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Polar and Steric Contributions of Saturated Substituents to the Acid-Base Equilibria of Aqueous Amines*

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Summary

A simple algebraic technique permits an unambiguous separation of polar and steric contributions of saturated substituents to the modification of the fundamental acidity of substituent ammonium ions. Two assumptions are made: (1) an empirical mathematical relationship between the acidic dissociation constant and the polar and steric factors for the substituents, and (2) the steric effect of a hydrogen atom is constant in all types of amine. Extensive data then show that (a) each substituent group possesses a characteristic polar and steric factor, (b) the polar effects obey a purely additive combination law, and (c) the steric effects of a given substituent are accumulative and consist of the product of a characteristic steric factor and the total number of substituents borne by the nitrogen atom. The substituent factors may be used to compute the acidic ionization constant of any secondary or tertiary ammonium ion for whose substituents the corresponding factors are known. It is to be noted that these factors represent the first system in which polar and steric effects of substituents attached *directly* to a site of reaction have been calculated.

Introduction

The past three decades have witnessed a tremendous growth of data relating reactivity and chemical structures in the field of carbon chemistry, closely paralleled by intensive efforts to correlate such data into a coherent system of empirical knowledge. The most prolific area for such research has lain in the field of aromatic compounds, where the linear free energy concept[1] has provided a certain degree of theoretical foundation, and in recent years the principal efforts have been in the direction of refining both the data and the methods for their correlation.[2] In addition, extensions have been attempted to include the simultaneous influences of more than one substituent in an aromatic system.[3,4] A second line of development, vigorously prosectued by Ingold and his colleagues,[5] deals with efforts to correlate the inductive effects of substituents on reactivity in the aliphatic system of compounds. This area received important clarification first through the demonstration of the importance of steric substituent effects,[6] and second through correlations of both polar and steric influences with reactivity on a quantitative empirical basis.[7]

More recently, it has become increasingly evident that the broad linear free energy concept is inadequate to account for all the details of structure-reactivity correlations observed in the aromatic series.[8] This has led to a proliferation of specialized attempts at correlation,[9] all of which give clear evidence of efforts to force the linear free energy theory to provide a theoretical fundament beyond its capacity. The most perceptive insight into this problem has been provided by Taft, who recognized that the dimensions of the question require the separation of substituent influences into three classes,[10] namely polar (P), steric (S), and resonance (R) effects. Since all three effects are inter-related, the problem is extraordinarily difficult, and it appears that R-influences remain essentially undetermined. As a result, the P- and S-influences in aromatic systems necessarily remain very ill-defined. In aliphatic systems, where R-effects are frequently small or even negligible, more progress has been possible,[7] but it has heretofore not yet proved feasible to determine the P- and S-effects insofar as they *directly* influence the

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6 H. C. Brown, *Record Chem. Progr. 14* (1953) 83.

7 R. W. Taft, *J. Amer. Chem. Soc. 75* (1953) 4231.

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9 H. C. Brown, Y. Okamoto and T. Inukai, *J. Amer. Chem. Soc. 80* (1958) 4964, and following papers.

10 R. W. Taft, S. Ehrenson, I. C. Lewis and R. E. Glick, *ibid. 81* (1959) 5352.

reaction site. Thus, the Taft aliphatic parameters have required one atom of «insulation» between the substituent and the reaction center, and they fail entirely when applied to the alkyl moiety of an aliphatic ester (see however ref. [11]).

Our investigations into the basicities of certain alkanolamines[12] directed our attention to the inadequacies of present structure-reactivity correlations when we encountered difficulties in interpreting our data on the basis of structural variations. The most successful prior attempt toward such a correlation was that of HALL[13] based on the Taft σ^*-parameters. It leaves considerable to be desired because of the limitations to those parameters already noted. Hence, we have performed an extensive re-examination of relations between the structures of amines and the dissociation equilibria of their acid conjugates in aqueous solutions which has led to a straightforward separation of P- and S-contributions to the acidity of a wide variety of ammonium-type ions. Aryl substituents have been omitted for the present, to avoid complexities arising from R-effects.

