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TAUTOMERISM OF 4-HYDROXYPYRAZOLES AND 4-HYDROXYISOXAZOLES—II

ZWITTERIONIC TAUTOMERS

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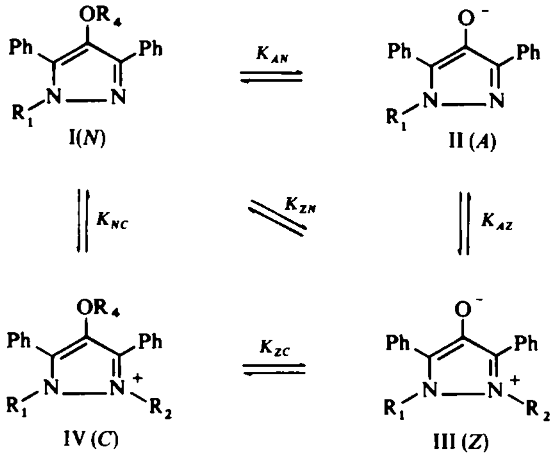
Abstract—The equilibrium constant for the formation of anhydro-4-hydroxy-3,5-diphenylpyrazole has been determined to be $3{\cdot}2 \times 10^{-5}$, using a spectroscopic/pK_a method similar to that used by Ebert[1] for aliphatic amino acids. A simple method of predicting equilibrium constants of zwitterions is proposed.

INTRODUCTION

IN PART I,[2] IR, UV and PMR evidence was presented strongly indicating that 4-hydroxy-3,5-diphenylpyrazole exists as the enolic tautomer (Ia) rather than as the ketonic form or the zwitterionic form (IIIa) both in the solid state and in solution.



	R_1	R_2	R_4
a	H	H	H
b	H	H	CH_3
c	CH_3	CH_3	H
d	CH_3	H	H

FIG A

IIIa must however exist in trace amounts in solution *via* the equilibria Ia ⇌ IIa ⇌ IIIa or Ia ⇌ IVa ⇌ IIIa. We were interested in determining the equilibrium constants for the equilibria for the following reasons. Firstly, the behaviour of Ia contrasts with that of 3-hydroxypyridine (V) which has been shown by Metzler and Snell[3] to be in *ca.* 1:1 equilibrium with its zwitterionic tautomer (VI) in aqueous solution, and this seemed surprising since V and VI are structurally related to I and III in the same way that benzene is related to pyrrole (by replacing a CH=CH unit by NH). Secondly, the topic is quite relevant to the view[4] that pyrazolin-5-one has strong contribution from a

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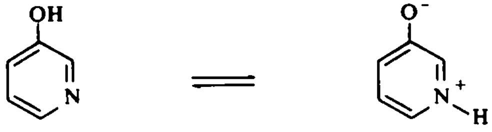
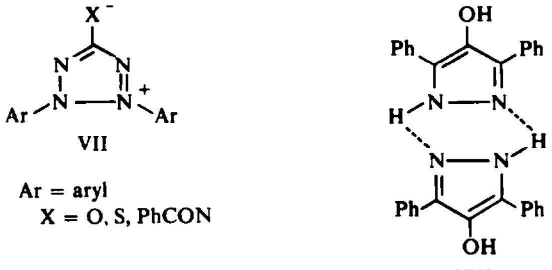


V VI

FIG B

zwitterionic resonance structure. Thirdly, there are a few examples in the literature[5, 6] of compounds represented by the general formula VII, which bears a close structural relationship to III.



VII

Ar = aryl
X = O, S, PhCON

VIII

FIG C

Derivation of equations

The following equations are derived here for use later in the results and discussion section.

