

A calculation of the relative protonation energies of amines in solution

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Relative protonation energies in the primary, secondary and tertiary aliphatic series of amines are calculated by a semiempirical method employing the virtual charge model. The method accounts quite well for the observed differences between the gas-phase protonation affinities and the protonation enthalpies in solution, but when allowance is made for steric shielding from the bulk solvent for “non-edge” atoms, some anomalies in the uncorrected model are removed. The calculated solute-solvent interactions are related to experimental enthalpies of solution and to trends expected from the Born model.

Key words: Virtual charge model—solvation effects—protonation of amines

1. Introduction

Most methods currently employed to perform electronic structure calculations on molecules in solution depend upon one of two approximations. In the *supermolecule approach* [1, 2] the solute molecule, together with a number of neighboring solvent molecules are explicitly included in various relative locations and orientations in a calculation on a system which models a solute molecule within its shells of bound solvent molecules. In a *continuum model* [2–5], on the other hand, the solvent is treated as a polarizable dielectric medium which responds to the charge distribution in the solute molecule by generating a reaction potential which in turn modifies the charge distribution on the solute molecule. The solute-solvent interaction is included in an effective hamiltonian $H(\psi)$ for the

solute molecule, thus defining a non-linear Schrödinger equation $H(\psi)\psi = E\psi$ which is solved iteratively.

Among the applications of continuum methods to account for empirical phenomena are those by Lamborelle and Tapia [6] in their investigation of the stabilities of tautomeric forms of aminoacids. Using self-consistent reaction field theory and the virtual charge model, these authors accounted for the observed reversal of the relative stabilities of the zwitterionic and non-zwitterionic forms of these systems, when their environment was switched from a gaseous to a polar medium, in terms of the polarization of the latter. Since CNDO/2 provides a good description of the proton affinities [7], it would be interesting to test the ability of a medium-polarization method to account for the trends in the experimental protonation energies within and between series of aliphatic amines in a polar solvent, and to compare the results with those expected in the gas phase.

2. Theory

2.1. Constant D

In Constanciel and Tapia's Virtual Charge Model (VCM) [5] to perform MO calculations on species in solution account is taken of solvent effects in an implicit manner by supposing that the molecule is placed in a polarizable cavity in a continuous medium. Each constituent atom A of the molecule, bearing a charge Q_A , polarizes the region of the medium in its immediate vicinity thereby generating a virtual charge Q'_A given by

$$Q'_A = -(1 - D^{-1})Q_A. \quad (1)$$

The "effective dielectronic constant" D of the homogeneous medium in the VCM is assumed to be constant for all atoms A and related to the true dielectric constant ϵ by $D = \sqrt{\epsilon}$.

The authors show that the total energy of a solute molecule in the VCM may be expressed as

$$E_{\text{total}} = E_{\text{solute}}^s + E_1 \quad (2)$$

where E_{solute}^s is the energy of the solute molecule subsystem S within the solvent medium including the interaction between the charges on the solute and the virtual charges, and E_1 the interactions between the virtual charges themselves. Within the framework of the CNDO/2 method [8] these contributions are, explicitly,

$$E_{\text{solute}}^s = \frac{1}{2} \sum_{\mu} \sum_{\nu} P_{\mu\nu} (H_{\mu\nu}^s + F_{\mu\nu}^s) - (1 - D^{-1}) \sum_A \sum_B Z_A Q_B \gamma_{AB} + \sum_{A>B} Z_A Z_B R_{AB}^{-1} \quad (3a)$$

$$E_1 = \frac{1}{2} (1 - D^{-1})^2 \sum_A \sum_B Q_A Q_B \gamma_{AB} \quad (3b)$$

where A and B are atoms of the solute molecule, μ and ν atomic orbitals, Z_A the charge on the core of atom A. The remaining quantities are standard CNDO

notation, except that the solvation-modified elements of the core and Fock matrices, $H_{\mu\nu}^s$ and $F_{\mu\nu}^s$ are obtained from the conventional, solvent-free elements by the addition of the matrix elements of the solvent field operator

$$\hat{G}(S) = (1 - D^{-1}) \sum_A \sum_{\mu}^{\varepsilon A} \sum_B Q_B \gamma_{AB} |\mu\rangle \langle \mu| \quad (4)$$

to each of them.

2.2. Atom-dependent D

An improvement in the theory might be expected to result from the lifting of the restriction which assigns the same value of effective dielectric constant to each atom in the molecule. An atom with a large number of neighboring atoms should be "shielded" from the solvent medium to a greater extent than one with a small number of neighbors.

