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Some studies on the tautomerism of heterocyclic and homocyclic compounds

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Abstract - The following hydroxy derivatives of heterocyclic compounds have been generated in solution and characterized by ^{1}H-NMR spectroscopy: 3-hydroxyfuran, 3-hydroxythiophene, 3-hydroxypyrrole, 3-hydroxy-1-methylpyrrole, 3-hydroxybenzofuran, 3-hydroxybenzothiophene, 3-hydroxyindole, 3-hydroxy-1-methylindole, 2-hydroxythiophene, 2-hydroxybenzothiophene, 2,5-dihydroxythiophene. The rate and equilibrium constants for their ketonization have been measured and are discussed. The following hydroxy derivatives of homocyclic compounds were also generated, characterized and investigated: 1-hydroxyindene, 2-hydroxyindene, 1-hydroxycyclohepta-1,3,5-triene, 3-hydroxycyclohepta-1,3,5-triene, hydroxycyclooctatetraene, and 3-hydroxy-cycloocta-1,3,5-triene.

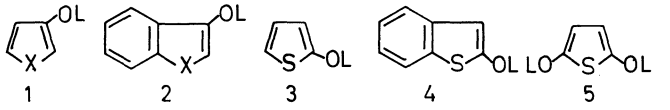
The mechanism of hydrolysis of heterocyclic methyl ethers derived from furan, thiophene, 1-methylpyrrole and their benzo-derivatives has been investigated and a change in rate limiting step from *C*-protonation to nuclophilic attack by water on the intermediate cation detected.

INTRODUCTION

There have been many investigations on the tautomerism of heterocyclic compounds (ref. 1-5) but most of these have been concerned with determining the structures of the stable tautomers. There have been relatively few investigations of unstable tautomers. In this lecture I wish to show how we have been able to generate in solution the unstable hydroxy tautomers (1-5) derived from furan, thiophene, pyrrole, 1-methylpyrrole and their benzo-derivatives, characterize them by NMR spectroscopy and start an investigation of their properties.

GENERATION OF UNSTABLE TAUTOMERS OF HETEROCYCLIC COMPOUNDS

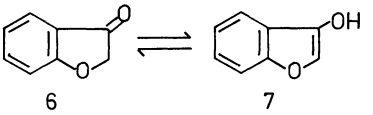
The first tautomeric pair to be investigated was 3-hydroxybenzofuran-3-benzofuranone (6 ⇌ 7). Previous investigators had shown that this compound exists exclusively as the keto-tautomer (6) in solutions in deuterated dimethyl sulphoxide and deuterated chloroform (ref. 6,7) and we confirmed this. The problem therefore is to find a way of generating the enol-tautomer (7).



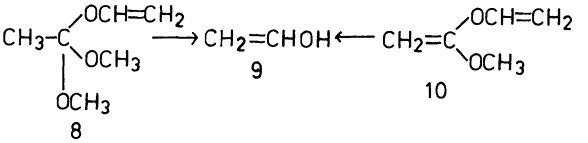
1 2 3 4 5

a X = O d X = NCH$_3$
b X = S e X = CH$_2$
c X = NH

L = H or D



6 7

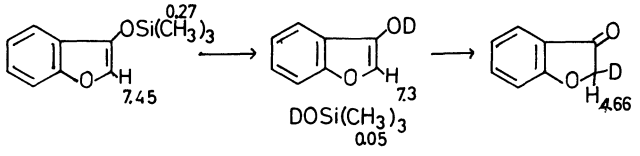


8 9 10

Earlier we had shown that vinyl alcohol (9) and other simple enols may be generated in solution by hydrolysis of precursors which have a labile protecting group which can be removed more rapidly than the enols ketonize (ref. 8). Thus for the generation of vinyl alcohol the two precursors 8 and 10 with ortho ester and ketene acetal protecting groups are particularly valuable. We therefore thought that it might be possible to generate the

enolic tautomer 7 by a similar method but that since the double bond is conjugated it was thought that this enol might not be so reactive as vinyl alcohol and that hence it would not be necessary to use such a labile protecting group. This was found to be so and the trimethylsilyl group could be removed from 3-trimethylsilyloxybenzofuran much faster than the resulting enol ketonized (ref.9).

