Tautomerism of the Monohydroxy[1] Derivatives of Five-Membered O, N, and S Heterocycles

Brian Capon* and Fu-Chiu Kwok

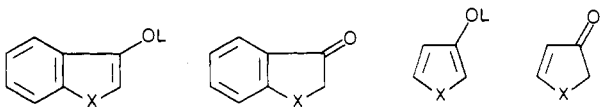
Contribution from the Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong. *Received July 11, 1988. Revised Manuscript Received December 12, 1988*

Abstract: The O-deuterated enolic tautomers 3-deuteroxybenzofuran, 3-deuteroxybenzothiophene, 3-deuteroxyindole, 3-deuteroxy-1-methylindole, 3-deuteroxyfuran, 3-deuteroxythiophene, 2-deuteroxybenzothiophene, and 2-deuteroxythiophene have been generated in solution in mixtures of CD_3COCD_3, CD_3CN, or CD_3SOCD_3 with D_2O by hydrolysis of their trimethylsilyl derivatives in the presence of DCl (10^{-3}–10^{-4} M) and characterized by ^1H NMR spectroscopy. Solutions of 3-hydroxypyrrole and of 3-hydroxy-1-methylpyrrole were obtained by methanolysis of their trimethylsilyl derivatives, evaporation of the methanol, and immediate dissolution in DMSO-d_6. The carbocyclic analogues of the bicyclic heterocyclic enols 3-deuteroxyindene and 2-deuteroxyindene were also generated in solution. Attempts to prepare solutions of 2-deuteroxyfuran, 2-deuteroxypyrrole, and 2-deuteroxy-1-methylpyrrole were unsuccessful. The kinetics of ketonization of the OH forms of these enols have been investigated in water or aqueous acetonitrile solution. The equilibrium constants for the keto–enol tautomerism were also determined either by direct measurement when sufficient enol was present at equilibrium or as the ratio of the rate constant for enolization of the keto form to that for ketonization of the enol form, the former being determined by the iodine-trapping technique. The effect of solvent on the equilibrium constants was also studied. Sufficient data were available for the equilibrium between 3-hydroxyindole and 3-ketoindole for them to be analyzed by the four-parameter equation of Mills and Beak to yield an *a* value of 2.4 and a *b* value of −3.0. The pK_as of the bicyclic enols were measured. 3-Hydroxybenzofuran and 3-hydroxybenzothiophene are stronger acids than 3-hydroxyindole and 3-hydroxy-1-methylindole. The ketonization reactions are general acid and general base catalyzed and their mechanisms are discussed.

There have been many investigations on the tautomerism of heterocyclic compounds,[2-7] 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 paper we show how a series of hydroxy derivatives of furan, thiophene, pyrrole, 1-methylpyrrole, and their benzo derivatives may be generated in solution and characterized by NMR spectroscopy and describe an investigation of the kinetics of the conversion of these species into their keto tautomers and measurements of the equilibrium constants of these reactions.

Methods Used for the Generation of Unstable Hydroxy Tautomers

It has been shown that vinyl alcohol 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.[8-12] It was thought that it should be possible to generate the enolic tautomers **1a–d** and **3a–d** by a similar

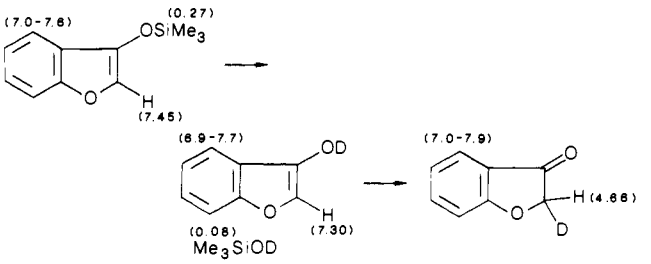


1 2 3 4

a, X = O; **b**, X = S; **c**, X = NH; **d**, X = NCH_3; **e**, X = CH_2; L = H or D

method and that since these are conjugated enols the protecting groups would not have to be so labile as those used for the generation of simple enols (e.g. ketene acetal and ortho ester). This was found to be so and all those enolic forms except the hydroxypyrroles could be generated in solution by hydrolysis of their trimethylsilyl ethers.[13]

Scheme I



Generation of 3-Hydroxybenzofuran in Solution. It was confirmed that the product obtained by standard synthetic procedures was the keto tautomer **2a**. The solid-phase IR spectrum (Nujol) showed a strong carbonyl absorption at 1720 cm^{-1} and no O–H stretching absorption in the range 3000–4000 cm^{-1} (cf. ref 16) and the ^1H NMR spectra of solutions in $CDCl_3$ and DMSO-d_6 showed only the presence of the keto form in agreement with previous work.[14-16] However, the enol form was generated by hydrolysis of its trimethylsilyl ether in a mixture of CD_3COCD_3 (90% v/v) and D_2O (10% v/v) which was 5×10^{-4} M in DCl at 32 °C (see Figures 1 and 2 and Scheme I). The ^1H NMR spectrum of the trimethylsilyl ether in CD_3COCD_3 (Figure 1a) showed signals at δ = 7.45 (s), 7.3 (m), and 0.27 (s) assigned as shown in Scheme I. On addition of D_2O/DCl to give the mixture indicated above, the spectrum changed rapidly and the signal of the trimethylsilyl group of the ether (δ = 0.27) was replaced by a new signal at $\delta = \sim 0.08$ thought to be that of trimethylsilanol (or of hexamethyldisiloxane)[17,18] (see Figure 1b). This change

(1) (a) Presented in part at the 8th IUPAC Conference on Physical Organic Chemistry, Tokyo, Japan, August 1986. (b) Preliminary communication: Capon B.; Kwok, F. C. *Tetrahedron Lett.* **1986**, *27*, 3275-3278.
(2) Katritzky, A. R.; Lagowski, J. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 311-338, 339-437; **1963**, *2*, 3-26, 27-81.
(3) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocyclic Compounds*; Academic Press: New York, 1976.
(4) Katritzky, A. R. *Chimia*, **1970**, *24*, 134-146.
(5) Bird, C. W.; Cheesman, G. W. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: London, 1984; Vol. 4, pp 34-38.
(6) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: Oxford, 1985; p 83.
(7) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman Publishing Ltd.: London, 1985.
(8) Capon, B.; Rycroft, D. S.; Watson, T. W. *J. Chem. Soc., Chem. Commun.* **1979**, 724-725.
(9) Capon, B.; Rycroft, D. S.; Watson, T. W.; Zucco, C. *J. Am. Chem. Soc.* **1981**, *103*, 1761-1765.
(10) Capon, B.; Zucco, C. *J. Am. Chem. Soc.* **1982**, *104*, 7567-7572.
(11) Capon, B.; Siddhanta, A. K. *J. Org. Chem.* **1984**, *49*, 255-262.
(12) Capon, B.; Siddhanta, A. K.; Zucco, C. *J. Org. Chem.* **1985**, *50*, 3580-3584.
(13) That the trimethylsilyl derivatives of enols are hydrolyzed with nucleophilic attack of water on silicon has already been demonstrated. Novice, M. H.; Seikaly, H. R.; Seiz, A. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1980**, *102*, 5835-5838.
(14) Schönberg, A.; Praefcke, K.; Kohtz, J. *Chem. Ber.* **1966**, *99*, 3076-3084.
(15) Huke, M.; Gorlitzer, K., *Arch. Pharm. (Weinheim, Ger.)* **1969**, *302*, 423-432.
(16) Amick, D. R. *J. Heterocycl. Chem.* **1975**, *12*, 1051-1052.
(17) See Fleming, I. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 3, p 576.

0002-7863/89/1511-5346$01.50/0

Figure 1. (a) The ^1H NMR spectrum of 3-[(trimethylsilyl)oxy]benzofuran in CD_3COCD_3 at 32 °C; (b) the spectrum 2 min after adding 10% D_2O–DCl (final concentration 5×10^{-4} M); and (c) the spectrum 16 min after b. The multiplet at $\delta = 2.02$ is that of HCD_2COCD_3 present in the solvent.

