The tautomerism of indazolinone in aqueous solution. A note on the 'principle of vinylogy'

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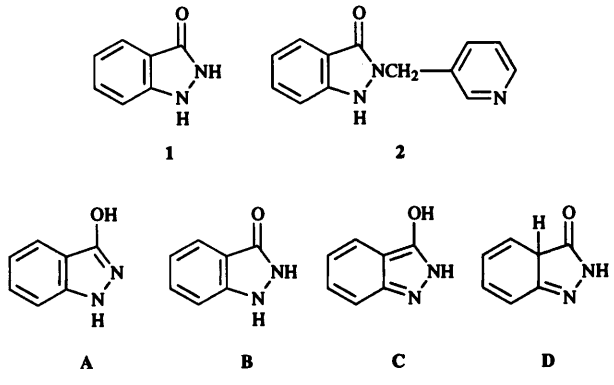
Correction factors derived in another study have been applied to the basic pK_a values of fixed model tautomers in order to elucidate the tautomeric balance for indazolinone 1 in aqueous solution. The oxo-form B dominates to the extent of *ca.* 95%; this is consistent with past studies in other solvents. Of the two possible hydroxy tautomers, the benzenoid form A accounts for almost all of the remainder, the proportion of the quinonoid form C being estimated as *ca.* $10^{-4.7}$. It has also proved possible to estimate all six of the microscopic acid pK_a values; as with the basic pK_as, the resultant of these agrees very closely with the measured, macroscopic pK_a of 1 itself.

1-Substitution engenders a switch to tautomer A; AM1 calculations suggest that the reason may be enforced planarity, leading to a severe (R)N–NH lone pair clash in B which destabilises this form.

Comparison with *N*-unsubstituted pyrazolones shows that benzene ring annelation has the expected effect of stabilising B and destabilising C. However, it is noted that A is more stable than C even when no quinonoid form is possible, and that this reflects a greater basicity for heterocycles in general when substituted with π-donors γ- rather than α- to aza-nitrogen. It is suggested that this effect applies equally in other contexts, as when C=O not C=N is the π-acceptor; that its origin lies in σ-bond-no-bond resonance which acts specifically to limit conjugation when π-donor and π-acceptor are contiguous; and that this phenomenon throws much light on the 'principle of vinylogy'.

Among the remaining problems in heteroaromatic tautomerism, that of indazolinone **1** (or 3-hydroxyindazole) arguably takes



1 **2**

A **B** **C** **D**

pride of place.[1] Three aromatic tautomers **A**–**C** are possible; a fourth, non-aromatic tautomer **D**, important (in non-polar solvents) for the related pyrazolones,[1a] may safely be discounted. Our present understanding is summarised by Elguero:[2a] that 1-substituted and 2-substituted indazolinones exist predominantly as **A** and **B** respectively, whereas the structure of *N*-unsubstituted indazolinones varies with their physical state. Unsurprisingly, in view of the general avoidance of quinonoid forms[1] (and see discussion below), tautomer **C** has never been detected.

The situation concerning **1** itself is particularly confused. Early IR evidence indicated it to exist as **B** in the solid state,[3] and this has recently been confirmed by a crystal structure determination.[4] However, UV spectra in ethanol[5] and a ^{13}C and ^{15}N NMR study in dimethyl sulfoxide (DMSO)[4] suggest a predominance of **A** in these solvents. The best quantitative evidence is that of Webb and co-workers,[6] who using the ^{13}C NMR spectra of model compounds, arrived at the conclusions of Table 1 (tautomer **C** had to be excluded from consideration through lack of an adequate model). Qualitatively, the rise in proportion of **B** with solvent proton donor ability (here designated as a_{solv})[7] throws open the question of its tautomeric form in the strong proton donor solvent water, $a_{solv} = 1.17$.

Table 1 Tautomer fraction of **1** as a function of phase[a]

Solvent	a_{solv}[b]	A	B
Solid state	—	—	✓
DMSO	0.00	0.75	0.25
MeOH	0.93	0.24	0.76
CF_3CH_2OH	1.51	0.03	0.97

[a] Ref. 6. [b] Ref. 7.

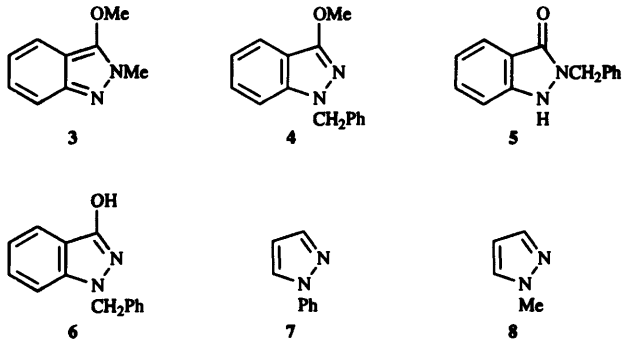
Recently, one of us has studied a number of 1- and 2-substituted indazolinones as 5-lipoxygenase inhibitors.[8,9] While activity was found in both series, only the latter were orally active, and in addition, their selectivity *vs.* inhibition of the enzyme cyclooxygenase was much superior; the outstanding compound in the series is the pyridyl derivative **2**. This pattern of activity strongly suggested that tautomeric form might be a contributory factor towards biological activity, and the present investigation was accordingly launched.

One result of this study has been to uncover, with the help of model pK_a values and on certain assumptions to be detailed below, the entire pattern of tautomerism in aqueous solution for indazolinone **1** itself. Another has been to throw light on the most curious feature of indazolinone tautomerism, namely the apparent discrepancy between the results of 1- and 2-substitution. We have been materially aided in this work by the preparation of the hitherto unavailable[4] model compound **3**, reported here for the first time. We conclude by comparing the present results with those we have previously reported[10] for the corresponding pyrazolones; some instructive resemblances and contrasts emerge.

