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THE REVERSIBLE CATION-ANION ISOMERISATION OF 2-IMINO-2H-PYRIDO [1,2-b][1,2,4]THIA(OXA)DIAZOLE HYDROBROMIDE

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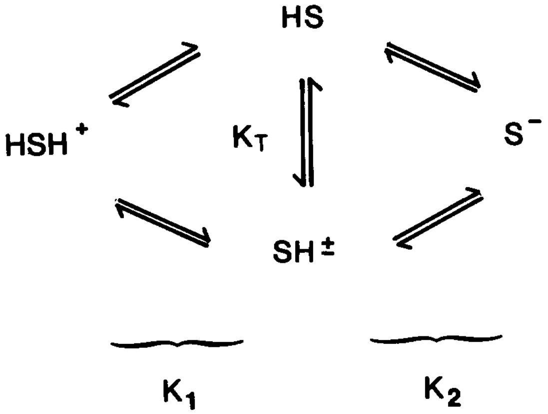
Abstract. The title compounds exist in pH-dependent equilibrium between cation and ring-opened anion; since $pK_2 < pK_1$, the hypothetical neutral species is always metastable.

It is well established that the equilibrium deprotonation of a diprotic species, as epitomised by the Scheme, possesses as one condition the relation of equation (i):

SCHEME



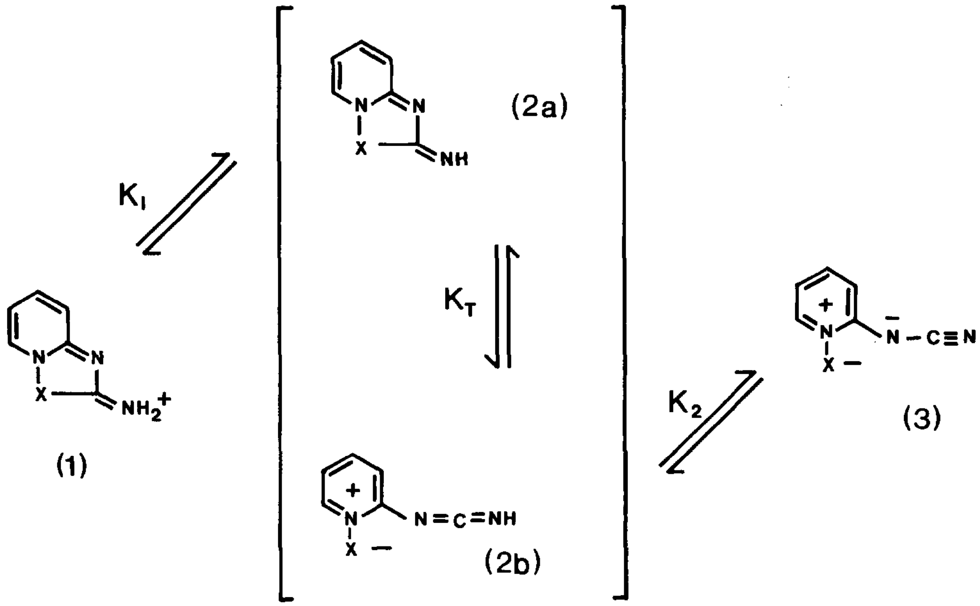
$$pK_2 \geq pK_1 + 0.60 \qquad \text{(i)}$$

for necessary statistical reasons.[1] Examples include diamines ($S=B^+$) and dicarboxylic acids ($S=A^-$) as well as formally neutral species; the latter class may be further sub-divided into essentially zwitterionic ($K_T \gg 1$; e.g. the α-aminoacids) or amphoteric ($K_T \ll 1$; e.g. the pyridones). In all such cases the minimum Δ pK = 0.60 is obtained at $K_T = 1$, i.e. when the two ionising groups are formally equivalent; in most cases, therefore, the difference will be greater than this.

It has been known for some years that the condition of equation (i) may be circumvented when the second deprotonation step involves a molecular rearrangement,[2] and a number of such examples have been reported.[2-7] Interest in this area has recently been rekindled by the work of Hünig and Schenk[3] on phenolphthalein and homophenolphthalein, who show that in each case $pK_2 < pK_1$; here a phenolic lactone ring opens to give a carboxylic acid. Conversely, amines that diprotonate more readily than they monoprotonate are to be found in the porphyrin series.[4]

An amphoteric substance for which $pK_2 < pK_1$ is arguably still more interesting, since here the effect of changing pH is to generate anion directly from cation, or vice versa, the intermediate neutral species being at all times metastable. The familiar example, which has been explored in some detail, is the equilibrium between diazonium cation and diazotate anion.[5] In heterocyclic chemistry, Eisenthal and Katritzky[6] have encountered such a case in the reversible ring opening of the N-methoxypyridinium cation, but no pK_a values were reported. We[7] have previously described a reversible ring opening process with $pK_1 > 14$ and $pK_2 < 6.5$, but the major reaction pathway involved an irreversible transformation, making this system unsuitable for extended study. The same disadvantage attaches in some degree to the other processes described above.