In his model to account for the destabilization of the α -helical conformation by a polar solvent Hopfinger [9] recognized a specific solvent environment for each atom depending on its position and on the local conformation of the chain. The contribution of an atom to the free energy of solvation of the molecule is reduced if its declared "volume of solvation" overlaps the van der Waals shells of other atoms. We can similarly take account of the inhomogeneous environment of a given atom A by assigning to it an effective dielectric constant D_A which depends on the position of A in the molecule and thus its degree of exposure to the solvent medium. A reasonable expression for D_A might be

$$D_A = \alpha_A D_s + (1 - \alpha_A) D_m \quad (5)$$

where α_A is the fractional solid angle subtended by the unobscured part of the solvent at atom A, while D_s and D_m are respectively the dielectric constants of the bulk medium (as in 2.1) and of the interior of the molecule. We decide on a value of 1.0 for D_m since interactions between atom A and the rest of the molecule are explicitly included in the calculation.

The total energy is still expressed by (2) but since the fundamental VCM Eq. (1) is now replaced by

$$Q'_A = -(1 - D_A^{-1}) Q_A \quad (6)$$

all the terms in (3) and (4) arising from the virtual charge must be modified in the same way, giving

$$E_{\text{solute}}^s = \frac{1}{2} \sum_{\mu} \sum_{\nu} P_{\mu\nu} (H_{\mu\nu}^s + F_{\mu\nu}^s) - \sum_A Z_A \sum_B (1 - D_B^{-1}) Q_B \gamma_{AB} + \sum_{A>B} Z_A Z_B R_{AB}^{-1} \quad (7a)$$

$$E_1 = \frac{1}{2} \sum_A (1 - D_A^{-1}) Q_A \sum_B (1 - D_B^{-1}) Q_B \gamma_{AB} \quad (7b)$$

$$\hat{G}(S) = \sum_A \sum_{\mu}^{\varepsilon A} \sum_B (1 - D_B^{-1}) Q_B \gamma_{AB} |\mu\rangle \langle \mu|. \quad (8)$$

2.3. Rules for solvent screening

The explicit calculation of fractional solid angles α_A as defined in 2.2 requires the use of some uncertain atomic radii and consequently quite lengthy computations. We feel that as a first measure the nature of the method proposed in this work is satisfied by estimating the degree of exposure of each atom to the solvent simply from the number and nature of the groups attached to it.

For the amine systems considered here we use the following rule to calculate α_A in (5):

- (1) A hydrogen atom does not screen an atom bonded to it;
- (2) A non-hydrogen atom screens each directly-bonded atom by 20%.

Thus, in triethylamine $\text{NEt}_2\text{C}^a\text{H}_2\text{C}^b\text{H}_3$ for example, we have

$$\alpha(\text{N}) = 0.4, \quad \alpha(\text{C}^a) = 0.6, \quad \alpha(\text{C}^b) = 0.8, \quad \alpha(\text{H}) = 0.8.$$

3. Results

3.1. Basicity parameter

The relationship between the protonation enthalpy in solution $\Delta H_p^{(s)}$ and the gas-phase basicity of the amine base PA is given by Aue et al. [10] as

$$\Delta H_p^{(s)} = -\text{PA} + \Delta H_s(\text{BH}^+) - \Delta H_s(\text{B}) - \Delta H_s(\text{H}^+) \quad (9)$$

where the ΔH_s terms are the solution enthalpies of the species indicated. Experimental values of $\Delta H_p^{(s)}$ and PA for the first few straight-chain members of the primary, secondary and tertiary amines (taken from Table 1 of Ref. [10]) are listed in the first two numerical columns of (our) Table 1. Since the solvation enthalpy difference between an amine and its protonated product amounts to $\sim 50 \text{ kcal mol}^{-1}$, while there is a large negative contribution from $\Delta H_s(\text{H}^+)$, it is not surprising that the absolute values of $\Delta H_p^{(s)}$ and of PA differ by an order of magnitude.

