Evaluation of Substituent Effects on the Enthalpies of Protonation of Amines. An Empirical Formula of Prediction

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An empirical formula is given which enables the enthalpy of protonation of amines to be calculated. The values of the heats of protonation of primary, secondary, and tertiary nitrogen having been fixed, it is necessary to add the positive effects of the carbon atoms or the negative ones of the nitrogen atoms, either charged or uncharged, present in the molecule, to get the enthalpy of protonation of amine. These effects decrease with increasing distance from the nitrogen being protonated. The calculated heats are compared with the experimental values for aliphatic mono- or poly-amines. Only the overall enthalpy of protonation has to be considered for amines containing different primary, secondary, or tertiary amino-groups in the one molecule. The formula can be used to evaluate the effect of other substituents on the heat of protonation of amino-groups. Two examples are given for the $-CO_2^-$ and the $-OH$ group in amino-acids or amino-alcohols.

THERE is interest in the determination of thermodynamic functions for the protonation or deprotonation of amines, amino-acids, and related substances. In solution, the thermodynamic functions of the amino-acids consist of two terms, one concerning the ionization of the acid group and the other the protonation of the amino-group. The electrostatic theory [1] satisfactorily accounts for ΔH and ΔS values of the ionization of carboxylic acids.[2] Schwarzenbach's model deals with protonation of amines.[3] Clark and Perrin [4] suggested a formula for predicting the strength of organic bases. Christensen *et al.*[5] put forward a formula for predicting the enthalpies and entropies of protonation of primary and secondary monoamines. We reported a formula for the calculation of the heats of protonation of aliphatic mono- and di-amines,[6] which we now extend to all aliphatic primary, secondary, and tertiary mono- or poly-amines. This formula also yields the micro-enthalpies [7] of protonation for an amine.

RESULTS AND DISCUSSION

Table 1 reports the prediction formula; the heat of protonation of an amine is equal to a constant α, different according to the type of primary, secondary, or tertiary nitrogen, plus the sum of the effects of the carbon, $\delta(C)$; nitrogen, $\delta(N)$; or charged nitrogen, $\delta(N^+)$ atoms on the enthalpy of protonation. These values were obtained by least-squares fitting of a number of reliable calorimetric data in the literature. They change according to the position in the chain of the reaction centre. An example is given at the bottom of Table 1. The effect of the carbon $\delta(C)$ in position 1 is zero,

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[1] E. J. King, in 'Acid–Base Equilibria,' vol. 4, ed. R. A. Robinson, McMillan, New York, 1965; Topic 15 of the International Encyclopaedia of Physical Chemistry and Chemical Physics, p. 210.

[2] J. J. Christensen, J. L. Oscarson, and R. M. Izatt, *J. Amer. Chem. Soc.*, 1968, **90**, 5949.

[3] G. Schwarzenbach, *Pure Appl. Chem.*, 1970, 307.

[4] J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.

[5] J. J. Christensen, R. M. Izatt, D. P. Wrathall, and L. D. Hansen, *J. Chem. Soc.* (*A*), 1969, 1212.

[6] R. Barbucci, P. Paoletti, and A. Vacca, *J. Chem. Soc.* (*A*), 1970, 2202.

[7] P. Paoletti, R. Barbucci, A. Vacca, and A. Dei, *J. Chem. Soc.* (*A*), 1971, 310.

i.e., the heats of protonation calculated for methylamine ($MeNH_2$), dimethylamine (Me_2NH), and trimethylamine (Me_3N) are equal to α for primary, secondary, or tertiary nitrogen. We have also assumed that $\delta(C)$ decreases with increasing chain length and halves from the fourth position onwards. We make a similar assumption for both $\delta(N^+)$ and $\delta(N)$. The values of these two effects were not calculated for positions 1 and 2 because the available data concern the polyamines with only ethylenic or longer chains between the amino-groups.