Experimental

Materials and methods

Compounds **1**,[11] **4**,[9] **5**[12] and **6**[5] were prepared as described.[9] Water was glass distilled; other reagents were of AnalaR grade.



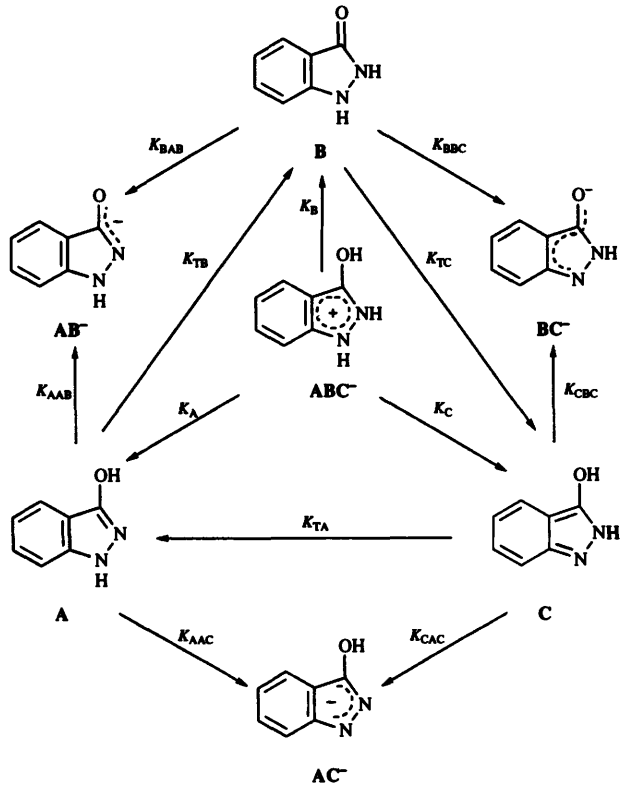
The NMR spectra of **3** were taken on a Jeol JNM-EX 400 NMR spectrometer at 400 MHz and 100 MHz for its ^1H and ^{13}C NMR spectra respectively, both in $CDCl_3$ solution and using tetramethylsilane as internal lock. Its mass spectrum (EI) was obtained on a VG 725 OSA mass spectrometer. UV spectra were run on a Beckmann DU7 UV spectrophotometer equipped with a thermostatted 1 cm cell. Basic pK_a values were obtained by standard techniques[13] from the UV spectra of a number of solutions at constant concentration in aqueous sulfuric acid of known H_0 value at 25 °C. The UV spectra were overlaid and there was no sign of any drift in the isosbestics that might have indicated decomposition. Evaluation of pK_a for **4** and **5** assumed the H_0 scale where H_A might have been more appropriate,[14] but since the two scales differ inappreciably in this range, no correction was thought necessary. Acid pK_a values were obtained potentiometrically, again by the standard methodology,[13] using a Radiometer TTT 80 titrator equipped with an ABU 80 autoburette and an Autocal PHM 83 pH meter carrying a Russell Type CMAWL combined electrode; the titration curve was plotted on a REC 80 Servograph recorder and indicated >98% purity in all cases. Results are included in Table 2.

Preparation of 2-methyl-3-methoxyindazole 3

A solution of diazomethane in diethyl ether prepared and titrated according to the method of Arndt[15] was added dropwise to a solution of 1,2-dihydro-2-methyl-3*H*-indazol-3-one[12] (2 g; 13.5 mmol) in a mixture of diethyl ether (50 cm^3) and ethanol (150 cm^3). After addition, the mixture was stirred for 1 h and washed first with dilute aqueous acetic acid, then water, dried ($MgSO_4$), and evaporated to dryness to give a mixture of **3** with 1,2-dihydro-1,2-dimethyl-3*H*-indazol-3-one[16] (1.8 g). The mixture was purified by column chromatography (SiO_2, 100 g) using methylene chloride–diethyl ether (50/50, v/v) and a gradient of methanol (1 cm^3 every 250 cm^3) as eluent to give 0.380 g (brown crystals, 17% yield) of pure **3** from the earlier fractions, mp 52.8–53.8 °C (Found: C, 61.0; H, 6.5; N, 16.4. $C_9H_{10}N_2O\cdot 0.75H_2O$ requires C, 61.5; H, 6.6; N, 15.9%); ν_{max}/cm^{-1} 1625, 1555, 1540, 1515, 1415, 1385, 1250, 1150; δ_H(400 MHz; $CDCl_3$) (All *J* in Hz) 3.94 (3 H, s, NCH_3), 4.32 (3 H, s, OCH_3), 6.90 (1 H, ddd, *J* 8.6, 6.5, 0.9, 5-*H*), 7.19 (1 H, ddd, *J* 8.8, 6.5, 1.0, 6-*H*), 7.49 (1 H, ddd, *J* 8.8, 0.9, 0.9, 7-*H*), 8.67 (1 H, ddd, *J* 8.6, 0.9, 1.0, 4-*H*); δ_C(100 MHz; $CDCl_3$) 34.99 (N-*C*H_3), 60.27 (O-*C*H_3), 106.72 (3a-*C*), 117.37 (7-*C*), 119.26 (5-*C**), 119.50 (4-*C**), 126.01 (6-*C*), 146.77 (3-*C***), 147.15 (7a-*C***); *m/z* (EI) 162 (80%, M$^+$), 147 (100%), 119 (9%), 105 (25%), 75 (23%).