A comparison of the trends between and within the primary, secondary and tertiary series shows that while the order of the gas-phase basicities is $|\text{PA}(\text{RNH}_2)| < |\text{PA}(\text{R}_2\text{NH})| < |\text{PA}(\text{R}_3\text{N})|$ with the order within each series being $\text{Me} < \text{Et} < \text{n-Pr} < \text{n-Bu}$, the effect of solvation is to reverse the order of the three series, while *retaining* the internal order of the alkyl groups R, increasing from Me to n-Bu. In order to find whether this effect is revealed also in CNDO calculations on these systems we need a measure of the relative basicities of the 12 amines that can follow from the CNDO results. For this purpose we simply define the ‘‘protonation energy’’ ΔE_p as the total energy of the protonated amine BH^+ relative to that of the amine:

$$\Delta E_p = E(\text{BH}^+) - E(\text{B}). \quad (10)$$

3.2. Gas phase basicities

The third numerical column of Table 1 lists the ‘‘*in vacuo*’’ protonation energies computed by applying (10) to the results of the conventional ($D=1$) CNDO

Table 1. Experimental and calculated protonation data on amines (experimental values taken from Aue et al. [10])

Amine	(B)	PA	$\Delta H_p^{(s)}$ (kcal mol ⁻¹)	Exptl. protonation energies (aq. soln)	Calculated protonation energies, $-\Delta E_p$ (a.u.)				VCM solvation energy (a.u.)			
					No solvation (D = 1)	No solvent screening (D = 5)	Solvent screening (D = 10)	Measured solvation enthalpies (kcal mol ⁻¹)	No solvent screening (D = 5)	Solvent screening (D = 10)	$-\epsilon(B)$	$-\epsilon(BH^+)$
MeNH ₂		218.4	13.18	0.4794	0.6497	0.6545	10.82	75.4	0.0126	0.1291	0.0125	0.1876
EtNH ₂		221.4	13.71	0.4912	0.6523	0.6567	13.05	75.2	0.0143	0.1262	0.0140	0.1795
n-PrNH ₂		222.8	13.84	0.4953	0.6526	0.6570	13.37	74.2	0.0150	0.1251	0.0147	0.1763
n-BuNH ₂		223.3	13.98	0.5027	0.6528	0.6571	14.11	74.6	0.0152	0.1244	0.0148	0.1741
Me ₂ NH		224.8	12.04	0.4947	0.6491	0.6539	12.69	69.7	0.0105	0.1202	0.0098	0.1689
Et ₂ NH		229.4	12.73	0.5105	0.6509	0.6550	15.31	68.4	0.0132	0.1158	0.0123	0.1568
n-Pr ₂ NH		231.4	13.17	0.5173	0.6512	0.6553	17.16	68.8	0.0145	0.1140	0.0135	0.1515
n-Bu ₂ NH		232.5	13.66	0.5206	0.6514	0.6554	18.81	69.9	0.0149	0.1127	0.0138	0.1486
Me ₃ N		228.6	8.82	0.5059	0.6479	0.6520	13.23	63.3	0.0088	0.1128	0.0074	0.1534
Et ₃ N		235.5	10.32	0.5236	0.6490	0.6522	16.76	61.4	0.0126	0.1075	0.0109	0.1395
n-Pr ₃ N		237.7	10.50	0.5317	0.6494	0.6528	—	—	0.0144	0.1053	0.0153	0.1334
n-Bu ₃ N		—	—	0.5358	0.6497	0.6530	—	—	0.0148	0.1037	0.0127	0.1229

method on the 12 amines and their protonation products. Because of uncertainties of the precise geometries of the alkyl groups all of them have been taken to be in all-*trans* conformations, although there is evidence that conformations are solvent-dependent [9, 11] and also that the protonation of an amine group may alter its conformation (see Ref. [6] for discussion and further references). However we assume that such changes are sufficiently systematic for Eq. (10) still to provide a valid comparison of energy changes. We observe that the $-\Delta E_p$ trend follows that of the PA values, to the extent of increasing in the direction primary to secondary to tertiary, and reproducing the order of the groups, $\text{Me} < \text{Et} < \text{n-Pr} < \text{n-Bu}$ within each series. In both experimental and calculated values there is a tendency for an incomplete separation of the values between the three series, which follows from the relatively low values for the methyl compounds in each series.

3.3. Solution basicities: Unscreened-solvent VCM

For the calculation of the basicities in aqueous solution it must be borne in mind that the procedures described in Sect. 2 do not fix the value of the solvent polarity parameter D or D_s unambiguously. The use of $D = \sqrt{\epsilon} \approx 9$ based on the bulk dielectric constant for water may not be appropriate for effects involving the immediate solute environment, even with the solvent-screening corrections described in Sects. 2.2 and 2.3. We therefore calculated basicities in solution using a range of D values from 1.0 to somewhat beyond the “bulk water” value of 9 in order to allow for the uncertainty in D and to investigate the effect of gradually increasing the dielectric constant.