The ^{1}H-NMR spectrum of 3-trimethylsilyloxybenzofuran in acetone-d_6 at *ca* 30°C showed signals at δ=7.45(s), 7.3(m), and 0.27(s). On addition of D_2O/DCl so that the concentration of D_2O was 10% v/v and that of DCl was 5×10^{-4}M the spectrum changed rapidly. The hydrolysis of the trimethylsilyl group was indicated by a decrease and eventual disappearance of the signal at δ=0.27 and formation of a signal at δ=0.05 which was ascribed to trimethylsilanol (or hexamethyldisiloxane) (ref. 10). At the same time the singlet which corresponded to H(2) of the trimethylsilyl ether at δ=7.45 was replaced by another singlet at δ=7.3 which was ascribed to H(2) of 3-deuteroxybenzofuran (see equation 1). These changes were complete after 18 minutes and the enol form appeared to be the only form present in solution as no signal ascribed to the methylene group of the keto form was discernable at δ=4.6-4.7. This solution was stable for several hours at 32°C but on addition of 5µL of 1 M HCl a multiplet at δ=4.66 corresponding to H(2) of the deuterated keto-form was formed over a period of about 15 minutes with concurrent disappearance of the signal at δ=7.3 of H(2) of the enol form. The multiplet of the protons on the benzene ring also changed to that of the keto form. These signals showed no further change but the signal of H(2) (δ=4.66) gradually disappeared and the signal of HDO increased as a result of exchange.



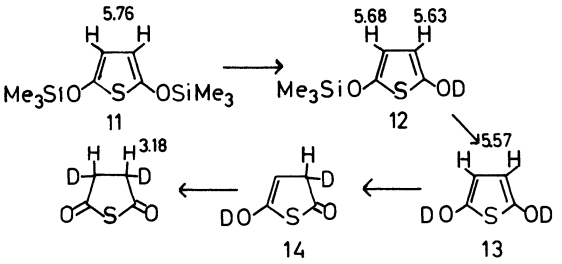
(1)

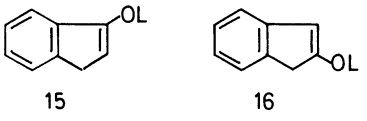
The enolic forms 3-hydroxybenzothiophene (2b, L=D) (ref. 7, 11), 3-hydroxyindole (2c, L=D) and 3-hydroxy-1-methylindole (2d, L=D) were generated similarly. The isolated solid forms of 3-hydroxybenzothiophene and 3-hydroxyindole were found to be the keto-tautomers as reported previously (ref. 7, 11, 12). On the other hand 3-hydroxy-1-methyl-indole was found to consist of a mixture of about 34% enol and 66% keto forms even after sublimation. The IR spectrum (nujol) showed a carbonyl stretching absorption (1665 cm^{-1}) and a broad OH stretching centred at 3180 cm^{-1} and the ^{1}H-NMR spectrum of a freshly prepared solution in DMSO-d_6 showed signals which corresponded to H(2) of both enolic and keto-forms. These three enolic forms (2b-2d) after generation in solution from their trimethylsilyl ethers ketonized in a similar way to that described for 3-hydroxybenzofuran except that when the keto-enol equilibria were established there were still detectable amounts of the enolic forms present.

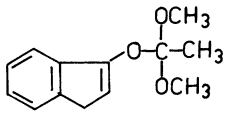
The monocyclic 3-hydroxy-compounds 1a and 1b were also generated from their *O*-trimethylsilyl ethers but the rates of ketonization were substantially greater. At equilibrium in water and in DMSO 3-hydroxyfuran exists greater than 99% in the keto-form (ref. 13) but a substantial amount of 3-hydroxythiophene was present at equilibrium (ref. 14). The trimethylsilyl derivatives are not suitable precursors for the generation of 3-hydroxypyrrole and 3-hydroxy-1-methylpyrrole (ref. 15) 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 these 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 (3, L=D) and 2-hydroxybenzothiophene (4, L=D) were also generated from their trimethylsilyl ethers. These may be regarded as the enolic forms of thioesters and they are converted into more than 99% of the keto-form at equilibrium (ref. 16). Attempts to generated the enolic forms of the corresponding furan and pyrrole heterocycles have so far been unsuccessful.

