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STRUCTURE-REACTIVITY CORRELATIONS FOR AZA-ARENES. PROTON AFFINITIES, pK_a VALUES, HYDROGEN-DEUTERIUM EXCHANGE RATES AND RADICAL-INDUCED ^{13}C SHIFTS

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Molecular reactivity parameters based on the concept of an effective electronic potential and defined as a simple function of the molecular charge distribution were applied in a study of various aspects of the chemical reactivity of azabenzenes and azanaphthalenes. Excellent linear correlations were obtained for proton affinities, pK_a values, H-D exchange rate exponents and ^{13}C shifts induced by the paramagnetic shift reagent TEMPO. In the last case, the predictions for quinazoline prompted a reinvestigation of the ^{13}C NMR spectrum of this compound, resulting in a reassignment of the spectrum relative to the assignment assumed by Grant and co-workers.

INTRODUCTION

Interpretation of the chemical reactivity associated with the π-systems of conjugated compounds in terms of electronic parameters derived from π-electron theory has a long and strong tradition,[1] but the derivation of first-order 'reactivity indices' for reactions involving primarily the σ-electron skeletons seems more problematic. In this work, a simple reactivity parameter based on the concept of an effective electronic potential was applied to various aspects of the chemical reactivity of aza-arenes (Scheme 1). Effective potentials have been shown to be successful in the prediction of relative pK_a values for ground and excited states of aza-aromatics;[2,3] in the following, the approach is refined and extended to aspects of the reactivity related to the CH acidity of these compounds.

EFFECTIVE ATOMIC POTENTIALS W

The electron distribution in a molecule is generally different from that of the corresponding superposition of formally isolated atoms. The effective atomic orbital (AO) energies W for an atom in a molecule can be approximated by a simple analytical function of the molecular charge distribution.[2,4,5] We shall assume that the energy W of a valence AO can be written as

$$W = W^{(0)} + W^{(1)} + W^{(2)} \qquad (1)$$

where $-W^{(0)}$ is an effective valence state ionization potential for the isolated neutral atom[6] and $W^{(1)}$ and $W^{(2)}$ are one- and two-centre molecular correction terms depending on the gross atomic valence populations Q. The functional form of the total one-centre contribution $W^{(0)} + W^{(1)}$ is chosen as the one suggested by Linderberg and Öhrn[7] on the basis of a study of differential ionization potentials,

$$W^{(0)} + W^{(1)} = -(\alpha + \beta\,\delta Q)^{3/2} \qquad (2)$$

where δQ is the formal net atomic charge, $\delta Q = (Z^{\text{core}} - Q)/|e|$, α is determined from $\alpha^{3/2} = -W^{(0)}$ and β is optimized[4] within a least-squares criterion to reproduce the valence-state ionization potentials for the positive and negative atomic ions[6] (the ionization potential for the positive ion is not defined for atomic hydrogen; two alternative parameterizations have been suggested for this atom[4]). The two-centre term $W_A^{(2)}$ for a valence AO on a centre A is taken as

$$W_A^{(2)} = -\sum_{B \neq A} \gamma_{AB}\,\delta Q_B \qquad (3)$$

where γ_{AB} represents the Coulomb repulsion between a valence electron on atom A and a valence electron on atom B. γ_{AB} is approximated by the expression[4]

$$\gamma_{AB} = [r_{AB}^2 + 2^{-2}(\gamma_A^{-1} + \gamma_B^{-1})^2]^{-1/2} \qquad (4)$$

where r_{AB} is the interatomic distance and the atomic parameters γ_A and γ_B are effective valence-shell electron repulsion terms derived from empirical atomic data.[8] Ordinary atomic parameters $W^{(0)}$, α, β and γ for the valence AOs of H, C, N, O and F are given in Table 1.

The effective atomic potentials described above were introduced more than 20 years ago[4,5] and have been