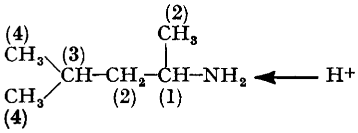
TABLE 1

Predicted heats of protonation/kcal mol^{-1} of amino-groups

Formula of prediction: $-\Delta H = \alpha + \sum_i \delta_i$.

α is 13·250, 11·970, or 8·827 for primary, secondary, or tertiary amines respectively.

Effect of the group	Position of the group relative to the reaction centre 1	2	3	4	5	6	7	8	9	10	11	12
$\delta(C)$	0·000	0·423	0·172	0·061	0·031	0·016	0·008	0·004	0·002	0·001		
$\delta(N)$			−1·751	−0·804	−0·402	−0·201	−0·101	−0·051	−0·026	−0·013	−0·007	−0·004
$\delta(N^+)$			−2·726	−1·457	−0·728	−0·364	−0·182	−0·091	−0·046	−0·023	−0·012	−0·006


$\overset{(4)}{CH_3}\!\diagdown^{(3)} \atop \underset{(4)}{CH_3}\!\diagup$ $CH{-}\underset{(2)}{CH_2}{-}\underset{(1)}{\overset{\overset{(2)}{CH_3}}{|}{CH}}{-}NH_2 \longleftarrow H^+$

Monoamines.—Table 2 shows calculated and experimental heats of protonation for monoamines. Column 4 reports the percentage differences between the calculated and experimental values. The agreement is considered satisfactory. Unfortunately, few heats of protonation for tertiary amines are available.

Diamines.—Table 3 shows calculated and experimental (stepwise and overall) heats for the protonation of symmetric and asymmetric diamines. The agreement is satisfactory for both the stepwise and overall heats of symmetric diamines, but the agreement is good only for the overall heats of asymmetric diamines. We can imagine protonation of these asymmetric diamines by two different routes: first on the primary and then on the secondary (or tertiary) nitrogen, or *vice-versa*. The values obtained are shown in Table 3. The stepwise experimental value agrees with neither of the two calculated heats but is between them. It is a reasonable hypothesis that there is, in every step, a tautomeric equilibrium between a species protonated on the primary nitrogen and one protonated on the secondary or tertiary nitrogen. This hypothesis seems likely for *N*-methylethylenediamine (the primary and secondary nitrogens have similar basicity constants) but is doubtful for *NN*-dimethylethylenediamine (tertiary nitrogen is much less basic than primary [7]). Trends of the stepwise heats could be accounted for by Schwarzenbach's electrostatic model,[3] being applicable to any association of ions in solution (not only to these reactions). By use of this model empirical values of ε_{eff}, the effective dielectric constant and $d\varepsilon_{eff}/dT$ can be calculated from ΔG and ΔH data, but since ε_{eff} and $d\varepsilon_{eff}/dT$ are not known *a priori* we cannot predict the ΔG or ΔH values.

Polyamines.—Primary, secondary, or tertiary nitrogen atoms are often present, simultaneously, in tri-, tetra-, penta-, and hexa-amines. The behaviour of these amines towards protonation is similar to that seen for the asymmetric diamines. The stepwise enthalpies calculated by our formula depend on the particular path so that the calculated values cannot agree with the experimental ones. On the other hand, the sum of the stepwise heats does not depend on the path, so that the overall heats can usefully be compared with experimental values. Some of these data are in Table 4. An example of application of our formula for 1,5,9,13-tetra-azatridecane $H_2N{\cdot}(CH_2)_3{\cdot}NH{\cdot}(CH_2)_3{\cdot}NH{\cdot}(CH_2)_3{\cdot}NH_2$ is reported in Table 5.