Scheme 1







We are also investigating the dihyroxy-derivatives of these heterocyclic systems but the only member of this series that we have so far been successful in detecting is 2,5-dihydroxythiophene (13) which was generated from the corresponding bis-trimethylsilyl derivative (11) (ref. 17); see Scheme 1. When the hydrolysis of the latter was followed by ^{1}H-NMR spectroscopy, the aromatic mono-(12) and di-(13)hydroxy compounds could be detected but not the non-aromatic hydroxy-keto compound (14).

In addition to generating these heterocyclic enols, for the benzo-series we have also generated the corresponding carbocyclic enols 15 and 16 to allow the effect of the hetero-atom to be studied. Enol 16 could be generated from its trimethylsilyl derivative but for the generation of enol 15 it was necessary to use the more labile ortho ester protecting group (see 17) similar to that used previously for other enols (ref. 8).

KINETICS AND MECHANISM OF KETONIZATION OF HETEROCYCLIC ENOLS AND HYDROLYSIS OF CORRESPONDING ENOL ETHERS

By the use of the methods described in the last section we are able to prepare solutions of the hydroxy tautomers and hence investigate their properties. We have made a start on this by measuring the rate and equilibrium constants for ketonization. The kinetics of ketonization were studied by UV spectroscopy. The pH-rate profiles in water are inverted bell-shaped curves following equation 2 with H^+, HO^-, and H_2O-catalysed reactions.

$$k_{obs} = k_H{+}10^{-pH} + k_{H_2O} + k_{HO^-}K_w/10^{-pH} \qquad (2)$$

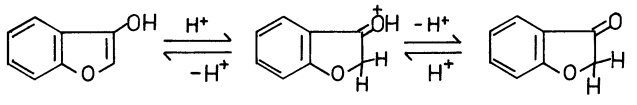
As some of the reactions were very fast some of the H_3O^+-catalysed reactions were also studied in acetonitrile-water mixtures. Detectable amounts of the 3-hydroxybenzothiophene (2b) the 3-hydroxyindoles (2c, 2d), 3-hydroxythiophene (1b), and the 3-hydroxypyrroles (1c, 1d) were present at equilibrium in water and the equilibrium constants were evaluated from the infinity absorbances. With the other compounds detectable amounts of the enol forms were not present at equilibrium so the rate constants for the H_3O^+-catalysed enolizations of the keto-forms were determined by the iodine-trapping method (ref. 18) and the equilibrium constants were determined from the rate constants for enolization and ketonization. These equilibrium constants (Table 1) indicate that 3-hydroxythiophene, 3-hydroxypyrrole, and their benzo-analogues are relatively more stable with respect to their keto-forms than 3-hydroxyfuran and its benzoanalogue are with respect to their keto forms. This is in agreement with the greater resonance energy of thiophene and pyrrole compared to furan (ref. 19). It has been pointed out that the resonance energy of benzofuran is very close to that of benzene and hence it was concluded that the furan ring of benzofuran is not aromatic (ref. 20).

Table 1 Rate and Equilibrium Constants for Ketonization at 25° (I = 1.00 M)

	$k_H{+}/M^{-1}s^{-1}$	K_{Enol}(E/K)
3-Hydroxybenzofuran	0.592	8.74×10^{-4}
3-Hydroxybenzothiophene	0.532	0.085
3-Hydroxyindole	3.44	0.086
3-Hydroxy-1-methylindole	5.82	0.303
1-Hydroxy-indene	903	1.85×10^{-8}
3-Hydroxyfuran	50.1	$<10^{-2}$
3-Hydroxythiophene	5.83	2.96
3-Hydroxypyrrole	2.38×10^4	0.13
3-Hydroxy-1-methyl-pyrrole	9.65×10^3	0.18

Nevertheless replacement of the CH_2 group of 1-hydroxyindene (2e) by an oxygen to give 3-hydroxybenzofuran (2a) has a substantial kinetic and thermodynamic effect on the stability of the enol: k_{H^+} for the ketonization of 1-hydroxyindene (2e) is about 1.5×10^3 greater than that for 3-hydroxybenzofuran (2a) and K_{Enol} is 4.7×10^4 less. Therefore despite the lack of aromaticity of the furan ring the oxygen has a substantial stabilizing effect on the double bond as might be expected from the work Hine and Flachskam (ref. 21).