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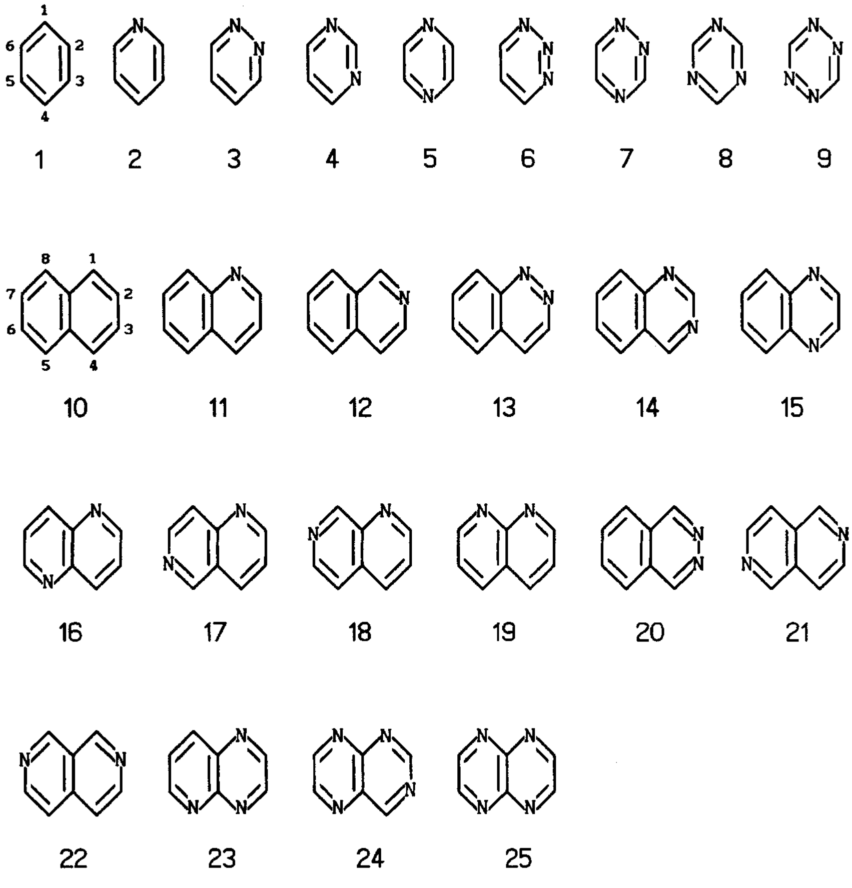
Table 1. Ordinary parameters[4] for effective atomic orbital energies $W_{A_\mu} = -(\alpha_{A_\mu} + \beta_{A_\mu}\delta Q_A)^{3/2} - \sum_{B \neq A} [r_{AB}^2 + 2^{-2}(\gamma_A^{-1} + \gamma_B^{-1})^2]^{-1/2}\delta Q_B$ (eV)

$A\mu$	$W^{(0)}$	α^a	β	γ
H1s	-13·595	5·6962120	4·870730	12·848
C2s	-19·42	7·2249162	2·936921	10·333
C2p	-10·93	4·9250817	3·559590	10·333
N2s	-25·58	8·6816118	3·009212	11·308
N2p	-13·94	5·7921773	3·852758	11·308
O2s	-32·30	10·1422664	3·234959	13·907
O2p	-14·61	5·9763150	4·536384	13·907
F2s	-39·39	11·5768566	3·385321	15·233
F2p	-18·11	6·8962389	4·153235	15·233

[a] $\alpha = |W^{(0)}|^{2/3}$.



Scheme 1

applied in a number of investigations, particularly of the ionization energies of aza-aromatics.[2,4,9] As previously pointed out,[2,4] the negative of the atomic potential W can be considered as an approximate *local ionization energy*, estimating the ease of partly removing a valence electron from the centre in question and thereby serving as an indicator of the local nucleophilicity. In this respect, the effective potential W is conceptually related to the molecular property $\bar{I}(\mathbf{r})$ introduced in 1990 by Politzer and co-workers.[10,11] $\bar{I}(\mathbf{r})$ can be interpreted as the average energy needed to ionize an electron at any particular point **r** in the space of the molecule and is rigorously defined within the framework of closed-shell Hartree–Fock theory. Average local ionization energies $\bar{I}(\mathbf{r})$ on molecular surfaces have been shown to be useful guides to the chemical reactivity for a variety of compounds, including the azines.[10,11] However, computation and mapping of the three-dimensional function $\bar{I}(\mathbf{r})$ on a suitable molecular surface is complicated, and analysis of the results in terms of intramolecular contributions is not straightforward. The less sophisticated, semiempirical parameter W have the advantage of great computational simplicity, and they are readily analysed in terms of atomic contributions, facilitating discussions of the origin of the predicted trends.[2] Moreover, their definition is not restricted to closed-shell systems; for example, W values for excited states have been shown to be of great predictive value.[3] Further evidence for the predictive power of this approach is provided by the results of the ensuing study.

Table 2. Calculated δW_N values (eV), predicted and observed proton affinities (kcal mol^{-1}) and pK_a values for the azabenzenes **2–9**; values in italics are predicted on the basis of the calculated δW_N values

Compound	δW_N	*PA*[a]	*PA*[b]	*PA*[c]	pK_a[d]	pK_a[e]
2	1·95	235·8	*223·2*	222·0	*4·72*	5·17
3	1·73	229·5	*217·3*	218·3	*2·67*	2·30
4	1·63	224·2	*214·6*	215·5	*1·74*	1·23
5	1·49	219·9	*210·8*	210·8	*0·44*	0·67
6 N-1	1·34	214·2	*206·7*		*−0·96*	
N-2	1·36	216·4	*207·3*		*−0·77*	
7 N-1	1·26	212·5	*204·6*		*−1·71*	
N-2	1·39	216·8	*208·1*		*−0·50*	
N-4	1·15	205·5	*201·6*		*−2·73*	
8	1·24	211·6	*204·0*	203·3	*−1·89*	−1·7[f]
9	0·84	196·4	*193·2*		*−5·62*	

[a] Proton affinities calculated by *ab initio* Hartree–Fock theory at the 3–21+G//3–21G level.[15]
[b] Proton affinities predicted by equation (7).
[c] Observed proton affinities.[16] The values in Ref. 17 are 1–2 kcal mol^{-1} smaller.
[d] pK_a predicted by equation (9).
[e] Observed pK_a.[18]
[f] pK_a for *s*-triazine estimated by extrapolation from observed data for methyl derivatives.[19]