TABLE 2

Experimental and calculated heats of protonation, $-\Delta H$/kcal mol^{-1}, of primary, secondary, and tertiary monoamines [a]

	Calc.	Found	Δ%
Primary			
$MeNH_2$	13·25	13·29	−0·29
$EtNH_2$	13·67	13·71	−0·26
Pr^nNH_2	13·85	13·84	0·07
Pr^iNH_2	14·10	13·97	0·93
Bu^nNH_2	13·91	13·98	−0·51
Bu^iNH_2	14·02	13·92	0·70
Bu^sNH_2	14·27	14·03	1·70
Bu^tNH_2	14·52	14·43	0·62
$n\text{-}C_5H_{11}{\cdot}NH_2$	13·94	13·98	−0·29
$Bu^iCH_2{\cdot}NH_2$	13·97	14·03	−0·43
Secondary			
Me_2NH	11·97	12·04	−0·58
Et_2NH	12·82	12·73	0·67
$Pr^n{}_2NH$	13·66	13·55	0·82
Bu^nMeNH	12·63	12·57	0·45
$Bu^n{}_2NH$	13·28	13·66	−2·74
$Bu^i{}_2NH$	13·51	13·38	0·94
$Bu^s{}_2NH$	14·01	14·03	−0·16
$(Bu^iCH_2)_2NH$	13·41	13·39	0·13
Tertiary			
Me_3N [b]	8·83	8·86	−0·36
Et_3N [b]	10·10	10·38	−2·72

[a] The experimental values are those reported in ref. 5 at 25·0 °C and $\mu \to 0$ except as indicated. [b] P. Paoletti, J. H. Stern, and A. Vacca, *J. Phys. Chem.*, 1965, **69**, 3759 at 25·0 °C and μ = 0·1M-KCl.

TABLE 3

Experimental and calculated heats of protonation, $-\Delta H$/kcal mol^{-1}, for symmetric and asymmetric diamines [a]

		Calc.		Found	Δ%
Symmetric [b]					
$H_2N\cdot(CH_2)_2\cdot NH_2$	Step 1	11·92		12·18	−2·12
	Step 2	10·95		10·90	0·42
	Overall	22·87		23·08	−1·34
$H_2N\cdot(CH_2)_3\cdot NH_2$	Step 1	13·04		13·09	−0·36
	Step 2	12·39		12·63	−1·91
	Overall	25·43		25·72	−1·12
$H_2N\cdot(CH_2)_4\cdot NH_2$	Step 1	13·51		13·58	−0·54
	Step 2	13·18		13·16	0·14
	Overall	26·69		26·74	−0·18
$H_2N\cdot(CH_2)_5\cdot NH_2$	Step 1	13·74		13·86	−0·88
	Step 2	13·57		13·41	1·22
	Overall	27·31		27·27	0·14
$H_2N\cdot(CH_2)_6\cdot NH_2$	Step 1	13·85		13·91	−0·40
	Step 2	13·77		13·71	0·45
	Overall	27·62		27·62	0·00
$MeHN\cdot(CH_2)_2\cdot NHMe$ [c]	Step 1	10·70		10·74	−0·34
	Step 2	9·73		9·67	0·60
	Overall	20·43		20·41	0·09
$Me_2N\cdot(CH_2)_2\cdot NMe_2$ [c]	Step 1	7·62		7·40	3·01
	Step 2	6·65		6·64	0·11
	Overall	14·27		14·04	1·63
Asymmetric [c]					
$MeNH\cdot(CH_2)_2\cdot NH_2$	Step 1	N_I 11·98	N_{II} 10·64	11·25	
	Step 2	N_{II} 9·67	N_I 11·01	10·34	
	Overall	21·65	21·65	21·59	0·27
$Me_2N\cdot(CH_2)_2\cdot NH_2$	Step 1	N_I 12·04	N_{III} 7·50	10·42	
	Step 2	N_{III} 6·62	N_I 11·07	8·42	
	Overall	18·57	18·57	18·84	−1·43

[a] At 25·0 °C and μ = 0·5M-KNO_3. [b] Experimental values from ref. 6. [c] Experimental values from ref. 7; N_I, N_{II}, or N_{III} indicate the type of nitrogen (primary, secondary, or tertiary respectively) for which we calculate the enthalpy of protonation.

