0.12			0.12
42	NH_2	0.10	0.17	0.08		0.17
43	NHMe		0.13	0.03		0.13
44	NMe_2	0.10	0.17	0.15		0.17
45	CH_2NH_2	0.00		0.04		0.08[i]
46	$CH_2CH_2NH_2$					0.04[i]
47	$NHNH_2$	0.15		0.22		0.22
48	NHPh		0.30	0.22		0.30
49	N(Me)Ph		0.15			0.15
50	NHCOMe	0.28	0.28	0.31	0.19[k]	0.28
51	NHCOPh		0.28	0.13		0.28
52	$CH_2NHCOMe$		0.09	0.12		0.09
53	$CH_2NHCOPh$					*j*
54	NHC(Me)=NPh[i]			0.38		0.38[i]
55	1-Pyrazolyl				0.30[l]	0.30
56	1-Imidazolyl				0.51[l]	0.51
57	$N{=}C(CF_3)_2$			0.32		0.32
58	$N{=}CCl_2$			0.26		0.26
59	$N{=}CH_2$				0.20[m]	0.20
60	N=CHPh			0.14	0.13[m]	0.13
61	N=C(Me)NHPh[i]					<0.15[i]
62	$N{=}C(NH_2)_2$				−0.01[k]	<0.1[i]

[a] Ref. 4. [b] Ref. 6. [c] Ref. 7. [d] Assumed equal to CH_2CO_2R. [e] Assumed equal to $CONH_2$. [f] Assumed equal to CH_2OMe. [g] Assumed equal to CH_2CH_2OH. [h] Assumed equal to CH_2OCOMe. [i] See the text. [j] Assumed equal to NHCOMe. [k] Ref. 13. [l] J. Elguero, C. Estopa and D. Ilavsky, *J. Chem. Res. (S)*, 1981, 364. [m] M. Charton, in *The Chemistry of Double-bonded Functional Groups*, ed. S. Patai, Wiley, New York, 1989, p. 239.

An alternative approach to the possible differences between primary, secondary and tertiary amines is to compare pK_a values directly, using the primary set as standards. Equations (11) and (12) result.

$$pK_a(\text{sec}) = 0.54\,(0.39) + 0.97\,(0.04)\,pK_a(\text{prim}) \quad (n = 7, r^2 = 0.990, s = 0.18, F = 487) \qquad (11)$$

$$pK_a(\text{tert}) = -1.64\,(0.46) + 1.10\,(0.05)\,pK_a(\text{prim}) \quad (n = 9, r^2 = 0.984, s = 0.27, F = 438) \qquad (12)$$

These are much better equations than the foregoing and there are no outliers even though both sets contain substituents, such as CN and CF_3, which have caused problems in the regressions discussed above. This suggests very strongly that factors may be present which are independent of the usual

Table 2 pK_a Values for amines of formula $R^1R^2NCH_2X$

	X	σ_I	$R^1,R^2 = H$	$R^1 = H, R^2 = Me$	$R^1,R^2 = Me$
1	H	0.00	10.62	10.73	9.81
2	Me	−0.01	10.70		
3	Et	−0.01	10.69		
4	CF_3	0.40	5.70	6.05	4.75
5	CHF_2	0.32	7.09		
6	CH_2F	0.15	8.79		
7	CCl_3	0.38	5.47		
8	$CHCl_2$	0.31	7.25		
9	$C{\equiv}CH$	0.29	8.15		6.97
10	$CH{=}CH_2$	0.11	9.49	10.11	8.64
11	Ph	0.12	9.38	9.54	8.91
12	CH_2Ph	0.03	9.84		
13	CN	0.57	5.34		4.2
14	CH_2CN	0.20	7.80	8.10	
15	CH_2COMe	0.15			8.37
16	CO_2Me	0.32	7.59		
17	CO_2Et	0.30	7.64		
18	$CONH_2$	0.28	7.95	8.31	
19	CONHMe	0.28		8.24	
20	$CONMe_2$	0.28		8.82	
21	CH_2OH	0.11	9.50	9.77	9.26
22	CH_2CH_2OH	0.06	9.96		
23	CH_2OMe	0.11	9.45		8.96
24	CH_2OCOMe	0.15	9.1		8.35
25	CH_2OCOEt	0.15			8.29
26	CH_2SH	0.12	8.27		
27	CH_2SMe	0.12	9.34		
28	CH_2NH_2	*a*	9.63[b]		
29	$CH_2NH_3^+$	*a*	7.15[b]		
30	$CH_2CH_2NH_2$	*a*	10.00[b]		
31	$CH_2CH_2NH_3^+$	*a*	8.59[b]		
32	$CH_2NHCOMe$	0.09	9.25		
33	$CH_2NHCOPh$	0.09	9.13		