Results and discussion

The neutral and ionised forms of **1** comprise three neutral tautomers **A**, **B** and **C**, three tautomeric anions **AB**$^-$, **BC**$^-$ and **AC**$^-$, and a common cation **ABC**$^+$ related as set out in Scheme 1. Here (and elsewhere) the lines represent equilibria while the arrow indicates the direction in which that equilibrium is defined. The subscripts are coded to relate these species in what is hoped will be an obvious manner. As a helpful mnemonic they are single for basic pK_a values, treble for acid pK_a values, and double (as *e.g.* K_{TA}) for the three tautomeric ratios.



Scheme 1

Derivation of tautomeric ratio

This is readily obtained from the basic pK_a of suitable model compounds,[1] where suitability is a function of (*a*) an unequivocal ionisation pathway, and (*b*) the absence of perturbing factors relative to the ionisation process being modelled. As to the first, the cations of **3** and **4** can only deprotonate in the sense of K_C and K_A respectively, so these *a priori* are suitable models. The cation of **5** could in principle deprotonate to a mixture of **B** and **C**, but the latter is so enormously disfavoured (*vide infra*) that any such effect must be negligible. Hence this criterion is satisfied throughout.

The second criterion is more complex. While the *N*-substituent of **3** is methyl, those of **4** and **5** are benzyl, and we need to correct for this. We proceed as follows. The difference ΔpK between the pK_a values of *N*-phenylpyrazole **7** and *N*-methylpyrazole **8** (Table 2) is 1.65, whereas the σ_I values of phenyl, methyl and benzyl are 0.12, −0.01 and 0.03 respectively.[17] If as expected the effect of this substituent is primarily inductive, then a 'two-point correlation' leads to the prediction of ΔpK +0.5 for the replacement of *N*-benzyl by *N*-methyl in this situation, and hence in **4**. Given ΔpK 1.41 for **9** and **10** and σ_I 0.15 for CH_2CF_3,[17] a similar calculation using these as models for the amide **5** leads to ΔpK +0.4. These are small but significant corrections and seem reasonable; the result of using them appears as the 'normalised' basic pK_a values of Table 2.

However, a second correction is also in principle required. The use of *N*-methyl and *O*-methyl derivatives to model the corresponding NH and OH tautomers has to assume either that methylation has no effect on pK_a, or has the same effect in both cases. For most published calculations this approximation, which we have termed[18] the 'naive basicity' assumption, has been adopted *faute de mieux*. In fact, there is ample evidence that neither assumption holds.[16] The reason for this lies in the

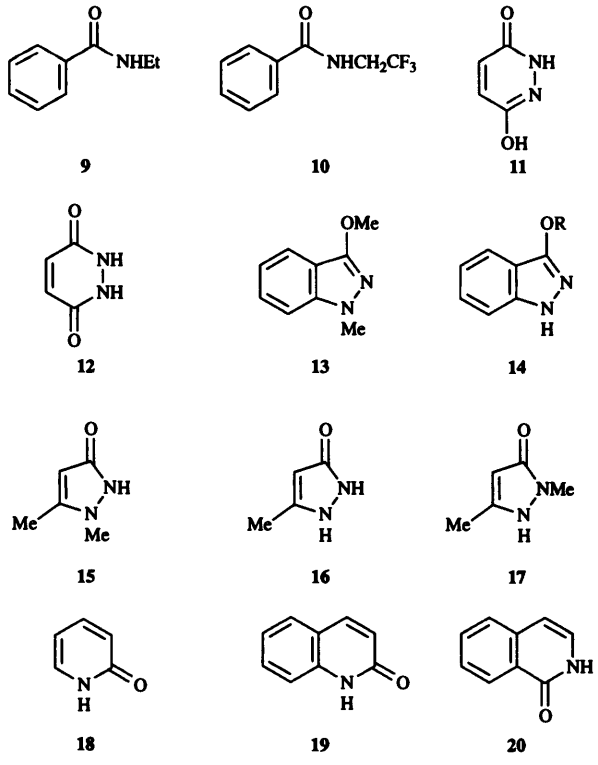


Table 2 Model compound pK_a values

Compound	Basic pK_a	'Normalised' basic pK_a[a]	Acid pK_a
1	0.33 ± 0.10		8.28
3	3.25 ± 0.05		
4	−0.65 ± 0.10	−0.15	
5	−0.55 ± 0.03	−0.15	8.44
6			7.21
7[b]	0.44		
8[b]	2.09		
9[c]	−1.92		
10[c]	−3.33		
25[d]	−2.08 ± 0.05		
26[d]	−1.36 ± 0.05		
27	−0.89 ± 0.01		6.06

[a] See the text. [b] J. Elguero, E. Gonzalez and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1963, **60**, 469. [c] D. W. Farlow and R. B. Moodie, *J. Chem. Soc. B*, 1970, 335. [d] Ref. 29.

Table 3 Correction factors for *O*- and *N*-methylated cations[a]

Cation derived from:	ΔpK_a
C=NNMe ⟶ C=NNH	0.73
O=CNMe ⟶ O=CNH	0.43
N=COMe ⟶ N=COH	1.0

[a] Ref. 10.

poorer solvation that results on alkylation, and which is more important for the cation since NH^+ and OH^+ are much more powerful proton donors, so much more heavily solvated, than NH and OH.[19] Hence the unsubstituted compound is expected to be a stronger base than its NMe or OMe derivative, contrary to what might have been anticipated on electronic grounds, and the pK_a values for the latter need to be corrected for this. It is possible in certain cases to estimate these corrections with reasonable accuracy, as for 1,2,3-triazole[18] and some pyrazolones.[10] The corrections we have found to work in the latter case, and which might reasonably be expected to give the right answer

Table 4 'Corrected' pK_a values[a] for the tautomers of indazolinone **1**

Species	pK_a
A	1.6
B	0.3
C	5.0

[a] To nearest 0.1; see the text.

here, appear in Table 3.† The derived 'true' pK_a values for **A**, **B** and **C**, rounded off to 0.1, are given in Table 4.