(a) *Ebert-type equation.* In a set of equilibria between a neutral species (N), an anion (A), a zwitterion (Z) and a cation (C) such as Ia, IIa, IIIa and IVa, the following equations[7] hold for dilute solutions. Square brackets denote molar concentrations.

$$K_{AN} = [A][H^+]/[N] \quad (1) \qquad K_{AZ} = [A][H^+]/[Z] \quad (2)$$

$$K_{ZC} = [Z][H^+]/[C] \quad (3) \qquad K_{NC} = [N][H^+]/[C] \quad (4)$$

$$K_{ZN} = [Z]/[N] \quad (5)$$

$$K_{ZN} = K_{ZC}/K_{NC} \quad (6) \qquad K_{ZN} = K_{AN}/K_{AZ} \quad (7)$$

Taking logarithms in equation (6) gives

$$\log K_{ZN} = pK_{NC} - pK_{ZC} \tag{8}$$

Thus, $\log K_{ZN}$ and hence K_{ZN} may be calculated if pK_{ZC} and pK_{NC} can be determined. pK_{ZC} may be determined directly for IIIc by the spectrophotometric/pK_a method,[8] and the value should not be greatly different for IIIa. For this work we will assume that pK_{ZC} is identical for IIIa and IIIc. pK_{ZC} may then be determined from the observed pK_a of the equilibrium mixture of Ia and IIIa (represented by $pK_C = -\log K_C$) by using the following relationship.[7]

$$K_C = K_{NC} + K_{ZC} \tag{9}$$

i.e.

$$pK_{NC} = -\log(K_C - K_{ZC}) \tag{10}$$

Combination of equations (8) and (10) leads to

$$\log K_{ZN} = -\log(K_C - K_{ZC}) - pK_{ZC} \tag{11}$$

This equation may be used to calculate log K_{ZN} and K_{ZN} since both K_C and K_{ZC} can be measured. This method of determining K_{ZN} is very similar to that of Ebert[1] used on aliphatic amino acids, the difference being that in his case, use was made of the spectrum of a molecule fixed in the neutral form (an amino acid ester), whereas in the present case a fixed zwitterionic species (IIIc) is involved.

(b) *Standard free energy equations.* For the equilibrium $N \rightleftharpoons Z$, the free energy ΔF_{ZN} of converting N to Z in their standard states is given by

$$\Delta F_{ZN} = -2{\cdot}303\, RT \log K_{ZN} \tag{12}$$

and similarly for the equilibrium $N + Z \rightleftharpoons A + C$ we have

$$\Delta F_{ACNZ} = -\ 2{\cdot}303\, RT \log K_{ACNZ} \tag{13}$$

where

$$K_{ACNZ} = [A]\,[C]/[N]\,[Z] \tag{14}$$

Equations (13) and (14) can be adapted as follows:

$$\Delta F_{ACNZ} = -2{\cdot}303\, RT \log\left[\frac{[A]\,[H^+]}{[N]} \times \frac{[C]}{[N]\,[H^+]} \times \frac{[N]}{[Z]}\right] \tag{15}$$

Substitution of equations (1), (4) and (5) into (15) leads to

$$\Delta F_{ACNZ} = -2{\cdot}303\, RT \log\left[K_{AN} \times \frac{1}{K_{NC}} \times \frac{1}{K_{ZN}}\right] \tag{16}$$

$$= 2{\cdot}303\, RT(pK_{AN} - pK_{NC} + \log K_{ZN}) \tag{17}$$

$$\log K_{ZN} = \frac{\Delta F_{ACNZ}}{2{\cdot}303\, RT} - pK_{AN} + pK_{NC} \tag{18}$$

RESULTS AND DISCUSSION

Table 1 shows the results of the pK_a determinations on Ia, Id and Ic. K_{ZN} was calculated *via* equation (10) using the pK_{AN} and pK_{NC} values for Id rather than those for Ia, because of the suspicion that the figures for Ia are anomalous owing to the occurrence of dimeric-type structures such as VIII in solution. The anomaly is manifested in the higher values for pK_{AN} and pK_{NC} for Ia compared with those for Id, which is the opposite of what one might expect by consideration of the greater electron donating power of the Me group compared with hydrogen.