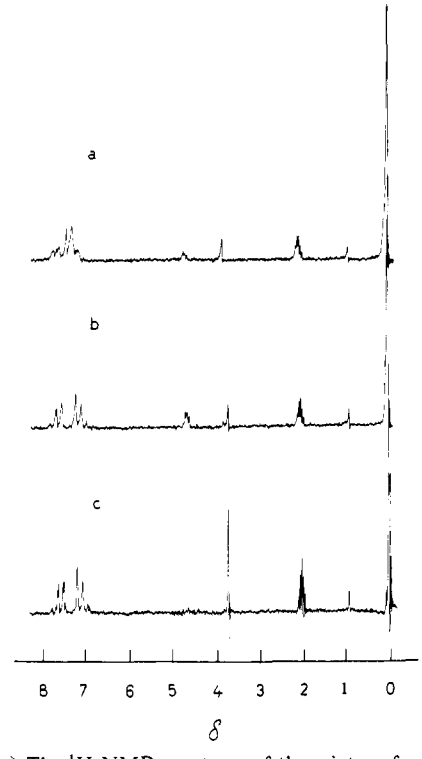


Figure 2. (a) The ^1H NMR spectrum of the mixture from Figure 1c immediately after the addition of 5 μL of 1 M DCl; (b) the spectrum 15 min after a; and (c) the spectrum 2 days later. The signal at $\delta = \sim 3.75$ is that of HOD.

was accompanied by the disappearance of the singlet at $\delta = 7.45$ ascribed to H-2 of the trimethylsilyl ether and its replacement by a new singlet at $\delta = 7.30$, which was ascribed to H-2 of 3-deuteroxybenzofuran. The complex multiplet centered on $\delta = 7.3$ of the protons attached to the benzene ring remained unchanged. These changes were complete after 18 min (Figure 1c) and the enol form appeared to be the only form present in solution as no signal ascribable to the methylene group of the keto form was discernible at $\delta = 4.6$–4.7. This solution was stable for several hours at 32 °C, but on addition of 5 μL of 1 M HCl a multiplet at $\delta = 4.66$ corresponding to H-2 of [2-^{2}H]-3-benzofuranone was formed with concurrent disappearance of the signal at $\delta = 7.3$ of H-2 of the enol form (Figure 2a). This change was complete after 15 min (Figure 2b) when the signals of the aromatic protons were identical with those of the keto form **2a** measured independently. These signals showed no further change but the signal of H-2 at $\delta = 4.66$ gradually disappeared and the signal of HDO increased as a result of exchange (Figure 2c). Similar experiments were carried out with DMSO-d_6 (80% v/v)–D_2O (20% v/v) which contained DCl (1×10^{-3} M to 1×10^{-4} M) as solvent. Solutions of **1a** (L = D) obtained in this way were stable for 1 day at room temperature and were used as stock solutions in kinetic experiments.

Generation of 3-Hydroxybenzothiophene in Solution. There are conflicting reports as to whether 3-hydroxybenzothiophene (**1b**) or 3-benzothiophenone (**2b**) is the more stable tautomer. Holt and co-workers concluded on the basis of infrared spectroscopic evidence that they had isolated the keto form (**2b**) in the solid state and that this was the only tautomer present in $CHCl_3$ and CS_2 solution.[19] Buu-Hoi and co-workers on the other hand concluded on the basis of its ^1H NMR spectrum that the species that they had isolated had the enolic structures (**1b**, L = H) in $CDCl_3$ and CF_3CO_2H solution.[20] The NMR spectrum that they reported had signals for five "aromatic protons" between $\delta = 6.9$ and 7.8 which they assumed to include the signal of the proton at position 2 of the enolic tautomer (**1b**). As they were also unable to detect any signal due to the proton at position 2 of the keto form (**2b**), they concluded that their solutions contained only the enolic form. Later workers however reported that the NMR spectra in CCl_4 and $CDCl_3$ correspond to greater than 95% of the keto form.[15,21] This discrepancy was later considered to arise from slow equilibration of the tautomers.[22,3,5] However, in other solvents (DMSO, CH_3OH, CD_3COCD_3) both tautomers could be detected at equilibrium, and the signal of the proton at C-2 of the enolic form (**2a**) does not occur in the region $\delta = 6.9$–7.8 as claimed[20] but at $\delta = 6.47$.[15,21] It therefore seems likely that Buu-Hoi and co-workers must have been studying some other species. Rubaszewska and Grabowski[22] were able to generate the enol form in solution by protonation of the enolate ion and studied it by UV spectroscopy. They measured the kinetics of conversion of the enol form into the keto form and from their results the half-life can be calculated to be ca. 3 min at pH 2.3 and 20 °C.

The solid material that we obtained by standard methods[21,23] was the keto tautomer (**2b**) both before and after sublimation. The solid-phase IR spectrum (Nujol) showed a strong carbonyl absorption at 1690 cm^{-1} but no absorption between 3000 and 4000 cm^{-1} that corresponded to the O–H stretching vibration. When this solid was dissolved in DMSO-d_6, the initial ^1H NMR spectrum corresponded mainly to the keto form **2b** ($\delta(CH_2) = 3.99$), but this changes over the course of about 1 day into an equilibrium mixture which contains 87% of the enol form (**1b**).[24] Huke and Gorlitzer reported that there is 29% of the enol form present in DMSO-d_6 but did not state whether they allowed the system to reach equilibrium.[15] On the other hand, the ^1H NMR spectrum

(18) When the spectra were measured at 90 MHz, the signal of trimethylsilanol ($\delta = 0.102$) was resolved from that of hexamethyldisiloxane ($\delta = 0.071$) and the conversion of the former into the latter could be followed.

(19) Holt, S. J.; Kellie, A. E.; O'Sullivan, D. G.; Sadler, P. W. *J. Chem. Soc.* **1958**, 1217–1223. See also: Krohnke, F. *Chem. Ber.* **1959**, *92*, 114.

(20) Buu-Hoi, N. P.; Bellavita, V.; Ricci, A.; Grandolini, G. *Bull. Soc. Chim. Fr.* **1965**, 2658–2659.

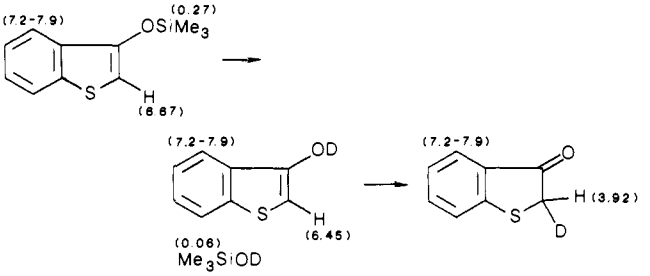
(21) Stridsberg, B.; Allenmark, S. *Chem. Scr.* **1974**, *6*, 184–192.

(22) Rubaszewska, W.; Grabowski, Z. R. *Tetrahedron* **1969**, *25*, 2807–2814.

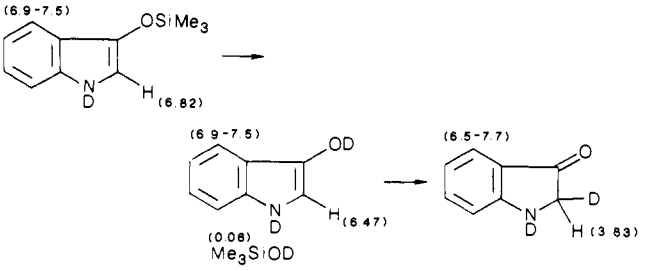
(23) Hansch, C.; Lindwall, H. G. *J. Org. Chem.* **1945**, *10*, 381–385.

(24) The rate of change depends on the water content of the DMSO-d_6, the greater the water content the faster the enolization.

Scheme II



Scheme III



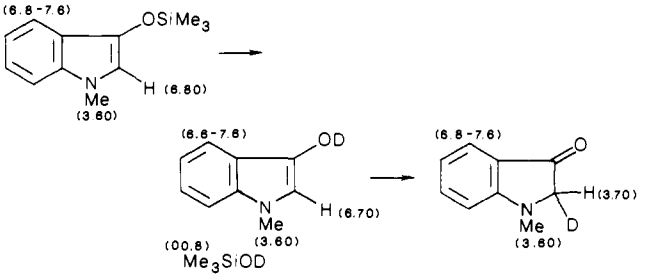
in $CDCl_3$ solution showed only the presence of the keto tautomer and this remained unchanged over 2.5 years. We therefore agree with Stridsberg and Allenmark[21] that the stable form in this solvent is the keto form. As discussed below, generally enols are much more stable in hydrogen bonding accepting solvents such DMSO than in solvents like $CDCl_3$ which do not accept hydrogen bonds.

3-Hydroxybenzothiophene could be generated in 100% yield as the enol form (**1b**, L = D) by hydrolysis of its trimethylsilyl ether in a way similar to that used for the generation of 3-hydroxybenzofuran, **1a** (see Scheme II). After 15 min at 32 °C the trimethylsilyl ether in 90% CD_3COCD_3–10% D_2O (5×10^{-4} M DCl) was converted into **1b** (L = D) (δ(CH) = 6.45) and no keto form, **2b** ($\delta(CH_2)$ = 3.92), could be detected. Under these conditions the enol form has a half-life of ca. 1 day and changes slowly to an equilibrium mixture which contains approximately 40% of the keto form.

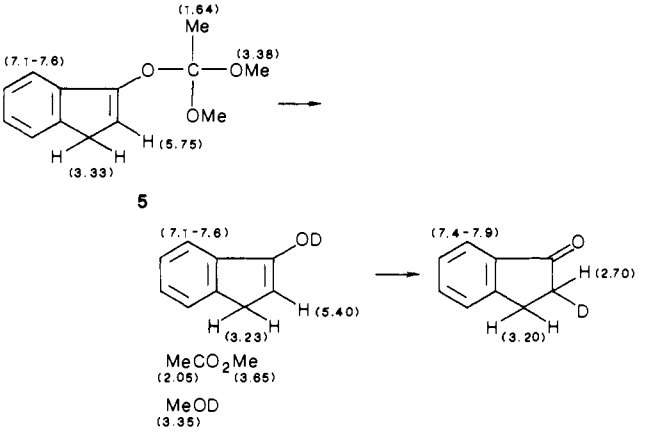
Generation of 3-Hydroxyindole in Solution. The solid sample of indoxyl that was isolated from its diacetate[25] and purified by sublimation was the keto form **2c** in agreement with the conclusions of Kirby and Shah.[26] The infrared spectrum (Nujol) shows a strong carbonyl absorption at 1685 cm^{-1} and N–H absorption at 3360 cm^{-1}, but no OH absorption. The ^1H NMR spectrum of a freshly prepared solution in DMSO-d_6 showed only the presence of the keto form ($\delta(CH_2)$ = 3.98, J = 2 Hz). However, over a period of 24 h the spectrum changed to that of the enol form (**1c**, L = H) (>90%), with δ(CH) = 6.72, $J_{1,2}$ = 2.5 Hz. The O,N-dideuterated enol form was generated by hydrolysis of its trimethylsilyl ether in 80% DMSO-d_6–20% D_2O (DCl = 5×10^{-4} M) and the signal of the methine proton of this species was a singlet (δ = 6.74) (see Scheme III).

