A Structure–Reactivity Relationship for the Basicity of Aza-arenes

Jens Spanget-Larsen
Royal Danish School of Educational Studies, Department of Chemistry, Emdrupvej 115 B, DK-2400 Copenhagen NV, Denmark

A semi-empirical reactivity index for the simple prediction of nitrogen basicities (pK_a values) of aza-arenes is presented, based on the concept of an effective potential W for the valence electrons on aza-nitrogen. Analysis of results for aza-benzenes and -naphthalenes indicates that the basicities are highly sensitive to intramolecular long range effects.

One of the most important chemical properties of aza-aromatic compounds such as pyridine, quinoline, *etc.*, is their ability to act as proton acceptors. This property is associated with the so-called non-bonding pair of electrons at the aza-nitrogen position and is reflected by the basic character of many of these compounds and by their ability to participate in hydrogen bonding. Considerable interest has been devoted to the problem of establishing a correlation between the electronic structure of an aza-aromatic compound and its pK_a value.[1–6] However, the results of a number of investigations seem to indicate that a first order 'reactivity index' does not exist.[5,6] In this communication, a promising approach towards solution of this problem is outlined. A simple reactivity parameter is discussed, which allows the prediction of relative pK_a values for a series of aza-arenes to the accuracy of *ca.* 0.5 pK_a units, with differentiation between individual sites of protonation for polyaza-compounds.

Theory

It is frequently assumed that the relative pK_a values for aza-aromatic compounds are determined by the relative proton affinities, and that the proton affinity associated with a particular aza-position is closely related to the electrostatic potential of the molecule in the region of this position.[4–7] In the present investigation, we shall assume that the proton affinity of an aza-arene can be related to the effective potential energy of the valence electrons on aza-nitrogen: the lower the potential energy of the valence electrons, the less energy is released when the H^+ ion is attached. The effective atomic potential can be interpreted as measuring the ease of partly removing an electron from the centre in question; the potential should thus correspond to the negative of the local binding energy of a valence electron on aza-nitrogen.[8] This assumption is supported by the results of Brogli *et al.*,[3] who established a correlation between the pK_a value and mean nitrogen lone-pair ionization energy for aza-benzenes and -naphthalenes.

According to the data of Karlsson and Mårtensson,[9] the valence state binding energy of a $2p$ electron on a free nitrogen atom can be set equal to 13.94 eV (1 eV $\approx$ 96.48 kJ mol^{-1}). In the molecule, the effective binding energy is modified as a result of the interaction with the molecular surroundings. The effective potential W_μ^A for an atomic orbital μ on atom A can generally be considered as a function of all gross atomic valence populations in the molecule.[8] The first term in equation (1)

$$W_\mu^A = W_\mu^A(q_A) + \sum_{B \neq A} W_\mu^A(q_B) \qquad (1)$$

relates W_μ^A to the gross population q_A of atom A, and the summation term relates W_μ^A to the population of all other

centres. The functional form of $W_\mu^A(q_A)$ used in this study is the one suggested by Linderberg and Öhrn.[10] The constants a

$$W_\mu^A(q_A) = -(a + b\,q_A)^{\frac{1}{2}} \qquad (2)$$

and b are determined by adjustment to 'observed' valence-state binding energies[9] for the neutral atom A and the atomic ions A^+ and A^-. The constants are adjusted such that complete agreement is obtained for the neutral atom, while the energies for the positive and negative ions are approximated according to a least squares criterion. The resulting function for the $2p$ electrons on nitrogen is given by equation (3) with the function

$$W_{2p}^N(q_N) = -(25.0560 - 2.8528\,q_N)^{\frac{1}{2}} \qquad (3)$$

values of equations (4). Empirical valence-state binding

$$\begin{aligned} W_{2p}^N(4) &= -29.95 \text{ eV } (29.12 \text{ eV}) \\ W_{2p}^N(5) &= -13.94 \text{ eV } (13.94 \text{ eV}) \\ W_{2p}^N(6) &= -2.70 \text{ eV } (0.80 \text{ eV}) \end{aligned} \qquad (4)$$

energies[9] are given in parentheses. Corresponding functions for the s and p type valence orbitals of H, C, N, O, and F are found in the literature.[8] The last term in equation (1) relates W_μ^A to the deviations from electroneutrality on the remaining centres [equation (5)]. Z_B^{core} is equal to the number of valence electrons

