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THE TAUTOMERISM OF HYDROXY DERIVATIVES OF FIVE-MEMBERED OXYGEN, NITROGEN, AND SULFUR HETEROCYCLES

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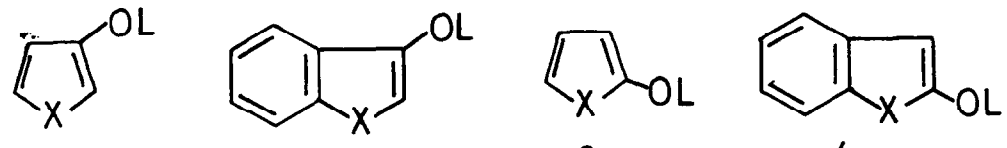
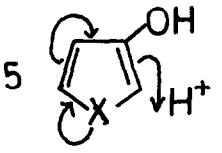
Abstract: The unstable enolic tautomers 3-hydroxyfuran, 2-and 3-hydroxythiophene, 3-hydroxy-pyrrole, 3-hydroxy-1-methyl-pyrrole and their benzo-derivatives have been generated in solution and the rate and equilibrium constants for their ketoization determined.

Most hydroxy derivatives of unsubstituted furans, thiophenes, pyrroles and their benzo-derivatives are unstable with respect to their keto-tautomers and have never been isolated or detected.[1] We now report that the 3-hydroxy compounds 1a - 1b and 2a - 2d may be generated in mixtures of CD_3CN, CD_3COCD_3 or CD_3SOCD_3 with D_2O by hydrolysis of their trimethylsilyl derivatives under slight acidic conditions and characterised by NMR spectroscopy. The method is similar to that used previously to generate vinyl alcohol and other enols in which a highly reactive orthoester or ketene acetal protective group is removed much faster than the enol tautomerizes.[2] However the 3-hydroxy compounds 1a - 1b and 2a - 2d are more stable with respect to their keto-tautomers and therefore the less labile trimethylsilyl group is sufficiently reactive to be removed faster than the enolic tautomers are converted into their keto-forms.

The technique used is illustrated with 3-hydroxybenzofuran. The material obtained by standard synthetic procedures is the keto-form[3] but the enolic form, 2a, L = D was generated from its trimethylsilyl derivative in a mixture of CD_3COCD_3 (90% v/v) and D_2O (10% v/v) which was 5 x 10^{-4} M in DCl at 32°. The ^{1}H-NMR spectrum of the trimethylsilyl ether in CD_3COCD_3 showed signals at δ = 7.45(s), 7.3(m), and 0.27(s). On addition of D_2O/DCl to give the mixture indicated above the spectrum changed rapidly and the singlet at δ = 7.45 corresponding to H(2) of the trimethylsilyl ether was replaced by a signal at δ = 7.3 which was ascribed to H(2) of 3-deuteroxy-benzofuran and at the same time the signal of the trimetylsilyl group (δ = 0.27) was replaced by that of trimethylsilanol (δ = 0.05). The solution so obtained was stable for several hours at 32°C but on addition of 5μL of 1M HCl the spectrum changed to that of the deuterated keto form. The enolic forms 3-hydroxybenzothiophene[4] (2b, L = D), 3-hydroxyindole[5] (2c, L = D), 3-hydroxy-1-methylindole[6] (2d, L = D), 3-hydroxyfuran[7] (1a, L = D) and 3-hydroxythiophene[8] (1b, L = D) were generated similarly but the trimethylsilyl derivatives are not suitable precursors for the generation of 3-hydroxypyrrole and





3-hydroxy-1-methylpyrrole[9] as these enols ketonize faster than the trimethylsilyloxy groups are removed. These compounds can be prepared as unstable easily resinifiable oils which consist of 30 - 35% enol and 70 - 65% of the keto-form by methanolysis of their trimethylsilyl ethers but when they were dissolved in DMSO-d_6 the ^{1}H-NMR spectra indicated the presence of *ca* 100% of the enol forms.

The enolic forms 2-hydroxythiophene (3b, L = D) and 2-hydroxy-benzothiophene (4b, L = D) were also generated from their trimethylsilyl ethers. These may be regarded as the enolic forms of thio esters and they are converted more than 99% into the keto-form at equilibrium.[10] Attempts to generate the enolic forms of the corresponding furan and pyrrole heterocycles (3a, c, d, 4a, c,d) have so far been unsuccessful.