The prediction of Table 4 is that **B** predominates to the extent of *ca.* 95% in water, with 5% of **A** and a negligible proportion of **C**. This is entirely consistent with the data of Table 1, according to which the proportion of **B** should lie somewhere between the 76% for methanol and the 97% for trifluoroethanol. In addition, pK_{ABC^+} may be calculated from eqn. (1) as 0.28, which

$$K_{ABC^+} = K_A + K_B + K_C \quad (1)$$

compares well with the measured value of 0.33 for **1** (Table 2). By contrast, the 'naive basicity' method predicts about 50% each of **A** and **B**, with pK_a *ca.* −0.45 for **1**.

The effect of 1-substitution on tautomeric form

Species **B** can deprotonate to the anion in two ways but compound **5** only in one, so it is unsurprising that **1** should be a slightly stronger acid (Table 1). On the same reasoning, **6** if in the oxo-form should also be a slightly weaker acid than **1**. In fact, it is more than 10 times stronger. Consistently with other evidence,[1c,2,5] this indicates a switch by **6** to the hydroxy-tautomer.

Other explanations can be discounted. This increase in acidity is far too great to be an electronic effect due to the benzyl group, and in any case, there is no remotely similar effect in **5**. Furthermore, alkyl substitution is not expected to affect anion solvation, *vis-à-vis* that of the neutral species, remotely to the extent it affects that of the cation: the weak proton donor properties of amides and amines[20] are likely to be still further reduced in the anion. Hence, for anions, little or no correction should be required to the pK_a value of the alkylated model compound.

In an attempt to trace the source of this discrepancy, we have carried out AM1[21] calculations for **A**, **B** and **C** with and without geometry optimisation. The results are set out in Table 5. With geometry optimisation, **B** is the favoured tautomer; if planarity is enforced, **A** and even **C** become more favoured. While it is well established that gas phase calculations greatly exaggerate the differences in stability between rival tautomers relative to solution, and that in addition solvation will change and may even reverse the tautomeric balance so predicted,[22,23] these results nevertheless allow a rationalisation. It is known[24] that lone pair orbitals of the same geometry on adjacent heteroatoms, by repelling one another, have a strongly destabilising effect which can be powerful enough to cause a switch in tautomeric form when this possibly is open. One such example is maleic hydrazide[23] whose preferred (and unusual) tautomeric form is **11**,[1d] in which the lone pairs on NH and imino-nitrogen are orthogonal so that stereoelectronic repulsion is avoided. The same favourable >C=NNH− arrangement is found in tautomers **A** and **C**. This repulsion can also be avoided in **B** provided that the 1-*N* atom is at least partly pyramidal, which is likely since this is essentially amine not amide nitrogen, in contrast to that in the disfavoured diamide structure **12** (there is no suggestion of tautomeric form **11** where free rotation can occur, as in diacylhydrazines). In fact, the crystal structure of **1** shows

† Elguero *et al.*[1e] suggest +0.9 for the C=NNMe ⟶ C=NNH correction in indazole itself; we use that of Table 2 for consistency with our previous treatment.[10]

Table 5 AM1 calculations on the tautomeric forms of indazolinone[a,b]

Tautomer	Relative energy[c]	Relative energy[d]
A	0	0
B	−5.6	7.6
C	6.6	6.6

[a] ΔH_f/kcal mol^{-1} relative to **A**. [b] 1 cal = 4.184 J. [c] With geometry optimisation. [d] With planarity enforced.

1-*N* to be partly pyramidal,[4] and since the solid state tends to enforce planarity, it is likely that, in solution, this lone pair clash is largely avoided. If 1-benzylation brings about a sufficient degree of planarity to make **A** the favoured tautomer,‡ then **6** becomes a suitable starting point for the calculation of pK_{AAB}; we pursue this argument below.

Calculation of the acid pK_a values

Elguero and co-workers[25] have shown that linear relations exist between the acidic and basic pK_a values of all azoles for which the requisite data are known. In fact there are two such relations, one for pyrazoles and one for the rest; and since benzimidazoles as well as imidazoles obey the latter relation, we may confidently predict that indazoles will follow the former. The relevant equation is (2), where pK_{st} is the statistically corrected

$$pK_{st} = 0.943\ pK_{NMe} + 11.83 \quad (2)$$

acid pK_a of the NH form and pK_{NMe} is the basic pK_a of its NMe derivative. Since indazoles unlike pyrazoles are unequivocally in the 1-*H* form,[1e] statistical correction is not required here and the constant in eqn. (2) becomes 12.13.

The 'normalised' pK_a of **4** in Table 2 is that calculated for **13**; application of the appropriate correction factor from Table 3 leads to a predicted basic pK_a value of 0.85 for **14**. This is the species required in eqn. (2) for the calculation of pK_{AAC}. There results pK_a 12.9, which makes **14** a stronger acid than pyrazole and presumably a stronger acid than indazole itself, as would be expected since OR adjacent to imino-nitrogen is generally base-weakening in heterocycles[26] (see Appendix). Given pK_{TA} 3.4 (Scheme 2), pK_{CAC} 9.5 follows by difference.

