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Tautomerism in some aromatic Schiff bases and related azo compounds: an LSER study

Liudmil Antonov,[1] Walter M. F. Fabian[2] and Peter J. Taylor[3]*

[1]National Forestry University, Faculty of Ecology, 10 Kliment Ohridski Avenue, Sofia 1756, Bulgaria
[2]Karl-Franzens University, Institut für Chemie, Heinrichstrasse 28, A-8010 Graz, Austria
[3]AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK

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ABSTRACT: An LSER study on the tautomerism of some aromatic Schiff bases and related azo compounds has vindicated the picture presented by previous *ab initio* studies and added further detail of its own. As predicted, the aminoenone tautomer is always the more polar (positive π^* term) and, in addition, is specifically favoured by proton donor solvents (α term positive) through binding to the second lone pair on carbonyl. As expected for chelates, the Schiff bases are unaffected by proton acceptors (β term zero) but owing to the poor proton acceptor properties of the azo linkage, those of the azo compounds are partially broken. Tautomer preference as earlier calculated by *ab initio* methods is linearly related to log K_T in the gas phase as estimated by LSER. Comparison with other compounds clearly shows the effect of aromatization in reducing K_T; for 1-[(*E*)- methyliminomethyl]naphthalen-2-ol this is quantitatively similar to that for 2-pyridone, of which it is a kind of vinylogue. However, the effect of benzo fusion is similar only in part, and a further apparent anomaly lies in the near-identical K_T values, for water, of Schiff bases and azo compounds. This is discussed in terms of their differing 'intrinsic' tautomeric bias, leading to a fortuitous cancellation of effects. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: tautomeric ratio; Schiff bases; azo compounds; LSER; *ab initio* calculation; hydrogen bonding; chelate formation

INTRODUCTION

Change in phase has long been known to affect the rates and equilibria of chemical reactions, but it is only in recent years that an attempt has been made to identify the solvent properties that underlie these variations and to use them in a quantitative manner. The most generally successful attempt has been the linear solvation energy relationship (LSER) methodology of Taft, Kamlet and co-workers, whose most comprehensive solvent parameter listing[1a] dates from 1983, with additions and emendations from 1988.[1b] Three solvent properties (solvatochromic parameters)[1] are found sufficient as descriptors in most cases (for partitioning *between* solvents, extra parameters are necessary). These are: α, a measure of solvent proton donor ability; β, a measure of its ability as a proton acceptor; and π^*, a less readily definable quantity which appears to consist in some blend of dipolarity with polarizability. The typical LSER equation may then be summarized as

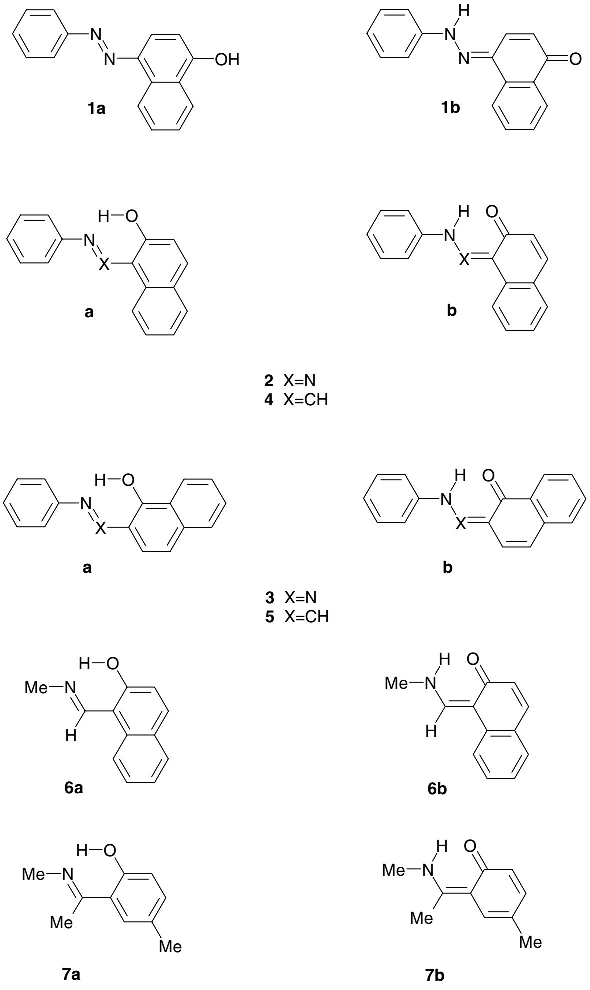
$$\log Q = c + s\pi^* + a\alpha + b\beta \qquad (1)$$

