The Tautomerism of 1,2,3-Triazole in Aqueous Solution

Adrien Albert
Australian National University, Faculty of Science (Chemistry), GPO Box 4, Canberra ACT 2601, Australia
Peter J. Taylor*
ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG

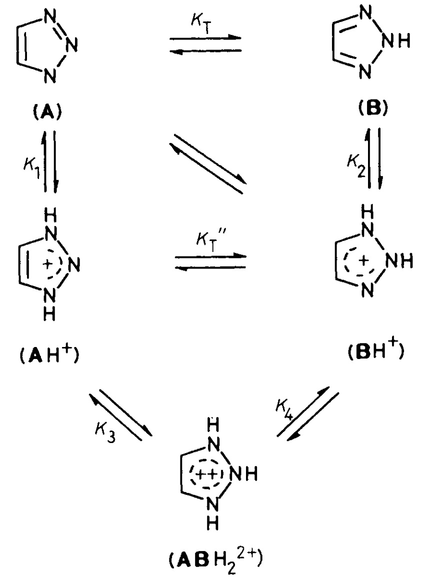
Two circumstantial but independent arguments both confirm that the 2*H*-tautomer of 1,2,3-triazole is favoured in aqueous solution by a factor of *ca.* two. Lone-pair repulsion is the probable cause; evidence from the solvent dependence of the tautomeric ratio is discussed.

The tautomerism of 1,2,3-triazole has been described[1a] as 'still the most confused of all the cases of annular tautomerism.' We present here evidence which, while circumstantial, plausibly defines its position for aqueous solution within quite close limits.

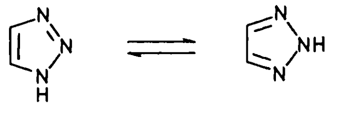
The Argument from Basicity.—If two tautomers (**A**) and (**B**) are related through a common cation, and if fixed forms of these tautomers can be prepared using bland substituents *e.g.* methyl, then on what we shall call the 'naive basicity' hypothesis, log K_T as defined *via* equation (1) is simply the difference in

$$K_T = [\mathbf{B}]/[\mathbf{A}] \qquad (1)$$

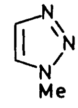
pK_a of these two forms. The situation for 1,2,3-triazole is set out in Scheme 1. Unfortunately, there is no common monocation, since the 1*H*-tautomer (**A**) prefers to give the cation ($\mathbf{AH}^+$).[1a] If formation of ($\mathbf{BH}^+$) from (**A**) is negligible, Scheme 1 could still be solved given good models for (**A**) and (**B**) and were all the pK_a values pK_1 – pK_4 to be obtained. However, 2-methyl-1,2,3-triazole (**3**) as a model for (**B**) is too weak a base for pK_2 to be accessible.[2] A recent theoretical treatment of basicity by Elguero and his co-workers[3] extrapolates to give pK_a *ca.* – 3.5 for (**3**), ($\mathbf{BH}^+$) being very unstable. Up to the present time, the problem has been abandoned at this point.



Scheme 1.



(1)



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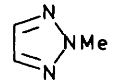


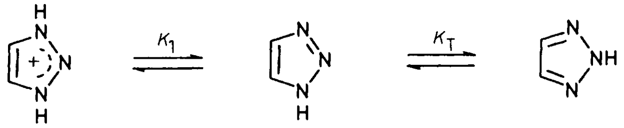
(3)

pK_a values for (**1**) and for 1-methyl-1,2,3-triazole (**2**) are known[2] (see the Table). If (**B**) is of negligible basicity, then protonation of (**1**) in aqueous solution is entirely due to the 1*H*-tautomer (**A**) and Scheme 1 collapses to give Scheme 2. We now have the relations of equations (2) and (3), where pK_{tot} is the

$$K_{tot} = [\mathbf{A} + \mathbf{B}][\mathrm{H}^+]/[\mathbf{AH}^+] \qquad (2)$$

$$K_1 = [\mathbf{A}][\mathrm{H}^+]/[\mathbf{AH}^+] \qquad (3)$$

observed overall pK_a of (**1**). Here $K_1 = 2K_{NMe}$ where pK_{NMe} is that for (**2**) since ($\mathbf{AH}^+$) can deprotonate in two equivalent ways. We also require a correction factor $K_{NH} = fK_{NMe}$ to allow for any difference in basicity which may arise from methylation.[1b] Incorporation of all these correction factors leads to equation (4) as the complete description of Scheme 2.