[a] See the text. [b] Statistically corrected.

Table 3 pK_a Values for alkanols of formula $R^1R^2R^3COH$

	R^1	R^2	R^3	pK_a	$\Sigma\sigma_I$	Ref.
34	H	H	H	15.09	0.00	*a*
35	H	H	Me	15.93	−0.01	*a*
36	H	H	CF_3	12.37	0.40	*a*
37	H	H	CHF_2	13.3	0.32	*a*
38	H	H	CCl_3	12.24	0.38	*a*
39	H	H	$CHCl_2$	12.89	0.31	*a*
40	H	H	CH_2Cl	14.31	0.17	*a*
41	H	H	$C{\equiv}CH$	13.55	0.29	*a*
42	H	H	$CH{=}CH_2$	15.52	0.11	*a*
43	H	H	Ph	15.4	0.12	*a*
44	H	H	CH_2OH	15.37[c]	0.11	*a*
45	H	H	CH_2OMe	14.82	0.11	*a*
46	H	H	CH_2OEt	15.12	0.11	*a*
47	H	H	CH_2OPh	15.1	0.15	*a*
48	OH	H	H	13.57[c]	0.24	*b*
49	OH	H	Me	13.87[c]	0.23	*b*
50	OH	H	Pr^i	14.07[c]	0.25	*b*
51	OH	H	CF_3	10.50[c]	0.64	*b*
52	OH	H	CCl_3	10.34[c]	0.62	*b*
53	OH	Ph	CF_3	10.30[c]	0.76	*b*
54	OH	CF_3	CF_3	6.88[c]	1.04	*b*
55	OH	CHF_2	CHF_2	9.09[c]	0.88	*b*

[a] S. Takahishi, L. A. Cohen, H. K. Miller and E. G. Peake, *J. Org. Chem.*, 1971, **36**, 1205. [b] J. Hine and G. F. Koser, *J. Org. Chem.*, 1971, **36**, 1348. [c] Statistically corrected.

σ_I/σ_R dichotomy (Charton[6] has convincingly shown that no resonance effect, as commonly understood, is present). One such possible factor is σ-resonance, as we have previously adduced in a somewhat similar context.[10] Here it would take the form $R_2NCH_2X \longleftrightarrow R_2N^+{=}CH_2\ X^-$ and is most likely to be important when the substituent X is highly electronegative and forms a stable anion, as is the case *e.g.* for CN and CF_3 but not, for instance, for COR. Such forces are important only at close range, as for XGY where G = CH_2, and are not expected in the defining situation where G is a benzene ring. Alternatively, some so far unrecognised steric perturbation may be present.[11]

We conclude that primary and secondary amines give the same ρ_I value to within the limits of error, and that tertiary amines differ by no more than could result from one or two mildly inaccurate pK_a values. Hence we adopt $\rho_I = -9.2 \pm 0.4$ as the common value for these amines.