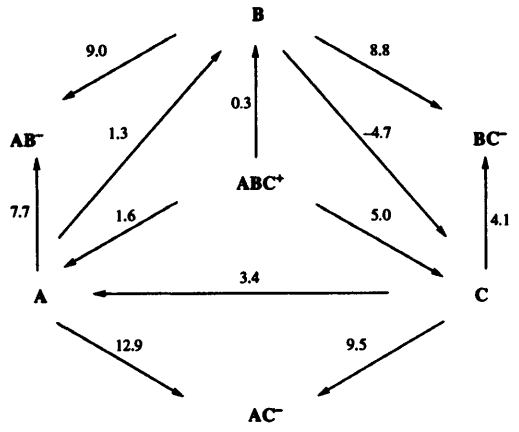
An interesting consequence of the near-unit slope of eqn. (2) is that substituents are expected to have near-identical effects on acidic and basic pK_a values. Hence we may use the correction factors of Table 2 equally to correct the measured acidic pK_a values of **5** and **6** to the appropriate model species. Compound **5** as model for **B** can ionise only to give the anion BC^-; correction by +0.4 gives pK_{BBC} 8.8. Similarly, **6** as model for **A**, corrected by +0.5, will give pK_{AAB} 7.7; this estimate is less certain since **6** may contain a little of **B**, but even 20% of **B** could only produce an error of ΔpK 0.1. Finally, pK_{BAB} and pK_{CBC} follow by difference.

The final picture appears as Scheme 2; here the numbers are pK_a or pK_T values, rounded to 0.1, and the arrowed lines have the same significance as in Scheme 1. As a final check, we may attempt to estimate the global or overall acidic pK_a of **1** *via* eqn. (3), in which x_A, x_B and x_C are the mole fractions of **A**, **B** and **C**

$$K(1) = x_A(K_{AAB} + K_{AAC}) + x_B(K_{BAB} + K_{BBC}) + x_C(K_{AAC} + K_{CAC}) \quad (3)$$

respectively. Solution of eqn. (3) using the values of Scheme 2 results in $pK(1) = 8.3$, the measured value being 8.28. We have seen above that its basic pK_a is predicted with equal success. We

‡ It is not clear why this should happen; it may simply be a ponderal effect, in which case methylation might not have the same consequences. This possibility is suggested by the different behaviour of **15** as discussed below.



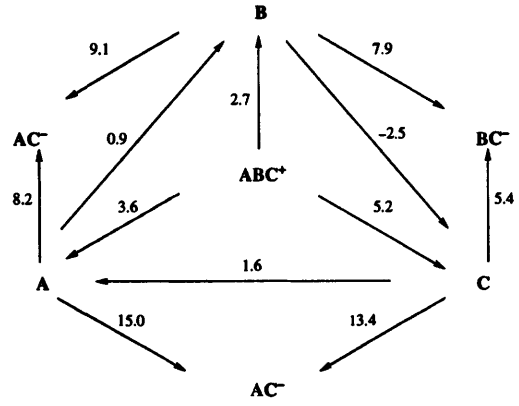
Scheme 2 Figures here and in Scheme 3 are pK_a or log K_T values (see the text)

believe that Scheme 2 represents as accurate a picture of indazolinone tautomerism as is possible at the present time.

Tautomerism in the pyrazolones

Katritzky and Maine[27] have studied the tautomerism of the pyrazolones **15** and **16**, obtaining pK_a data which we have reinterpreted[10] to derive tautomer balances, and overall basic pK_a values, closely in agreement with those observed,[27] in a parallel investigation to the present one. The correction factors of Table 3 were first used in that study. Our results for **16**[10] are exhibited in the central portion of Scheme 3. Here **B** is not quite so predominant, with 90% of the oxo-form actually present[27] (we calculate[10] 88%). Interestingly, 70% of the oxo-form is still present in **15** (calculated value 75%) so the effect of 1-methyl in that case is very much less than that of 1-benzyl here, consistently with the ponderal effect suggested above. This similarity is useful in that **15** becomes a reasonable model for the ionisation of **16** (either tautomer) to give the anion AB^-.

We may now complete Scheme 3 by carrying out estimations



Scheme 3

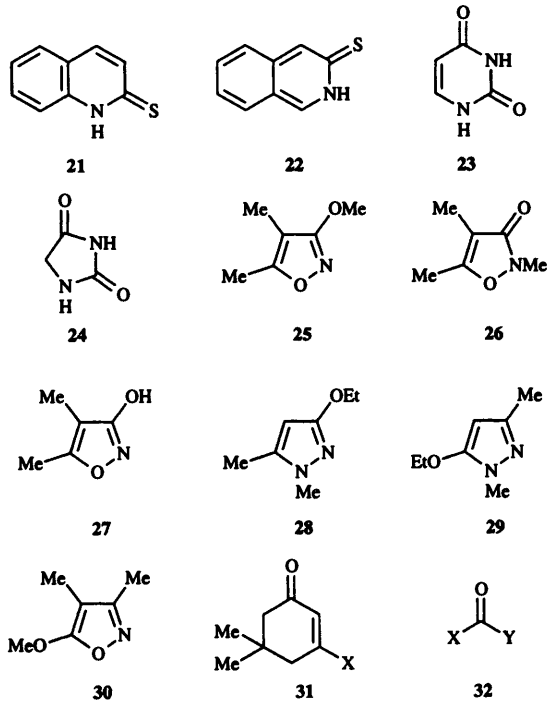
of the acidic pK_a values on the lines set out above. Given that **C** is once again greatly disfavoured, pK_a 7.94 for **17**[27] may be used unchanged for pK_{BBC}. As noted above, pK_a 8.91 for **15** does not refer unequivocally to either ionisation pathway, but nevertheless, given pK_{TB} 0.9, it can be factored to give pK_{BAB} and pK_{AAB}. Here we correct for the slightly different tautomer balance in **15** *vs.* **16** by adjusting this macro-p*K* value by +0.2 to 9.1 on the lines of their different basic macro-p*K* values.[10,27] [This correction is once again based on the implications of eqn. (2).] Finally, we use the estimated[10] basic pK_a of **15** as form **A**, 3.05, to calculate its acidic pK_a according to eqn. (2); pK_{AAC} 15.0 results. The remaining values, for pK_{CBC} and pK_{CAC}, follow