Separation of P- and S-Effects

The acidic dissociation constant of an ammonium-type cation is considered to consist of a product of the polar parameters, P_i and steric factors, S_i belonging to the various N-substituents in the neutral amine. Thus, in general,

$$\prod_1^3 (P_i S_i) = K_a , \qquad (1)$$

and the corresponding expressions for ammonium ion and the primary, secondary and tertiary ammonium ions respectively are

Ammonium:	$P_H^3 S_H^3 = K_{a,0}$	(1a)
Alkylammonium:	$P_H^2 S_H^2 P_R S_R = K_{a,1}$	(1b)
Dialkylammonium:	$P_H S_H P_R S_R P_{R'} S_{R'} = K_{a,2}$	(1c)
Trialkylammonium:	$P_R S_R P_{R'} S_{R'} P_{R''} S_{R''} = K_{a,3}$	(1d)

With respect to the steric factors, there can be no doubt that, from the standpoint of spatial requirements, hydrogen, the smallest possible substituent, possesses the least steric influence. Therefore, as a point of reference, it seems reasonable to set $S_H = 1$. Larger substituents will clearly impart a release of strain in the process of dissociation of the tetrahedral ammonium-type ion to the less crowed trigonal free amine molecule. Therefore, it is expected that the various S_R will be greater than unity.

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[12] a) H.WEIDMANN and H.K.ZIMMERMAN, *Texas J. Sci. 11* (1959) 212.
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Now prior experience[6] has shown that the steric influences of a particular type of substituent in a homo-substitued series of amines differ according to the degree of substitution. Thus, for example, the steric influence of two methyl groups in dimethylamine is greater than that of two primary methyl groups, while the effect of three methyl groups in trimethylamine is greater than that of three primary methyl groups. Thus, although it is tenable to regard the polar contributions, P_R, to be alike in each member of such a series, it is generally accepted that $S_R^{tert} > S_R^{sec} > S_R^{prim}$. Heretofore, the relationship among these steric factors has not been clear. However, if one examines several series of homo-substituted amines, it is observed that, to a very good approximation, the effect of *each* tertiary S_R^{tert} is the cube of the primary S_R^{prim}, while the effect of *each* secondary S_R^{sec} is the square of the primary S_R^{prim}. Thus, one finds the following relations:

$$S_R^{prim} = S_R \qquad (2a)$$

$$S_R^{sec} = S_R^2 \qquad (2b)$$

$$S_R^{tert} = S_R^3 \qquad (2c)$$

When the foregoing ideas are introduced into Equations (1a – d), together with the simplified notations that $p = -\log P$, $x = -\log S$, and $pK = -\log K$, the general expressions for the acidic dissociations become

$$3p_H = pK_{a,0} \qquad (3a)$$

$$2p_H + p_R + x_R = pK_{a,1} \qquad (3b)$$

$$p_H + p_R + p_{R'} + 2x_R + 2x_{R'} = pK_{a,2} \qquad (3c)$$

$$p_R + p_{R'} + p_{R''} + 3x_R + 3x_{R'} + 3x_{R''} = pK_{a,3} \qquad (3d)$$

For use in calculating the p_R and x_R parameters from experimental data, Equations (3a – d) can be combined in three ways not involving redundancy, namely (3a) with (3b), (3a) with (3b) and (3c), and (3a) with (3c) and (3d). These combinations lead to the following general expressions:

$$pK_{a,1} - \frac{2}{3} pK_{a,0} = p_R + x_R \qquad (4a)$$

$$pK_{a,2} - pK_{a,1} + \frac{1}{3} pK_{a,0} = p_{R'} + x_R + 2x_{R'} \qquad (4b)$$

$$pK_{a,3} - pK_{a,2} + \frac{1}{3} pK_{a,0} = p_{R''} + x_R + x_{R'} + 3x_{R''} \qquad (4c)$$

Their solution in order to determine individual substituent p_R and x_R values obviously requires a certain amount of reduction in generality. Two cases have been used in the present work, as follows:

Case I, $R = R' = R''$:

The simplest case one can consider is that of a homo-substituted group of amines, wherein Equations (4b) and (4c) reduce to

$$pK_{a,2} - pK_{a,1} + \frac{1}{3} pK_{a,0} = p_R + 3x_R \quad (5a)$$

$$pK_{a,3} - pK_{a,2} + \frac{1}{3} pK_{a,0} = p_R + 5x_R \quad (5b)$$

The combinations, (4a) and (5a), (5a) and (5b), and (4a) and (5b) lead respectively to

$$x_R = \frac{1}{2} (pK_{a,2} + pK_{a,0}) - pK_{a,1} \quad (6a)$$

$$x_R = \frac{1}{2} (pK_{a,3} + pK_{a,1}) - pK_{a,2} \quad (6b)$$

$$x_R = \frac{1}{4} (pK_{a,3} + pK_{a,0} - pK_{a,2} - pK_{a,1}) \quad (6c)$$

by which x_R may be obtained in three different ways. If the mean value of x_R so determined is then introduced into Equations (3b – d), taking account of the identies of the substituents, the following three independent expressions for calculating p_R result.

$$p_R = pK_{a,1} - \frac{2}{3} pK_{a,0} - x_R \quad (7a)$$

$$p_R = \frac{1}{2} (pK_{a,2} - \frac{1}{3} pK_{a,0}) - 2x_R \quad (7b)$$

$$p_R = \frac{1}{3} pK_{a,3} - 3x_R \quad (7c)$$

Case II, $R^{prim} = R^{sec} = R^{tert} = R'^{sec} = R'^{tert} = R''^{tert}$:

When one has available experimental data for a series of amines, RNH_2, $RNHR'$, RNR'_2, as in the case of ethylamine, ethyl-methylamine and ethyldimethylamine for example, the resulting simplifications of (3c) and (3d), together with their combinations with each other and with (3b), yield the following expressions for x_R:

$$x_R = pK_{a,3} - pK_{a,2} + \frac{1}{3} pK_{a,0} - p_{R'} - 4x_{R'} \quad (8a)$$

$$x_R = \frac{1}{2} (pK_{a,3} - pK_{a,1}) + \frac{1}{3} pK_{a,0} - p_{R'} - 3x_{R'} \quad (8b)$$

$$x_R = pK_{a,2} - pK_{a,1} + \frac{1}{3} pK_{a,0} - p_{R'} - 2x_{R'} \quad (8c)$$

Again, the values of x_R (which are now secondary values, since they depend on a previous determination of $p_{R'}$ and $x_{R'}$ by the methods of Case I) can be introduced into Equations (3b – d), again taking account of existing identities among substituents, to yield the following expressions which, together with Equations (7a) give the value of p_R.

$$p_R = pK_{a,2} - \frac{1}{3} pK_{a,0} - p_{R'} - 2x_{R'} - 2x_R \quad (9a)$$

$$p_R = pK_{a,3} - 2p_{R'} - 6x_{R'} - 3x_R \quad (9b)$$

Case III, $R = R' \neq R''$:

A closely related case of some interest is that involving R_2NH and R_2NR'', in which R is a symmetrical difunctional substituent. An example of such a pair would be ethyleneimine and N-methyl ethyleneimine. In this case, application of Equations (3a), (3c) and (3d), with due regard for identities of substituent, R, leads to the expression,

$$x_R = \frac{1}{2} (pK_{a,3} - pK_{a,2} + \frac{1}{3} pK_{a,0} - p_{R''} - 3x_{R''}) \quad (10)$$

Introduction of the resulting x_R-value into Equation (3d) produces the following expression which, together with Equation (7b) can be used to determine p_R:

$$p_R = \frac{1}{2} pK_{a,3} - \frac{1}{2} (p_{R''} + 3x_{R''}) - 3x_R \quad (11)$$

Derived Parameters

Table 1 lists the polar and steric parameters which have been deduced from experimental data according to the procedures outlined above. In the cases of the ammonium ion and the cations of the primary and secondary amines, the experimental data have been subjected to statistical corrections to account for the fact that, in these instances, the acidic dissociation measured by the dissociation constant can occur in more than one way. In the cases where three amines were available for analysis, it has been possible to check the precision (i. e., internal consistency) of the p- and x-values determined. When only two amines were available, only one equation for the x-parameter and two for the p-parameter could be used, with a resulting loss in the confidence which can be attached to the values listed.