where Q is the quantity under study and not all terms are necessarily significant. When Q is the tautomeric ratio and solvent–water partitioning is also measured, it then becomes possible to analyse the properties of the individual tautomers, as has been carried out for compound **2** in the present study, the dyestuff Sudan I, by Abraham *et al*.[2]

Otherwise, surprisingly few LSER studies of tautomerism have been published since the pioneering work of Beak and co-workers on β-diketones[3] and on pyridones.[4] Recently however, Antonov and co-workers have published a number of papers[5–10] concerning the Schiff bases **1, 4** and **5** and the related azo- compounds **2** and **3** (Scheme 1), which include data[5–8,10,11] in a variety of solvents that have proved eminently suitable for the present LSER analysis. These data appear in Table 1 along with those from a study by Dudek and Dudek[12] on the related Schiff base **6** (Scheme 1); the resulting LSER equations are given in Table 2. As previously,[5–10] K_T is defined in terms of a shift from the hydroxy (**a**) to the oxo (**b**) form: $K_T = [\mathbf{b}]/[\mathbf{a}]$.

The essential virtue of LSER analysis is that it replaces vague concepts of solute or solvent 'polarity' and 'specificity' by precisely defined relationships which possess a recognizable chemical meaning. Although some of the conclusions from this study have already appeared,[10]

Correspondence to: P. J. Taylor, 7 Radnormere Drive, Cheadle Hulme, Cheadle, Cheshire SK8 5JX, UK.
E-mail: pjtaylor@ukinf.com



Scheme 1

this paper presents for the first time the evidence on which they are based. Another virtue of LSER is its ability to allow cross-comparison between the behaviour of chemical classes by extrapolation to a common phase in a way which gives rise to chemical insights; we pursue this aim in the section overview.

RESULTS AND DISCUSSION

LSER analysis

The LSER regression equations for compounds **1–6** and **8–11** appear in Table 2. The Schiff bases **4–6** show significant terms in π^* and α but not in β. This parallels the behaviour of acetylacetone (**8**) (Scheme 2), where the absence of a β term is attributed[3] to the presence of an intramolecular hydrogen bond too strong to be broken by the solvent. For **4–6** there is competition between NH$\cdots$O and OH$\cdots$N bonding with similar effect since both bonds are strong, as is confirmed by calculation.[10] Despite this, **4–6** all show positive α terms, since the second lone pair on carbonyl, unlike the first and that on aza nitrogen in the **a** forms, is accessible to the solvent. The larger coefficient for α in **6** than in **4** or **5** is expected since NHMe is a better electron donor[13] than NHPh so carbonyl in **6b** should be a better proton acceptor.[14,15] The positive coefficients for π^* in all three cases firmly identify the **b** forms as the more polar, as is supported by calculation[8–10] and by thermodynamic studies.[10] For both α and π^* the coefficients are greatest for **6**, which is therefore expected to have the highest K_{T} value in polar solvents, as is found.

Despite their parallelism in structure, the azo compounds **2** and **3** do not entirely parallel **4** and **5** in their behaviour. For both compounds the π^* and α terms are again positive, for similar reasons,[9,10] but each now possesses a *negative* β term. Hence intramolecular bonding must be weaker, as is confirmed by calculation,[10] and so can be broken by proton acceptor solvents. Its negative sign is consistent with other evidence[14,16] that OH is generally a better proton donor than NH. Their π^* terms are small and for **2** may not exist; cf. Eqns (3) and (4). However Abraham *et al.*,[2] who also examined **2**, obtained an equation almost identical with Eqn (3) using a different selection of solvents, so we believe it to be genuine. These small π^* terms presumably result from an attenuation of the difference between the dipolarity of the rival tautomers caused by replacing X = CH by X = N (Scheme 1). Following these authors who find K_{T} for **2** to be anomalous for formamide, we also omit it. However, we have not followed them in using data obtained for aqueous ethanol, (a) because this is not available across the series and (b) since the α and β values for the pure solvents which come from the same compilation[17] differ from those elsewhere accepted,[1] hence there is a potential problem of incompatibility in their use.