The kinetics of ketonization were studied by UV spectroscopy. The pH-rate profiles were inverted bell shaped curves with H^+, HO^-, and H_2O-catalysed reactions. The values of k_{H^+} and the equilibrium constants are given in Table I. These will be discussed in detail in the full paper but the following salient points may be noted. The 3-hydroxybenzo-compounds 2a - 2d undergo ketonization much more slowly than their carbocyclic analogue 1-hydroxy-indene (2e) and the 3-hydroxy-indoles react faster than 3-hydroxybenzofuran and 3-hydroxybenzo-thiophene. At equilibrium none of the enolic forms of 3-hydroxybenzofuran (2a) and 1-hydroxyindene (2e) are detectable but there are substantial amounts of 3-hydroxybenzothiophene (2b) and of the 3-hydroxyindoles (2c and 2d). The equilibrium constants for the enolization of the keto-forms of the latter two compounds could therefore be determined directly but those of the keto-forms of 3-hydroxybenzofuran and 1-hydroxyindene had to be determined by measuring the rate constants for their hydronium-ion catalysed enolizations using the iodine trapping technqiue and combining these with the rate constants for ketonization of the enolic forms determined as described above. The effect of replacing the CH_2 group of 1-hydroxyindene (2e) by an oxygen is to make the enolic form about 5 x 10^4 times more stable with respect to the keto-form (see Table I). The greater stability still of 3-hydroxybenzothiophene and of the 3-hydroxyindoles is presumably the result of the greater aromaticity of the thiophene and pyrrole rings.[11]

Table I Rate and Equilibrium Constants for the Ketonization of Hydroxy-Heterocyclic Compounds at 25° (I = 1.00 M)

	$k_H+/M^{-1}s^{-1}$ [a]	$k_H+/M^{-1}s^{-1}$ [b]	$K_{enol}(H_2O)$	K_{enol}(DMSO)
3-Hydroxy-benzo-series				
2a	0.592	0.865	8.70×10^{-4}	$<2\times10^{-2}$
2b	0.532	0.31 (0.0699)[c]	0.085	6.7
2c	3.44	-	0.086	28.3
2d	5.82	-	0.303	11.4
1-Hydroxy-indene(2e)[e]	9.03×10^{2}[f]	3.28×10^{2}	1.85×10^{-8}	$<2\times10^{-2}$
3-Hydroxy-series				
1a	50.1	29.7	$<10^{-2}$	$<2\times10^{-2}$
1b	5.83	(1.78)[c]	2.96	$>10^{2}$
1c	2.38×10^{4}	-	0.13	$>10^{2}$
1d	9.65×10^{3}	-	0.18	$>10^{2}$
2-Hydroxy-benzo-series				
4b	-	12.4	3.42×10^{-6}	$<2\times10^{-2}$
2-Hydroxy-indene(4e)[g]	83	2.79	$<10^{-2}$	$<2\times10^{-2}$
2-Hydroxy-series				
3b	-	(11.5)[c,d]	$<10^{-2}$	$<2\times10^{-2}$

[a] Water, I - 1.00 M

[b] Water-acetonitrile (10% - 90% v/v)

[c] Water-acetonitrile (50% - 50% v/v)

[d] Total rate constant to yield 3-thiolene-2-one(20%) and 4-thiolene-2-one(80%)

[e] Generated from 1-indenyl dimethyl orthoacetate

[f] Extrapolated value

[g] Generated from its trimethylsilyl derivative

The monocyclic 3-hydroxy-compounds(1a - 1d) undergo ketonization 11 to 6.9 x 10^3 times faster than their benzo-analogues (2a - 2d) presumably as a result of the mesomeric effect symbolised by 5 which is more effective when X is N causing the 3-hydroxypyrroles (1c and 1d) to ketonize faster than 3-hydroxyfuran and 3-hydroxythiophene. Again substantial amounts of the more aromatic 3-hydroxythiophene (1b) and 3-hydroxypyrroles (1c and 1d) are present at equilibrium but no detectable amount of the less aromatic 3-hydroxyfuran.

2-Hydroxythiophene undergoes ketonization to yield a mixture of 3- and 4- thiolene-2-one the composition of which depends on the catalyst and the solvent. The H_3O^+-catalysed ketonization with protonation at C-3 to yield 4-thiolene-2-one is about five times faster in water-acetonitrile (50% - 50% v/v) than the H_3O^+-ketonization of 3-hydroxy-thiophene which occurs with protonation at C-2. The initial protonation steps in these reactions are similar to the initial steps of proton-exchange and other electrophilic substitutions which normally occur much faster at C-2 of thiophene than at C-3.[12] The presence of the hydroxy groups is therefore affecting the relative rates, and the formation of the thioester group at C-2 is kinetically as well as thermodynamically favoured over formation of the keto-group at C-3. Benzothiophene normally undergoes electrophilic

substitution at the 3-position more rapidly than at the 2-position[1,2] so both this and formation of the thioester group favour ketonization of 2-hydroxy-benzothiophene which occurs 40 times faster than ketonization of 3-hydroxy-benzothiophene. The rapid rate of ketonization of the thio-ester enol 2-hydroxy-benzothiophene is also indcated by its 4.4 fold greater rate of ketonization compared to 2-hydroxyindene which contrasts with what is found with 3-hydroxy-benzothiophene and 1-hydroxyindene.

It is suggested that it may be possible to generate many other hitherto inaccessible unstable tautomers of heterocyclic compound by methods similar to those reported in this paper.

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