We wish to report the discovery of a new cation-anion transformation process for which $pK_2 < pK_1$, which depends similarly on a heterocyclic rearrangement, and which appears to be rapidly and perfectly reversible, insusceptible to side reactions on even repeated re-cycling.[8]



2-Pyridylthiourea in glacial acetic acid was oxidised with bromine to give (1,X=S) as its bromide.[9] Titration of this salt with aqueous sodium hydroxide gave an "abnormal" (i.e. flattened) titration curve of the type illustrated by Schwarzenbach and Zollinger[2] for the case of $pK_2 < pK_1$. It was surmised that ring opening might have occurred to give the anionic species (3,X=S), but decomposition took place in alkaline solution and no characterisable product could be isolated. Attention therefore switched to the known[10] oxygen analogue, which was prepared as its hydrobromide.[11] Treatment of this salt in aqueous solution with caustic liquor precipitated a solid which analysed for the sodium salt of the anion (3,X=O).[12] Its infrared spectrum contained a very strong band at 2150 cm^{-1}, as expected for an electron-rich cyanamide, and a new strong band at 1214 cm^{-1}, consistent with an N-oxide structure. The aqueous u.v. spectra of cation and anion are well characterised; changing the pH of the solution produces a smooth transition with sharp isosbestics and no sign of any intermediate species.

Potentiometric titration of (1,X=S) and (1,X=O) at 23°C in water leads to the pK_a values of the Table. These were obtained by deconvoluting the titration curves using a computerised version of Speakman's method for the treatment of overlapping pK_a values.[13] For (1,X=S) $pK_2 > pK_1$, but by less than the theoretical minimum of equation (i). For (1,X=O) $pK_2 \ll pK_1$, and the nature of the ionisation steps is confirmed by the results for 80% methanol, since this solvent is expected to lower basic and raise acidic pK_a values.[14] Strictly however it should be noted that, in the absence of any information as to the equilibrium between (2a) and (2b), these pK_a values are apparent; they possess their face values only if $K_T = 1$.

These pK_a values have proved entirely insensitive to titration speed up to the point at which "electrode drag" would in any case be expected. Resonance stabilisation of the N-oxide linkage[15] may provide the driving force for the rapid formation of (2b) from (2a), whereas there are good precedents for a rapid re-cyclisation.[7] Re-cycling has been carried out, for (1,X=O), a number of times without change in pK_a or diminution of the titre. It seems that this reversible system is particularly robust and could form the basis for a systematic appraisal of this phenomenon.[16]

Table. pK_a Values for Compounds (1)

Compound	Solvent	pK_1	pK_2
X = S	Water	7.85 ± 0.11	8.06 ± 0.04
X = O	"	7.77 ± 0.16	6.60 ± 0.14
X = O	80% Methanol	7.54 ± 0.09	7.01 ± 0.08

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(8) It should be noted that strong alkali will hydrolyse (1,X=O) to the oxo-derivative; see ref. (10).

(9) Recryst. twice from water, m.pt. 221-3°C (decomp.); found: C, 31.3; H, 2.8; N, 17.9; Br, 34.8; required for $C_6H_6BrN_3S$: C, 31.1; H, 2.6; N, 18.3; Br, 34.5; ν / cm^{-1} (nujol): main peaks at 3300-3000 (NH_2^+), 1640 (NH_2^+), 1615, 1565, 1525, 1455 (ring modes and $C=N^+$), and 770 (CH).

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(11) Recryst. methanol-ethanol, m.pt. 242-3°C (decomp.), lit.[10] 232-3°C (decomp.); found C, 33.4; H, 2.8; N, 19.2; Br, 36.4; required for $C_6H_6BrN_3O$: C, 33.3; H, 2.8; N, 19.5; Br, 37.0; ν/cm^{-1} (nujol): main peaks at 3200-2900 (NH_2^+), 1694 ($C=N^+$), 1632 (NH_2^+), 1616, 1578, 1500, and 1453 (ring modes). The NH_2^+ modes were confirmed by their removal on deuteriation. λ_{max} (nm): pH2 in water, 238 (log ε 4.29) and 298 (log ε 3.73); pH10 in water, 236 (log ε 4.38), 270 (log ε 4.23), and 326 (log ε 3.69).

(12) M. pt. 250-300°C with slow decomposition; found: C, 45.6; H, 2.6; N, 25.9; required for $C_6H_4N_3ONa$. 1/8 H_2O: C, 45.2; H, 2.5; N, 26.3; ν/cm^{-1}(nujol): main peaks at 2250 (C≡N), 1608, 1552, 1507, 1444 (ring modes), 1214 (NO), and 740 (CH).

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(16) A referee points out that pyridine N-sulphides such as (3,X=S) are so far unknown as isolable species. This is not contradicted by the present result, which shows the titration of (1, X=S) to be accurately reversible on a time-scale of 1-2min, but not if left in alkali for 10 min or more.

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