Generation of 3-Hydroxy-1-methylindole. In contrast to what was found with indoxyl, the solid sample of *N*-methylindoxyl that was isolated by hydrolysis of the acetate[25] and purification by sublimation was a mixture of the enol (**1d**, L = **H**) and keto (**2d**) forms. The infrared spectrum (Nujol) showed a carbonyl-stretching absorption at 1665 cm^{-1} and a broad OH stretching at ca. 3180 cm^{-1}. When this material was dissolved in DMSO-d_6, a solvent in which tautomerization is slow, and the spectrum run immediately, 34% enol (**1d**, L = H) and 66% keto form (**2d**) were present. After 18 h at room temperature an equilibrium mixture which contained 92% of the enol form was obtained. When the solid was dissolved in $CDCl_3$, a solvent in which tautomerism is rapid, the ^1H NMR spectrum indicated the presence of ca. 97% keto form and ca. 3% enol form. This was confirmed by the IR spectrum of the solution which showed only a very weak OH absorption.

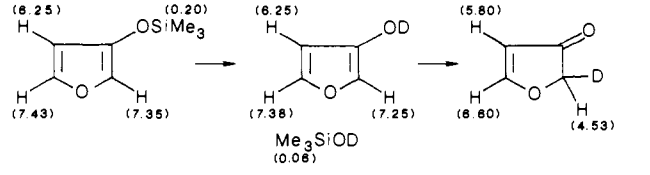
Scheme IV



Scheme V



Scheme VI



A solution which contained 100% of the O-deuterated enol form (**1d**, L = D) was generated by hydrolysis of its trimethylsilyl ether in DMSO (80%)–D_2O (20%)–DCl (5×10^{-4} M) at 32 °C (see Scheme IV). Under these conditions the enol form was generated immediately and was converted over a period of several hours into an equilibrium mixture which contained ca. 6% of the keto form.

Generation of 3-Hydroxyindene. In order to compare the ketonization of the 3-hydroxy bicyclic enols (**1a–d**) with the analogous carbocyclic compound, 3-hydroxyindene (**1e**) was also studied. When the corresponding trimethylsilyl ether was hydrolyzed in CD_3COCD_3 (80% v/v)–D_2O (20% v/v) which contained DCl (5×10^{-4} M), 3-hydroxyindene was detected, but its maximum concentration was only ca. 20% of the starting concentration of the precursor. A similar result was obtained when DMSO-d_6 was used instead of CD_3COCD_3, and it was therefore concluded that the trimethylsilyl ether was not a satisfactory precursor for this enol. Therefore recourse was made to the ortho ester derivative, **5**, analogous to the precursors used for the generation of other enols.[11] When this was hydrolyzed in CD_3COCD_3 (80%)–D_2O (20%) which contained DCl (10^{-3} M) at 32 °C, it was converted rapidly (<3 min) into the enol (**1e**, L = D). This was stable for at least 15 min but on addition of more acid (5 μL of 0.1 M DCl to 0.5 mL) was converted into the keto form (see Scheme V).

Generation of 3-Hydroxyfuran in Solution. 3-Hydroxyfurans exist exclusively in the keto form at equilibrium unless there is a keto substituent at position 2.[27-29]

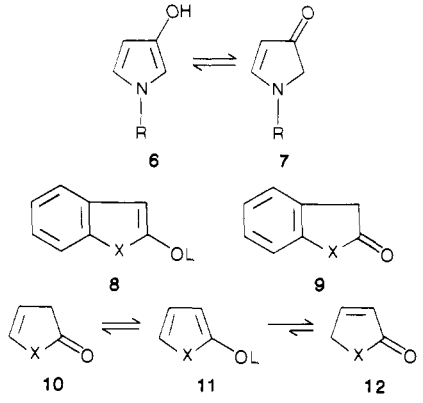
(25) Holt, S. J.; Sadler, P. W. *Proc. R. Soc. London, B* **1958**, 148–481.
(26) Kirby, G. W.; Shah, S. W. *Chem. Commun.* **1965**, 381.
(27) De Kijke, D.; Boelens, H. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 731–738.
(28) Meister, C.; Scharf, H. D. *Synthesis* **1981**, 733–737.

A solution which contains ca. 95% of the enol form **3a** (L = D) was generated from its trimethylsilyl ether in DMSO-d_6 (80%)–D_2O (20%) which contained DCl (5×10^{-4} M) at 32 °C (see Scheme VI). Over a period of several hours this was converted into the keto tautomer deuterated at position 2. In all the solvents used (CCl_4, DMSO-d_6, CD_3COCD_3, CD_3OD), no detectable amount of the enol was present at equilibrium.

Generation of 3-Hydroxythiophene in Solution. 3-Hydroxythiophene was first reported by Fiesselmann, Schipprak, and Zeitler in 1954 as an unstable oil,[30] but it was not completely characterized. It was prepared again in 1956 by Ford and MacKay, who showed by infrared spectroscopy that it exists as a mixture of keto (**4b**) and enol (**3b**) forms in the pure liquid state and in CCl_4 solution.[31]

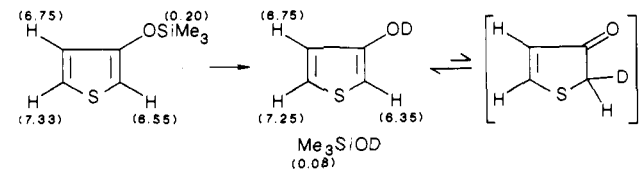
Alkyl- and dialkyl-3-hydroxythiophenes are more stable, but they still exist as mixtures of both forms in the liquid state and in solution. Lantz and Hörnfeldt[32] determined the equilibrium constants for the tautomerization of a series of 2,5-dialkyl-3-hydroxythiophenes in CS_2 solution. It was reported that the keto–enol equilibria were established very rapidly. The 2,5-dimethyl compound was studied in five solvents (C_6H_{12}, CS_2, $CHCl_3$, CH_3COCH_3, CH_3CN) and the values of K (keto (K)/enol (E)) varied from 8.09 in $CHCl_3$ to 1.04 in acetone. In our investigation crude 3-hydroxythiophene was prepared by the method of Ford and Mackay[31] and converted into its trimethylsilyl ether, which was purified by distillation. This was methanolyzed and evaporation of the methanol and trimethylsilanol yielded 3-hydroxythiophene with an infrared spectrum identical with that reported by Ford and Mackay.[31] Like previous workers, we found that this compound is resinified rapidly, but it is sufficiently stable to have its NMR spectrum run in a solvent. The percentage enol present was estimated to be as indicated in the following solvents: DMSO-d_6 (100%); CD_3COCD_3 (100%); CH_3OH (100%); dioxane–water (9:1) (~95%); CCl_4 (~60%).[33] Deuteroxythiophene can also be generated from its trimethylsilyl derivative in CD_3COCD_3–D_2O (4:1 v/v)–DCl (10^{-3} M) (see Scheme VII). The keto form was not detectable in this solvent, but the signal of H-2 of the enol form (δ = 6.30) slowly disappeared through exchange with the solvent and the signals of H-4 and H-5 were simplified.

3-Hydroxypyrroles. Momose and co-workers showed the 1-methyl, 1-benzyl, and 1-phenyl derivatives to exist as the keto tautomers (**7**, R = CH_3, $C_6H_5CH_2$, C_6H_5) in $CDCl_3$ solution by ^1H NMR spectroscopy.[34] Attempts to prepare the unsubstituted compound (**6** ⇌ **7**, R = H) were unsuccessful. The 1-*tert*-butyl

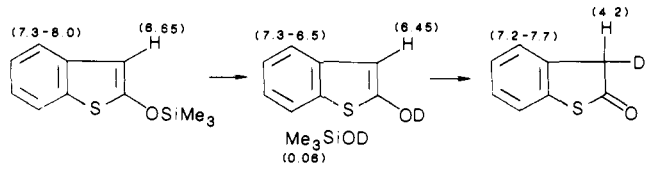


and 1-phenyl compounds were prepared by McNab and Monahan[35] and shown to exist as the keto tautomers (**7**, R = *t*-Bu, Ph)

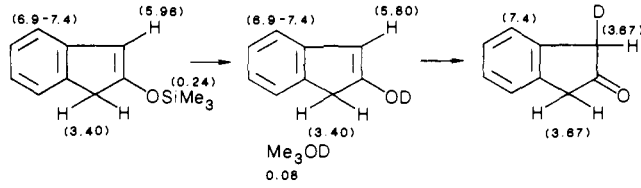
Scheme VII



Scheme VIII



Scheme IX



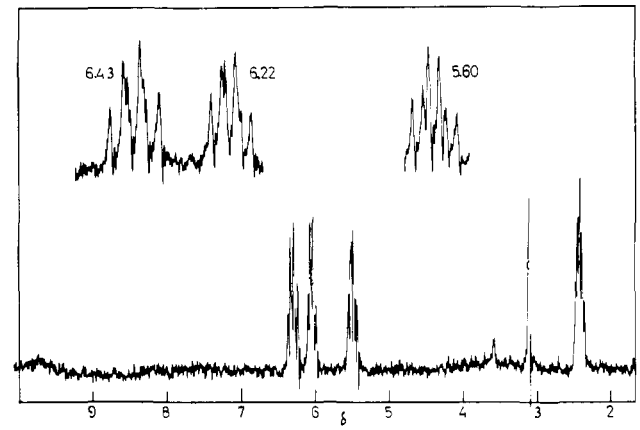


Figure 3. The ^1H NMR spectrum of 3-hydroxypyrrole in DMSO-d_6 at 32 °C. Inset: expansion of signals of protons at positions 2, 4, and 5.

in $CDCl_3$ solution. However, in DMSO-d_6 solution the enol forms (**6**, R = *t*-Bu, Ph) were present to the extent of 85–95%.