In the present application to the aza-arenes, the net atomic charges δQ are computed by a charge-iterative version of the energy weighted maximum overlap (EWMO) method.[12–14] Details of the calculation procedure were given in previous publications,[2,4,5] where also references to the molecular geometries used in the calculations can be found.[2] The computed shifts of the effective AO energies,

$$\delta W = W - W^{(0)} = W^{(1)} + W^{(2)} \qquad (5)$$

are treated as chemical reactivity indices; the shift δW_A for an atom A other than hydrogen shall be taken as δW_{A2p} (δW_{A2s} and δW_{A2p} are essentially identical for A = C or N). Positive δW corresponds to an increased electronic potential (relative to the isolated atom). In general, the more positive is δW, the higher *basic* and *nucleophilic* character should be associated with the corresponding region of the molecule. δW_N for the aza centres in a series of aza-arenes thus tend to correlate with the pK_a values of the compounds[2–4] (see below). On the other hand, the more negative is δW, the more

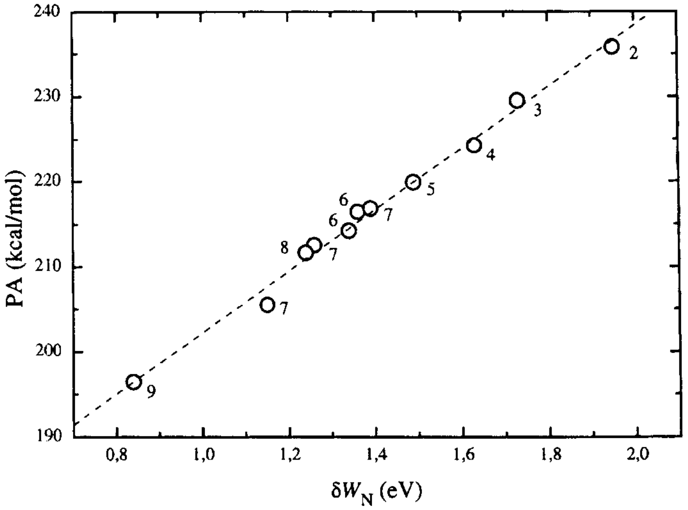
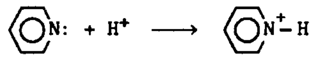


Figure 1. Linear regression of *ab initio* Hartree–Fock proton affinities[15] (*PA*) on δW_N values for azabenzenes. The regression equation is PA/kcal mol^{-1} = 166·11 + 36·12311δW_N/eV (SD = 1·03 kcal mol^{-1}, R = 0·996)

acidic and *electrophilic* should be the corresponding part of the molecule. For example, as we shall show, δW_C and δW_H values for CH bonds serve as a basis for the definition of reactivity indices for the CH acidity of the aza-arenes.

PROTON AFFINITIES

One of the most important chemical properties of aza-arenes such as pyridine and quinoline (Scheme 1) is their ability to act as proton acceptors, e.g.



(6)

The gas-phase proton affinity, *PA*, is defined as the negative of the enthalpy change $\Delta H°$ associated with this reaction. *PA*s for several azabenzenes calculated by *ab initio* Hartree–Fock theory[15] are given in Table 2, together with the computed δW_N values. An excellent linear correlation exists between the two sets of theoretical data, as shown in Figure 1. There is also a very convincing correlation with the experimental *PA*s reported by Meot-Ner[16] (Table 2); the observed *PA*s are reproduced to an accuracy of about 0.5% by the expression

$$PA/\text{kcal mol}^{-1} = 170{\cdot}54 + 27{\cdot}01221\ \delta W_N/\text{eV} \qquad (7)$$

(SD = 1·15 kcal mol^{-1}, $R = 0{\cdot}991$) (1 kcal = 4·184 kJ). The correlation of the observed *PA*s with δW_N is superior to the corresponding correlation with local surface ionization energies $\bar{I}_{S,\min}$ computed within *ab initio* Hartree–Fock theory by Politzer and co-workers[11] (SD = 1·74 kcal mol^{-1}, $R = 0{\cdot}978$).

*PA*s for 1,2,3-triazine (**6**), 1,2,4-triazine (**7**) and *s*-tetrazine (**9**) estimated on the basis of equation (7) are given in Table 2. Tentative *PA* predictions for azanaphthalenes are given in Table 3. Tentative *PA* predictions for azanaphthalenes are given in Table 3. Only a few experimental values are available to test these results, but the predicted increase in the *PA* by about 7 kcal mol^{-1} on annelation of a benzene ring to pyridine (**2**), pyridazine (**3**) and pyrazine (**5**) is in keeping with the experimental evidence[16] (Table 3).