The pK's were determined in 4% MeOH in H_2O because of poor solubility of Ia and Id in water. Under these conditions the pH recorded by the electrometric method is no longer correct, but a correction increment (addition of 0·1 units to the measured pK_a) is available from the work of Ligny *et al.*[9] The pK_a so corrected is then the value for that particular solvent system (4% MeOH) and will of course differ slightly from the pK_a value in water. This correction was not applied in this paper since it is small, and the most significant quantities (log K_{ZN} and log K_{ACNZ}) are independent of it.

TABLE 1

		Nye and Tang*		Metzler and Snell†,[3]
pK_{AN}	Ia	9·48	IV	8·26
	Id	9·29		
pK_{NC}	Ia	2·01‡	IV	5·44
	Id	1·96		
pK_{ZC}	Ic	6·46	V	5·37
K_{ZN}		$3{\cdot}2 \times 10^{-5}$		1·2
log K_{ZN}		$-4{\cdot}50$		$-0{\cdot}07$
ΔF_{ZN} (Kcal/mole)		6·15		0·1

* 25° in 4% MeOH in H_2O.
† 25° in H_2O.
‡ Since IVa is a dibasic acid, log 2 must be added to this value if it is to be validly compared with the pK_a of the monobasic acid IVd.

A second correction which ought strictly to be applied is to make allowance for the difference in the pK_{ZC}'s of III(d) and III(c), but since it was found unnecessary to make such a correction in analogous work on aliphatic amino acids,[10] no correction was made in this paper either.

The values of K_{ZN} and ΔF_{ZN} obtained for I are compared in Table 1 with those determined by Metzler and Snell[3] for V, and it is seen that while the free energies of 3-hydroxypyridine (V) and its zwitterion (VI) are roughly equal, the 4-hydroxypyrazole (I) is more stable than its zwitterion (III) by about 6 Kcal/mole. Inspection of the pK_{AN}, pK_{NC}, K_{ZN} and log K_{ZN} values of a range of zwitterionic compounds taken from the literature (Table 2), shows their behaviour to be quite variable. For example K_{ZN}'s range from *ca.* 10^5 to $^{10-5}$.

Order is brought to the data when the $-\log K_{ACNZ}$ and ΔF_{ACNZ} values are calculated (using equations (13) and (16)). The ΔF_{ACNZ} values (i.e. the standard free energy of formation of an anion and a cation from a neutral compound and its zwitterionic tautomer) fall within a narrow range between 0·5 and 4·4 Kcal/mole. This quantity can be thought of as an approximate indication of the degree of interaction between the positive and negative charges within the zwitterion. If the acidic and basic ends of the molecule were completely independent of each other, ΔF_{ACNZ} would be zero.

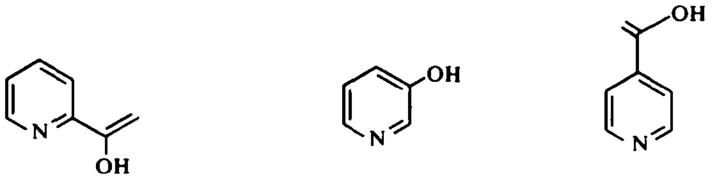
Kirkwood and Westheimer[11] have produced a theoretical treatment of aliphatic amino acids in which they considered zwitterions as ellipsoids of dielectric constant 2, with point positive and negative charges located below the surface and the solvent as having a homogeneous dielectric constant surrounding the ellipsoid. Using this model, distances of separation of the positive and negative charges were calculated from the observed pK_a values. The results were found to be in reasonable agreement with the charge separation distances obtained by consideration of known bond lengths and angles. Thus the variation of ΔF_{ACNZ} (Kcal/mole) from 2·72 for α-aminoacetic acid to 0·51 for ε-amino-n-caproic acid is consistent with a simple electrostatic theory. The same treatment of zwitterions in which there is considerable