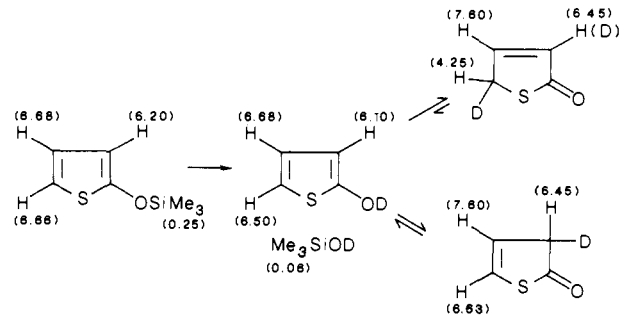
We have prepared the unsubstituted 3-hydroxypyrrole (**6**, R = H) by hydrogenolysis (and decarboxylation) of benzyl 3-hydroxypyrrole-2-carboxylate in ethanol with 10% Pd/C. The reaction was followed by withdrawing small samples from the reaction mixture and measuring the NMR spectra. After about 1.5 h, when reaction was complete, the catalyst was filtered off and the ethanol was removed with an oil pump, allowing the temperature to fall below room temperature. The crude material was converted to its trimethylsilyl ether, which was purified by distillation. This was methanolyzed (2–4 h) and the methanol and trimethylsilanol were evaporated (rotary pump). This yielded an unstable oil which resinified very rapidly. When it was dissolved immediately in DMSO-d_6, the ^1H NMR spectrum (Figure 3) of the solution was that expected for 3-hydroxypyrrole with δ = 5.60 (m, 1 H, H-4), 6.22 (m, 1 H, H-2), 6.43 (m, 1 H, H-5), and 9.76 (br s, 1 H, H-1 or HO).

A solution of 3-hydroxy-1-methylpyrrole (**6**, R = CH_3) was prepared similarly: δ = 3.28 (s, 3 H, NCH_3), 5.34 (dd, 1 H, J = 2.0, 2.6 Hz, H-4), 5.94 (dd, 1 H, J = 2.0, 2.6 Hz, H-2), 6.10 (t, 1 H, J = 2.6 Hz, H-5), 7.65 (br s, 1 H, OH).

Generation of 2-Hydroxybenzothiophene in Solution. As reported by a number of workers,[36] the isolated solid and its solutions

(29) Hofmann, A.; Philipsborn, W. v.; Eugster, C. H. *Helv. Chim. Acta* **1965**, *48*, 1322–1331.
(30) Fiesselman, H.; Schipprak, P.; Zeitler, L. *Chem. Ber.* **1954**, *87*, 841–848.
(31) Ford, M. C.; Mackay, D. *J. Chem. Soc.* **1956**, 4985–4987.
(32) Lantz, R.; Hörnfeldt, A. B. *Chem. Scr.* **1972**, *2*, 9–15.
(33) The ^1H NMR spectrum of the keto form in CCl_4 has been reported recently. Camici, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1986**, *27*, 5155. Our spectrum of a CCl_4 solution shows clearly the presence of both tautomers.
(34) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1979**, *27*, 1448–1453.
(35) McNab, H.; Monahan, L. C. *J. Chem. Soc., Chem. Commun.* **1985**, 213–214.

Scheme X



consist wholly of the keto tautomer **9** (X = S). We have generated the enol form (**8**, X = S, L = D) from its trimethylsilyl derivative in CD_3COCD_3–D_2O (9:1 v/v)–DCl (10^{-4} M) at −34 °C. On hydrolysis, the signal of the trimethylsilyl group of the ether at δ = 0.35 is replaced by that of trimethylsilanol (δ = ~0.08) with concurrent disappearance of the signal of H-3 of the ether at δ = 6.65 and the appearance of a new signal at δ = 6.45 ascribed to H-3 of 2-hydroxybenzothiophene. After 15 min at −25 °C the spectra had changed to that of [3-^{2}H]-2-benzothiophenone with a broad singlet at δ = 4.20 for H-3 (see Scheme VIII).

Generation of 2-Hydroxyindene in Solution. This was best carried out by hydrolyzing the trimethylsilyl derivative in CD_3SOCD_3–D_2O (4:1 v/v)–DCl (2 × 10^{-4} M) at 32 °C. The hydrolysis was complete in 4 min and the enol was stable for about 1 hour (see Scheme IX).

Generation of 2-Hydroxythiophene in Solution. 2-Hydroxythiophene (**11**, X = S, L = H) has two keto tautomers: 4-thiolen-2-one (**10**, X = S) and 3-thiolen-2-one (**12**, X = S). The tautomerism of 5-substituted 2-hydroxythiophenes was extensively studied by Lawesson and co-workers[37] and by Hörnfeldt.[38] With 5-alkyl-substituted compounds, only the keto forms were detected, but substantial amounts of the enol forms were present at equilibrium when the 5-substituent was phenyl, thienyl, or carbethoxy.

The unsubstituted 2-hydroxythiophene (or its tautomer) was first prepared as an unstable liquid by Hurd and Kreuz,[39] who concluded on the basis of its infrared spectrum that it was a mixture of enol and keto forms in CCl_4 solution. However, a reinvestigation by Gronowitz and Hoffman[40] using ^{1}H NMR spectroscopy led to the conclusion that only 3-thiolen-2-one (**12**, X = S) was present in the neat liquid and this was confirmed by Hawkins.[41]

In our investigation the hydrolysis of 2-[(trimethylsilyl)oxy]-thiophene in CD_3SOCD_3 (80% v/v)–D_2O (pD 4.52, 20% v/v) at 32 °C was followed by ^{1}H NMR spectroscopy. The spectrum of the trimethylsilyl derivative in DMSO-d_6 showed coincident signals for H-4 and H-5 at δ = 6.68, a triplet for H-3 at δ = 6.20 (J = 2.6 Hz), and a singlet at δ = 0.20 (Me_3Si). On addition of the D_2O (pD 4.52, 20% v/v), the trimethylsilyl derivative was converted immediately into 2-deuteroxythiophene as indicated by replacement of the signal of the trimethylsilyl group by that of trimethylsilanol (δ = 0.08) and by the relatively small changes that occurred in the rest of the spectrum. The signals of H-4 had the same chemical shift with δ = 6.68 (dd, J = 3.6 and 5.2) and those of H-3 and H-5 were shifted upfield slightly with δ = 6.10 (dd, J = 2.0 and 3.6 Hz) and 6.50 (dd, J = 2.0 and 5.2 Hz). After about 10 min the 2-deuteroxythiophene was converted into a mixture of [5-^{2}H$_1$]-3-thiolene-2-one (ca. 65%) and [3-^{2}H$_1$]-4-thiolen-2-one (ca. 35%) as shown in Scheme X. The 4-thiolen-2-one was unstable and after 45 min it was converted into 3-thiolen-2-one which was partially deuterated at positions 3 and 5, but not at position 4.

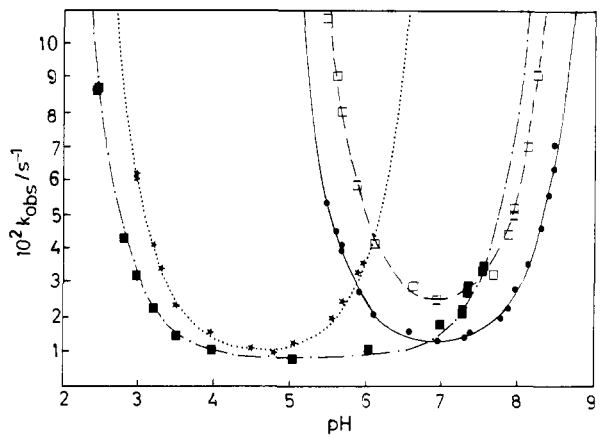


Figure 4. pH profiles for the ketonization of 3-hydroxyfuran (★), 3-hydroxythiophene (■), 3-hydroxypyrrole (□), and 3-hydroxy-1-methylpyrrole (●) at 25 °C (I = 1.10 M). The points are experimentally determined and the lines are drawn according to eq 1 with the parameters listed in Table 1. Full results are tabulated in Tables S5–S8.