The success of the δW approach is remarkable. For example, the δW_N values adequately account for the relative *PA*s of the diazines pyridazine (**3**), pyrimidine (**4**) and pyrazine (**5**), where sophisticated procedures such as MNDO and AM1 fail.[15] Previous analysis has demonstrated that the Coulombic two-centre terms $W_N^{(2)}$ are essential for reproduction of the experimental trend, indicating that the nitrogen basicity of aza-heterocycles is sensitive to electronic long-range effects.[2] This result is consistent with previous observations that the base strengths of nitrogen heterocycles do not correlate with calculated nitrogen gross charges.[20]

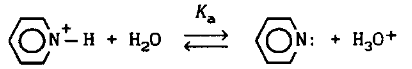
Table 3. Calculated δW_N values (eV), predicted and observed proton affinities (kcal mol^{-1}) and pK_a values for the azanaphthalenes **11–25**; values in italics are predicted on the basis of the calculated δW_N values

Compound		δW_N	*PA*[a]	*PA*[b]	pK_a[c]	pK_a[d]
11		2·20	*230·0*	227·6	*4·94*	4·90
12		2·18	*229·4*	227·5	*5·43*	5·40
13	N-1	1·92	*222·4*	224·3	*2·01*	
	N-2	1·91	*222·1*		*2·61*	2·37
14	N-1	1·97	*223·8*		*2·53*	2·01[e]
	N-3	1·90	*221·9*		*2·50*	
15		1·80	*219·2*	217·1	*0·75*	0·56
16		1·97	*223·8*		*2·53*	2·84
17	N-1	1·92	*222·4*		*2·01*	
	N-6	1·98	*224·0*		*3·34*	3·76
18	N-1	1·89	*221·6*		*1·70*	
	N-7	1·98	*224·0*		*3·34*	3·61
19		2·06	*226·2*		*3·48*	3·36
20		2·04	*225·6*		*3·97*	3·47
21		1·87	*221·1*		*2·19*	
22		1·90	*221·9*		*2·50*	
23	N-1	1·57	*212·9*		*−1·66*	
	N-4	1·67	*215·7*		*−0·61*	
	N-5	1·84	*220·2*		*1·17*	1·2
24	N-1	1·52	*211·6*		*−2·18*	−2·5[f]
	N-3	1·43	*209·2*		*−2·42*	
	N-5	1·14	*201·3*		*−6·16*	
	N-8	1·29	*205·4*		*−4·58*	
25		1·44	*209·4*		*−3·02*	−3·0[g]

[a] Proton affinities predicted by equation (7).
[b] Observed gas-phase proton affinities.[16]
[c] pK_a predicted by equations (10) and (11).
[d] Observed pK_a.[23]
[e] pK_a for quinazoline determined by fast reaction techniques.[26]
[f] Estimated pK_a for pteridine.[23]
[g] Average of estimated pK_as for pyrazino[2,3-*b*]pyrazine.[23,27]

pK_a VALUES

While calculation of gas-phase *PA*s seems to be relatively straightforward, prediction from first principles of the corresponding pK_a values in solution is very difficult. The pK_a value for an aza-arene in aqueous solution refers to a thermodynamic equilibrium, e.g.



(8)

The equilibrium constant K_a depends on entropy changes and solvent effects that are not easily calculated theoretically.[21] However, the pK_a values of nitrogen heterocycles are important in biological structure–activity work, and considerable interest has been devoted to the problem of establishing effective empirical or semi-empirical procedures for pK_a prediction.[20–23]

In aqueous solution, the solvent attenuation of the basicity is essentially different for azabenzenes and azanaphthalenes, and for the latter the attenuation is different for aza centres in α- and β-positions; the differences have been discussed in terms of steric inhibition of solvation.[16] It is thus preferable to estimate pK_a values by treating independently the three types of nitrogen positions. For azabenzenes we apply the relationship[2]

$$\mathrm{p}K_a = -13{\cdot}436 + 9{\cdot}30964\ \delta W_N/\mathrm{eV} \qquad (9)$$

(SD = 0·48 pH units, $R = 0{\cdot}986$) (in the applications reported in this paper, δW was not weighted by statistical factors for compounds with two or more equivalent reaction centres; it is sometimes unclear if experimental data in the literature have already been corrected for 'statistical effects'). For nitrogen atoms in naphthalene α-positions, we refer to the linear regression for the series quinoline (**11**), quinoxaline (**15**), 1,5-naphthyridine (**16**), 1,8-naphthyridine (**19**), pyrido[2,3-*b*]pyrazine (**23**) and pyrazino[2,3-*b*]pyrazine (**25**):[2]

$$\mathrm{p}K_a = -18{\cdot}098 + 10{\cdot}47277\ \delta W_N/\mathrm{eV} \quad (\alpha\text{-nitrogen}) \qquad (10)$$

(SD = 0·19 pH units, $R = 0{\cdot}998$). Insufficient empirical data are available for the calibration of a similar relation for β-positions; we shall apply equation (10) also for β-positions, but add 0·7 pH units to the predicted pK_a to obtain agreement with the observed pK_a for isoquinoline (**12**), i.e.

$$\mathrm{p}K_a = -17{\cdot}398 + 10{\cdot}47277\ \delta W_N/\mathrm{eV} \quad (\beta\text{-nitrogen}) \qquad (11)$$

The resulting correlation between observed and estimated pK_a values for 5 azabenzenes and 13 azanaphthalenes is shown in Figure 2. The standard deviation (SD) is 0·3 pH units. This is probably an indication of the kind of accuracy that may be expected in carefully calibrated predictions based on δW_N values within series of aza-arenes. In general, the relationship

$$\mathrm{p}K_a \approx c + 10\ \delta W_N/\mathrm{eV} \qquad (12)$$

may be useful for rough estimates of relative pK_a values.[2] This relationship was applied in studies of aminopyrimidines and aminoquinoxalines,[3] where δW_N was computed on the basis of net charges predicted by INDO/S calculations. In particular, the δW_N values so obtained were used to estimate protonation site and relative pK_a values for ground and excited states of several aminoquinoxalines; the results were consistent with the experimental evidence.[3]