by difference. From eqn. (3) we now calculate the acidic pK_a of **16** as 7.6; unfortunately, no experimental value has been reported.

Tautomeric preference in indazolones and pyrazolones

From Scheme 2 for indazolinone **1** and Scheme 3 for the pyrazolone **16** it is now possible to highlight similarities and differences that throw considerable light on the often conflicting factors which influence tautomeric form in compounds of this sort.

As long realised,[1] both come into the interesting category of compound whose tautomeric preference, as regards **A** *vs.* **B**, cannot be assumed. In fact, both in water favour the oxo-form, but not by very much; as we have noted above, and as our AM1 calculations help to bear out, the reason for this lies in the stereoelectronic factors that destabilise –NHNH– relative to >C=NNH– when planarity is enforced.[24] Other factors also show themselves. It has been noted that benzene ring annelation generally increases the bias in favour of the oxo-form, since conjugation in the annelated ring is unaffected and overall aromaticity, whose loss has to be offset against the gain of amide resonance, is now much less diminished; compounds **18**, **19** and **20** possess pK_T 3.0, 3.9 and 4.8, respectively, in favour of the oxo-form.[1f] In fact the effect reported here, while present (ΔpK_T *ca.* 0.4) is much less than normal, possibly indicating that the pyrazole ring itself is much less aromatic than that *e.g.* of pyridine. Another factor is that quinonoid forms tend to be strongly disfavoured; the thiones **21** and **22** are favoured by



margins of pK_T 5.1 and 3.0, respectively, over the corresponding thiols.[1f] The difference between pK_{TA} 1.6 for **16**, and pK_{TA} 3.4 for **1**, is very much in line with the factor of *ca.* 10^2 that appears normal in such cases, and virtually identical with that of $10^{1.7}$ known to apply in aqueous solution to indazole itself.[1,22c]

Other features, not hitherto identified, appear on closer inspection. One of these is that the nominal amine NH of **16**, and even by a small margin that of **1**, appears to be the one that preferentially loses its proton. Surprisingly, this has precedent: uracil **23** ionises preferentially by loss of a proton from *N*-1,[28] despite the fact that *N*-3 is nominally that of an imide and is certainly the site of loss from hydantoin **24**. The likely reason for this, for both **16** and **23**, is that the anion is better conjugated, *i.e.* the resulting anionic charge is spread across a greater distance. Hence BC^- is the predominant (>90%) anion for **16**, though a nearly equal mixture with AB^- is found for **1**. Another point of interest concerns the tautomeric balance between **A** and **C**. Even for the pyrazolone **16** where no quinonoid form exists, **A** is preferred, **C** being the stronger base; which can only mean that OH is a better electron donor to imino-nitrogen from the more remote substituent position. These and other aspects of vinylogous conjugation are considered further in the Appendix.

3-Hydroxy-4,5-dimethylisoxazole: a cautionary tale

3-Hydroxyisoxazoles[1,29] are among the few potential oxoheterocycles in which evidence for predominance of the hydroxy tautomer, under all known circumstances, is compelling. Katritzky and co-workers[29] have prepared and investigated a number of compounds which include the fixed tautomers **25** and **26** as well as the parent compound **27**. All the evidence suggests that **27** exists as shown: its solid-state IR spectrum (as well as those examined in solution) is that of a hydroxy derivative, and the same is true of its solution UV spectra. Only in water, where the UV spectra of **25** and **26** are not readily distinguishable, is the situation in any way obscure, though in point of fact, *ab initio* calculations carried out at the 6-31G** level with molecular dynamics simulation for aqueous solution predict a predominance of the hydroxy tautomer in this case as well.[22b]

The pK_a values of **25** and **26** are included in Table 2. On 'naive basicity' assumptions, this indicates 84% of the hydroxy tautomer **A**. Application of the corrections from Table 3 translates these pK_a values to −1.08 and −0.93 respectively, implying 59% of **A**, *i.e.* still a predominance, but not by so much. For **27**, pK_a −1.31 is then predicted. The value found is pK_a −0.89. Hence eqn. (1) is incommensurable.

Rationalisations can be suggested but do not help. It seems clear that the correction factors of Table 3 are very specific, and do not translate to other situations—we had already discovered this for maleic hydrazide.[23] In particular, the correction factor for OMe ⟶ OH of 1.0, applicable to **25**, needs to be at least 1.3 before eqn. (1) can be applied. It would not be too surprising if both correction factors need to be increased, since OH^+ in this more electron-deficient molecule may require still heavier solvation, and the even more severe lone pair repulsion in –ONH– than in –NHNH– that presumably helps to determine tautomeric preference may have similar consequences. As far as one can see the relatively high acidity of **27**, pK_a 6.06, as compared with pK_{AAB} in Schemes 2 and 3, does qualitatively suggest the predominance of tautomer **A**, consistently with all the other evidence.