The absence of an intramolecular hydrogen bond in **1** produces significant differences. Its larger positive π^* term reflects its longer dipole and greater electronic flux, relative to **2** and **3**, while its much larger negative β term confirms the greater proton donor ability of OH than of NH. Nevertheless, this is much smaller than that for the β-diketone **9** (Table 2; note the change in sign, reflecting the different sign of K_{E}), which signals the pure effect of enolic OH in the absence of competition. Comparison of the β term for **1** with those for **2** and **3** emphasizes that the intramolecular bond of the latter pair can only be partly broken. These facts taken together imply that aza nitrogen is a poorer proton acceptor than that of the corresponding imine, and independent evidence exists for this. Table 3 lists the octanol–water fragment values ('*f* values')[18] for key fragments A in the context of PhAPh.[19] These '*f* values' are (logarithmic) indices of hydrophobicity, becoming more positive as this increases, and although hydrophobicity also rises with fragment volume, these fragments are near enough isosteric for that factor to be unimportant. It will be seen that, whereas the replacement in stilbene of one CH by N reduces hydrophobicity by almost two orders of magnitude, replacement of both cancels half that effect. Clearly

Table 1. Variation of $\log K_T$ with solvent for compounds **1–6**

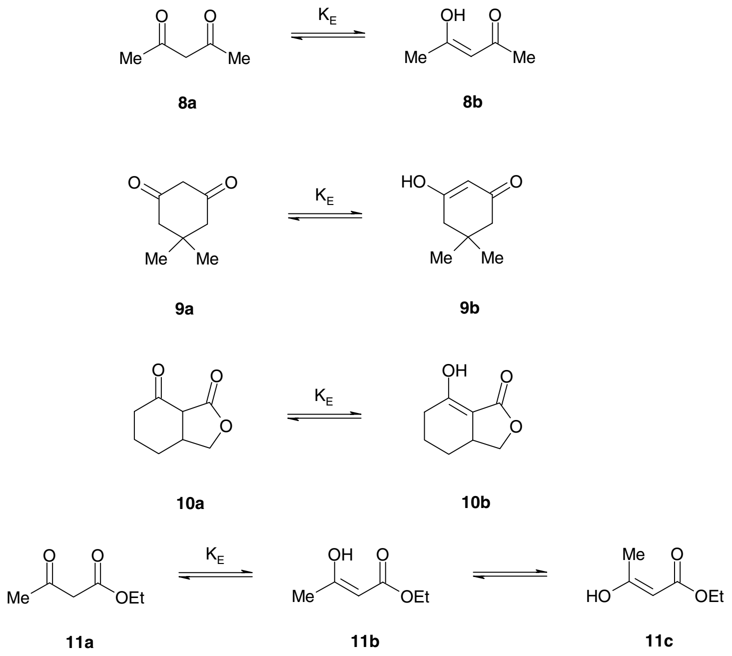
	Solvent[a]			Log K_T[b,c]					
Compound	π^*	α	β	**1**	**2**	**3**	**4**	**5**	**6**
MeOH	0.60	0.93	0.62	−0.59	0.19	0.31	−0.02	0.06	0.95
EtOH[d,e]	0.54	0.83	0.77	−0.85	−0.21	0.30	−0.03	0.17	
Pr^i-OH	0.48	0.76	0.95					0.00	
Et_2O	0.27	0	0.47				−0.87	−0.62	
Me_2CO	0.71	0.08	0.48	−0.43		0.25	−0.48	−0.35	
EtOAc	0.55	0	0.45	−0.59		0.26		−0.46	
MeCN	0.75	0.19	0.31	−0.24	−0.18	0.35	−0.25		
$HCONH_2$	0.97	0.71	0.60	0.17	0.45[f]				
DMF	0.88	0	0.69	−1.06		0.20		−0.31	
DMSO	1.00	0	0.76	−0.90		0.22	−0.12	−0.08	0.30[g]
Pyridine	0.87	0	0.64						0.30
PhMe	0.54	0	0.11					−0.52	
$(CH_2Cl)_2$	0.81	0	0			0.36			
CH_2Cl_2	0.82	0.30	0	0.20	−0.08	0.40	−0.23	−0.19	
$CHCl_3$	0.58	0.44	0	0.13	0.17	0.40	−0.28		0.40
CCl_4	0.28	0	0		−0.25	0.33	−0.83	−0.66	−0.55
C_6H_{12}	0	0	0			0.21		−0.70	
Hexane	−0.08	0	0				−1.06		
Isooctane	−0.08	0	0	−0.94	−0.31	0.18			

