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ALL-VALENCE ELECTRON CALCULATIONS AND PROTON AFFINITY OF AMINES

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With the recently introduced technique of ion cyclotron resonance (ICR) spectroscopy [1-4], precise values of the intrinsic gas-phase basicity of many compounds became available. Gas-phase basicities are particularly attractive due to the absence of solvent effects which complicate the interpretation of the basicity of compounds. Thus the knowledge of the intrinsic basic strength should help one to identify the effects which are primarily due to solvation and those which are inherent in the protonation reaction itself.

The proton affinity (PA) of a base is defined as the heterolytic bond dissociation energy, D $(B\text{-}H^+)$ for removing a proton from the conjugate acid BH^+

$$BH^+ \rightleftharpoons B + H^+$$
$$D(B-H^+) \equiv PA(B) = \Delta H \qquad (1)$$

Since the energy of a proton at infinite distance is taken as zero, the calculated proton affinity ΔE is given by the energy difference between the neutral and protonated species

$$\Delta E = E_B - E_{BH^+}$$

Previous work has shown that quantum chemical calculations reproduce the experimental trends of the experimental gas-phase acidities of alcohols [4,5,6] and basicities of amines [3,4,6,7]. However, all these studies, at least as far as the amines are concerned deal with a relatively small series excluding the biologically important ones such as piperidine, quinuclidine etc. In doing so the applicability of the quantum chemical calculations is restricted to a relatively narrow range of proton affinities (PA). Therefore it was considered of sufficient interest to test the predictive value of the CNDO/2 [8] and PCILO [9] methods with respect to an extensive series of amines with PA's ranging from that of 2,2,2-trifluoroethylamine to that of $n\text{-}Bu_3N$.

All bond angles were taken as 109.47°. The following bond lengths were used : C-C = 1.54 Å ; C-N = 1.48 Å ; C-H = 1.09 Å ; N-H = 1.0 Å. The $N\text{-}H^+$ bond length was determined from the potential curve $E = f(d_{N-H^+})$ in the neighbourhood of the expected equilibrium distance i.e. between 0.8 Å and 1.2 Å in steps of 0.1 Å. Both the PCILO and CNDO/2 calculations invariably showed this distance to be 1.1 Å which compares favourably with d(N-H) = 1.07 Å obtained from a geometry optimization [3].

The most important results of both theoretical methods are listed in Table 1. Using the AQSARF programme [10] all C^n_r (n=9 ; r=1,2) regression equations with PA as the dependent variable were generated with the following variables : the change of the charge density on the N atom in going from base to protonated species (ΔQ_N), the group charge density $Q_{NH_x}{}^+$, the PCILO calculated polarity difference between B and BH^+ either of the whole molecule $\Delta \Sigma_1^n del(I)$, or that part of the molecule directly involved in the protonation process $\Delta\Sigma\, del(I)\ NH_x{}^+$ and $\Delta\Sigma_1^4 del(I)$ (the summation taken over the four ligands of the N atom), the polarity of the NH^+ bond del(I) NH^+ and the variables listed in Table 1. The analysis yielded the following "best" regression equations

	r	S	F	
$PA = \underset{(45.645)}{0.712}\ \Delta E_{PCILO} - 5.328$	0.997	0.796	2083.4	(2)
$PA = \underset{(25.560)}{0.643}\ \Delta E_{CNDO/2} + 18.911$	0.911	1.413	653.3	(3)
$PA = \underset{(-12.063)}{-0.389}\ HOMO + 347.334$	0.961	2.904	145.5	(4)

where r is the correlation coefficient, S the standard error of the estimate, F the overall statistical significance of the equation and the figures in parentheses the Student's t-test values.

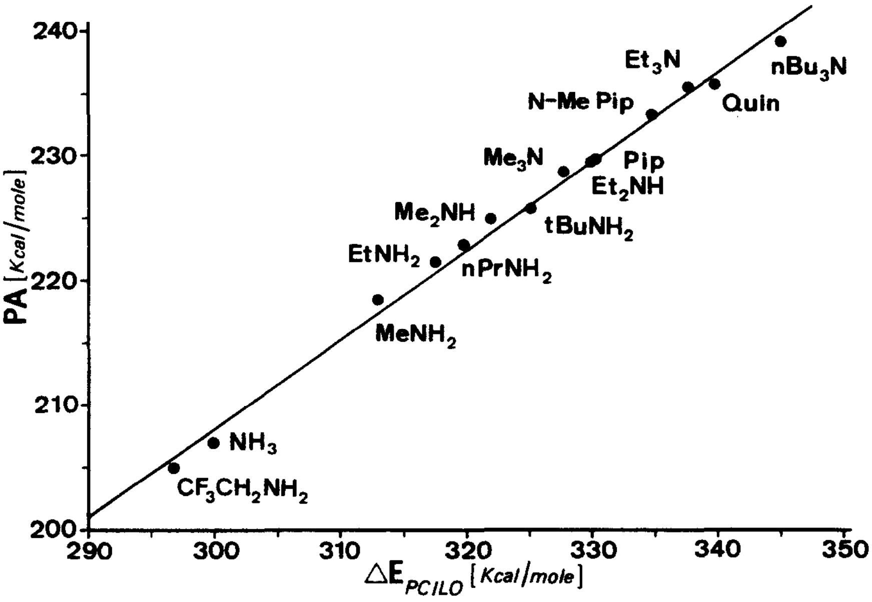
The analysis further revealed PA to be inversely proportional to del(I) NH^+ and $Q_{NH_x}{}^+$ with $r = 0.952$, $S = 3.220$ and $r = 0.902$, $S = 4.542$ respectively. The remainder of the equations either show r values less than 0.88 or not statistically significant.