ρ_I *Values for Alcohols of Type* $R^1R^2R^3COH$.—The data used by Fox and Jencks[1] to derive $\rho_I = -8.2$ for these are given in Table 3 and we confirm this value using the full set [eqn. (16), Table 4]. However, a plot of the data reveals two outliers, compounds **53** and **55**, which carry inordinate weight; at the same time, MeOH is also an outlier (not an unusual characteristic for the first member of a homologous series). Elimination of all three leads to eqn. (18) with $\rho_I = -9.0 \pm 0.3$ which we believe to be the best available compromise.

ρ_I *Values for Amines of Type* $NH_2CH_2CH_2X$.—This can also be addressed from the data of Table 2, and the appropriate eqns. (13)–(15) appear in Table 4. Eliminating SH, as for CH_2SH in the NH_2CH_2X set, greatly improves the correlation, and the choice lies between eqns. (14) and (15). In fact there is little to choose, and as a compromise we suggest the average value, $\rho_I = -4.4 \pm 0.4$. Charton[6] reports a value of −4.82. Ours involves an attenuation factor of 2.1 relative to the NH_2CH_2X set, rather less than the normal factor of 2.5 as used by Fox and

Table 4 Regression equations for pK_a *vs.* σ_I

Eqn.	Cons.	$-\rho_I$	n	r^2	s	F
NH_2CH_2X						
(2)	10.39 (0.15)	10.02 (0.63)	25	0.916	0.46	250
Eliminate CH_2SH:						
(3)	10.45 (0.14)	10.15 (0.59)	24	0.931	0.42	298
Eliminate CH_2SH, CN:						
(4)	10.55 (0.14)	10.90 (0.65)	23	0.930	0.39	279
Eliminate CH_2SH, CF_3, CCl_3:						
(5)	10.37 (0.10)	9.21 (0.44)	22	0.956	0.29	437
Eliminate CH_2SH, CN, CF_3, CCl_3:						
(6)	10.42 (0.11)	9.57 (0.57)	21	0.937	0.29	283
$MeNHCH_2X$						
(7)	10.93 (0.35)	10.53 (1.54)	9	0.87	0.54	47
Eliminate CF_3:						
(8)	10.67 (0.32)	8.51 (1.62)	8	0.82	0.45	27
Me_2NCH_2X						
(9)	10.03 (0.19)	11.01 (0.75)	11	0.960	0.38	216
Eliminate CF_3:						
(10)	9.96 (0.10)	10.11 (0.43)	10	0.986	0.20	564
$NH_2CH_2CH_2X$						
(13)	10.54 (0.20)	4.71 (0.69)	12	0.825	0.37	47
Eliminate SH:						
(14)	10.60 (0.10)	4.59 (0.33)	11	0.954	0.18	188
Eliminate SH, CN:						
(15)	10.54 (0.10)	4.18 (0.41)	10	0.928	0.17	103
$R^1R^2R^3COH$						
(16)	15.88 (0.13)	8.23 (0.31)	22	0.972	0.41	698
Eliminate (53), (55):						
(17)	15.97 (0.13)	8.78 (0.33)	20	0.976	0.35	728
Eliminate (34), (53), (55):						
(18)	16.08 (0.10)	9.01 (0.27)	19	0.985	0.29	1092

Table 5 σ_I Values for amines and imines[a]

	σ_I		σ_I
$-NHCOCF_3$	0.38	$-N{=}C(CF_3)_2$	0.32
$-CH{=}NPh$	0.33	$-N{=}CHPh$	0.13
Imidazol-1-yl (–NC=N)	0.51	Pyrazol-1-yl (–NN=C)	0.30
$-NHC(Me){=}NPh$[b]	0.38	$-N{=}C(Me)NHPh$	< 0.15
$-NHCONH_2$	0.23	$-N{=}C(NH_2)_2$	< 0.1

[a] Table 1 or ref. 6. [b] See the text.

Jencks[1] and subsequently (or that of 2.40 found by Charton),[6] and must therefore be regarded as very provisional.