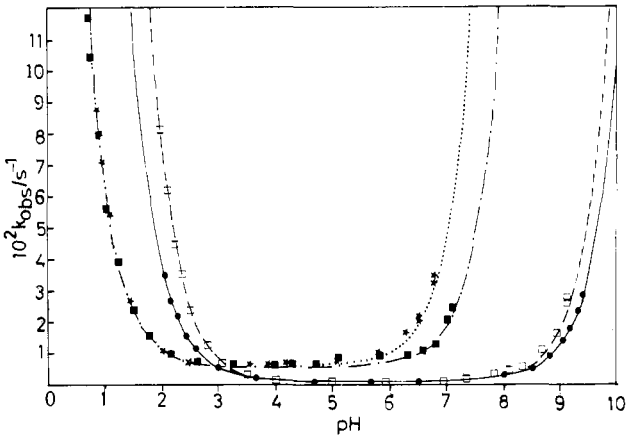


Figure 5. pH–rate profiles for the ketonization of 3-hydroxybenzofuran (★), 3-hydroxybenzothiophene (■), 3-hydroxyindole (□), and 3-hydroxy-1-methylindole (●) at 25 °C (I = 1.0 M). The points are experimentally determined and the lines are drawn according to eq 1 with the parameters listed in Table 1. Full results are tabulated in Tables S1–S4.

Attempted Generation of 2-Hydroxyfuran. 2-Hydroxyfuran (**11**, X = O, L = H) is tautomeric with 2-oxo-2,3-dihydrofuran (**10**, X = O) and 2-oxo-2,5-dihydrofuran (**12**, X = O). At equilibrium the conjugated keto form (**12**, X = O) is stable,[38] but the unconjugated keto form (**10**, X = O) has been prepared.[42] The hydroxy form (**11**, X = O) has never been detected and our attempts to generate its O-deuterated analogue have been unsuccessful. Thus, hydrolysis of its trimethylsilyl ether in CD_3COCD_3–D_2O (97.5:2.5 v/v)–DCl (2.5 × 10^{-3} M) at −45 °C and in DMSO-d_6–D_2O mixtures at room temperature yielded only the deuterated 2-oxo-2,3-dihydrofuran. Methanolysis of the trimethylsilyl ether makes an alternative method of preparation of this unstable keto form (see the Experimental Section).

Attempted Generation of 2-Hydroxypyrrole and 2-Hydroxy-1-methylpyrrole. 2-Hydroxypyrrole and 2-hydroxy-1-methylpyrrole have, like 2-hydroxyfuran, two keto tautomers, both of which are known.[42-46] Attempts to generate the 2-hydroxy derivatives by hydrolysis of trimethylsilyl derivatives in mixtures of CD_3COCD_3

(36) Iddon, B.; Scrowston, R. M. *Adv. Heterocycl. Chem.* **1970**, *11*, 296. Stacy, G. W.; Wollner, T. E. *J. Org. Chem.* **1967**, *32*, 3028–3032.
(37) Jakobsen, H. J.; Larsen, E. H.; Lawesson, S. O. *Tetrahedron* **1963**, *19*, 1867–1882.
(38) Hörnfeldt, A. B. *Sven. Kem. Tidskr.* **1968**, *80*, 343–356.
(39) Hurd, C. D.; Kreuz, K. L. *J. Am. Chem. Soc.* **1950**, *72*, 5543–5546.
(40) Gronowitz, S.; Hoffman, R. A. *Ark. Kemi* **1960**, *15*, 499–511.
(41) Hawkins, R. T. *J. Heterocycl. Chem.* **1974**, *11*, 291–294.
(42) Nasman, J. A. H.; Pensar, K. G. *Synthesis* **1985**, 786–787.
(43) Bordner, J.; Rapoport, H. *J. Org. Chem.* **1965**, *30*, 3824–3828.
(44) Bocchi, V.; Chierici, L.; Gardini, G. P.; Mondelli, R. *Tetrahedron* **1970**, *26*, 4073–4082. Gardini, G. P.; Bocchi, V. *Gazz. Chim. Ital.* **1972**, *102*, 91.
(45) Mondelli, R.; Bocchi, V.; Gardini, G. P.; Chiericic, L. *Org. Mag. Res.* **1971**, *3*, 7–22.
(46) Baker, J. T.; Sifniades, S. *J. Org. Chem.* **1979**, *44*, 2798–2800.

Table I. Rate and Equilibrium Constants for the Ketonization of Hydroxy Heterocyclic Compounds at 25 °C in Water (I = 1.00 M)[a,b]

	k_{H^+}, M^{-1} s^{-1}	$10^{-5}k_{HO^-}$, M^{-1} s^{-1}	$10^3k_{H_2O}$, s^{-1}	K_{enol}
		3-Hydroxybenzo Series		
1a (L = H)	0.592 (0.592)[d]	4.05 (4.05)	6.41 (6.41)	8.70×10^{-5}
1b	0.534 (0.579)	1.14 (1.24)	5.59 (6.07)	$8 \times 50 \times 10^{-2}$
1c	3.43 (3.73)	0.00994 (0.0108)	1.05 (1.14)	8.60×10^{-2}
1d	5.82 (7.58)	0.0134 (0.0175)	1.00 (1.31)	0.303
1e	903[c,d]			1.85×10^{-8}
		3-Hydroxy Series		
3a (L = H)	50.1 (50.1)	27.9 (27.9)	8.60 (8.60)	$<10^{-2}$
3b	5.83 (23.1)	0.187 (0.739)	2.22 (8.78)	2.96
3c	2.49×10^4 (2.81×10^4)	0.346 (0.391)	17.1 (19.3)	0.13
3d	1.17×10^4 (1.38×10^4)	0.154 (0.182)	8.90 (10.5)	0.18

[a] The experimentally determined rate constants (k_{obs}) are the sums of the rate constants for ketonization of the enol forms and enolization of the keto forms. The rate constants for the H^+-, HO^--, and H_2O-catalyzed reaction obtained from the pH–rate profiles that use these constants ($k^l_{H^+}$, $k^l_{HO^-}$, $k^l_{H_2O}$) are therefore also the sum of the rate constants for ketonization and enolization; these are the values given in parentheses. The rate constants for ketonization of the enols (k_{H^+}, k_{HO^-}, k_{H_2O}) were obtained by dividing these by 1 + K_{enol}. [b] The estimated standard deviations for k_{H^+} were 0.2–1% (benzo series) and 1–3.7% (monocyclic series); for k_{HO^-} they were 1.3–6.7%, and for k_{H_2O} they were 2.5–11% except for **2e** and **2d** for which it was ca. 20%. (See Tables S1–S8.) [c] Extrapolated from the value for 90% CH_3CN–10% H_2O (v/v) (Table II) by multiplying by the ratio of the rate constants for the hydrolysis of 3-methoxyindene in water (102.7 M^{-1} s^{-1}) and 90% CH_3CN–10% H_2O (37.3 M^{-1} s^{-1}). [d] Rate constants for enolization of the keto forms were determined by iodine-trapping method to have the following values: 3-ketobenzofuran, k_{H^+} = 5.15×10^{-5} M^{-1} s^{-1} and 3-ketoindan, k_{H^+} = 1.67×10^{-5} M^{-1} s^{-1}.

or DMSO-d_6 and H_2O or D_2O in the presence of HCl or DCl (10^{-4} M to 2×10^{-3} M) were unsuccessful. 1-(Trimethylsilyl)-2-[(trimethylsilyl)oxy]pyrrole yielded a mixture of Δ^3- and Δ^4-keto forms in the ratio of 9:1, but hydrolysis of 1-methyl-2-(trimethylsiloxy)pyrrole in 90% (v/v) CD_3SOCD_3–D_2O–DCl (10^{-4} M) yielded a solution of the unstable Δ^4-keto form after 15 min which was slowly converted into the stable Δ^3 form.

Kinetic Measurements

The kinetics of ketonization were studied by UV spectroscopy. As there were usually appreciable amounts of both tautomers present at equilibrium, the experimentally determined rate constants, k_{obs}, are the sums of the rate constants for ketonization of the enol and enolization of the keto forms. These were plotted against pH to yield U-shaped curves (Figures 4 and 5 and Tables S1–8) which followed eq 1 and the parameters $k^l_{H^+}$, $k^l_{HO^-}$, and

$$k_{obs} = k^l_{H^+} \times 10^{-pH} + k^l_{H_2O} + k^l_{HO^-}K_w/10^{-pH} \quad (1)$$

$k^l_{H_2O}$, which were evaluated by a generalized least-squares method are also the sums of rate constants for the ketonization and enolization. The rate constants for ketonization of the enols, k_{H^+}, k_{HO^-}, and k_{H_2O} (Table I) were obtained from these by dividing by 1 + K_{enol} [$k_{H^+} = k^l_{H^+}/(1 + K_{enol})$, etc.].

When there were detectable amounts of both tautomers present at equilibrium as with **1b–d** and **3b–d** (L = H), the equilibrium constants were estimated from the infinity absorbances. When detectable amounts of the enol forms were not present at equilibrium, as with 3-hydroxybenzofuran (**1a**) and 3-hydroxyindene (**1e**), the rate constants for the H^+-catalyzed enolization of the keto forms were determined by the iodine-trapping method[47] and the equilibrium constants were determined from the rate constants for enolization (now the experimentally determined constants) and ketonization. The rate of enolization of the keto form of 3-hydroxyfuran (**3a**, L = H) could not be determined by the iodine-trapping method as the disappearance of iodine was not zero order, possibly because there is a direct addition of iodine to the double bond.

The two 2-hydroxy heterocyclic compounds studied (**8**, **11**, X = S) underwent a particularly rapid spontaneous or water-catalyzed tautomerization; so in order to slow this down, their reactions were studied in aqueous acetonitrile solution; for comparison, the ketonization of some of the 3-hydroxy compounds were also studied under these conditions (Table II). No detectable amounts of the enolic forms of 2-hydroxythiophene (**11**, X = S) and 2-hydroxybenzothiophene (**8**, X = S) are present at equilibrium under these conditions or in DMSO-d_6, one of the best solvents for stabilizing nonintramolecularly hydrogen-bonded enols.