Possible Extension of the Formula.—Our formula allows one to calculate the influence of other groups such as CO_2^-, $-OH$, $-Cl$, $-CN$, *etc.* if good experimental, preferably calorimetric, data on the protonation of amino-groups are available. As an example we report the heats of protonation of amino-groups in molecules containing CO_2^- groups in Table 6. Column 2 shows the heats calculated by our formula, without accounting

TABLE 4

Experimental and calculated heats of protonation, $-\Delta H$/kcal mol^{-1}, for tri-, tetra-, penta-, and hexa-amines

	No. of protonated nitrogens					
Amine [a]	prim.	sec.	tert.	Calc.	Found	Δ%
den	2	1		30·83	30·35	1·56
dpt	2	1		36·30	35·75	1·52
trien	2	2		38·74	38·64	0·24
tetren	2	3		46·64	47·51	−1·83
tpt	3		1	45·27	44·77	1·11
ptetraen	4		1	50·80	51·90	−2·12

[a] Experimental values are valid at 25·0 °C and μ = 0·1M-KCl except as indicated. den = diethylenetriamine, M. Ciampolini and P. Paoletti, *J. Phys. Chem.*, 1961, **65**, 1224; dpt = 3,3′-diaminodipropylamine, P. Paoletti, F. Nuzzi, and A. Vacca, *J. Chem. Soc.* (*A*), 1966, 1385; trien = triethylenetetramine, P. Paoletti, M. Ciampolini, and A. Vacca, *J. Phys. Chem.*, 1963, **67**, 1065; tetren = tetraethylenepentamine, P. Paoletti and A. Vacca, *J. Chem. Soc.*, 1964, 5051; tpt = 3,3′,3″-triaminotripropylamine, A. Vacca and P. Paoletti, *J. Chem. Soc.* (*A*), 1968, 2378; ptetraen = *NNN′N′*-tetrakis-2-aminoethyl-1,3-diaminopropane, P. Paoletti, R. Walser, A. Vacca, and G. Schwarzenbach, *Helv. Chim. Acta*, 1971, **34**, 243, at μ = 0·1M-KNO_3.

TABLE 5

1st step: assumed protonation on one of the two primary nitrogens

(i) α of primary nitrogen	13·250
(ii) Total effect of the carbon atoms in positions 1, 2, 3, 5, 6, 7, 9, 10, and 11	0·653
(iii) Effect of the amino-groups in positions 4, 8, and 12	−0·859
Total	13·044

2nd step assumed protonation on the other primary nitrogen

(i) + (ii) above	13·903
(iv) Effect of amino-groups in positions 4 and 8	−0·855
(v) Effect of a protonated nitrogen in position 12	−0·006
Total	13·042

3rd step assumed protonation on one of the two secondary nitrogens

(vi) α of secondary nitrogen	11·970
(vii) Effect of the carbon atoms in positions 1, 1, 2, 2, 3, 3, 5, 6, and 7	1·245
(viii) Effect of an amino-group in position 4	−0·804
(ix) Effect of the two protonated nitrogens in positions 4 and 8	−1·548
Total	10·863

4th step, protonation on the last nitrogen

(vi) + (vii) above	13·215
(x) Effect of the three protonated nitrogens in positions 4, 4, and 8	−3·005
Total	10·210

Overall $-\Delta H_{\rm calc}$ = 47·16 kcal mol^{-1}. Overall $-\Delta H_{\rm exp}$ = 47·20 kcal mol^{-1}.[8]

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[8] R. Barbucci, L. Fabbrizzi, and P. Paoletti, *J.C.S. Dalton*, 1972, 745.

for the CO_2^- group, and column 4 shows the difference between $-\Delta H_{calc}$ and $-\Delta H_{exp}$. These differences, that is the effect of the CO_2^- group (in position 2) on the protonation of amine, are near enough to the median value (—2·85). Owing to the very few heats of protonation available for amino-acids with CO_2^- either in position 3 or 4, we can only get the individual values reported at the foot of Table 6 as the effect of a CO_2^- group in these positions. However we observe a decreasing of the effect of the CO_2^- group with the distance.