Further Consideration of σ_I *Values.*—Comment is required on entries 54 and 61 of Table 1. The HLT compendium[7] contains a value of $\sigma_I = 0.38$ for the unit **56A**. Almost certainly, this value attaches to its tautomer **56B**. In the first place, **56B** is established as the dominant tautomer where the

$$\underset{\mathbf{56A}}{-N{=}C(Me)NHPh} \rightleftharpoons \underset{\mathbf{56H}}{-NH \simeq C(Me) \simeq NHPh^+} \rightleftharpoons \underset{\mathbf{56B}}{-NHC(Me)C{=}NPh}$$

link is to alkyl.[12] Secondly, we assemble evidence in Table 5 which will demonstrate a simple distinction between high σ_I values for species in which the C=X dipole is aligned away from the probe (left-hand column) and the nearest equivalent species (exact equivalence is rarely possible) where this dipole is reversed (right hand column); this second set of σ_I values is much lower. Our estimate of σ_I for **56A** uses the data for guanidines of Heesing and Schmaldt,[13] making allowance for their tendency to underestimate σ_I for other groups by 0.05–0.1 (*cf.* Table 1).

Entries 45 and 46 derive from compounds **28** and **30** after statistical correction of their pK_a values; the sequence 42 → 45 → 46 shows about the same attenuation factor as for 27 → 28 → 29, as would be expected.

σ_I *Values for Charged Species.*—It is well established[14,15] that poles and dipoles must not be mixed in Hammett-type correlations, the main reason being that the distance-dependence of their effects is quite different; indeed, σ-values for the former are meaningless unless the system is clearly defined. Nevertheless, it would be useful to have values we can use, alongside those for neutral species, in equations of type (1).

$$\Delta = \rho_L\sigma_L + \delta^B \qquad (19)$$

Wepster and co-workers[14] describe the effect of charged substituents on ionisation of the probe Y in terms of eqn. (19), where $\rho_L = \rho_I$ for the uncharged substituent X and δ^B is a factor whose sign depends on that of the charge and whose magnitude is a function only of distance. Unfortunately, none of their values is any help here, since the minimum distance between probe and substituent is that of the benzene ring, and extrapolation to the very short distance involved in XCH_2Y is simply not possible. It will be seen that eqn. (19) is in line with the treatment of Jencks[1] in the case of $T^\pm$ (see above), where substitution of some other amine Y for -NHMe is handled by a correction of the form $\rho_I(\sigma_{I(Y)} - \sigma_{I(NHMe)})$.

In adapting Wepster's treatment, we proceed as follows. It is first of all useful to re-write eqn. (19) as (20), where δ^B is replaced by $\rho_I\delta^\pm$ so that protonation (or deprotonation) of a given substituent simply adds a distance-dependent term to σ_I; for a cation, $\sigma_I^\pm = \sigma_I + \delta^\pm$. We next consider the case[1] of $MeNH_2{}^+CH_2OH$, pK_a = 9.98. Relative to MeOH, we have Δ pK_a = 5.11; dividing by $\rho_I = -9.1$ gives $\sigma_I^\pm = 0.56$ which, subtracting $\sigma_I = 0.13$ for -NHMe, results in $\delta^\pm = 0.43$ for the case of XCH_2Y. This same value of $\delta^\pm$ can be derived from 'σ_I' = 0.60 as given for $-NH_3{}^+$ by De Tar[3b] (Table 6).

$$\Delta\,pK_a = \rho_I\sigma_I{}^\pm = \rho_I(\sigma_I + \delta^\pm) \qquad (20)$$

The (statistically corrected) pK_a values for $NH_2(CH_2)_2NH_2$ and $NH_2(CH_2)_3NH_2$ (Table 2) may be used to derive the appropriate σ_I and $\sigma_I^\pm$ values for $-CH_2NH_2$ and $-CH_2CH_2NH_2$ (Table 6). We now attempt to calculate these $\sigma_I^\pm$ values from σ_I and $\delta^\pm$. Since the expected[15] distance dependence for the action of a dipole on a pole is $1/r^2$, but that for a pole on a pole is $1/r$, the attenuation factor of 2.5 per methylene (or heavy atom) link adduced by Jencks[1] for the former should fall to ≈1.6 in the latter case. Use of this factor to attenuate $\delta^\pm$ leads successively to values of 0.43, 0.27 and 0.17 for zero, one and two interposed linkages. The fit observed to $\sigma_I^\pm$ is exact (Table 6).