Conclusions

With the help of correction factors originally derived for certain pyrazolones,[10] we have established tautomer ratios and micro-pK_a values in aqueous solution for indazolinone **1** itself. Comparison with the above analysis for the pyrazolone **16** shows resemblances and differences that are readily interpretable in terms of established chemical principles:[1] the increased proportion of the oxo-form **B** on benzene ring annelation; and the further effect of this in disfavouring tautomer **C** which contains a quinonoid arrangement of double bonds. On the basis of AM1 calculations, the effect of 1-substitution in inducing a switch to the hydroxy-form **A** is attributed to an enforced molecular planarity which results in strong –(R)NNH– lone pair repulsion. In **16**, the predominant anion is that formed by loss of a proton from nominally amine NH; this is probably due to charge delocalisation, which will also help to explain why **A** is the more stable of the rival hydroxy-forms.

The above correction factors fail for the isoxazole **27**;[29] along with a similar failure for maleic hydrazide **11**,[23] this unfortunately seems to indicate their extreme specificity.

Appendix

The 'principle of vinylogy'[30]

There is ample and growing evidence that vinylogous conjugation is much more pronounced than that of the contiguous sort: vinylogous amides are much stronger bases than amides themselves;[31] their carbonyl frequences are lower;[32] and not only carbonyl but many other π-acceptor groups become much more powerful proton acceptors when separated from the π-donor atom by a carbon double bond.[33] The present results, added to those of some previous studies, may be used to throw considerable light on this phenomenon.

It appears to be a general feature of aza-heterocycles that γ-substitution of an electron donor enhances basicity more than α-substitution. This is the feature remarked on above, concerning the preference for tautomer **A** over tautomer **C** in the case of the pyrazolones. This result partly reflects the behaviour of the fixed tautomers **28** and **29**, which possess pK_a values of 2.05 and 3.51 respectively.[27] In a similar way, the related isoxazoles **25**[29] and **30**[34] possess pK_a values, respectively, of −2.08 and −1.47. Indeed, the first in each pair is not only a weaker base than the second; it is a weaker base than the corresponding compound lacking alkoxy substitution.[27,34]

4-Methoxy- and 2-methoxy-pyridine possess pK_a values of 6.58 and 3.06 respectively, and the second result mirrors those above in an even more extreme fashion, given pK_a 5.23 for pyridine itself. Taft and co-workers[26] have analysed this case. They demonstrate that, while σ_I is already more important than σ_R^+ in correlating the pK_a values of 4-substituted pyridines ($\rho_I = -5.15$, $\rho_R^+ = -2.69$), its dominance in the 2-position is overwhelming ($\rho_I = -10.60$, $\rho_R^+ = -1.39$). Hence the resonance donor effect of methoxy is swamped by its inductive acceptor properties. A similar effect can be anticipated for OH in **1** and **16**; it may well operate in the pyrazoles and isoxazoles discussed above, and for (the usually unobservable) hydroxy-heterocyles in general.

The carbonyl group as π-acceptor is similar to aza-nitrogen and there is some evidence that the same factors operate. Carbonyl frequency in the unsaturated ketones **31** depends almost equally on σ_I and σ_R^+ for the substituent X ($\rho_I = 33.21$, $\rho_R^+ = 29.92$).[35] However, for CH_3COX, σ_I is dominant ($\rho_I = 204.53$, $\rho_R^+ = 46.85$).[35] Similarly in **32**, σ_I (for X + Y) dominates ΔG for complexation with iodine ($\rho_I = 2.63$, $\rho_R^+ = 0.94$).[36] Hence we have at least a partial rationale for the observed superiority of vinylogous conjugation over the contiguous sort in the evidently much greater ability of π-donor atoms to exercise their resonance donor properties when not directly attached to the π-acceptor group. As to what lies behind that rationale itself, we have elsewhere suggested[37] that contiguous conjugation loses out through the operation of 'σ-resonance'—σ-bond-no-bond resonance[38]—*i.e.* interaction between the C–X antibonding orbital and the neighbouring π-acceptor lone pair, as has indeed been demonstrated for esters by Huyskens *et al.*[39] That is: we owe the superiority of vinylogous conjugation not to any special feature it may possess, but to a deficiency inherent in the contiguous variety. Amides, esters *etc.* are undoubtedly conjugated structures, but with the restraints of σ-resonance removed, their vinylogues are even more so.