TABLE 2

No.	Compound	pK_{AN}	pK_{NC}	K_{ZN}	log K_{ZN}	−log K_{ACNZ}	ΔF_{ACNZ} Kcal/mole	Ref.
1	NH_2CH_2COOH	4·30	7·73	$2{\cdot}6 \times 10^5$	5·42	1·99	2·72	13
2	$NH_2(CH_2)_2COOH$	4·66	9·13	$3{\cdot}4 \times 10^5$	5·53	1·06	1·45	13
3	$NH_2(CH_2)_3COOH$	4·95	9·71	$3{\cdot}0 \times 10^5$	5·48	0·72	0·98	14
4	$NH_2(CH_2)_4COOH$	4·89	10·15	$7{\cdot}6 \times 10^5$	5·88	0·62	0·85	14
5	$NH_2(CH_2)_5COOH$	4·81	10·37	$8{\cdot}7 \times 10^5$	5·94	0·38	0·51	13
6	*o*-amino benzoic acid	4·92	2·09	$2{\cdot}0 \times 10^{-1}$	−0·70	2·13	2·8	15
7	*m*-amino benzoic acid	4·27	3·56	2·3	0·36	1·07	1·4	15
8	*p*-amino benzoic acid	4·86	2·38	$1{\cdot}3 \times 10^{-1}$	−0·87	1·61	2·2	16
9	*o*-dimethylamino benzoic acid	4·3	5·55	$1{\cdot}1 \times 10$	4·1	2·85	3·9	17
10	pyridine-2-carboxylic acid	4·13	3·21	$1{\cdot}5 \times 10$	1·18	3·08	4·2	18
11	pyridine-3-carboxylic acid	3·75	3·13	$1{\cdot}0 \times 10$	1·00	1·64	2·2	18
12	pyridine-4-carboxylic acid	3·44	3·26	$2{\cdot}5 \times 10$	1·40	1·58	2·2	18
13	3-hydroxy-quinoline	8·01	4·33	$6{\cdot}4 \times 10^{-2}$	−1·19	2·49	3·3	19*
14	6-hydroxy-quinoline	8·87	5·18	$1{\cdot}4 \times 10^{-2}$	−1·85	1·84	2·5	19*
15	8-hydroxy-quinoline	9·87	5·15	$3{\cdot}5 \times 10^{-2}$	−1·46	3·27	4·4	19*
16	4-hydroxyiso-quinoline	7·80	5·48	3·76	0·58	2·90	3·9	19*
17	5-hydroxyiso-quinoline	8·43	5·42	$3{\cdot}8 \times 10^{-2}$	−1·42	1·59	2·1	19*
18	7-hydroxyiso-quinoline	8·86	5·71	$3{\cdot}8 \times 10^{-2}$	−1·42	1·73	2·3	19*
19	3-hydroxypyridine (IV)	8·26	5·44	1·2	−0·07	2·75	3·7	3
20	3-methanesulfon-amidopyridine	7·0	3·5	$8{\cdot}1 \times 10^{-2}$	−1·1	2·5	3·4	20
21	Id	9·29	1·96	$3{\cdot}2 \times 10^{-5}$	−4·50	2·77	3·8	†

Determinations were run at 25° and in H_2O or under unstable conditions except: * run at 20°, and † run in 4% MeOH in H_2O. Data not taken directly from the literature were calculated using equations (5) to (17). Ref. 19 also contains similar data on the acridines which are not valid for comparison since the K_{ZN}'s were determined in solutions of high alcohol concentration.

charge delocalization such as aromatic compounds, is not possible, since the method assumes point charges. However, we wish to point out that there is a qualitively correlation between ΔF_{ACNZ} values and formal charge separation. Inspection of the ΔF_{ACNZ} values for the compounds in Table 2 which have partial formulae IX, X and XI reveals that the values fall between different limits for each of the three types. [IX has ΔF_{ACNZ} (Kcal/mole) between 4·2 and 4·4 (compounds **10** and **15**); X, between