Scheme 2.

$$\log(K_T + 1) = \mathrm{p}K_{NMe} - \mathrm{p}K_{tot} - \log 2 - \log f \qquad (4)$$

The 'naive basicity' method assumes $f = 1$, *i.e.* that *N*-methylation has substantially no effect on pK_a. In that case, equation (2) leads to a negative K_T; *i.e.* the result is meaningless. However, both *N*- and *O*-methylation are expected to be base-weakening since replacement of NH or OH leads to poorer solvation in the cation.[4] Studies of annular tautomerism confirm this[1d] and, for some 1,2,4-triazoles which form the nearest analogy to the present case, a mean value of –0.68 for log f may be deduced. Equation (4) now solves to give K_T 1.88; *i.e.* 1,2,3-triazole (**1**) in aqueous solution contains 65% of the 2*H*-tautomer.

The Argument from Partitioning.—Mobile sub-species possess their own micro-partition coefficients[5] which sum to give that observed according to equation (5), where x_A is the mole

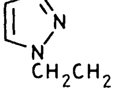
$$P_{tot} = x_A P_A + (1 - x_A)P_B \qquad (5)$$

Table. Physical data for some 1,2,3-triazoles.

Compound	pK_a[a]	log P
1,2,3-Triazole (**1**)	1.17	−0.29[b]
1-Methyl-1,2,3-triazole (**2**)	1.25	
1-Phenethyl-1,2,3-triazole (**4**)		1.12[b]
2-Phenethyl-1,2,3-triazole (**5**)		1.90[b]
Benzotriazole (**6**)		1.34[c]
1-Methylbenzotriazole (**7**)		1.13[c]
2-Methylbenzotriazole (**8**)		1.64[c]

[a] Ref. 2. [b] This work. [c] Ref. 19.

fraction of species (**A**) and $x_B = (1 - x_A)$ by definition. If P_A and P_B may be estimated and P_{tot} is known, then x_A and K_T follow. We start from the phenethyl derivatives (**4**) and (**5**), the octanol–water log P values[6] of which are in the Table. Given fragment values (*f*-values)[7] of 0.70 for CH_3, 0.53 for CH_2, and 1.90 for Ph, we obtain calculated log P values of −1.14 and −0.36 for (**2**) and (**3**) respectively. We have next to allow for the effect of *N*-methylation. This is very variable and generally positive,[6] but exceptions arise when NH is a good proton donor since proton donating ability aids extraction into octanol[8,9] and this can offset the expected effect of an alkyl group.[10] In fact the triazoles are excellent proton donors[11] and this explains the negative effect of *N*-methylation on log P for (**7**) relative to (**6**).



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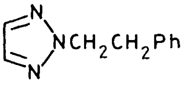

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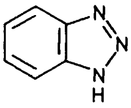

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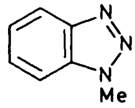


(7)

Since (**6**) is known to exist overwhelmingly as the 1*H*-tautomer shown,[1a] Δlog P between (**6**) and (**7**) may be used to supply the correction factors for (**2**) and (**3**). Hence the predicted log$P$ values for (**A**) and (**B**) are −0.93 and −0.15, respectively. Given log P −0.29 for (**1**) itself, then from equation (5), K_T 2.03 results; *i.e.* 1,2,3-triazole in aqueous solution contains 67% of the 2*H*-tautomer.