$$W_\mu^A(q_B) = \gamma_{AB}\,(q_B - Z_B^{core}) \qquad (5)$$

in the neutral atom B and γ_{AB} represents the Coulomb repulsion between a valence electron on atom A and a valence electron on atom B, approximated by formula (6)[8] where R_{AB} is the

$$\gamma_{AB} = [R_{AB}^2 + 2^{-2}\,(\gamma_A^{-1} + \gamma_B^{-1})^2]^{-\frac{1}{2}} \qquad (6)$$

internuclear distance and the atomic parameters γ_A are taken from the tables of Sichel and Whitehead.[11] Equation (6) is closely related to the Dewar–Sabelli–Ohno–Klopman relation.[12]

It only remains to evaluate the atomic valence populations q_A for all atoms in the molecule. We shall estimate the q_A values by means of a Mulliken population analysis on the basis of the results of an Energy Weighted Maximum Overlap (EWMO)[13] calculation. In the present application, the atomic orbital energy parameters entering the EWMO formalism are set equal to the

population-dependent potentials W_μ^A discussed above, requiring an iterative approach to the solution of the model (in early work referred to as MIEHM).[8,14] This and other aspects of the calculational procedure,[8,14] as well as the results of applications to the photoelectron spectra of aza-arenes,[15,16] have been discussed in previous publications.

In the following, pK_a values for aza-benzenes and -naphthalenes are correlated with the computed self-consistent W_{2p}^N energies; for brevity, we shall simply denote the latter quantities
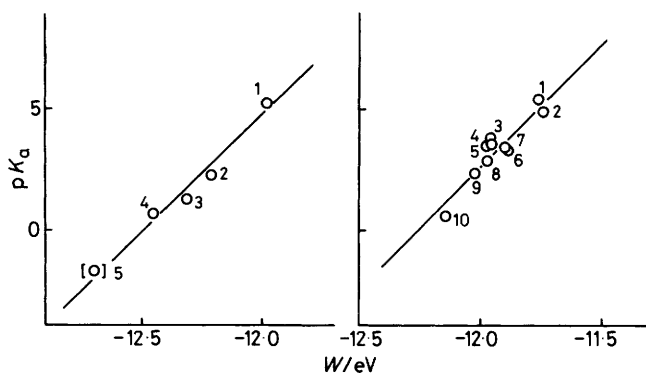
Figure 1. Correlation between observed pK_a values[18,19] and computed W values for azabenzenes (left: 1, 1-; 2, 1, 2-; 3, 1,3-; 4, 1,4-; 5, 1,3,5-) and azanaphthalenes (right: 1, 2-; 2, 1-; 3, 1,6-; 4, 1,7-; 5, 1,3-; 6, 2,3-; 7, 1,8-; 8, 1,5-; 9, 1,2-; 10, 1,4-)
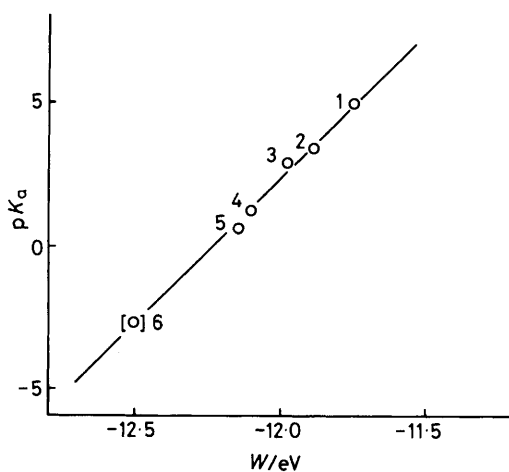
Figure 2. Correlation between observed pK_a values[18,20,21] and computed W values for the series of α-azanaphthalenes: 1, 1-; 2, 1,8-; 3, 1,5-; 4, 1,4,5-; 5, 1,4-; 6, 1,4,5,8-

Table. Calculated quantities in relation to equation (1) (writing W for W_{2p}^N) and experimental pK_a values for pyridine, pyridazine, pyrimidine, pyrazine, s-triazine, and 1,2,4,5-tetrazine