[a] Solvatochromic parameters π^*, α and β from Ref. 1.
[b] At ambient temperature.
[c] For sources of data, see text.
[d] Absolute EtOH (Ref. 11).
[e] Slight discrepancies between some values and those of Ref. 10 result from the use there of $\Delta G = \Delta H - T\Delta S$ to calculate $\log K_T$.
[f] Outlier (see text).
[g] Estimated from value for **7** using the close parallelism between other values for **6** and **7**.

Table 2. LSER correlation equations [Eqns (2)–(12)] for compounds **1–11**[a,b]

Compound	Eqn	c	s	a	b	n	r^2	s	F
1	(2)	−0.81 (0.17)	1.17 (0.26)	0.63 (0.19)	−1.50 (0.26)	11	0.856	0.21	13.9
2	(3)	−0.29 (0.10)	0.11 (0.19)	0.79 (0.27)	−0.68 (0.28)	7	0.81	0.12	4.2
2	(4)	−0.25 (0.06)		0.85 (0.22)	−0.70 (0.25)	7	0.79	0.11	7.4
3	(5)	0.23 (0.02)	0.17 (0.04)	0.16 (0.03)	−0.23 (0.03)	13	0.867	0.03	19.5
4	(6)	−1.05 (0.04)	0.85 (0.07)	0.60 (0.06)		10	0.976	0.07	143
5	(7)	−0.76 (0.06)	0.55 (0.10)	0.63 (0.07)		12	0.943	0.08	74
6	(8)	−0.87 (0.12)	1.25 (0.16)	1.17 (0.11)		5	0.987	0.09	74
8	(9)[c,d]	1.50 (0.09)	−1.58 (0.14)	−0.18 (0.10)		18	0.905	0.16	71
9	(10)[c,d]	−1.78 (0.24)	0.54 (0.33)	0.70 (0.20)	4.38 (0.21)	14	0.981	0.21	171
10	(11)[c,d]	0.38 (0.14)	−1.90 (0.23)		−0.28 (0.18)	14	0.89	0.18	42
11	(12)[c,d]	0.11 (0.10)	−1.33 (0.20)	−0.42 (0.14)		14	0.82	0.18	25

[a] See Eqn (1) for the definitions of c, s, a and b.
[b] n = number of points, r = correlation coefficient, s = standard error, F = Fisher's F-statistic.
[c] For $\log K_E$, where K_E = [enol]/[keto]; see text.
[d] Ref. 24.



Scheme 2

—CH═N— is much more hydrophilic than —N═N— and, although no direct measurement exists, it follows that the latter must be a much poorer proton acceptor; consistently, our homodesmotic treatment of intramolecular bonding[10] predicts that the azo compounds will have the weaker bonds.

Extrapolation to the gas phase

Calculations for the isolated molecule implicitly refer to the gas phase, and there is a common assumption that behaviour in alkane solvents must be similar. This is not necessarily true. Laurence *et al.*[20] obtained $\pi^* = -1.23$ for the gas phase, as far from $\pi^* = 0$ for cyclohexane in one direction as $\pi^* = 1.09$ for water in the other. Hence the gas phase will match expectation for an alkane solvent only if the π^* term is unimportant, which is not the case here.