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References

1 J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, *The Tautomerism of Heterocycles*, Academic Press, New York, 1976, (*a*) pp. 339 *et seq.*; (*b*) p. 20; (*c*) p. 352; (*d*) p. 124; (*e*) p. 291; (*f*) p. 204 *et seq.*
2 J. Elguero, in *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, vol. 5 (ed. K. T. Potts), p. 167, Pergamon, Oxford, 1984, (*a*) p. 215; (*b*) p. 211.
3 D. G. O'Sullivan, *J. Chem. Soc.*, 1960, 3278.
4 P. Ballasteros, J. Elguero, R. M. Claramunt, R. Faure, M. De la Concepción Foces-Foces, F. H. Cano and A. Rousseau, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1677.
5 J. Schmutz, F. Hunzicker and W. Michaelis, *Helv. Chim. Acta*, 1964, **47**, 1986.
6 W. Schilf, L. Stefaniak, M. Witanowski and G. A. Webb, *Magn. Reson. Chem.*, 1985, **23**, 784.
7 M. J. Kamlet, J.-L. M. Abboud, M. H. Abraham and R. W. Taft, *J. Org. Chem.*, 1983, **48**, 2877.
8 S. J. Foster, P. Bruneau, E. R. H. Walker and R. M. McMillan, *Brit. J. Pharmacol.*, 1990, **99**, 113.
9 P. Bruneau, C. Delvare, M. P. Edwards and R. M. McMillan, *J. Med. Chem.*, 1991, **34**, 1028.
10 O. G. Parchment, D. V. S. Green, P. J. Taylor and I. H. Hillier, *J. Am. Chem. Soc.*, 1993, **115**, 2352.
11 F. M. Stephenson, *Org. Synth., Collect.*, Wiley, New York, 1955, vol. 3, p. 475.
12 S. Wyrick, P. Voorstad, G. Cocolas and I. Hall, *J. Med. Chem.*, 1984, **27**, 768.
13 A. Albert and E. P. Serjeant, *Ionisation Constants of Acids and Bases*, Methuen, London, 1962.
14 C. H. Rochester, *Acidity Functions*, Academic Press, New York, 1970.
15 F. Arndt, *Org. Synth., Collect.*, Wiley, New York, 1943, vol. 2, p. 165.
16 G. Palazzo and G. Corsi, *Ann. Chim. (Rome)*, 1965, **55**, 583.
17 M. Charton, *Prog. Phys. Org. Chem.*, 1981, **13**, 119.
18 A. Albert and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1903.
19 E. Spinner and G. B. Yeoh, *J. Chem. Soc. B*, 1971, 279.
20 M. H. Abraham, P. L. Grellier, D. V. Prior, P. P. Duce, J. J. Morris and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1989, 699; M. H. Abraham, P. P. Duce, D. V. Prior, D. G. Barratt, J. J. Morris and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1355.
21 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
22 See, *e.g.* (*a*) M. J. Scanlan and I. H. Hillier, *J. Chem. Soc., Chem. Commun.*, 1984, 102; (*b*) S. Woodcock, D. V. S. Green, M. A. Vincent, I. H. Hillier, M. F. Guest and P. Sherwood, *J. Chem. Soc., Perkin Trans. 2*, 1992, 2151; (*c*) J. Catalán, J. L. G. de Paz and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 1996, 57.
23 N. A. Burton, D. V. S. Green, I. H. Hillier, P. J. Taylor, M. A. Vincent and S. Woodcock, *J. Chem. Soc., Perkin Trans. 2*, 1993, 331.
24 See, *e.g.*, R. W. Taft, F. Anvia, M. Taagepera, J. Catalán and J. Elguero, *J. Am. Chem. Soc.*, 1986, **108**, 3237; J. Catalán, J. L. G. de Paz, M. Yanez and J. Elguero, *Chem. Scr.*, 1984, **24**, 84; J. Catalán, M. Sanchez-Cabezudo, J. L. G. de Paz, J. Elguero, R. W. Taft and F. Anvia, *J. Comput. Chem.*, 1989, **10**, 426.
25 J. Catalán, M. Menendez and J. Elguero, *Bull. Soc. Chim. Fr.*, 1985, 30.
26 S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, 1973, **10**, 1.
27 A. R. Katritzky and F. W. Maine, *Tetrahedron*, 1964, **20**, 299; 315; A. R. Katritzky, F. W. Maine and S. Golding, *Tetrahedron*, 1965, **21**, 1693.
28 J. Gut, M. Prystas and J. Jonas, *Coll. Czech. Chem. Commun.*, 1961, **26**, 986.
29 A. J. Boulton, A. R. Katritzky, A. M. Hamid and S. Øksne, *Tetrahedron*, 1964, **20**, 2835.
30 J. March, *Advanced Organic Chemistry*, John Wiley, New York, 1985, p. 418.
31 J. V. Greenhill, *Chem. Soc. Rev.*, 1977, **6**, 277.
32 J. Dabrowski and U. Dabrowska, *Chem. Ber.*, 1968, **101**, 2365; 3392; P. J. Taylor, *Spectrochim. Acta, Part A*, 1970, **26**, 165; 1976, **32**, 1471; D. Smith and P. J. Taylor, *Spectrochim. Acta, Part A*, 1976, **32**, 1477.
33 See, *e.g.* R. W. Taft, J. F. Gal, S. Geribaldi and P. C. Maria, *J. Am. Chem. Soc.*, 1986, **108**, 861; M. Berthelot, M. Helbert, J.-Y. Le Questel, F. Anvia and R. W. Taft, *J. Chem. Soc., Perkin Trans. 2*, 1993, 625; F. Desseau, C. Laurence and M. Berthelot, *J. Chem. Soc., Perkin Trans. 2*, 1994, 485; C. Laurence, M. Berthelot, M. Lucon and D. G. Morris, *J. Chem. Soc., Perkin Trans. 2*, 1994, 491.
34 A. J. Boulton and A. R. Katritzky, *Tetrahedron*, 1961, **12**, 41.

35 M. Azzaro, J. F. Gal, S. Geribaldi and N. Novo-Kremer, *Spectrochim. Acta, Part A*, 1978, **34**, 225.
36 C. Laurence, G. Guiheneuf and B. Wojtkowiak, *J. Am. Chem. Soc.*, 1979, **101**, 4793.
37 M. H. Abraham, P. P. Duce, D. V. Prior, D. G. Barratt, J. J. Morris and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1355.
38 See, *e.g.* J. E. Baldwin and R. K. Norris, *J. Org. Chem.*, 1981, **46**, 697; A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag, Berlin, 1983.
39 P. L. Huyskens, H. Marshal and Th. Zeegers-Huyskens, *J. Mol. Struct.*, 1987, **158**, 379.

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