Aza-benzene	q_N	$W(q_N)/eV$	$\Sigma W(q_B)/eV$ B	W/eV	pK_a
1-	5.343	−9.46	−2.53	−11.99	5.3[a]
1,2-	5.192	−11.36	−0.85	−12.21	2.2[a]
1,3-	5.341	−9.48	−2.83	−12.31	1.2[a]
1,4-	5.302	−9.96	−2.49	−12.45	0.6[a]
1,3,5-	5.337	−9.52	−3.18	−12.70	−1.7[b]
1,2,4,5-	5.153	−11.87	−1.23	−13.10	<0[a]

[a] Ref. 18. [b] Extrapolated value; ref. 19.

by W. The calculations were based on experimental or estimated geometries as previously described;[8,15] the calculations for the azanaphthalenes were based on geometries derived from the experimental geometry of naphthalene.[17]

Results and Discussion

Figure 1 shows the correlation between observed pK_a values[18] and calculated W values for aza-benzenes and -naphthalenes. Very satisfactory correlations are obtained, leading to regression lines of the approximate form (7) where c is a constant

$$pK_a = c + 10\ W/eV \qquad (7)$$

characteristic for the isoconjugate series ($c \approx 125$ for aza-benzenes, ≈ 122.5 for azanaphthalenes; standard error of estimate $\approx 0.5\ pK_a$ units). Evidently, the quantity W represents to a good approximation those factors which are responsible for the shifts in pK_a value within such a series.

As defined in the preceding section, $W \equiv W_{2p}^N$ is computed as the sum of a one-centre and a two-centre contribution. To elucidate the relative importance of the two contributions, calculated data for pyridine, the diazines, s-triazine, and 1,2,4,5-tetrazine are given in the Table. It is quickly seen that although the one-centre term $W_{2p}^N(q_N)$ represents by far the largest contribution, this term does not at all parallel the observed basicities. For example, essentially identical one-centre terms are predicted for pyridine, pyrimidine, and s-triazine, in marked contrast to the widely differing pK_a values observed (or estimated)[18,19] for these compounds. It is only after inclusion of the two-centre summation term that the experimental trend is reproduced, indicating that the nitrogen basicity of an aza-aromatic compound is very sensitive to electronic long-range effects. This result is consistent with previous observations that pK_a values for aza-aromatic compounds do not correlate with calculated nitrogen gross electron populations.[1,2,5]

The computed W value can be used to predict the basicity of those aza-arenes for which pK_a cannot be measured, for instance when the proton affinity is small and protonation is slow relative to hydration or other processes in H_2O solution. The pK_a value of s-triazine, for example, cannot be determined experimentally, but a value close to −1.7 has been estimated by correlation with data for the series of methyl derivatives.[19] As indicated in Figure 1, this estimate is pleasingly consistent with the calculated value. The W parameter obtained for 1,2,4,5-tetrazine indicates a pK_a value of the order of −6. It is difficult to judge the significance of this much extrapolated value, but it is probably more realistic than the value −1.5 tentatively estimated by Brogli et al.[3] The most convincing correlations and predictions can be established for selected series of closely related compounds, as illustrated by the results for α-azanaphthalenes displayed in Figure 2. Armarego[21] has estimated a pK_a value of −2.7 for 1,4,5,8-tetra-azanaphthalene; this value is perfectly consistent with the calculated W parameter, as shown in Figure 2.

In the case of aza-aromatic compounds with two or more non-equivalent aza-positions, the calculated W values can be used to predict the preferred site of protonation. For example, the W values for the 1-, 2-, and 4-position of 1,2,4-triazine are −12.68, −12.55, and −12.76 eV, respectively.[15] The 2-position is clearly predicted as the most basic site, with an estimated pK_a value of −0.5; 1,2,4-triazine is thus predicted to be significantly more basic than its isomer s-triazine. In contrast to the case of 1,2,4-triazine, the electronic structure of 1,2,3-triazine is in many aspects strikingly similar to that of s-triazine.[15] The computed W values for the 1,2,3-isomer are −12.60 eV for the 1- and 3-position and −12.58 eV for the 2-position, suggesting a pK_a value close to −1 with no particularly preferred protonation

site. An example from the naphthalene series is provided by the case of 1,4,5-triazanaphthalene. The calculated W values are -12.37, -12.27, and -12.10 eV for the 1-, 4-, and 5-position, respectively. As anticipated, the 5-position is predicted to be far more basic than the other two aza-positions, and only the W value for this position is consistent with the measured[20] pK_a value of 1.2 eV (see the correlation in Figure 2).