The basicities calculated as the protonation energies ΔE_p by the solvent-unscreened VCM method of Constanciel and Tapia (Sect. 2.1) are plotted, relative to MeNH_2 , against the solvent polarity parameter D in Fig. 1. The curves clearly show how the order of the basicities of the three amine series in the gas phase is changed in a polar medium, eventually (at $D \approx 3$) reversing as the polarity of the environment increases, while retaining the order of the alkyl groups Me to n-Bu within each series. This result is in agreement with the trend of the experimental PA and (aqueous) $-\Delta H_p^{(s)}$ values evident in Table 1, thus providing encouraging support for the VCM method. However a comparison of the ΔE_p values in the polar region with the experimental solution protonation enthalpies $\Delta H_p^{(s)}$ shows that while the measured basicities of the secondary and tertiary amines are distinct, our calculated values (ΔE_p) show a separation of these two series which is not quite (but almost) complete. Also, although the experimental basicities of the primary and secondary amines do not separate completely, the reference primary amine MeNH_2 is found within the range of the secondary, not the tertiary amines as the VCM method predicts.

3.4. Solvent-screened VCM

We next tried the solvent-screening method described in Sect. 2.2 and 2.3, and summarize the results in Fig. 2. There is still no obvious value at which to fix

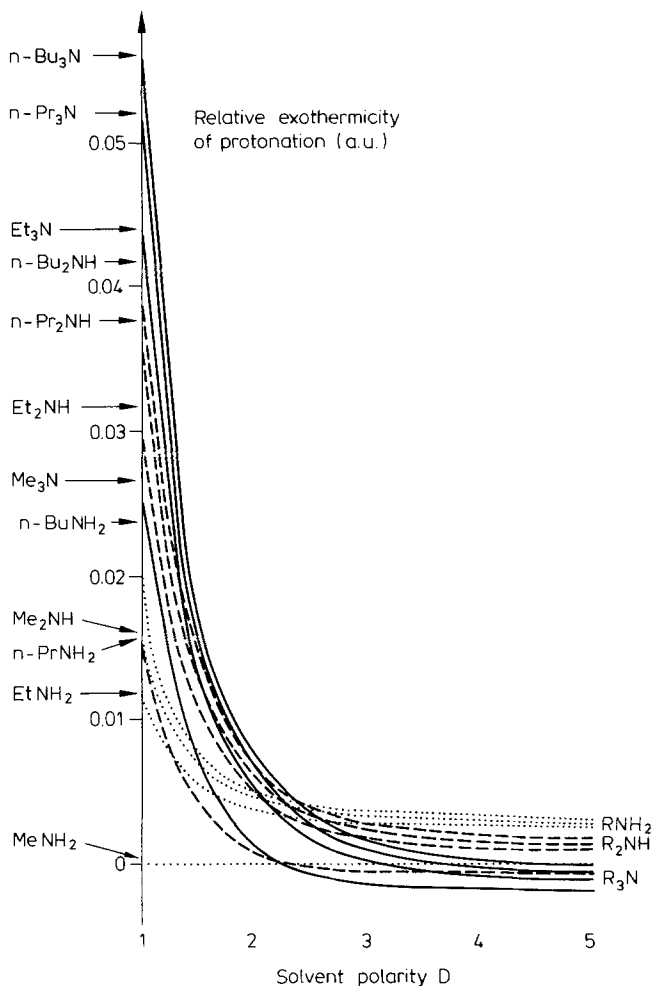


Fig. 1. Relative values of the unscreened-VCM-calculated protonation enthalpies $-\Delta E_p$, with respect to that for methylamine, as a function of the polarity parameter D . There is no significant change in the curves beyond the D range shown

D_s , but it is reasonable to suppose that since less assumptions are now being made about the continuous nature of the solvent medium (by explicitly modifying the dielectric constant in the immediate environment of the solute) the D_s value might be closer to that measured for the bulk solvent.

Fig. 2 shows the results of the solvent-screening calculations. The order of the relative ΔE_p values is now sensitive to a greater range of D_s , and the figure shows that at the "bulk-water" value (≈ 9) the order of the calculated basicities is almost exactly that of the experimental protonation energies in aqueous solution, $\Delta H_p^{(s)}$: the secondary and tertiary amines are now separated, and ΔE_p for the reference molecule MeNH_2 is close to that for $n\text{-Pr}_2\text{NH}$, in agreement with the $\Delta H_p^{(s)}$ data.