When one examines the polar parameters, they appear in a general way to follow the familiar polarity sequence well known to organic chemists, i.e. alkyl groups tend to diminish the acidity as compared to the effect of a proton, while electron-withdrawing groups appear to enhance acidity. However, closer examination reveals that an exact parallelism between these parameters and other so-called polar substituent constants does not occur.

The absence of such a 1–1 correspondence is probably a result of the reflection, in the conventional substituent «constants» of an element traceable to the concurrent steric influence of the various substituents. As the results in Table 1 show, this steric effect reveals numerous unanticipated anomalied when judged in terms of earlier work. Thus, although the shift of x on going from methyl to ethyl to isopropyl to tertiary butyl substituents is in the expected direction, increasing chain length in a straight-chain substituent produces a minimum in x before becoming approximately constant for long chains.

Also the much-assumed «tie-back» affect of cyclic imino substituents seems to operate in the opposite direction to that which one would anticipate. Moreover, the steric influence of the supposedly rather small hydroxyl and methoxyl groups turns out to be surprisingly large, in fact on a scale comparable with that of the very bulky trimethylsilylmethyl group. It is thus apparent that a considerable further study of these phenomena (now proceeding in our laboratories) is necessary.

Application of Results

The steric and polar parameters given in Table 1 make it clear that the basicity of a particular amine cannot be judged in either polar or steric terms alone, but rather as a composite of these effects as contributed by the various substituents present on the nitrogen atom. By means of the parameters which have been determined, it is now possible to make estimations of basicity in quantitative terms. This ability will be useful in many areas, particularly in work on reaction kinetics and mechanisms where the factors contributing polar and steric influences are often of paramount importance.

In order to give an idea of the precision with which such quantitative judgements can be made, the parameters of Table 1 have been introduced into Equations (3c) and (3d) to calculate the ionization constants of a variety of secondary and tertiary ammonium ions for which experimental values are known. The comparison of the calculated values with the experimental ones is given in Table 2. From these results it is evident that the steric and polar parameters can reproduce the experimental pK_a values within one or two tenths of a pK-unit

Table 1. Polar and Steric Factors Calculated from the pK_a of Aqueous Ammonium Ions at 25°