Conclusions.—The results presented in this paper demonstrate the existence of a useful semi-empirical reactivity index W for the prediction of the relative pK_a values for a series of aza-arenes. It is noteworthy that the simple approach succeeds where highly sophisticated electrostatic potential calculations failed.[5] This can probably be explained by the characterization of W as an effective binding energy, calculated with reference to empirical atomic data and thereby implicitly incorporating higher order terms.

Acknowledgements

References

1 T. Nakajima and A. Pullman, *Bull. Soc. Chim. Fr.*, 1958, 1502; A. Veillard and A. Pullman, *J. Theor. Biol.*, 1963, **4**, 37.

2 R. Zahradnik and C. Párkányi, *Collect. Czech. Chem. Commun.*, 1965, **30**, 355.

3 F. Brogli, E. Heilbronner, and T. Kobayashi, *Helv. Chim. Acta*, 1972, **55**, 274.

4 R. Bonaccorsi, A. Pullman, E. Scrocco, and J. Tomasi, *Theor. Chim. Acta*, 1972, **24**, 51.

5 J. Almlöf, H. Johansen, B. Roos, and U. Wahlgren, *J. Electron Spectrosc. Relat. Phenom.*, 1973, **2**, 51.

6 E. Scrocco and J. Tomasi, *Adv. Quantum Chem.*, 1978, **11**, 115.

7 D. E. Williams, and R. R. Weller, *J. Am. Chem. Soc.*, 1983, **105**, 4143.

8 J. Spanget-Larsen, *J. Electron Spectrosc. Relat. Phenom.*, 1973, **2**, 33.

9 G. Karlsson and O. Mårtensson, *Theor. Chim. Acta*, 1969, **13**, 195.

10 J. Linderberg and Y. Öhrn. 'Propagators in Quantum Chemistry,' Academic Press, New York, 1973, p. 64.

11 J. M. Sichel and M. A. Whitehead, *Theor. Chim. Acta*, 1967, **7**, 32.

12 M. J. S. Dewar and N. L. Hojvat (Sabelli), *J. Chem. Phys.*, 1961, **34**, 1232; *Proc. R. Soc. London*, 1961, **A264**, 431; M. J. S. Dewar and N. L. Sabelli, *J. Phys. Chem.*, 1962, **66**, 2310; K. Ohno, *Theor. Chim. Acta*, 1964, **3**, 219; G. Klopman, *J. Am. Chem. Soc.*, 1964, **86**, 4550.

13 J. Linderberg and Y. Öhrn, ref. 10, p. 82.

14 J. Spanget-Larsen, QCPE, 1974, **11**, 246 (using the ordinary set of atomic parameters described in ref. 8).

15 R. Gleiter, M. Kobayashi, H. Neunhoeffer, and J. Spanget-Larsen, *Chem. Phys. Lett.*, 1977, **46**, 231; R. Gleiter, J. Spanget-Larsen, R. Bartetzko, H. Neunhoeffer, and M. Clausen, *ibid.*, 1983, **97**, 94.

16 J. Spanget-Larsen, *J. Electron Spectrosc. Relat. Phenom.*, 1974, **3**, 369; D. M. W. van den Ham, M. Beerlage, D. van der Meer, and D. Feil, *ibid.*, 1975, **7**, 33; D. M. W. van den Ham, D. van der Meer, and D. Feil, *ibid.*, 1974, **4**, 111; E. W. Thulstrup, J. Spanget-Larsen, and R. Gleiter, *Mol. Phys.*, 1979, **37**, 1382; R. Gleiter, J. Spanget-Larsen, and W. L. F. Armarego, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1517.

17 D. W. J. Cruickshank, *Acta Crystallogr.*, 1957, **10**, 504.

18 D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

19 B. A. Korolev and M. A. Mal'tseva, *Zh. Obshch. Khim.*, 1976, **46**, 1605.

20 A. Albert and C. Pedersen, *J. Chem. Soc.*, 1956, 4683.

21 W. L. F. Armarego, *J. Chem. Soc.*, 1963, 4304.