Table II. Kinetics of Ketonization of Enols in Aqueous Acetonitrile Solution at 25.0 °C

	k_{H^+}, M^{-1} s^{-1} (esd)	$10^3k_{H_2O}$, s^{-1} (esd)	K_{enol} (E/K)
	90% CH_3CN–10% H_2O (v/v)		
3-hydroxyfuran	29.7 (0.3)	*a*	$<10^{-2}$
3-hydroxybenzofuran	0.865 (0.036)	*a*	
3-hydroxybenzothiophene	0.314 (0.016)[b]	*a*	0.312
3-hydroxyindene	328 (4.0)		
2-hydroxythiophene	2.10 (0.04)[c]	2.04[c]	$<10^{-2}$ [d]
2-hydroxybenzothiophene	12.4 (0.20)	18.0	
2-hydroxyindene	2.79 (0.13)	*a*	
	50% CH_3CH–10% H_2O (v/v)		
3-hydroxythiophene	1.78 (0.046)	*a*	7.76
3-hydroxybenzothiophene	0.0705 (0.0029)	0.366 (0.0075)	0.56
2-hydroxythiophene	11.5 (0.5)[e]	23[e] (.80)	$<10^{-2}$ [d]

[a] Within experimental error zero. [b] $k^l_{H^+}$ = 0.412 M^{-1} s^{-1}; $k_{H^+} = k^l_{H^+}(1 + K_{enol})$. [c] Rate constant for ketonization with protonation at C-3 and C-5; $k^3_{H^+} \approx 0.21$ M^{-1} s^{-1}, $k^5_{H^+} \approx 1.89$ M^{-1} s^{-1}; $k^3_{H_2O} \approx 1.02 \times 10^{-3}$ s^{-1}, $k^3_{H_2O} \approx 1.02 \times 10^{-3}$ s^{-1}. [d] Based on 3-thiolen-2-one. [e] Rate constant for ketonization with protonation at C-3 and C-5.

Presumably, the aromatic stabilization of the enol form is counterbalanced by stabilization of the keto form by delocalization in the thioester group.

Equilibrium Constants for Enol–Keto Tautomerism in Water. These equilibrium constants indicate that 3-hydroxythiophene and 3-hydroxypyrrole and their benzo analogues are relatively more stable with respect to their keto forms than 3-hydroxyfuran and its benzo analogue are with respect to their keto forms (Table I). This is in agreement with the greater resonance stabilization of thiophene and pyrrole compared to that of furan and of benzothiophene and indole compared to that of benzofuran.[48] Thus the Dewar resonance energies of thiophene,[49] pyrrole,[50] and furan[50] are respectively 6.5, 5.3, and 4.3 kcal mol^{-1} and those of benzothiophene,[49] indole,[51] and benzofuran[51] are 24.8, 23.8, and 20.3 kcal mol^{-1}. The resonance energy of benzofuran is almost identical with that of benzene and Dewar and his co-workers concluded that the five-membered ring of the former is not aromatic.[51] Nevertheless, the replacement of the methylene group of 3-hydroxyindene by an oxygen to give 3-hydroxybenzofuran has a large effect on the equilibrium constant, K_{enol}, and the rate constant

(47) Feather, J. A.; Gold, V. *J. Chem. Soc.* **1965**, 1752–1761.

(48) Cook, M. J.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem.* **1974**, *17*, 255–356.

(49) Dewar, M. J. S.; Trinajstic, N. *J. Am. Chem. Soc.* **1970**, *92*, 1453–1459.

(50) Dewar, M. J. S.; Trinajstic, N. *Theor. Chim. Acta* **1970**, *17*, 235–238.

(51) Dewar, M. J. S.; Harget, A. J.; Trinajstic, N.; Worley, S. D. *Tetrahedron* **1970**, *26*, 4505–4516.

Table III. Solvent Effect on Equilibrium Constants for Enolization (K_{enol} = E/K) or Monocyclic Compounds.

solvent	3-hydroxy-pyrrole[a]	3-hydroxy-*N*-methyl-pyrrole[a]	3-hydroxy-thiophene[a]
CCl_4	resinified	resinified	1.11
$CDCl_3$	resinified	resinified	0.522
CD_3CN	0.93	1.11	>50
CD_3NO_2		0.61	
acetone-d_6			>50
dioxane-H_2O (4:1 v/v)			>50
CH_3CN-H_2O (1:1 v/v)			7.76
CH_3OH	0.406	0.458	>50
H_2O	0.133	0.184	2.96
DMSO-d_6	>50	>50	>50
pure compound	0.435	0.554	9.00

[a] Generalized least-squares fitting of the data to eq 2 (ref 85) did not lead to convergence, probably because there are too few observations.

for the H_2O^+-catalyzed ketonization. The 4700-fold difference between K_{enol} for 3-hydroxyindene and 3-hydroxybenzofuran suggests that the ring oxygen is stabilizing the enol form by ca. 5 kcal mol^{-1}. This is similar to the ca. 5 kcal mol^{-1} stabilizing effect of a methoxy group on a double bond attributed to electron delocalization "arising from overlap of the filled 2p orbitals on the substituent with the 2pπ systems of the carbon–carbon double bond".[52] The greater stability of 3-hydroxybenzofuran compared to 3-hydroxyindene therefore does not necessarily imply that the furan ring of the benzofuran is aromatic as an oxygen substituent attached to the double bond of the enol should stabilize it whether or not this is so.

To compare K_{enol} for 2-hydroxybenzothiophene with that of its homocyclic analogue 2-hydroxyindene, the value of the former in H_2O–CH_3CN (9:1 v/v) (Table II) was extrapolated to water by assuming that the solvent effect was the same as for K_{enol} for 3-hydroxybenzothiophene. This yields a value of 6.24×10^{-6} compared to 8.16×10^{-5} for 2-hydroxyindene. As indicated above, the aromatic stabilization of the enolic form of 2-hydroxythiophene is counterbalanced by the thio lactone conjugation of the keto form.

Solvent Effects on the Equilibrium Constants for Keto–Enol Tautomerism. The effect of solvent on the equilibrium constants K_{enol} (E/K) is shown in Tables III and IV. As with other enols which cannot form an intramolecular hydrogen bond,[53,54] the enols we have studied are much more stable with respect to their keto forms in hydrogen bonding accepting solvents than in aprotic solvents. For example, there is no detectable amount at equilibrium of the enol form of 3-hydroxybenzothiophene in benzene-d_6, CCl_4, $CDCl_3$, and CD_2Cl_2, but there are appreciable amounts present in methanol and aqueous solvents, and it is the predominent form in pyridine-d_5, DMF-d_6, and DMSO-d_6 (see Table IV). This behavior can be quantified when sufficient data are available by a multiparameter equation (eq 2) used by Mills

$$\Delta G_s^\circ = (\epsilon - 1)/(2\epsilon + 1) + a\alpha + b\beta + \Delta G_v^\circ \qquad (2)$$

and Beak[54] which is based on the solvent parameters derived by Taft and his co-workers.[55] In equation 2, ΔG_s° is the difference in free energy between tautomers in a particular solvent; the term $(\epsilon - 1)/(2\epsilon + 1)$ is the Kirkwood–Onsager reaction-field term; α is a measure of the hydrogen-donating ability of the solvent, and β is a measure of its hydrogen bonding accepting ability; ΔG_v° is formally the difference in free energy between tautomers in the gas phase, but along with k, a, and b, ΔG_v° is treated as a disposable parameter. For hydroxylic solvents, instead of using δ, Mills and Beak used the β_2 value of Taft, which they termed β'. They found that the equilibrium between 5,5-dimethyl-1,3-cyclohexadienone and its monoenol is controlled almost completely

Table IV. Solvent Effect on Equilibrium Constants for Enolization (K_{enol} = E/K) Bicyclic Compounds

solvent	3-hydroxy-benzo-thiophene[a]	3-hydroxy-indole[a]	3-hydroxy-1-methylindole
benzene-d_6	<0.01	insoluble	0.14
CCl_4	<0.01	insoluble	0.14
$CDCl_3$	<0.01	<0.01	0.03
CD_2Cl_2	<0.02	0.086	0.09
CD_3CN	0.11	0.58	0.70
CD_3NO_2	0.025	0.18	0.28
acetone-d_6	0.63	7.80	1.29
CH_3CO_2H	0.075		0.21
CH_3CN-H_2O (9:1 v/v)	0.312		
CH_3CN-H_2O (1:1 v/v)	0.56		
CH_3OH	0.75		4.00
H_2O	0.085	0.086	0.303
pyridine-d_5	2.11	8.7	8.8
DMF-d_7	4.8	16.1	13.5
DMSO-d_6	11.5	28.4	11.2
pure state	0	0	0.52

[a] Generalized least-squares fitting of the data to eq 2 (ref 85) did not lead to convergence, probably because there are too few observations.

by the hydrogen bonding accepting ability of the solvent, i.e. in eq 2 the term $b\beta$ was dominant and b had a large negative value, −6.0, which corresponds to stabilization of the enol form by solvents which are hydrogen-bond acceptors. The term $a\alpha$ was much less important and a had a small negative value, −0.53, which suggests that solvents that are hydrogen-bond donors stabilize the enol slightly more than the keto form.

