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Theoretical Study on the Protonation of AZA-Aromatics

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The protonation of azanaphthalenes and azabenzenes has been studied theoretically using CNDO/2 wavefunctions and perturbation theory in order to examine the correlation between pK_a values and quantum-mechanical quantities.

Key words: Aza-aromatics, protonation of ~

1. Introduction

Much attention has been given in the past to the theoretical study of protonation reactions [1–3]. These early works were rather limited, because of the use of very simplified methods, mainly π-electron theories. In the last ten years, however, more advanced methods have become available, semi-empirical as well as *ab initio*, which have been used for a study on this subject [4–9]. In this paper we present the results of a theoretical study on the protonation of aza-aromatics. This study, which is based on the CNDO/2 method and perturbation theory, is concerned with the correlation between the experimentally determined pK_a values of the azanaphthalenes [10] and the theoretical calculations.

2. Theory

The energy change in solution (ΔE_l) accompanying the proton transfer reaction

$$RH^+ \rightarrow R + H^+ \tag{1}$$

can be calculated from the gas phase protonation energy ΔE_g and the solvation energy terms E_s as follows:

$$\Delta E_l = -\Delta E_g + E_s(R) - E_s(RH^+) + E_s(H^+) \tag{2}$$

where ΔE_g is defined by:

$$\Delta E_g = E_g(RH^+) - E_g(R)\,. \tag{3}$$

In our study ΔE_g has been calculated quantum-mechanically (see below). The solvation energies of R and RH^+ are obtained using the classical model of Hylton *et al.* [11] and $E_s(H^+)$ is a constant known from experiment.

In view of the large size of the molecules to be studied, ΔE_g has been determined using the CNDO/2 method [12–14] and perturbation theory. This calculation has been carried out in three steps.

First we have performed a CNDO/2 calculation on the neutral molecule R in order to obtain $E_g(\mathrm{R})$ and the corresponding wave-function. In the second step the position of the proton has been determined by calculating the molecular electrostatic potential [15] of the molecule R, following a procedure similar to that of Petrongolo and Tomasi [16]. The electrostatic potential gives a first order approximation of ΔE_g, commonly called the Coulomb energy (E_C). By evaluating E_C at several points in space one or more minima may be found which correspond – to first order – to the sites of protonation in the molecule. This type of calculation is much less time consuming than minimization of $E_g(\mathrm{RH}^+)$ by a full CNDO/2 calculation.

In the final step – with the proton placed at one of the E_C minima – we have first carried the perturbation approach – of which E_C is the first order term – to higher order. In this way we obtain the induction energy E_I, resulting from polarization of the molecular charge distribution in the field of the proton [17, 18]. It has been shown that reliable values for E_I can be obtained, employing a slightly modified second order energy expression based on Brillouin-Wigner perturbation energy [19] (see Ref. [18] for further details). Secondly, polarization as well as charge transfer is taken into account by performing a CNDO/2 calculation on the protonated species, giving $E_g(\mathrm{RH}^+)$. Subtracting $E_g(\mathrm{R})$ from $E_g(\mathrm{RH}^+)$ we obtain the gas phase protonation energy ΔE_g.

However, it is well known that these protonation energies are overestimated by the CNDO/2 method [4, 16]. Since they appear to be about 4/3 times as large as the corresponding energies obtained from minimal basis set *ab initio* calculations, we have scaled down our ΔE_g values by a factor 3/4.

Having determined the various terms which contribute to ΔE_l, the energy change in solution, it is necessary to make some assumptions before we can correlate ΔE_l with experimental $\mathrm{pK_a}$ values. At 298 °K the latter are related to the free energy difference in solution (ΔG_l) as follows:

$$\Delta G_l = -RT \ln K_a = 1.36\ \mathrm{pK_a} \tag{4}$$

where ΔG_l is in kcal/mole.

If we assume that, apart from a symmetry factor, the entropy difference of the reaction is constant and that changes in volume can be neglected, Eq. (4) reduces to:

$$\Delta E_l = 1.36\ \mathrm{pK'_a} + \text{constant} \tag{5}$$

where $\mathrm{pK'_a}$ incorporates the symmetry factor mentioned above ($\mathrm{pK'_a} = \mathrm{pK_a} - 0.30$ for the symmetrical diazanaphthalenes and $\mathrm{pK'_a} = \mathrm{pK_a}$ otherwise). Since the solvation energy of the proton ($E_s(\mathrm{H}^+)$) is also constant, it is convenient to rewrite Eq. (5) as:

$$-\Delta E = 1.36\ \mathrm{pK'_a} - E_s(\mathrm{H}^+) + \text{constant} \tag{6}$$

where ΔE is defined by [cf. Eq. (2)]:

$$\Delta E = \Delta E_g - E_s(\mathrm{R}) + E_s(\mathrm{RH}^+) \tag{7}$$

3. Results and Discussion

A difficulty in our calculations for the 12 azanaphthalenes is that the molecular structure is not known for all of them. We therefore assumed the "benzene" geometry for all molecules: $R_{CC} = R_{CN} = R_{NN} = 1.397$ Å, $R_{CH} = 1.084$ Å and all angles 120°.