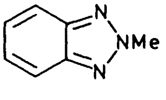
Discussion

As indicated at the outset, neither of these arguments is unassailable. Nevertheless, their agreement is impressive, and at least the sign of log K_T is probably not in doubt. It is interesting to consider how variation in phase affects K_T. Much published evidence is vitiated by concentration effects,[1a] but allowing for this, the 2*H*-tautomer is generally favoured to a greater extent in other solvents than in water. For example, a careful study by Lunazzi *et al.*[12] showed 80% of (**1**) to be present as (**B**) in dichloromethane and 97% in toluene, with (**A**) being relatively more favoured at high concentration. A similar concentration dependence was noted by Begtrup.[13] In methanol, the proportion of (**B**) is > 70% or > 90% according to the method of calculation.[14] We may obtain an approximate result for octanol through the box equilibrium of Scheme 3. Since K_T, P_A, and P_B are all known (see above), this solves to give K_T' *ca.* 12, *i.e.* 92% of (**B**) in octanol. The position is clearer cut for the isolated molecule, where microwave spectroscopy shows only (**B**) to be detectable in the gas phase.[15] This agrees with calculation, which predicts factors ranging from 400[15] to about ten[3] in favour of the 2*H*-tautomer. It should be noted, incidentally, that all these real and implied K_T values have in fact to be doubled, since two equivalent forms exist for (**A**). Hence (**B**) is favoured by a factor of four in water, possibly by as large a ratio as 60 in toluene, and by this sort of margin or more in the gas phase.

$$\begin{tikzcd}
\mathbf{A}_{oct} \arrow[r, shift left, harpoon, "K_T'"] \arrow[d, shift left, harpoon] & \mathbf{B}_{oct} \arrow[l, shift left, harpoon] \arrow[d, shift left, harpoon] \\
\mathbf{A}_w \arrow[u, shift left, harpoon, "P_A"] \arrow[r, shift left, harpoon, "K_T"] & \mathbf{B}_w \arrow[l, shift left, harpoon] \arrow[u, shift left, harpoon, "P_A"]
\end{tikzcd}$$

Scheme 3.

Finally we consider why this equilibrium should be as it is. In an interesting treatment of relative basicity for some heterocycles in the gas phase, Taft and his co-workers[16] identify, *inter alia*, two major destabilising factors: lone-pair repulsion between adjacent sp^2-nitrogens in the neutral species, and that between adjacent NH groups in the cation. Both are expected to be greatly attenuated in water. Quantitative sense can be made of the difference in basicity between the isomers imidazole and pyrazole;[16] the absence of a common cation, however, precludes extrapolation to the tautomers considered here. Qualitatively, the present results are clearly consistent with the predominant importance of lone-pair repulsion, *i.e.* the 'α-effect.'[17] Confirmatory evidence comes from solvent–water partitioning. Since lone-pair repulsion can be relieved by hydrogen bonding, and water is an exceptional proton donor,[18] octanol–water log P values for potential 'α-effect' heterocycles are always lower than for their isomers.[6,9,10] This is clearly shown throughout the set of homologues exemplified by (**7**) and (**8**),[19] for which an average Δlog P *ca.* 0.5 is found. These margins are much greater when the organic phase is aprotic[10] while, for similar reasons, the fixed 4*H*-tautomer (**9**) of *s*-triazole is a ten-fold better proton acceptor than its 1*H*-isomer (**10**).[11] A contrary effect shows itself in chloroform, which as a pure proton donor should tend to favour the stronger acceptor; here, exceptionally, (**A**) predominates.[20,21] Elsewhere however, form (**A**), as expected, is progressively disfavoured as the solvent becomes less polar and so lone-pair repulsion is enhanced.



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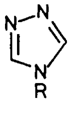

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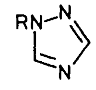
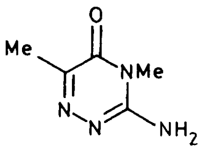
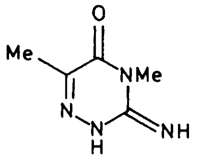


(10)

Elguero *et al.*[1d] have previously noted that the observed tautomeric preference in the triazoles is not as expected on simple Hammett grounds, and have tentatively invoked lone-pair repulsion as the cause. We regard that postulate as overwhelmingly confirmed. In fact we consider the data assembled here to constitute some of the best evidence there is for the importance of the 'α-effect' in heterocyclic chemistry, to be added to that previously adduced[22] from the unexpected tautomeric preference for species (**11b**) and (**12b**). In forthcoming publications[10,11] this argument will be taken further.



(11a)



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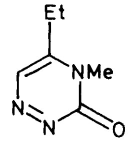
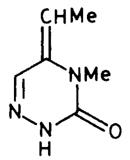


(12a)



(12b)

Experimental

log *P* values for (**1**), (**4**), and (**5**) were determined by standard methods.[23]

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