As for the ketonization of simple enols (ref. 8) there are two possible mechanisms for the ketonization of these heterocyclic enols as illustrated for 3-hydroxybenzofuran in equations 3 and 4. The two proton transfers can either occur in separate steps (eq. 3) or concertedly (eq. 4).



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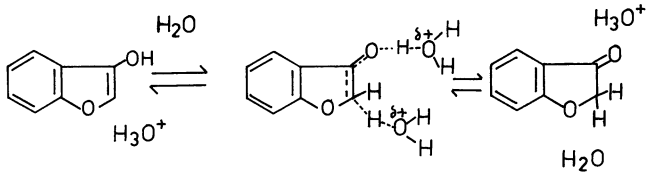


(4)

The mechanism which involves concerted proton transfers (analogous to eq. 4) was preferred for the ketonization of simple enols on the basis of a comparison of the kinetics of these reactions with the kinetics of the hydrolysis of the corresponding enol ethers (ref. 8). Similar behaviour to that found with simple enols was found when the ketonization of 3-hydroxybenzofuran was compared with the hydrolysis of 3-methoxybenzofuran. Thus k_{H^+} for the ketonization of 3-hydroxybenzofuran is 15.7 times greater than that for the hydrolysis of 3-methoxybenzofuran in water but about 2680 fold greater in water-DMSO mixture (17.2:82.8 mole %). This large difference in rates and the difference in the dependence of the rates on DMSO concentration suggests a strong interaction of the proton on the hydroxyl group with the solvent in the transition state for the ketonization of 3-hydroxybenzofuran which is best explained by the concerted mechanism (eq. 4).

CHANGE IN RATE-DETERMINING STEP IN HYDROLYSIS OF HETEROCYCLIC ENOL ETHERS

An attempt to extend the above type of investigation to the other heterocyclic enols lead to an unexpected result. The relative rates of their hydronium-catalysed ketonization compared to the hydrolysis of the corresponding methyl enol ethers is given in Table 2. With simple enols in water this ratio falls in the range 10 to 70 (ref. 8) but some of these heterocyclic enols values greatly in excess of this were obtained. This lead us to suspect that there might be a change in rate determining steps in the hydrolysis of the methyl ethers from rate limiting carbon protonation to rate limiting attack on the intermediate cation. The possibility that there might be a change in the rate-limiting step in the hydrolysis of enol ethers was first considered by Kresge and Chen (ref. 22) who also pointed out that in the extreme case of a phenol ether reversible protonation is much faster than hydrolysis. However their attempts to detect a change in the rate-determining step of the hydrolysis of simple enol ethers were unsuccessful (ref. 22, 23). Subsequently evidence for such a change was obtained by Okuyama and Fueno (ref. 24) with ketene dithioacetals as substrates and by Hevesi (ref. 25) with seleno enol ethers and ketene diseleno acetals. The evidence which includes the observation of deuterium exchange and *cis-trans* isomerisation concurrent with hydrolysis, the solvent isotope effects, and the observation of general-acid catalysis with a non-linear dependence on buffer concentration indicates that with ketene dithioacetals and seleno enol ethers that proton transfer and hydration of the cation occur at comparable rates but that with ketene diselenoacetals proton transfer is fast and reversible. Therefore it requires the presence of two sulphurs or one selenium to cause a partial change in rate-determining step and only when two seleniums are present is the change in rate-determining step complete. It was suggested (ref. 24) that for the ketene dithioacetals the partial change in rate-determining step resulted from hydration of the cation being slow rather than from its deprotonation being fast.