IX ΔF_{ACNZ} = 4·2–4·4

X 3·3–3·9

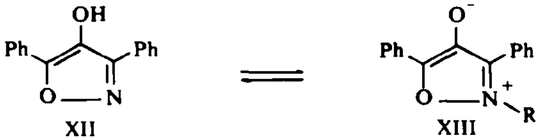
XI 2·1–2·2 Kcal/mole

FIG D

3·3 and 3·9 (compounds **13**, **16** and **19**); and XI, between 2·1 and 2·2 (compounds **12** and **17**)], and the energy decreases with increasing formal charge separation, as it does with the aliphatic amino acids. Note that the correlation is independent of whether the compound is a carboxylic acid or a phenol. In addition 3-methanesulfonamidopyridine (**20**) and the 4-hydroxypyrazole (Id) (**21**) have ΔF_{ACNZ} values within the limits for type X in spite of some modification of the system. More drastic modification of the system leads to ΔF_{ACNZ} values quite different from those observed for compounds containing the cited partial structures. For example α-aminoacetic acid has a similar geometry to that of IX in that they both contain a *cis* N—C—C—O arrangement, but their ΔF_{ACNZ} values are very different (2·72 and 4·2 to 4·4 respectively). This behaviour is not unexpected since ΔF_{ACNZ} will depend not only on formal charge separation, but on actual distribution of this charge over the delocalized system, and this is highly variable from system to system.‡

Consideration of the above correlations leads to the proposal of the rule that "aromatic compounds with similar geometry and electronic structure should have similar ΔF_{ACNZ} values". This rule should have great utility in predicting tautomeric equilibrium constants of zwitterions by applying equation (18), which only requires knowledge of the two pK_a's of the neutral species in addition to an estimated ΔF_{ACNZ} value. Application of the rule of course relies on the interpretation of the word "similar". Kirkwood and Westheimer's theory implies that ΔF_{ACNZ} values will depend on the shape of the molecule appreciably and bulky substituents for example might have a noticeable effect. On the other hand probably the largest factor arises from charge distribution. Many more examples are needed before the rule can be applied in a quantitative manner with confidence.

There are certain cases nevertheless, when the rule should be quite reliable. A case in point is that of 4-hydroxy-3,5-diphenylisoxazole XII, and its potential zwitterionic tautomer XIIIa, which should have almost identical geometry and



XII XIII

	R
a	H
b	Me

FIG E

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‡ A more detailed discussion of the correlation of ΔF_{ACNZ} with structure will be published later.

electronic structure to that of 4-hydroxy-3,5-diphenylpyrazole Ia and its zwitterionic tautomer IIIa. According to the rule, these compounds will have very similar ΔF_{ACNZ} values. Insertion of the ΔF_{ACNZ} value determined for I together with the known* values of pK_{AN} (7·21) and pK_{NC} (−3·25) for XII in equation (18) leads to

$$\log K_{ZN} = \frac{3{\cdot}8}{2{\cdot}303\,RT} - 7{\cdot}21 - 3{\cdot}25 = -7{\cdot}7 \tag{19}$$

This prediction that the zwitterion XIIIa should be quite unstable relative to XII is in accord with the lack of spectroscopic evidence[2, 12] for the presence of XIIIa in solutions or solid samples of XII.

Further quantitative testing of the rule is in progress.

CONCLUSIONS

The enol, 4-Hydroxy-3,5-diphenylpyrazole (Ia) is more stable than its zwitterionic tautomer, anhydro-4-hydroxy-1,2-dimethyl-3,5-diphenyl pyrazolium hydroxide (III) by about 6·15 Kcal mole^{-1}. This result is in fact not unexpected if we propose that the free energy of formation of the cation and anion from a compound and its zwitterionic tautomer (ΔF_{ACNZ}) should lie close to the values observed for related systems (3·3 to 3·9 Kcal/mole).

EXPERIMENTAL

The materials were prepared[2] and the pK_a's determined[8] according to known methods. Absorption spectra were determined on a Unican SP 800 spectrophotometer on 7×10^{-6} M 4% methanolic solutions in 10 cm quartz cells at 25·0 ± 0·3°. The pH was measured for each buffered solution at the same temperature with a Radiometer pH Meter 28.

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