$$\log K_{\mathrm{T}} = -1.78(0.07) - 0.81(0.06)\Delta H_f \quad (n = 6, r^2 = 0.978, s = 0.17, F = 180) \qquad (13)$$

$$\Delta G = 2.42 + 1.10\Delta H_f \qquad (14)$$

Table 4 contains our LSER-derived log K_{T} values for **1**–**6** in the gas phase, along with our calculated[10] differential energies of formation. The relation between them is given by Eqn (13), which may be further transformed into Eqn (14). This reveals that, to almost within the limits of error (±0.08), the tautomeric equilibrium is driven in the gas phase entirely by this enthalpy difference, except for a small constant quantity which is plausibly an entropy

Table 3. Fragment values (octanol–water) for compounds of type PhAPh[a]

A	*f*-Value
—CH═CH—	1.08
—CH═N—	−0.86
—N═N—	0.14
>C═0	−0.50

[a] Ref. 19.

Table 4. Tautomer ratio in water and the gas phase

Compound	Log K_{T}			
	Water[a]	Water[b]	Gas phase[c]	ΔH_{f}[d]
1	>0[e]	0.61	−2.25	0.62
2[f]		0.48	−0.43	
	0.07			−1.57
2[g]		0.46	−0.25	
3	—	0.51	0.02	−2.28
4	0.43	0.58	−2.10	0.60
5	0.49	0.58	−1.44	−0.33
6	—	1.86	−2.41	0.45
8	−0.83[h]	−0.43[j]		
9	1.28[i]	1.38[j]		

[a] Experimental, by extrapolation.
[b] From the appropriate equation in Table 2 using values of $\pi^* = 1.09$, $\alpha = 1.17$ and $\beta = 0.4$. This value for β derives from a recent survey of the conflicting evidence (Ref. 24).
[c] From the appropriate equation in Table 2 using values of $\pi^* = -1.23$, $\alpha = \beta = 0$. For the value for π^* see, Ref. 22.
[d] For the process **a** → **b** (B3LYP/6–311 + G**) in kcal mol^{-1} (Ref. 10).
[e] The relation between log K_{T} and solvent composition in aqueous ethanol is too non-linear to permit extrapolation.
[f] For Eqn (3).
[g] For Eqn (4).
[h] Ref. 32.
[i] Ref. 3.
[j] Ref. 24.

term. If so, its sign (ΔS negative in the forward direction) is such as to imply a more rigid structure for the **b** form. This is in apparent conflict with the greater strength of OH$\cdots$N bonding[10] but may be reconciled with it if we take into consideration the fact that ΔS refers to an overall process which includes, *inter alia*, the presence in the **b** tautomer of rigid exocyclic double bonds, C=C and C=O. It may be significant here that **1**, which cannot form an intramolecular bond, fits Eqn (13) as well as any other compound. Nevertheless, we regard this matter as *sub judice*.

Statistics and experiment related comments

The experimental procedures for the synthesis of compounds **1–5** and the spectral measurements, by UV–visible spectrophotometry, are described in detail elsewhere.[5–8,10] Since in solution the tautomers **a** and **b** coexist and cannot be isolated experimentally, quantitative analysis is in general impossible by means of classical spectrophotometric analysis. Therefore, the tautomeric constants were estimated by using an advanced spectral data processing method based on resolution of overlapping bands.[21] Its reliability has been proved by analysis of simulated and model mixtures[22] and in real chemical systems.[23]

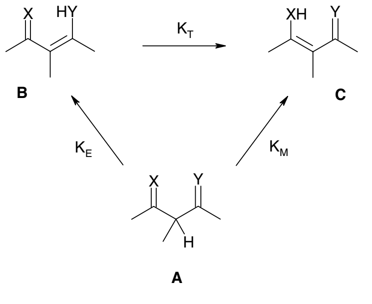
The statistics require comment. For the three azo compounds, these are fairly poor, and this is certainly not because the experimental data are less accurate than elsewhere. Any linear free energy analysis depends for its success on precise characterization of the system being examined. If this is compromised, e.g. by the presence of molecular species not part of the analysis, that analysis may be at risk. This is most obviously true for **2** and **3** since both probably contain unchelated material, which, for either component or both, may vary with solvent in a way that does not reflect the behaviour of the dominant subspecies. Also, this unchelated material, being spectrally almost identical with the chelated material (otherwise no clear isosbestic points can be observed), cannot be recognized by the chemometric approaches (see above) used for calculation of K_T. To a lesser extent it may also be true for **1**, where conformational complications are possible. By contrast, the tight chelate bonding of **4** and **5** leads to clearly defined systems whose statistics show a marked improvement. A somewhat similar contrast is shown by **8** and **9**; whereas **9** is a rigid system **8** is not, and this fact is again reflected in the latter's poorer statistics (Table 2).