Of the equilibria that we have studied, sufficient data to give an acceptable correlation were available only with 3-hydroxyindole (see Table S9) although in general terms it can be seen that the enols are relatively more stable in hydrogen bonding accepting solvents such as DMSO and DMF. With 3-hydroxyindole, again the most important term is the hydrogen bond accepting terms and the b value is −3. However the a value is quite large and positive (2.4), which must arise from the keto form being stabilized by hydrogen-bond donors. This is reasonable because when the hydroxyindole ketonizes the enamine type nitrogen is converted into a more basic amine-type nitrogen.

pK_as of Enolic and Keto Forms. The benzo series of enols (**1**) was sufficiently stable in the basic solution for their pK_as to be determined (Table V). The pK_as of the enol and keto tautomers are related by the equation

$$pK_a^{keto} = pK_a^{enol} + pK_{enol}$$

3-Hydroxybenzofuran and 3-hydroxybenzothiophene are stronger acids than the 3-hydroxyindoles [and phenol (pK_a = 9.98)], which can be attributed to the greater electron-withdrawing inductive effect of oxygen [σ_I(OR) = 0.27] and sulfur [σ_I(SR) = 0.25] compared to nitrogen [σ_I(NHR) = 0.17].[56]

Discussion of Kinetic Results

Examination of the pH–rate profiles (Figures 4 and 5) indicates that those for 3-hydroxyfuran and 3-hydroxythiophene are displaced to lower pHs than those of the 3-hydroxypyrroles (Figure 4), which is a result of the latter undergoing H^+ ketonization much faster. A similar but smaller effect is found in the benzo series (Figure 5). The effect of replacing the methylene group of 3-hydroxyindene by a heteroatom causes a decrease in k_{H^+} for the ketonization (Table I). The results suggest however that another factor beside the stability of the enol is important here. Thus 3-hydroxybenzofuran and 3-hydroxybenzothiophene undergo ketonization at similar rates despite the former being thermodynamically much less stable. This may be partly due to the slightly different inductive effects of the heteroatoms on the stability of the positively charged transition state or may arise

(52) Hine, J.; Flachskam, N. W. *J. Am. Chem. Soc.* **1973**, *95*, 1179–1185.
(53) Hine, J. *Structural Effects on Equilibrium in Organic Chemistry*; Robert E. Krieger Publishing Co.: New York, 1981; p 278.
(54) Mills, S. G.; Beak, P. *J. Org. Chem.* **1985**, *50*, 1216–1224.
(55) Kamlet, M. J.; Abboud, J. L.; Taft, R. W. *Prog. Phys. Org. Chem.* **1981**, *13*, 485–630.
(56) See: Exner, O. In *Correlation Analysis in Chemistry—Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; p 500.

Table V. pK_as of Enol and Keto Tautomers at 25 °C and β Values for Base-Catalyzed Ketonization of the Enolic Tautomers

	vinyl alcohol[4]	3-hydroxy-benzofuran	3-hydroxy-benzothiophene	3-hydroxy-indole	3-hydroxy-1-methylindole	phenol
pK_a^{enol}	10.50[a]	9.16	8.86	10.46	10.76	9.998[d]
pK_a^{keto}	16.73	13.22	9.93	11.52	11.28	ca. −1[e]
pK_{enol}	6.23	4.06	1.07	1.07	0.52	ca. −11[e]
β value	0.77[b]	0.59	0.50			
α value[c]	0.23	0.41	0.50			

[a] Reference 16. [b] Reference 12. [c] For C-protonation of the enolate ion. [d] Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*, 2nd ed.; Butterworth: London, 1959; p 533. [e] Tee, O. S.; Iyengar, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 455.

Table VI. Rate Constants[a] for the Hydronium Ion Catalyzed Ketonization of 3-Hydroxybenzofuran and Hydrolysis of 3-Methylbenzofuran in Mixtures of Dimethyl Sulfoxide and Water at 25 °C (I = 0.1 M)

Me_2SO, mol %	k_{H^+} for ketonization of 3-hydroxybenzofuran, M^{-1} s^{-1}	$10k_{H^+}$ for hydrolysis of 3-methoxybenzofuran, M^{-1} s^{-1}	ratio
0	0.528	33.1	16
7.8		13.2	
14.5	0.234	6.48	36
27.6	0.098	1.34	73
37.2	0.068	0.610	111
50.4	0.075	0.348	216
69.6	0.202	0.201	1005
82.8	0.402	0.115	3496

[a] Based on C_{H^+}.

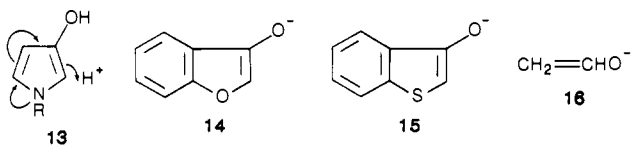
Table VII. Catalytic Constants for the General-Acid- and General-Base-Catalyzed Ketonization of 3-Hydroxybenzofuran and 3-Hydroxybenzothiophene at 25 °C (I = 1.00 M).

		3-hydroxy-benzofuran		3-hydroxy-benzothiophene	
acid	pK_a (25 °C)[a]	k_{A^-}, M^{-1} s^{-1}	k_{HA}, M^{-1} s^{-1}	k_{A^-}, M^{-1} s^{-1}	k_{HA}, M^{-1} s^{-1}
cyanoacetic	2.470	0.0816	0.152	0.0718	*b*
chloroacetic	2.870	0.0286	0.106	0.219	0.0685
formate	3.752	0.810	*b*	0.582	*b*
acetate	4.756	2.21	*b*	1.32	*c*
pivalate	5.050	4.02	*c*	1.85	*c*

[a] Reference 36, p 124. [b] General-acid catalysis detected but catalytic constant not accurately defined by the data. [c] No general-acid catalysis detected.

from their being different amounts of proton transfer in the transition state.

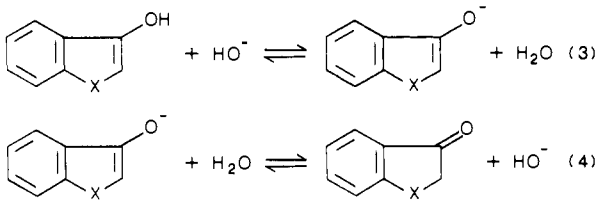
The monocyclic 3-hydroxy compounds **3** undergo H^+-catalyzed ketonization 11 to 6.9 × 10^3 times faster than their benzo analogues **1** presumably as a result of the mesomeric effect symbolized by **13**, which is more effective when X is N than when it is O or S, causing the 3-hydroxypyrroles (**3c**, **3d**) to ketonize faster than 3-hydroxyfuran (**3a**) and 3-hydroxythiophene (**3b**).



13 **14** **15** **16**

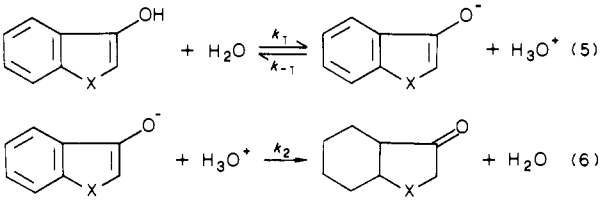
In DMSO–water mixtures, the ketonization shows behavior similar to that of vinyl alcohol.[10] In water k_{H^+} for the ketonization of 3-hydroxybenzofuran is 16 times greater than that for the hydrolysis of 3-methoxybenzofuran, which occurs with rate-limiting C-protonation,[57] but in a water–DMSO mixture with 82.8 mol % DMSO it is 3496 times greater (Table VI). This large difference in rates suggests that there is a strong interaction between the proton of the hydroxyl group and the solvent in the transition state, which is best explained by a concerted mechanism.[57-59]

The rate constants for the hydroxide ion catalyzed ketonization of 3-hydroxybenzofuran and 3-hydroxybenzothiophene are more than 100 times greater than those for the ketonization of the 3-hydroxyindoles (Table I). On the basis of the normally accepted mechanism for the hydroxide ion catalyzed ketonization (eq 3 and 4), this difference could arise from a more favorable equilibrium



constant for formation of the anion or from a more favorable rate constant for C-protonation of the anion by water. It seems that both of these factors are important, since although 3-hydroxybenzofuran and 3-hydroxybenzothiophene are stronger acids than the 3-hydroxyindoles (Table V), the difference in the pK_as is usually less than the difference in the log k_{HO^-} values, so the greater electron-withdrawing effect of the oxygen and sulfur stabilizes the transition states for C-protonation of the anions as well as the anions themselves.

All the enols studied show a spontaneous or water-catalyzed ketonization. A possible mechanism for this involves two steps as shown for the bicyclic enols in eq 5 and 6. This is similar to



the mechanism proposed for general-base catalysis (see below), and for it to be a valid mechanism two conditions must be met:[10] (i) $k_1 > k_{H_2O}$ and (ii) k_2 must be smaller than the diffusion-controlled limit, 10^{10}–10^{11} M^{-1} s^{-1}. If a value of 5 × 10^{10} M^{-1} s^{-1} is assumed for k_{-1}, k_1 for 3-hydroxybenzofuran, 3-hydroxybenzothiophene, 3-hydroxyindole, and 3-hydroxy-1-methylindole is calculated to be 34.6, 69.0, 1.73, and 0.87 s^{-1}, respectively. These values are 5400, 1.24 × 10^4, 1650, and 870 times larger than the corresponding values of k_{H_2O}, and hence the first condition is met. The values of k_2 calculated on the basis of this mechanism ($k_2 = k_{H_2O}/k_a$) are 9.27 × 10^6, 4.05 × 10^6, 3.03 × 10^7, and 5.81 × 10^7 M^{-1} s^{-1}. These values are much smaller than the diffusion-controlled limit, so the second condition is also fulfilled and the mechanism of eq 4–6 is a reasonable one. However, they are much larger than the values of k_{H^+} for ketonization of the corresponding enols, so as with vinyl alcohol,[10,60] the rate constants for C-

(57) Capon, B.; Kwok, F. C. *Tetrahedron* **1987**, *43*, 69–76.