Table 2 Relative Rates of Ketonization of Heterocyclic Enols compared to the Rates of Hydrolysis of the Corresponding Enol Ethers in water at 25°C (I = 1.00 M)

	k_H^+(keto)/k_H^+(hyd.)
3-Hydroxyfuran	204
3-Hydroxythiophene	3.49×10^4
3-Hydroxybenzothiophene	63.2
3-Hydroxyindole	554
3-Hydroxy-1-methylindole	1658

Table 3 Solvent Isotope Effects (k_H^+/k_D^+) for the Hydrolysis of Heterocyclic Enol Ethers

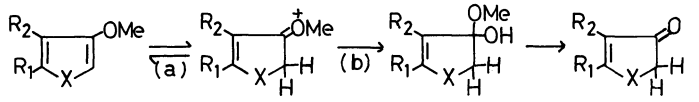
	k_H^+/k_D^+*	k_{ex}/k_{hyd}**
3-Methoxybenzofuran	3.08	<.05†
3-Methoxybenzothiophene	1.36	31
3-Methoxyfuran	0.51	83
3-Methoxy-1-methylindole	0.44	1.3×10^3
3-Methoxythiophene	0.52	2.6×10^4

*In water at 25°

**In CD_3CN:D_2O(9:1v/v) at 32°

†(Exchange not detected)

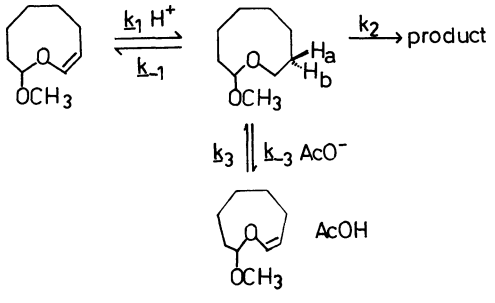
The results shown in Table 3 suggest that there is a regular change in the mechanism of hydrolysis on going from 3-methoxybenzofuran to 3-methoxythiophene. 3-Methoxybenzofuran behaves as a normal enol ether. The isotope effect k_H/k_D=3.08 and no exchange could be detected when the hydrolysis was followed by ^{1}H-NMR in CD_3CN-D_2O mixture. With 3-methoxythiophene however k_H/k_D=0.52 and exchange is about 2.6×10^4 times faster than hydrolysis. 3-Methoxy-1-methylindole and 3-methoxyfuran behave similarly but 3-methoxybenzothiophene shows intermediate behaviour with k_H/k_D=1.36 and k_{ex}/k_{hy}=31 in the CD_3CN-D_2O mixture. It therefore seems that as the heterocyclic system becomes more aromatic there is an increase in the tendency of the intermediate cation to undergo deprotonation (a in eq. 5) and re-aromatise relative to undergoing nucleophilic attack (b). With this series compounds we are therefore able to obtain a complete spectrum of the possible reaction mechanisms of the hydrolysis of oxygen-enol ethers.



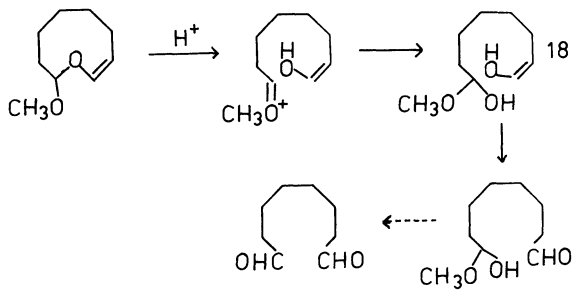
$R_1 = R_2 = H$ or $R_1R_2 = C_4H_4$ (5)

Reversible protonation in the hydrolysis of an oxygen-enol ether has been claimed previously (ref. 26) for the hydrolysis of 9-methoxy-oxacyclonon-2-ene at high buffer concentrations. It was proposed that in the absence of buffer the rate limiting step was protonation of the double bond (k_1 in Scheme 2) but that at high buffer concentration ($C_{AcO^-} > \sim 0.01$ M) the protonation step became rapid and reversible and the rate limiting step became "some subsequent reaction" tentatively identified as reaction of the cation with water. As pointed out by Kresge and co-workers (ref. 27) there are a number of problems with this mechanism. One of these is that at high buffer concentrations there should be exchange of the hydrogen at position 3 with the solvent but this was not detected when the reaction was carried out in D_2O (C_{NaOAc}=0.017 M) and it was therefore necessary to postulate that H_a and H_b in the intermediate cation (see Scheme 2) undergo exchange at significantly different rates. It is now suggested that the mechanism shown in Scheme 3 explains the experimental observations better.