There is further evidence from another source. Water is an extreme and sometimes badly behaved solvent and there is evidence for its anomalous behaviour from some LSER studies.[24] As an example, we contrast the β-keto esters **10** and **11** (Scheme 2), for which $\log K_E$ in water is -1.62[3] and -1.06[25], respectively. According to our LSER analysis[24] (Table 2), the corresponding calculated values are -1.80 and -1.83, so that although agreement is reasonable for the rigid molecule **10**, for **11** it is not; much more enol is present than extrapolation from other solvents would predict. This is plausibly due to the presence, in water much more than elsewhere, of unchelated enols such as **11c**, their presence the result of its exceptional amphiprotic properties. Because of these discrepancies we do not include water in any of the LSER analyses in Table 2.[24] Instead, our calculated values are compared with the sometimes ill-defined experimental values in Table 4. The direction of the discrepancy for **2**, $\Delta\log K_T \approx -0.4$, implies preferential ring opening for **2a**, consistent with other arguments. This is considerably less than that for **11** and about equal, although in the opposite direction, to that for **8** (note for the latter the opposite sign for $\log K_E$). The Schiff bases **4** and **5** escape these problems through possessing tighter chelates. Similar but smaller random variations elsewhere are presumably responsible for the poorer statistics of **2** and **3**.

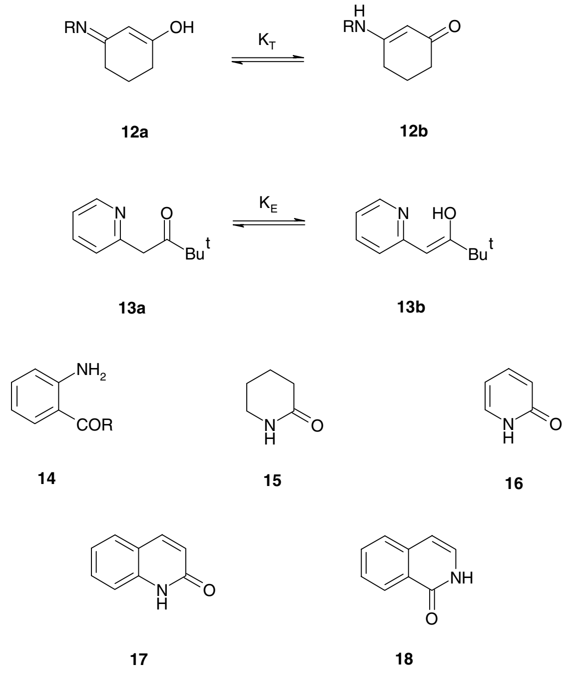
OVERVIEW

We may attempt to place these results in context. The present study exemplifies a much more general situation which is set out in Scheme 3. In this three-way equilibrium, a species **A** containing two hetero-double bonds C=X and C=Y separated by a saturated carbon atom can enolize to give either or both of the species **B** and **C**. Here we use single-headed arrows to define the direction of each equilibrium, i.e. $K_M = K_E K_T$. For symmetrical molecules such as **8** and **9**, $K_E = K_M$ so that $K_T = 1$. Among asymmetric molecules a pertinent example (Scheme 4) is **12** (R = alkyl), for which $K_T > 10^8$ in water[26] and species **A** is undetectable.