Predicted pK_a values for several azabenzenes and azanaphthalenes are given in Tables 2 and 3. The pK_a value for 1,2,3-triazine (**6**) is predicted to be *ca* −1. Inthe case of 1,2,4-triazine (**7**), the 2-position is clearly predicted as the most basic site. This is consistent with the recent results of Politzer and co-workers;[11] however, their prediction of a pK_a value of −1·8 is at variance with the result of the present procedure, yielding a pK_a value of *ca* −0·5.[2] The pK_a value for *s*-tetrazine (**9**) is estimated to be *ca* −6. It is difficult to judge the significance of this much extrapolated value, but it is probably more realistic than the value of −1·5 estimated by Brogli *et al.*[24] The pK_a values for the β,β-naphthyridines **21** and **22** are, surprisingly, predicted to be appreciably smaller than that reported for phthalazine (**20**). In the α,β-diaza derivatives **13**, **17** and **18**, the β-nitrogen is predicted to be more basic than the α-nitrogen, but in quinazoline (**14**) similar pK_a values are predicted for the two nitrogen positions. In pteridine (**24**), the 1-position is predicted to be slightly more basic than the 3-position;[9] the predicted pK_a value of −2·2 is consistent with the value of −2·5 estimated by Perrin *et al.*[23]

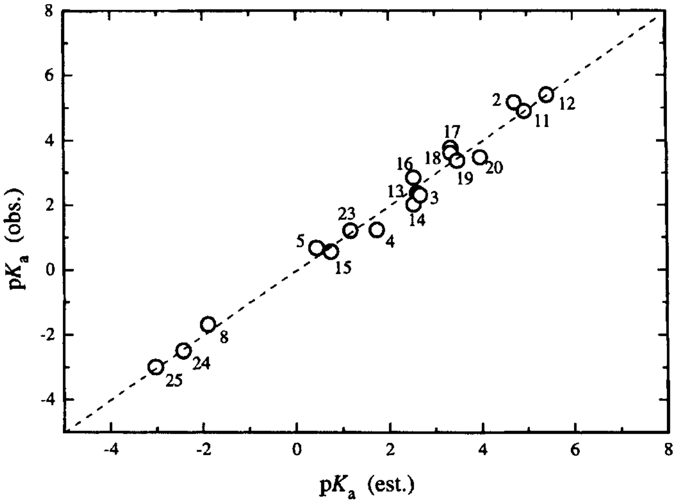
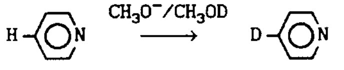


Figure 2. Correlation of observed and estimated pK_a values for azabenzenes and azanaphthalenes (SD = 0·32 pH units)

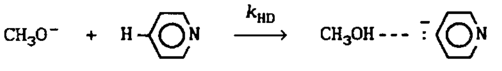
HYDROGEN-DEUTERIUM EXCHANGE RATES

Replacement of a CH unit in an aromatic hydrocarbon by a nitrogen atom introduces a basic centre. At the same time, the introduction of an electronegative heteroatom in the ring may be expected to increase the acidity of the remaining CH groups by means of an inductive effect, thereby facilitating the formation of carbanions. Zoltewicz *et al.*[28] investigated this hypothesis by measuring the rates of H–D exchange of pyridine and the diazines in CH_3ONa–CH_3OD, e.g.



(13)

The rate-determining step can be considered to be deprotonation by strong base to give an H-bonded carbanion,[29] e.g.



(14)

However, contrary to expectation, it was found that nitrogen does not facilitate anion formation at adjacent positions to the degree that it facilitates anion formation at more removed centres. For pyridine (**2**), it was found that exchange of the *meta*- and *para*-hydrogens proceeded about 10 times as fast as exchange of the *ortho*-hydrogens.[28]

The transition state of the deprotonation reaction must correspond to a situation where the CH bond is largely broken. We tentatively define a simple 'bond potential' δW_{CH} for the CH bond:

$$\delta W_{CH} = \tfrac{1}{2}(\delta W_C + \delta W_H) \qquad (15)$$

δW_{CH} may be thought of as a qualitative measure of the effective electronic potential in the CH bond region. The lower is δW_{CH}, the more thermodynamically stable should be the CH bond but, at the same time, the more electrophilic should be the bond, and the faster should it react with base to form a carbanion, corresponding to larger k_{HD} (smaller pk_{HD}). The computed δW_{CH} values for the *ortho*, *meta* and *para* positions in pyridine (**2**) are +0·20, +0·04 and −0·04 eV, respectively, in agreement with the relative ordering of the observed k_{HD} values $3{\cdot}2\times10^{-6}$, $3{\cdot}0\times10^{-5}$ and $3{\cdot}8\times10^{-5}\,\mathrm{l\,mol^{-1}\,s^{-1}}$. The unusual relative exchange rates discussed by Zoltewicz *et al.*[28] are thus easily explained by the relative CH bond potentials. The relative reactivities cannot be explained by the local net charges; the calculated charge distribution for **2** suggests that the positively charged *ortho* positions should be far more electrophilic and acidic than the *meta* and *para* positions, as expected on the basis of an inductive effect. However, consideration of two-centre Coulombic interaction terms leads to a large increase in the effective atomic potentials in the *ortho* positions, and thereby to agreement with the observed trend. It is interesting that the relative CH bond lengths in **2**[29] show the opposite ordering to the exchange rates k_{HD}; this is probably a reflection of the expected inversal of the ordering of thermodynamic and kinetic stabilities.