Table 6

The effect of CO_2^- substitution on the protonation enthalpy, $-\Delta H$/kcal mol^{-1}, of amino-groups [a]

	Calc.	Found	$-\delta(CO_2^-)$ / kcal mol^{-1}	
$H_2N{\cdot}CH_2{\cdot}CO_2$	13·250	10·57 [b]	2·68	
$H_2N{\cdot}CHMe{\cdot}CO_2^-$	13·673	10·91 [c]	2·67	
$H_2N{\cdot}CHEt{\cdot}CO_2^-$	13·845	10·86 [d]	2·98	
$H_2N{\cdot}CMe_2{\cdot}CO_2^-$	14·096	11·57 [d]	2·53	
$H_2N{\cdot}CHPr^i{\cdot}CO_2^-$	14·017	10·73 [d]	3·28	
$H_2N{\cdot}CHBu^n{\cdot}CO_2^-$	13·937	11·05 [e]	2·89	
		Average	2·85	position 2
$H_2N{\cdot}(CH_2)_2{\cdot}CO_2^-$	13·673	11·30 [d]	2·37	position 3
$H_2N{\cdot}(CH_2)_3{\cdot}CO_2^-$	13·845	12·45 [d]	1·39	position 4

[a] Experimental values are valid at 25·0 °C and $\mu = 0$. [b] J. A. Partridge, J. J. Christensen, and R. M. Izatt, *J. Amer. Chem. Soc.*, 1966, **88**, 1649. [c] J. M. Sturtevart, *J. Amer. Chem. Soc.*, 1942, **64**, 762. [d] Ref. 2. [e] P. K. Smith, A. C. Taylor, and E. R. B. Smith, *J. Biol. Chem.*, 1937, **122**, 109.

Table 7 shows a similar calculation to evaluate the effect of an OH group in position 3. The value obtained from amino-alcohols with primary or secondary nitrogen atoms is near to the median value (—1·4), but from amino-alcohols with tertiary nitrogens a far lower value is obtained (—0·5). We are not able to explain this different behaviour, but we have observed that the tertiary amines themselves show large differences between calculated and experimental values.

Table 7

The effect of −OH substitution on the protonation enthalpies, $-\Delta H$/kcal mol^{-1}, of amino-groups

	Calc.	Found	Δ	$-\delta(OH)$ / kcal mol^{-1}
$H_2N{\cdot}(CH_2)_2{\cdot}OH$	13·67	12·04 [a]	1·63	1·63
$H_2N{\cdot}CMe_2{\cdot}CH_2OH$	14·52	12·93 [a]	1·59	1·59
$H_2N{\cdot}CMe(CH_2OH)_2$	14·52	11·93 [a]	2·59	1·30
$H_2N{\cdot}C(CH_2OH)_3$	14·52	11·35 [a]	3·17	1·06
$HN(CH_2{\cdot}CH_2OH)_2$	12·82	10·01 [b]	2·81	1·40
$HNMe{\cdot}CH_2{\cdot}CH_2OH$	12·39	11·06 [b]	1·33	1·33
$Et_2N{\cdot}CH_2{\cdot}CH_2OH$	10·10	9·66 [b]	0·44	0·44
$Me_2N{\cdot}CH_2{\cdot}CH_2OH$	9·25	8·74 [b]	0·51	0·51
$N(CH_2{\cdot}CH_2{\cdot}OH)_3$	10·10	8·16 [b]	1·94	0·65

[a] G. Øjelund and I. Wädso, *Acta Chem. Scand.*, 1968, **22**, 2691 at 25 °C and $\mu = 0{\cdot}05$M. [b] Ref. 5 at 25·0 °C and $\mu = 0$.

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