Scheme 2



Scheme 3



9-Methoxyoxacyclonon-2-ene is a mixed alkoxy-vinyloxy-acetal and would be expected to behave like a mixed alkoxy-phenoxy-acetal (ref. 28) and undergo fission of the C-O bond to the vinyloxy group. This would lead to the simple enol 18 and the rate of its ketonization should be approximately equal to that of *cis*-prop-1-enol for which $k_H+=2.80\ M^{-1}s^{-1}$ at 15° (ref. 8). The rate constant measured by Cooper, Vitullo, and Whalen for reaction of 9-methoxyoxacyclonon-2-ene in the absence of buffer is $8.1\ M^{-1}s^{-1}$ at 25.1° (ref. 27) and hence it would be reasonable that the process whose rate is being measure is ketonization of enol. The isotope effect $k_H+/k_D+=4.2 \pm 0.2$ is also a reasonable value for ketonization of an enol (cf ref. 8), and as isotope effects for the hydrolysis of enol ethers are rarely greater than 3.6 (ref. 29), is perhaps better explained by the mechanism of Scheme 3 than by that of Scheme 2. The change in rate determining step on increasing the buffer concentration can also be explained by Scheme 3 as the ketonization of enols is strongly general base catalysed (ref. 8) so at high buffer concentration the ketonization step would become fast and the rate-limiting step would be hydrolysis of the mixed acetal.

ACID-CATALYSED KETONIZATION OF 2-HYDROXY COMPOUNDS: COMPARISON WITH ELECTROPHILIC SUBSTITUTION

The ketonization of the two 2-hydroxy-compounds studied, 2-hydroxybenzothiophene and 2-hydroxythiophene, show a relatively fast spontaneous or water catalysed reaction which it necessary to study the kinetics in acetonitrile-water mixture. In contrast to what is found with 3-hydroxy compounds, 2-hydroxybenzothiophene undergoes ketonization faster than its carbocyclic analogue 2-hydroxyindene and it also undergoes ketonization faster than 3-hydroxybenzothiophene (Table 4). This behaviour presumably arises from 2-hydroxybenzothiophene being an enol at the carboxylic acid level of oxidation and from the thio-ester delocalization being partly developed in the transition state.

2-Hydroxythiophene ketonizes more slowly than 2-hydroxybenzothiophene. The ketonization of 3-hydroxythiophene could not be studied in a 9:1 (v/v) mixture of acetonitrile-water as in this solvent the equilibrium strongly favoured the enol form but in a 1:1 (v/v) mixture 2-hydroxythiophene ketonizes about 6.5 times faster than 3-hydroxythiophene.

The rate-limiting step in the acid-catalysed ketonization of these enols is analogous to that for electrophilic substitution in the heterocyclic rings (ref. 30). Thus the ketonization of the 3-hydroxy compounds is analogous to electrophilic substitution in the 2-position and ketonization of the 2-hydroxy compounds to form the Δ^4 keto-compounds analogous to substitution in the three position (see Scheme 4). The ketonizations of the hydroxy compounds are however many orders of magnitude faster than proton exchange of the parent heterocycles but the same relative rate sequences are found when comparing benzothiophene and thiophene for reaction at either the 2- or 3-position (see Scheme 5). When however reaction at the 2-position is compared with reaction at the 3-position the relative rate sequences for electrophilic substitution and ketonization are different (Scheme 6). As mentioned above there must be some additional stabilization of the transition state for ketonization of the 2-hydroxy-compound as a result of delocalization in the developing thioester group.