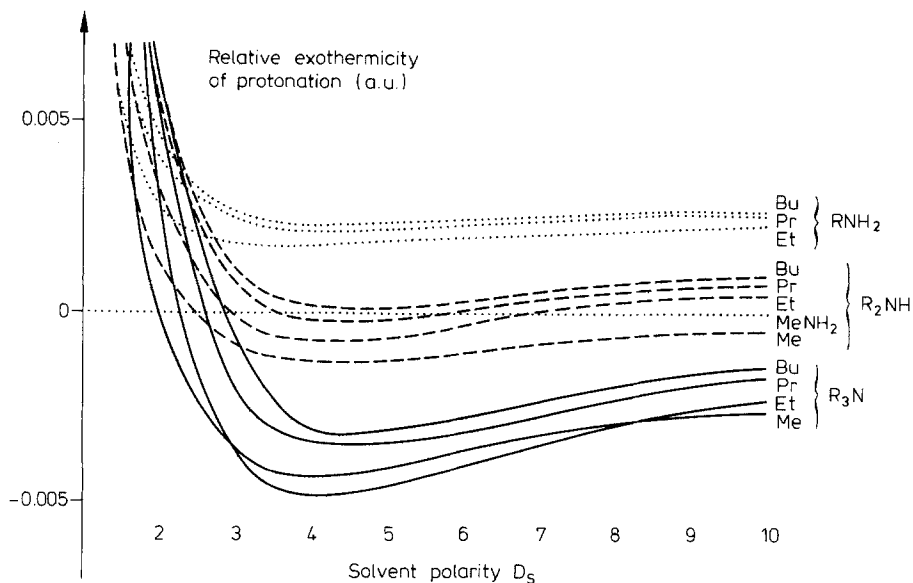


Fig. 2. Relative enthalpies as in Fig. 1 but with solvent screening

3.5. Solvation energies

In the second half of Table 1 the effects on the experimental solvation enthalpies ΔH_s of changing the alkyl group in the three amine series, are shown. Aue et al. [10] discuss the increase in $-\Delta H_s(B)$ with lengthening the chain in terms of the greater hydrophobic interactions in a long alkyl chain. They account for the diminishing $-\Delta H_s(BH^+)$ values with chain length by representing the protonated amines by the Born model [12] of a charged spherical ion in a continuous medium, with corrections made for the hydrophobic interactions.

The quantities (B) and (BH^+) listed in the table represent the change in the total energies of the amines B on solvation as implied by Eq. (2). We note that the opposite trends of the solvation enthalpies for the unprotonated and protonated amines is reproduced by both versions of the VCM method, thus supporting the validity of the Born model in both the latter theory and in the interpretation of the $\Delta H_s(B)$ and $\Delta H_s(BH^+)$ trends in Ref. [10].

4. Discussion

The virtual charge model predicts the inversion of the relative protonation energies of the primary, secondary and tertiary amines on switching their environment from a gas to a dielectric medium, while retaining the order of the alkyl groups within each series. The agreement of this result with experiment, as well as the correct prediction of the trends in solvation energies for the protonated

and unprotonated amines, supports the validity of representing the solute-solvent interaction (in these systems at least) as a polarization of the medium by point charges on the atoms. Such an interaction can thus embrace polarization effects which are sometimes described more specifically in hydrogen bonding, non-bonded interactions, etc. between the solute and its neighboring solvent molecules. In this respect our results are consistent with the conclusions of Terryn et al. [13] who performed CNDO/2 calculations on a system consisting of amine molecules in spherical cavities within a solvent continuum.

A small improvement is seen to obtain when account is taken of the different exposure to the bulk solvent of the atoms in different parts of the molecule. While the application of the principles discussed in the present work has been to amines constituting simple models of more complex biomolecules we might expect more pronounced effects in systems whose sizes and structures facilitate the steric shielding of a more substantial proportion of atoms from the effects of the bulk solvent. For example Sinanoğlu and Abdulnur [14] discuss the double-helix-stabilizing effect of water as a solvent for DNA, in comparison with less polar solvents which tend to dissociate the structure into two random coils. They explain the effect as a lower surface energy which is required to create one cavity than that to create two smaller cavities in the solvent medium—an effect which is more pronounced in a more polar medium than in a less polar one. In order to account for such a solvation effect by a continuum-type quantum chemical method, it would be essential to recognize the different environments of atoms within, and on the outside of, the polynucleotide chain. The same remarks apply to proteins, whose tertiary structures (chain configurations) and quaternary structures (inter-chain associations) are highly, and anisotropically, solvent dependent.

Acknowledgment. We should like to thank Dr. R. Constanciel for helpful advice and Professor R. Daudel and Dr. O. Chalvet for discussions, hospitality and the use of computing facilities and programs during the stay of one of us (D.A. M.-B.) at the C.M.O.A. in Paris. We should also like to acknowledge a maintenance grant (for D.M.D.) from An Roinn Oideachais.

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Received July 21, 1983