For X = NR, Y = O there are three ways in which the basic structure of Scheme 2 can be aromatized. If C=N is part of an aromatic system, the result is to favour species **A** and **B** at the expense of **C**. An example is **13**,[27] where **13b** attains parity with **13a** only in the most non-polar solvents and $\log K_E = -1.7$ may be calculated for water.[24] The LSER equation for **13**[27] is dominated by π^* and α, as it is for **8** (Table 2), both forming chelates. If C=C in **C** is part of an aromatic ring, the dominance of this tautomer is reinforced to the point where the



Scheme 3



Scheme 4

resulting compounds, such as **14**, would not ordinarily be considered capable of tautomerism at all. If, however, C═C in **B** is aromatized, the result is effectively to abolish tautomer **A** and reduce the dominance of **C** to the point where the outcome as to K_T is open. That is the situation in compounds **1**–**7**, which we now consider.

No K_T value is known for a simple chelated aminoenone, but since $OH \cdots N$ bonding is generally much stronger than $NH \cdots O$ bonding, as seen above, some attenuation relative to $>10^8$ in **12** would be expected, and this is backed up by calculation,[24] which suggests a value closer to 10^6. Our closest comparison is with **7**. Full LSER analysis is impossible through the paucity of data, but where the same solvents have been employed $\Delta \log K_T$ between **6** and **7** is so nearly constant as to suggest $K_T \approx 10$ for the latter, a fall therefore of $\sim 10^5$-fold relative to a hypothetical non-aromatic precursor. For the attenuation of K_T for 2-pyridone (**16**) relative to 2-pyrrolidinone (**15**) (Scheme 4), also in water, we estimate[24] a drop of $\sim 10^4$-fold, a closely similar factor. There is a further parallel in the effect of substitution on nitrogen. The effect of substituting NMe in **6** by NPh in **4** is to reduce the dominance of the oxo form in water by $\Delta \log K_T \approx -1.3$ (Table 4), whereas the process MeCONHMe to MeCONHPh results in $\Delta \log K_T \approx -2.1$;[24] both shifts result from the poorer electron donor properties of NHPh[13] and together demonstrate a similarity between the behaviour of amides and their vinylogues which is not far from quantitative.

The results of benzo fusion do not compare so closely. In monocyclic heterocycles its effect is straightforward: K_T in water is increased by $\Delta \log K_T = 1.0 \pm 0.1$ in water if NH occupies the α-position as in 2-quinolone (**17**) (Scheme 4) or by $\Delta \log K_T = 2.0 \pm 0.1$ if in the β-position as for isoquinolone (**18**).[24] In **6** vs **7**, which may be regarded as vinylogues of **16** and **17**, this pattern is followed, with $\Delta \log K_T$ probably ca 0.9 (Table 4). However, K_T is virtually identical for **4** and **5** (and probably for **2** and **3**) which, on this analogy, should not be the case. It is difficult to account for this anomaly but, by contrast with the oxo heterocycles, none of these azo compounds or Schiff bases is a truly rigid molecule, and its origin may be found here. At all events, the near equality of K_T for 2-quinolone (**17**) and 4-quinolone[28] is echoed by **2** and **1** (Table 4), so some degree of regularity is present here.

The near equality in water of K_T for Schiff bases and the corresponding azo compounds, which is greater for the first but typically only by a factor of three,[24] is another anomaly, since aza nitrogen is an electronegative substituent and it is clear, both from these LSER results (reduced π^*) and by calculation,[10] that it severely attenuates the electron donor properties of NH. There are two plausible explanations, both of which may contribute. One is a change in the relative strength of $OH \cdots N$ and $NH \cdots O$ bonding, chiefly due to the weakness of the azo group as a proton acceptor (Table 3). The other and possibly more important factor lies in the strong tendency of azo compounds to tautomerize to the hydrazone even when no through-conjugated structure can result; for example, $Me_2CHN{=}NPh$ in hexane goes irreversibly to $Me_2C{=}NNHPh$,[29] whereas $PrN{=}NPr$ in *tert*-butanol gives, at equilibrium, 98.4% of $EtCH{=}NNHPr$[30] ($\log K_T \approx 1.8$). By contrast, enamines $R^1CH{=}CHNHR^2$ are disfavoured relative to their imine $R^1CH_2CH{=}NR^2$ tautomers,[31] typically in water by ca 10^2-fold. A countervailing factor of probably $>10^3$ from this cause, set against the expected reduction in K_T relative to Schiff bases brought about in azo compounds by their greater electronegativity, should be ample to account for the near equivalence observed.

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