δW_{CH} values computed for benzene and several azabenzenes (using the 'hydrogen-corrected' parameters defined in Ref. 4) are given in Table 4 together with the pk_{HD} values reported by Zoltewicz *et al.*[28] As shown in Figure 3, a convincing linear correlation is observed between the two sets of data, thereby supporting the

Table 4. Calculated δW_{CH} and δW_H values (eV), predicted and observed hydrogen–deuterium exchange rate exponents pk_{HD} and radical-induced ^{13}C shifts $\Delta\delta_f$ (ppm) for benzene (**1**) and the azabenzenes **2–9**; values in italics are predicted on the basis of the calculated δW_{CH} or δW_H values

Compound		δW_{CH}	pk_{HD}[a]	pk_{HD}[b]	δW_H	$\Delta\delta_f$[c]	$\Delta\delta_f$[d]
1		+0·450	*6·85*	6·88	−0·240	*5·07*	5·64
2	H-2	+0·196	*5·55*	5·50	−0·362	*6·19*	6·91
	H-3	+0·041	*4·75*	4·52	−0·630	*8·67*	8·13
	H-4	−0·040	*4·34*	4·42	−0·677	*9·10*	8·55
3	H-3	−0·259	*3·21*	2·85	−0·809	*10·32*	10·91
	H-4	−0·513	*1·91*	1·69	−1·128	*13·28*	13·86
4	H-2	−0·136	*3·84*	3·94	−0·520	*7·65*	7·55
	H-4	−0·336	*2·82*	3·41	−0·830	*10·52*	12·68–13·99[e]
	H-5	−0·414	*2·42*	2·26	−1·059	*12·63*	14·16–15·79[e]
5		−0·242	*3·30*	3·52	−0·780	*10·06*	11·02
8		−0·694	*0·98*		−0·995	*12·04*	14·93
9		−1·064	*−0·91*		−1·386	*15·66*	

[a] pk_{HD} predicted by the regression equation in Figure 3.

[b] Observed pk_{HD}.[28]

[c] $\Delta\delta_f$ predicted by the regression equation in Figure 4.

[d] Observed $\Delta\delta_f$ induced by the shift reagent TEMPO.[30]

[e] $\Delta\delta_f$ dependent on the concentration of the shift reagent.[30]

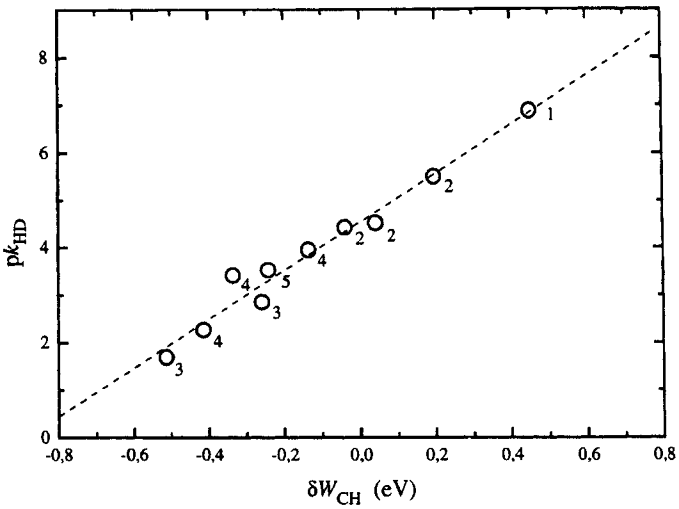


Figure 3. Linear regression of observed H–D exchange rate exponents pk_{HD}[29] on δW_{CH} values for benzene (**1**), pyridine (**2**) and the diazines (**3**–**5**). The regression equation is $pk_{HD} = 4{\cdot}542 + 5{\cdot}12812\delta W_{CH}/\mathrm{eV}$ (SD = 0·29, $R = 0{\cdot}984$)

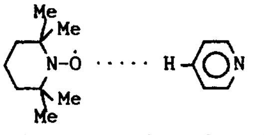
assumption that the relative exchange rates can be explained in terms of the bond potentials. On the basis of the present results, *s*-tetrazine (**9**) is predicted to exchange hydrogen about 80 times faster than *s*-triazine (**8**) and almost 10^8 times faster than benzene (**1**).