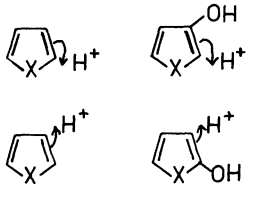
Table 4 The Kinetics of Ketonization of 2-Hydroxythiophene and 2-Hydroxybenzothiophene at 25°C

	$k_H+/M^{-1}s^{-1}$*
2-Hydroxybenzothiophene	12.4
2-Hydroxyindene	2.79
3-Hydroxybenzothiophene	0.314
2-Hydroxythiophene	2.10(11.5)+
3-Hydroxythiophene	(1.78)+
2,5-Dihydroxythiophene	7.06

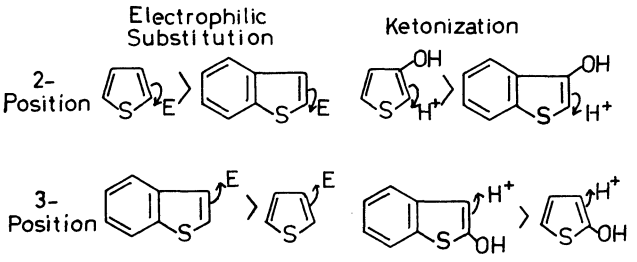
*In acetonitrile-water (9:1 v/v)

+In acetonitrile-water (1:1 v/v)

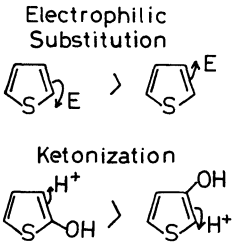
Scheme 4



Scheme 5

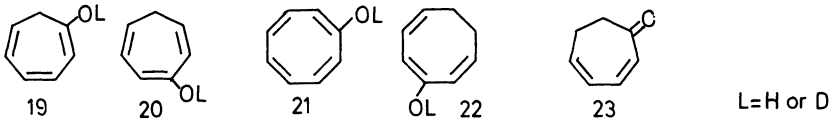


Scheme 6

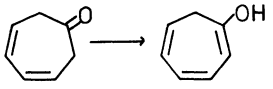


HOMOCYCLIC ENOLS

The technique that we have used to generate heterocyclic enols has also been used to generate the homocyclic enols 19 to 22 in aqueous DMSO or aqueous acetonitrile solution. Enols 19 and 20 are derived from cycloheptatriene and if cycloheptatriene were stablized by homoaromaticity, which has sometimes been claimed (ref. 31) but sometimes disputed (ref. 32), they would be expected to be stabilized with respect to their keto forms as compared to analogous acyclic trienols.



Ketonization of cyclohepta-1,3,5-trienol yields 3,5-cyclohaptadienone as the kinetically controlled product. This ketone has been synthesized several times before and variable results have been reported for its UV spectrum (ref. 33) which have sometimes been attributed to the presence of 2,4-cycloheptadienone (23). It seemed to us that these results might partly be due to the presence of variable amounts of cyclohepta-1,3,5-trienol and to see if 3,5-cycloheptadienone would enolize we measured its NMR spectrum in DMSO-d_6, a solvent which is particularly favourable for stabilization of enols. Over a period of 15-30 minutes the ^{1}H-NMR spectrum changed with formation of signals due to the trienol the most obvious of which were those at δ=2.38 due to H-7 and δ=9.4 due to the OH. At equilibrium there was *ca* 35% of cyclohepta-1,3,5-trienol present. An analogous change was found in the UV spectrum of a DMSO solution of 3,5-cycloheptadienone when there is an increase in absorbance at 297 nm. Support for this being due to formation of cyclohepta-1,3,5-trienol was obtained by injecting a small amount of an equilibrated DMSO solution into acetonitrile when the maximum, now at 286 nm, decreases to a new equilibrium value.



(6)

We have studied the kinetics of ketonization of these cyclic enols. The kinetics of the enolization of 3,5-cycloheptadienone has also been measured by the iodine-trapping method (ref. 18) which gives an equilibrium constant of 1.2×10^{-3} for the enolization shown in equation 6. Clearly this enol is more stable than vinyl alcohol for which K_{enol} is 2×10^{-7} (ref. 8) but is much less stable than phenol for which $K_{enol}=10^{11}$ (ref. 34).

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