A check on this treatment is provided by species **56**. Protonation of **56A** to the cation **56H** involves formal protonation at the α-position, $\delta^\pm = 0.43$. Protonation of **56B** to the same common cation involves formal protonation at the γ-position, $\delta^\pm = 0.17$. Virtually the same value of $\sigma_I^\pm$ is produced by either means (Table 6). We shall take the mean value, $\sigma_I^\pm = 0.56$, as that to use for the dihydroquinazolinium cation as encountered elsewhere.[5] Values for both protonated forms of hydrazine may be derived in a similar manner (Table 6).

If preferred, these $\delta^\pm$ values may be multiplied by ρ_I to obtain Δ pK_a directly; this results in values of 3.91, 2.46 and 1.55 respectively for zero, one and two extra linkages relative to

Table 6 Effective σ_I values for cations

Neutral species	σ_I[a]	Cation	$\delta^{\pm}$	$\sigma_I^{\pm}$[b] calc.	obs.[c]
$-NHMe$	0.13	$-NH_2Me^+$	0.43	0.56[c]	
$-NH_2$	0.17	$-NH_3^+$	0.43	0.60	0.60[d]
$-CH_2NH_2$	0.08[c]	$-CH_2NH_3^+$	0.27	0.35	0.35
$-CH_2CH_2NH_2$	0.04[c]	$-CH_2CH_2NH_3^+$	0.17	0.21	0.19
$-NHNH_2$	0.22	$-NH_2^+NH_2$	0.43	0.65	
$-NHNH_2$	0.22	$-NHNH_3^+$	0.27	0.49	
$-NHC(Me)=NPh$	0.38	$-NHC(Me)=NHPh^+$	0.17	0.55[c]	
$-N=C(Me)NHPh$	< 0.15	$-NH^+=C(Me)NHPh$	0.43	< 0.58[c]	

[a] Consensus value from Table 1. [b] $\sigma_I^{\pm} = \sigma_I + \delta^{\pm}$. [c] See the text. [d] Ref. 3(*b*).

X–C–Y. The first is appreciably less than Jencks' estimate[1] of 4.8, the difference resulting chiefly from the revised amine σ_I values. The second and third compare with Δ pK_a 2.15 and 0.96 for the mutual effect of charge in the series $NH_2(CH_2)_nCO_2H$ where $n = 1$ or 2 (since the negative charge is on oxygen),[16] though the latter comparison may not be entirely fair since some conformational distortion due to mutual charge attraction is possible.

Conclusions

Basing our results on Charton's[6] σ_I values as appropriate to the aqueous or near-aqueous conditions in which tetrahedral intermediates are commonly observed, we have derived new ρ_I values of -9.1 ± 0.4 for the effect of substituent X on the pK_a of probe Y in X–C–Y, and of -4.4 ± 0.4 when X–C–C–Y is involved. While the former lies within the limits -8.4 ± 1 suggested by Fox and Jencks,[1] it is more tightly drawn and we believe it to be more satisfactory. The chief doubt concerning these (or any) ρ_I values attaches to the possibility of saturation effects, which would of course reduce them. This is partly contra-indicated by the presence of tetrasubstituted compounds among the data set of Table 3, but only further work can resolve this point.

We also draw attention to the possibility of assigning σ_I values to charged substituents, and a methodology for converting σ_I for a base to $\sigma_I^{\pm}$ for its cation is derived. (By subtracting instead of adding $\delta^{\pm}$ this should work equally well for anions, but we have no direct information on this point.) As is well established,[14,15] any such value must be used with care, but there are contexts in which their use may prove convenient.[5]

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