Comparison of eqs (2) and (3) shows that the PCILO calculations have a much better predictive value than the CNDO/2 calculations. Fig.1 shows the excellent correlation between PA and ΔE_{PCILO}. As can be seen from Fig.1, the primary amines do not appear to deviate from the overall regression line into a separate one as noted by Aue et al. [3] The present results suggest that the ammonia-methylamine PA difference, $\Delta PA = 11.4$ Kcal/mole assigned by Aue et al. [3] is somewhat too large. A more appropriate value of ΔPA thus seems to be ca 9 Kcal/mol. [11, 12]

It is interesting to note that the slopes of eq (2) and (3) are very much smaller than those reported for the CNDO/2 [3] and *ab initio* calculations [3, 7] on the series NH_3, $MeNH_2$, Me_2NH and Me_3N. Equation (4) indicates a rough linear inverse proportionality between PA and the CNDO/2 calculated energies of the HOMO of the amines.

In all cases, except for NH_3 and t-Bu NH_2, the nitrogen atom acquires a net positive charge upon protonation. It should be noted, however, that the tendency of the nitrogen atom to become more positive in the series primary, secondary, tertiary amine with the same alkyl group, is reversed by increasing the size of the alkyl group within a series of primary, secondary or tertiary amines.

The conclusions of an electron population analysis are qualitatively in agreement with a charge-induced dipole moment interaction model [3, 13], in the sense that upon protonation the carbon atoms adjacent to the nitrogen atom become more negative whereas the attached



hydrogen atoms acquire a positive charge.

In summary, the present results indicate that the PCILO calculations perform much better than CNDO/2 calculations in predicting the PA's of a variety of amines.

Table I. Proton affinities, PCILO and CNDO/2 results for amines [a]

Amine	PA [b]	ΔE_{PCILO}	$\Delta E_{CNDO/2}$	HOMO [c]
2, 2, 2-Trifluoro-ethylamine	205	296.69	292.85	347.12
NH_3	207	299.84	294.63	370.03
$MeNH_2$	218.4	312.95	307.90	330.37
$Et\ NH_2$	221.4	317.55	313.0	323.91
n-Pr NH_2	222.8	319.78	315.62	322.28
$Me_2\ NH$	224.8	322.00	317.68	313.30
t-Bu NH_2	225.7	325.25	322.55	308.28
Me_3N	228.6	327.79	325.03	301.69
$Et_2\ NH$	229.4	329.96	326.59	307.53
Piperidine	229.7	330.37	326.83	307.34
N-Methylpiperidine	233.2	334.77	332.56	299.0
Et_3N	235.5	337.73	336.26	290.02
Quinuclidine	235.7	339.91	341.27	277.22
n-Bu_3N	239.1	345.06	344.03	282.24

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[a] All values in Kcal/mole. [b] Taken from ref.4. [c] CNDO/2 calculations

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REFERENCES

1. J.D. Baldeschwieler and S.S. Woodgate, Accounts Chem.Res., 4, 114 (1971).
2. D.H. Aue, H.M. Webb, and M.T. Bowers, J.Am.Chem.Soc., 94, 4726 (1972).
3. D.H. Aue, H.M. Webb, and M.T. Bowers, ibid., 98, 311 (1976).
4. D.H. Aue, H.M. Webb, and M.T. Bowers, ibid., 98, 318 (1976).
5. R.H. Hermann, ibid., 92, 5298 (1970).
6. J.P. Lewis, Tetrahedron, 25, 4117 (1969).
7. W.J. Hehre and J.A. Pople, Tetrahedron Letters, 2959 (1970).
8. QCPE 141 Program, University of Indiana, Bloomington, US.
9. QCPE 220 Program, Ibid.
10. J.P. Tollenaere, H. Moereels, and M. Protiva, Eur.J.Med.Chem. 11, 293 (1976).
11. See note added in proof of ref.3.
12. By taking PA of NH_3 as 209.4 Kcal/mol and excluding $CF_3CH_2NH_2$, the following regression equation obtains : $PA = 0.662\ \Delta E_{PCILO} + 11.029$ ($n = 13$) ; $r = 0.998$; $S = 0.466$; $F = 3613.9$; t-test value = 60.116. Note the remarkable improvement of the standard deviation !
13. J.I. Brauman, J.M. Riveros, and L.K. Blair, J.Am.Chem.Soc., 93, 3914 (1971).