RADICAL-INDUCED ^{13}C SHIFTS

In 1984 Grant and co-workers published an investigation of the NMR ^{13}C shifts induced by the free radical TEMPO (2,2,6,6-tetramethylpiperidinyl-1-oxy) for several nitrogen heterocyclic compounds.[30] The induced shifts $\Delta\delta_f$ were larger than those observed for the corresponding aromatic hydrocarbons,[31] indicating a stronger interaction between the nitrogen heterocycles and the shift reagent TEMPO. However, it was found that for aza-aromatics, the stronger interaction is not at the adjacent positions to the nitrogen atoms. For pyridine, for example, the induced shifts $\Delta\delta_f$ for the *ortho*, *meta* and *para* positions are 6·91, 8·13 and 8·85 ppm, respectively (compared with 5·64 ppm for benzene). Grant and co-workers showed that for pyridine (**2**), pyridazine (**3**), pyrazine (**5**) and *s*ctriazine (**8**), the $\Delta\delta_f$ values increase in an additive manner with increasing number of nitrogen atoms in the ring, but that pyrimidine (**4**) forms a striking exception. The interactions between pyrimidine and TEMPO appear to be stronger, consistent with the observation that the induced shifts in pyrimidine exhibit a much larger concentration dependence than in the other nitrogen heterocycles investigated (Table 4). Also, the results for quinazoline (**14**) were found to be problematic, with apparent inversion of the order of the induced shifts for C-2 and C-4 as compared with pyrimidine[30] (see below).

The order of the induced shifts for pyridine is similar to that of the CH acidities discussed in the preceding section, indicating that the relative strengths of the contact interactions may be somehow related to the relative acidities. We have found that an approximate linear correlation exists between observed $\Delta\delta_f$ values and calculated δW_H parameters, except for compounds with aza centres in a 1,3-arrangement (e.g. **4**, **8** and **14**). Figure 4 shows the linear regression for 23 methine positions in benzene (**1**), pyridine (**2**), pyridazine (**3**), pyrazine (**5**), naphthalene (**10**), quinoline (**11**) and isoquinoline (**12**); the standard deviation is 0·6 ppm. A number of trends are well accounted for by the computed δW_H values (Tables 4 and 5). For example, the large spread of the $\Delta\delta_f$ values for quinoline (**11**) relative to that for isoquinoline (**12**) is well reproduced. The largest and smallest shifts for **11** are correctly predicted in the 4- and 8-positions. The unusually small shift in the 8-position of **11** is correctly predicted to be even smaller than the shifts in naphthalene; this shift is apparently an exception to the general rule that the introduction of aza-nitrogen into an aromatic hydrocarbon causes an increase of the induced shifts.

Taken at its face value, the correlation in Figure 4 indicates that the induced shifts in these compounds are influenced by the electrophilicity of the exposed H atoms, which probably determines the relative strengths of the temporary contact interactions with TEMPO, e.g.



(16)

On the other hand, compounds such as **4**, **8** and **14** do not fit well into the correlation in Figure 4. In the case

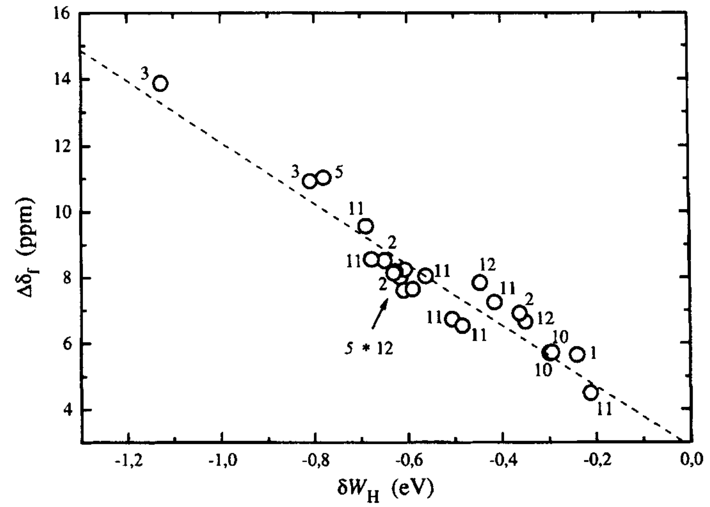


Figure 4. Linear regression of observed radical-induced ^{13}C chemical shifts $\Delta\delta_f$[32] on δW_H values for benzene (**1**), pyridine (**2**), pyridazine (**3**), pyrazine (**5**), naphthalene (**10**), quinoline (**11**) and isoquinoline (**12**). The regression equation is $\Delta\delta_f/\text{ppm} = 2{\cdot}848 - 9{\cdot}24038\,\delta W_H/\text{eV}$ (SD = 0·61 ppm, $R = 0{\cdot}915$)

Table 5. Calculated δW_H values (eV), predicted and observed radical-induced ^{13}C shifts $\Delta\delta_f$ (ppm) for naphthalene (**10**) and the azanaphthalenes **11**, **12** and **14**; values in italics are predicted on the basis of the calculated δW_H values

Compound		δW_H	$\Delta\delta_f$[a]	$\Delta\delta_f$[b]
10	H-1	−0·298	*5·60*	5·70
	H-2	−0·294	*5·56*	5·71
11	H-2	−0·415	*6·68*	7·25
	H-3	−0·649	*8·85*	8·51
	H-4	−0·689	*9·21*	9·56
	H-5	−0·561	*8·03*	8·04
	H-6	−0·505	*7·51*	6·72
	H-7	−0·483	*7·31*	6·52
	H-8	−0·212	*4·81*	4·49
12	H-1	−0·446	*6·97*	7·84
	H-3	−0·350	*6·08*	6·65
	H-4	−0·616	*8·54*	8·00
	H-5	−0·606	*8·45*	8·24
	H-6	−0·608	*8·47*	7·61
	H-7	−0·589	*8·29*	7·64
	H-8	−0·626	*8·63*	8·19
14	H-2	−0·491	*7·39*	6·80[c]
	H-4	−0·814	*10·37*	16·21[c]
	H-5	−0·886	*11·04*	12·92
	H-6	−0·801	*10·25*	9·91
	H-7	−0·796	*10·20*	9·51
	H-8	−0·522	*7·67*	6·23