R	RNH_2 $pK_{a,1}$ Corr.[b]	R_2NH $pK_{a,2}$ Corr.[c]	R_3N $pK_{a,3}$	x	p
—H			9.848[a,a]		3.283
—CH_3	11.102[β]	11.075[β]	9.800[β]	— 0.632 ± 0.005[i]	5.163 ± 0.003[j]
—C_2H_5	11.11[γ]	11.28[δ]	10.65[e]	— 0.47 ± 0.05[i]	4.98 ± 0.03[j]
—*n*-C_3H_7	11.01[γ]	11.30[ζ]	10.65[e]	— 0.46 ± 0.01[i]	4.92 ± 0.02[j]
—*n*-C_4H_9	11.07[γ]	11.55[ζ]	10.89[η]	— 0.47 ± 0.07[i]	5.03 ± 0.04[j]
—*i*-C_4H_9	10.90[δ]	11.12[δ]	10.32[δ]	— 0.46 ± 0.03[i]	4.82 ± 0.02[j]
—CH_2CHCH_2	9.97[δ]	9.59[ζ]	8.31[ζ]	— 0.36 ± 0.07[i]	3.82 ± 0.04[j]
—CH_2CH_2OH	9.976[θ]	9.184[ι]	7.762[κ]	— 0.388 ± 0.048[i]	3.758 ± 0.026[j]
—$CH_2Si(CH_3)_3$	11.44[λ]	11.70[λ]		— 0.67[k]	5.54[j]
—CH_2CH_2CN		5.56[μ]	1.1 ± 0.1[μ]	— 0.73[l]	2.58[j]
—*n*-C_5H_{11}	11.12[δ]	11.48[δ]		— 0.46[k]	5.01[j]
—*n*-C_6H_{13}	11.12[ν]	11.31[ν]		— 0.54[k]	5.10[j]
—C_8H_{17}	11.13[ν]	11.31[ν]		— 0.55[k]	5.12[j]
—*n*-$C_{12}H_{25}$	11.11[ν]	11.26[ν]		— 0.55[k]	5.10[j]
—*n*-$C_{13}H_{27}$	11.11[ν]	11.26[ν]		— 0.55[k]	5.10[j]
—*n*-$C_{15}H_{31}$	11.09[ν]	11.30[ν]		— 0.52[k]	5.04[j]
—*n*-$C_{18}H_{37}$	11.08[ν]	11.26[ν]		— 0.54[k]	5.06[j]
—*i*-C_5H_{11}	11.12[δ]	11.30[δ]		— 0.55[k]	5.10[j]
—*i*-C_3H_7	11.11[δ]	11.35[δ]	10.30[e,ε]	— 0.43 ± 0.05[o]	4,97 ± 0.06[p]
—*s*-C_4H_9	11.04[δ]	11.31[π]	10.40[e,ε]	— 0.35 ± 0.08[o]	4.80 ± 0.06[p]
—*t*-C_4H_9	10.93[δ]		10.52[e,ε]	— 0.19[m]	4.55[n]
—CH_2CCH	8.63[ξ]		7.05[e,o]	— 0.77[m]	2.84[n]
—$CH_2C_6H_5$	9.82[ϱ]		8.93[e,δ]	— 0.43[m]	3.68[n]
—OCH_3	5.08[σ]	5.05[d,σ]	3.65[e,ϱ]	— 0.70 ± 0.04[q]	— 0.77 ± 0.03[r]
—OH	6.45[σ]	6.26[d,σ]	5.20[e,ϱ]	— 0.61 ± 0.13[q]	0.43 ± 0.09[r]
—CH_2CH_2—		8.28[τ]	7.86[f,φ]	— 0.20[s]	2.90[t]
—$CH_2CH_2CH_2$—		11.59[φ]	10.40[f,φ]	— 0.59[s]	5.33[t]
—$CH_2CH_2CH_2CH_2$—		11.606[χ]	10.46[f,φ]	— 0.56[s]	5.29[t]
—$CH_2(CH_2)_3CH_2$—		11.52[φ]	10.08[f,φ]	— 0.73[s]	5.59[t]
cis-$CH_3CHCHCH_3$		9.02[τ]	8.56[g,τ]	— 0.37[s]	3.62[t]
—$(CH_2)_2O(CH_2)_2$—		8.66[ψ]	7.41[f,ω]	— 0.62[s]	3.91 ± 0.01[t]
—CH_2CN	5.82[μ]	0.50[μ]	4.55[g,μ]	— 0.73[o]	0.00 ± 0.04[j]
—cyclo-C_6H_{11}	11.12[δ]		10.70[h,z]	— 0.33[m]	4.88[n]

Table 2. Comparison of Calculated and Experimental Acidic Dissociation Constants for Ammonium Ions, RR′R″NH