The results of the calculations are shown in Table 1 (for atom numbering see Fig. 1). Using these results we have examined how the pK_a' values correlate with E_C, $E_C + E_I$, ΔE_g, and ΔE in order to establish the relative importance of these terms.

Table 1. Protonation energy terms for azanaphthalenes. All energies in kcal/mole

Compound	No.		$-E_C$	$-E_I$	$-\Delta E_g$ [a]	$-\Delta E$	pK_a' [b]
Cinnoline (1,2-diazanaphthalene)	1	α	88.35	75.00	256.41	290.85	2.27
		β	87.66	70.43	253.50	288.76	
Quinazoline (1,3-diazanaphthalene)	2	α	91.30	73.09	261.72	296.46	3.43
		β	85.84	72.17	256.96	292.34	
Quinoxaline (1,4-diazanaphthalene)	3		77.44	74.20	258.17	293.12	0.26
1,5-naphthyridine (1,5-diazanaphthalene)	4		88.23	75.16	259.88	295.27	2.61
1,6-naphthyridine (1,6-diazanaphthalene)	5	α	81.19	74.32	261.41	297.02	3.78
		β	83.32	70.87	258.44	294.00	
1,7-naphthyridine (1,7-diazanaphthalene)	6	α	78.75	73.79	260.06	295.57	3.63
		β	82.33	70.53	257.39	292.99	
1,8-naphthyridine (1,8-diazanaphthalene)	7		103.10	74.37	262.67	297.42	3.09
Phthalazine (2,3-diazanaphthalene)	8		81.08	70.41	257.44	292.19	3.17
2,6-naphthyridine (2,6-diazanaphthalene)	9		88.23	71.41	256.68	293.21	3.18
2,7-naphthyridene (2,7-diazanaphthalene)	10		90.11	71.56	257.69	294.04	3.43
Quinoline (1-azanaphthalene)	11		82.96	72.18	263.78	298.60	4.94
Isoquinoline (2-azanaphthalene)	12		96.26	72.99	258.93	294.10	5.40

[a] these values have been scaled down by a factor 3/4 (see text)

[b] for pK_a values see Ref. [10]

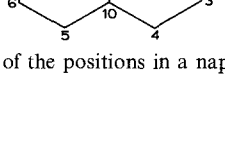

Fig. 1. Numbering of the positions in a naphthalene molecule

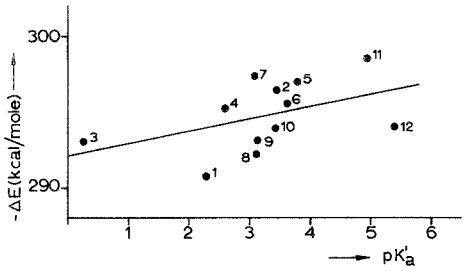

Fig. 2. Correlation between ΔE and pK'_a for azanaphthalenes. The numbers in the figure correspond to the numbers in Table 1

If we consider the Coulomb energy E_C we find hardly any correlation with pK'_a, the correlation coefficient c being 0.35. Especially the large Coulomb energy of 1,8-naphthyridine is striking. The correlation becomes even worse if we include the induction energy E_I: $c = 0.23$. The protonation energy in the gas phase ΔE_g gives a correlation with the pK'_a values slightly better than that of the Coulomb energy ($c = 0.41$).

Inclusion of the solvation energy terms gives a further improvement ($c = 0.46$). The correlation line corresponding to ΔE is shown in Fig. 2. The slope of this line is 0.82 which is somewhat less than the expected value of 1.36 [cf. Eq. (6)]. The intercept is 292.1 kcal/mole. This should be approximately equal to the solvation energy of the proton, as we expect the constant in Eq. (6) not to be larger than 10 kcal/mole [20]. Since the solvation energy of the proton is 261 kcal/mole [21], one may infer that the adjustment of ΔE_g (based on minimal basis set *ab initio* calculations) still leads to slightly overestimated protonation energies (cf. Ref. [9]).

Although ΔE gives a better correlation than E_C, $E_C + E_I$ or ΔE_g, the final correlation ($c = 0.46$) is not satisfactory. We will now consider some possible sources of error which may be responsible for this poor correlation.

a) We have placed the proton at the minimum of the Coulomb energy. In further calculations this position is not changed, though we might expect the optimized geometry of the protonated molecule to be different, not only with regard to the proton position, but also as a consequence of some deformation of the reacting molecule. However, it would cost a tremendous amount of computation time to find this geometry.

b) Another, perhaps a more serious, error is that for all molecules we have used the "benzene" structure, which may differ considerably from the experimental structure. We have investigated this error by performing similar calculations on four azabenzenes for which the experimental structure is known [22–25]. The various contributions to ΔE for both the "benzene" structure and the experimental structure have been determined in the same way as before.