[a] $\Delta\delta_f$ predicted by the regression equation in Figure 4.
[b] Observed $\Delta\delta_f$ induced by the shift reagent TEMPO.[30]
[c] $\Delta\delta_f$ corresponding to a reassignment (δC-2 = 155·21, δC-4 = 160·10 ppm) of the ^{13}C spectrum of quinazoline (see text)

of quinazoline (**14**), the agreement between the predicted shifts and those published by Grant and co-workers[30] is particularly poor, with deviations as large as 9 ppm; the predicted $\Delta\delta_f$ values for the C-2 and C-4 are 7·4 and 10·4 ppm (Table 5), in striking disagreement with the observed shifts 16·2 and 6·8 ppm.[30] However, the reported shifts for **14** are problematic; they are consistent only with a complete reversal of the general trend that induced shifts in positions adjacent to aza-nitrogen tend to be small.

The published assignments for C-2 and C-4 of quinazoline (**14**) diverge.[32–34] In view of the situation indicated above, we have reinvestigated the ^{13}C NMR spectrum of **14** in $DCCl_3$ using the COLOC technique.[35] The observation of a cross peak due to a long-range coupling (delay optimized for a long-range coupling of 5 Hz) between C-4 and C-5 unambiguously confirms the assignment in Ref. 34 and thus reverses the assignment published in Refs 32 and 33 and assumed by Grant and co-workers.[30] In Table 5, the induced shifts reported for the 2- and 4-positions in **14** have thus been reassigned, resulting in $\Delta\delta_f = 6{\cdot}80$ ppm for C-2 and 16·21 ppm for C-4. The reassignment leads to consistency with the induced shifts observed for **4** and to improved agreement with the predicted shifts (Table 5).

Figure 5 shows the correlation between observed $\Delta\delta_f$ values and computed δW_H parameters, with inclusion of results for the problematic ‘1,3-aza compounds’ **4**, **8** and **14**. It is apparent that the relatively small shifts (6–10 ppm) in the 2-position of **4** and the 2-, 6-, 7- and 8-positions of **14** are reasonably well predicted, but the large shifts (13–16 ppm) observed for **8** and for the

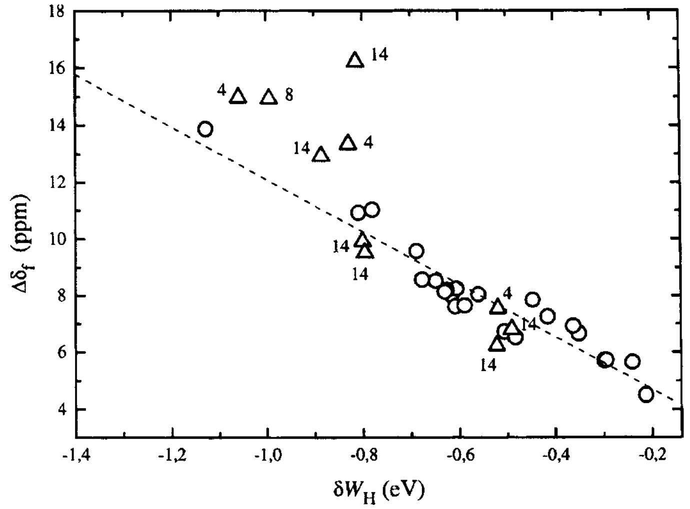


Figure 5. Same as Figure 4, but with inclusion of results for pyrimidine (**4**), *s*-triazine (**8**) and quinazoline (**14**), indicated by triangles. The points for **14** correspond to a reassignment of the ^{13}C shifts relative to that of Grant and co-workers[30] (see text). The regression line is that from Figure 4

4- and 5-positions in **4** and **14** are all underestimated. The induced shifts for these positions are apparently increased by some factors that are not represented by the atomic potentials δW_H. The largest deviation is for **14**, where the very large shift in the 4-position is underestimated by 6 ppm. It is possibly significant that fused pyrimidines such as **14** (and **24**) are considerably more chemically reactive than most other aza-aromatics; for example, they tend to undergo fast covalent hydration across the 3,4-bond in aqueous acidic media.[22,36]

CONCLUSION

The results for aza-heterocycles presented in this paper indicate that a promising approach towards the prediction of chemical reactivities may be based on a definition of effective atomic potentials as a simple function of atomic charges and interatomic distances, quantities that are easily estimated by standard molecular modelling procedures. The conceptual and computational simplicity of the procedure is appealing and facilitates analysis of the results in terms of atomic contributions.[2] Results relating to pK_a values for ground and excited states of aza-aromatics have been discussed previously,[2-4] but the approach seems valid also for very strong interactions, such as in H–D exchange reactions involving rupture of a covalent CH bond, and for very weak interactions, as with the free radical TEMPO.

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