R	R′	R″	pK_a^{exp}	pK_a^{calc} *	Error $(pK_a^{calc} - pK_a^{exp})$
H	CH_3	$CH_2C_6H_5$	9.58[ϱ]	9.70	0.12
H	C_2H_5	$CH_2C_6H_5$	9.68[ϱ]	9.84	0.16
H	CH_3	CH_2CHCH_2	10.11[π]	9.98	−0.13
CH_3	CH_3	C_2H_5	9.99[ε]	10.10	0.11
CH_3	CH_3	n-C_3H_7	9.99[ε]	10.07	0.08
CH_3	CH_3	n-C_4H_9	10.02[ε]	10.15	0.13
CH_3	CH_3	CH_2CHCH_2	8.72[ο]	9.27	0.55
CH_3	C_2H_5	C_2H_5	10.29[ε]	10.41	0.12
CH_3	CH_2CHCH_2	CH_2CHCH_2	8.79[π]	8.75	−0.04
CH_3	CH_2CH_2OH	CH_2CH_2OH	8.52[χ]	8.455	−0.065
C_2H_5	CH_2CH_2OH	CH_2CH_2OH	8.92[γ]	8.76	−0.16
n-C_4H_9	CH_2CH_2OH	CH_2CH_2OH	8.89[γ]	8.81	−0.08
i-C_3H_7	CH_2CH_2OH	CH_2CH_2OH	9.09[γ]	8.90	−0.19
t-C_4H_9	CH_2CH_2OH	CH_2CH_2OH	9.07[γ]	9.16	0.09
$CH_2C_6H_5$	CH_2CH_2OH	CH_2CH_2OH	7.68[γ]	7.58	−0.10
C_2H_5	C_2H_5	$CH_2C_6H_5$	9.48[δ]	9.53	0.05
C_2H_5	C_2H_5	CH_2CH_2CN	7.65[μ]	7.53	−0.12
C_2H_5	CH_2CN	CH_2CN	−0.6 ± 0.1[μ]	−0.81	−0.21
C_2H_5	CH_2CH_2CN	CH_2CH_2CN	4.55[μ]	4.33	−0.22
C_2H_5	$-CH_2CH_2-$		7.93[τ]	8.17	0.24
n-C_4H_9	$-CH_2CH_2CH_2CH_2-$		10.64[z]	10.84	0.20
$CH_2C_6H_5$	$-CH_2CH_2CH_2CH_2-$		9.50[z]	9.51	0.01
C_2H_5	$-CH_2CH_2CH_2CH_2CH_2-$		10.40[δ]	10.37	−0.03
CH_2CHCH_2	$-CH_2CH_2CH_2CH_2CH_2-$		9.68[ω]	9.54	−0.14
CH_2CN	$-CH_2CH_2CH_2CH_2CH_2-$		4.55[μ]	4.61	0.06
n-C_4H_9	$-CH_2CH_2CH_2CH_2CH_2-$		10.48[δ]	10.42	−0.06
C_2H_5	$-CH_2CH_2OCH_2CH_2-$		7.70[ω]	7.67	−0.03
CH_2CHCH_2	$-CH_2CH_2OCH_2CH_2-$		7.05[ω]	6.84	−0.21

* The statistical correction for the secondary amines has been removed from the values given in this column.

Notes to Table 1 and 2:

[a] Statistically corrected to $pK_{a,0} = pK_a^{exp} + \log 4$.

[b] Statistically corrected to $pK_{a,1} = pK_{a,1}^{exp} + \log 3$.

[c] Statistically corrected to $pK_{a,2} = pK_{a,2}^{exp} + \log 2$.

[d] Constants listed are for $RNHCH_3$.

[e] Constants listed are for $RN(CH_3)_2$.

[f] Constants listed are for $RNCH_3$, where R is bifunctional, cyclic.

[g] Constants listed are for RNC_2H_5, where R is bifunctional, cyclic.

[h] Constant listed is for $RN(CH_2)_5$.

[i] Average of values calculated from Equations (6a–c).

[j] Calculated from Equations (7a–c).

[k] Calculated from Equation (6a).

[l] Calculated from combination of Equations (5b) and (7c):
$x = \frac{1}{3} pK_{a,3} + \frac{1}{2}\left(\frac{1}{3} pK_{a,0} - pK_{a,2}\right)$.

[m] Calculated from Equation (8b), R′ = CH_3, C_2H_5 or $-(CH_2)_5-$ as required.

[n] Calculated from Equations (7a) and (9b).

[o] Average of values calculated from Equations (6a), (8b) and (8c).

[p] Average of values calculated from Equations (7a), (7b) and (9b).

[q] Calculated from Equations (8a–c), R′ = CH_3 or C_2H_5 as required.

[r] Calculated from Equations (7a), (9a) and (9b).

[s] Calculated from Equation (10).

[t] Calculated from Equations (7b) and (11).

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in most cases, and often much more closely. The deviations observed can, in many cases (e.g. the diethanolamine derivatives for which we have personal knowledge of the accuracy of the experimental data) be attributed to moderate errors in the experimental quantities used both in the comparison and in determining the parameters employed. On this basis one can conclude that the agreement observed is very good. It offers reason to believe that one can, in the cases for which substituent parameters are available, calculate with relatively good accuracy the protolytic equilibrium constant for any secondary or tertiary hetero-substituted amine.