The results are given in Table 2 and Fig. 3. From the correlation lines given in Fig. 3, which refer to ΔE versus pK'_a, it is seen that the influence of the structure is surprisingly small as far as the slope is concerned, both slopes being 0.89. However, the correlation coefficients differ considerably – $c = 0.70$ and

Table 2. Protonation energy terms for azabenzenes. All energies in kcal/mole

Compound	No.	$-E_C$	$-E_I$	$-\Delta E_g$ [c]	$-\Delta E$	pK'_a [d]
Pyridine	13[a]	83.77	67.83	252.36	297.49	5.23
(1-azabenzene)	13[b]	83.59	67.33	245.78	290.94	
Pyridazine	14[a]	84.65	68.96	246.31	291.02	2.03
(1,2-diazabenzene)	14[b]	81.08	66.33	241.98	287.18	
Pyrimidine	15[a]	83.71	68.96	249.08	294.68	1.00
(1,3-diazabenzene)	15[b]	77.50	67.96	242.50	288.08	
Pyrazine	16[a]	78.56	68.78	247.17	292.75	0.35
(1,4-diazabenzene)	16[b]	70.91	66.58	240.26	286.10	

[a] "benzene" structure

[b] experimental structure

[c] these values have been scaled down by a factor 3/4 (see text)

[d] for pK_a values see [28]

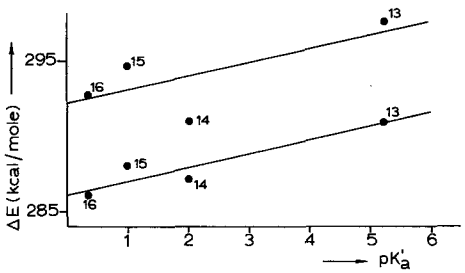

Fig. 3. Correlation between ΔE and pK'_a for azabenzenes. The upper line corresponds to the azabenzenes with "benzene" geometry, the lower line to the azabenzenes with experimental geometry. For numbering see Table 2

$c = 0.93$ – thus underlining the importance of the use of experimental geometries.

This difference in correlation coefficients is mainly due to the large deviation found for pyridazine ("benzene" structure). This is not surprising, since the departure from the "benzene" structure will be most pronounced when two nitrogen atoms are attached to each other. In the case of diazanaphthalenes the same phenomenon may be noticed for cinnoline and phthalazine (see Fig. 2).

Reasonable correlations for azabenzenes (experimental structure) are also obtained between pK'_a and E_C, $E_C + E_I$ and ΔE_g: $c = 0.84$, $c = 0.84$ and $c = 0.95$ respectively. These results indicate that for correlation with pK'_a values within a given series the induction and solvation energy terms are relatively unimportant.

It is seen from Fig. 2 and Fig. 3 that the correlation line of the azanaphthalenes and that of the azabenzenes ("benzene" structure) nearly coincide (as they should): both lines have the same intercept (292.1 kcal/mole) and about the same slope (0.82 and 0.89 respectively). This would not be the case if the solvation energy – which is largely dependent on the size of the molecules – had been omitted, a fact which has been noted before [26].

c) In the case of the asymmetrical diazanaphthalenes an additional difficulty is the fact that two different protonation sites are possible (we have always used the lowest energy value for our correlations). For cinnoline and quinazoline our results clearly indicate position 1 (the α-position) as the most favourable site of protonation. However, for 1,6- and 1,7-naphthyridine the Coulomb energy favours position 6 and 7 respectively (the β-position), whereas according to ΔE_g and ΔE, protonation will take place at the α-position. A similar discrepancy between E_C and ΔE_g is sometimes encountered in *ab initio* calculations (see e.g. the results for cyclopropene in Ref. [27]).

Experimental work to determine the actual site of protonation is in progress.

4. Conclusions

Our calculations on azanaphthalenes have resulted in a rather poor correlation between ΔE and pK_a'. However, similar calculations on azabenzenes have shown that to a large extent this may be due to the lack of experimental geometries in the former case.

For correlation with pK_a' values within a series of structurally similar molecules one should use either the Coulomb energy or – preferably – the gas phase protonation energy. The induction and solvation energy terms have been shown to be relatively unimportant.

With regard to the site of protonation in the asymmetrical diazanaphthalenes our results indicate that for cinnoline and quinazoline the α-position is the most favourable site of attack. However, for 1,6- and 1,7-naphthyridine the present results are not conclusive.

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