(58) See: Lienhard, G. E.; Wang, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 1146–1153. A referee has suggested that a stepwise mechanism which, at the transition state, employs stronger H bonding from $\cdots^{\delta+}$O–H to DMSO than to water seems a good explanation. This implies that the strength of the H bond from the transition state is increased by 5 kcal mol^{-1} more on going from water to 82.8 mol % DMSO than is the hydrogen bond from the initial state.

(59) A similar argument has been used in a discussion of the mechanism of the breakdown of hemiacetals: Funderburk, L. H.; Aldwin, L.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5444–5459.

protonation of the enolate ions are about 10^7 times greater than for C-protonation (with ketonization) of the corresponding enols.

General-acid–base catalysis of the ketonization of 3-hydroxybenzofuran and 3-hydroxybenzothiophene was studied in buffers of five carboxylic acids and their salts. With the weaker acids, general-acid catalysis was relatively unimportant compared to general-base catalysis and accurate values of k_{HA} were not obtained. Plots of log (k_A/q) vs $(pK_a + \log (p/q)$[61] for all five bases yielded straight lines with slopes, of $\beta = 0.59$ (esd = 0.06) (3-hydroxybenzofuran) and $\beta = 0.50$ (esd = 0.06) (3-hydroxybenzothiophene). On the assumption that the reaction mechanism involves general-acid-catalyzed protonation of the enolate anions, the α-values for this step are therefore 0.41 (**14**) and 0.5 (**15**), respectively. This compares to a value of $\alpha = 0.23$ for C-protonation of the anion of vinyl alcohol (**16**).[12] These values imply that the amount of proton transfer in the transition state for C-protonation increases in the order **16** < **14** < **15**, which parallels their order of stabilities as measured by pK_as of the keto forms which are 16.73 (**16**), 13.22 (**14**), and 9.93 (**15**) (see Table V). This is of course what would be expected on the basis of the Bema Hapothle (Hammond effect).[62] The two-point α-value for the ketonization of 3-hydroxybenzofuran is 0.39, similar to that reported for the ketonization of vinyl alcohol (0.45).

A Comparison of the Ketonization of Heterocyclic Enols with Electrophilic Substitution

The acid-catalyzed ketonization of the heterocyclic enols involves electrophilic attack on one of the ring-carbon atoms, so these reactions are analogous to proton exchange of the parent heterocyclic systems, and it is therefore relevant to compare ketonization with this and other electrophilic substitution reaction. The ketonization of the 3-hydroxy compounds and of the 2-hydroxy compounds to yield the Δ^3-keto tautomers therefore corresponds to electrophilic substitution at the 2-position, and ketonization of the 2-hydroxy compounds to yield the Δ^4-keto tautomers corresponds to substitution at the 3-position. In electrophilic substitution in the parent heterocyclic systems the relative rates are 1-methylpyrrole > pyrrole ≫ furan > thiophene,[63,64] and substitution at the 2-position occurs more rapidly than at the 3-position. A similar pattern is found in the ketonization of the hydroxy derivatives, but the reactions are many orders of magnitude faster. Thus, the rate of deuterium exchange of 2-deuteriothiophene was reported to be 1.40 h^{-1} at 24.6 °C in 57% aqueous sulfuric acid.[65] This corresponds to a second-order rate constant (based on h_0) of 2.75×10^{-8} M^{-1} s^{-1} whereas the rate constant for ketonization of 3-hydroxythiophene is 5.83 M^{-1} s^{-1} at 25 °C. Similarly, the rate constant for deuterium exchange of pyrrole at the 2-position in D_2O–dioxane (1:1, w/w) is 3.9×10^{-2} M^{-1} s^{-1} (at 32 °C)[66] compared to a value of 2.49×10^4 M^{-1} s^{-1} for the ketonization of 3-hydroxypyrrole in water at 25 °C. These differences may be compared with the approximately 10^5-fold greater rate of exchange of phenol compared to benzene (at 100 °C).[67]

The benzo derivatives of furan and thiophene undergo electrophilic substitution in the 2-position more slowly than their monocyclic analogues, but in the 3-position they undergo it more rapidly.[68] This difference is reflected in the rates of the H_3O^+-catalyzed ketonization of 2- and 3-hydroxybenzothiophene compared to 2- and 3-hydroxythiophene. Thus, 3-hydroxythiophene undergoes H^+-catalyzed ketonization 10^1–10^2 times faster than 3-hydroxybenzothiophene (Tables I and II), but 2-hydroxybenzothiophene ($k_{H^+} = 12.4$ M^{-1} s^{-1}) undergoes ketonization about 59 times faster in 90% CH_3CN–H_2O (v/v) than 3-hydroxythiophene undergoes ketonization with protonation at the 3-position ($k_{H^+} = 0.21$ M^{-1} s^{-1}) to yield the Δ^4-keto compound (Table II).

Table VIII. Wavelengths Used for Kinetic Studies[a]

compound	λ, nm	compound	λ, nm
3-hydroxybenzofuran	323	3-hydroxypyrrole	309
3-hydroxybenzothiophene	368	3-hydroxy-1-methylpyrrole	322
3-hydroxyindole	380	3-hydroxyindene	265
3-hydroxy-1-methylindole	417	2-hydroxybenzothiophene	262[b]
3-hydroxyfuran	258	2-hydroxythiophene	263
3-hydroxythiophene	322	2-hydroxyindene	262

[a] Appearance of keto form. [b] Disappearance of enol form.

Conclusion

The investigation described in this paper shows how solutions of the 3-enolic derivatives **1a–e** and **3a–d** may be prepared, many for the first time. These are formally enols at the ketone level of oxidation and are more stable than the 2-enolic derivatives **8** and **11**, which are formally enols at the carboxylic acid level of oxidation. Solutions of these could only be prepared when X = S and attempts to generate them when X = O, NH, or NMe were unsuccessful. This is presumably a reflection of the higher aromaticity of thiophene compared to furan and pyrrole and of benzothiophene compared to benzofuran and indole.[48]

The successful generation, detection, and characterization of 2-hydroxythiophene and 2-hydroxybenzothiophene is the first time that enols at the carboxylic acid level of oxidation have been detected, although recently a sterically crowded acyclic enol of an ester has been reported.[69]

The availability of these enols has enabled us to obtain much quantitative data on their properties and opens the door to a more thorough investigation of their chemical properties.

Experimental Section

Trimethylsilyl Derivatives Prepared by Reaction with Chlorotrimethylsilane and Triethylamine. 3-Benzofuranone,[70] 3-benzothiophenone,[23] 3(2*H*)-furanone,[28] and 3(2*H*)-thiophenone[34] were prepared by standard methods. 1-Methylindoxyl was prepared from 3-acetoxy-1-methylindole.[25] It was essential for the solutions of all the reagents to be deoxygenated (N_2 or Ar) and for all manipulations to be carried out with exclusion of oxygen. Sodium hydroxide solution (2 M, 100 mL) was added to 3-acetoxy-1-methylindole (4 g) and the mixture was refluxed until the solid had dissolved (15 min). The solution was cooled, acidified with 1 M HCl, and extracted with CH_2Cl_2 (3 × 25 mL). The combined CH_2Cl_2 extracts were washed with $NaHCO_3$, dried, and evaporated to give a yellow oil which solidified on stirring at −20 °C (yielded 3.2 g). The crude product was purified by sublimation at 50–55 °C (10^{-3} mm). The resulting yellow crystals were very sensitive to oxidation, rapidly turned dark brown on exposure to air, and more slowly were converted into a green liquid. Indoxyl was prepared similarly from 3-acetoxyindole (Aldrich).[26] 3-Hydroxypyrrole was prepared by hydrogenolysis of benzyl 3-hydroxypyrrole-3-carboxylate over 10% Pd/C at 1 atm.[34] The hydrogen was generated from sodium borohydride and passed through sodium hydroxide solution. After 90 min, when the reaction was complete (^1H NMR spectrum), the catalyst was filtered off and the ethanol was evaporated with an oil pump so that the temperature fell below 0 °C. The residue was trimethylsilylated immediately and the reaction yielded 30%. 3-Hydroxy-1-methylpyrrole was prepared similarly by hydrogenolysis of benzyl 3-hydroxy-1-methylpyrrole-2-carboxylate.[34] These compounds were converted into their trimethylsilyl enol ethers by treatment with chlorotrimethylsilane and dry triethylamine in dry tetrahydrofuran.[71] The products were isolated by a nonaqueous workup which

(60) Chiang, Y.; Hojatti, M.; Keeffe, J. R.; Kresge, A. J.; Schepp, N. P.; Wirz, J. *J. Am. Chem. Soc.* **1987**, *109*, 4000–4009.
(61) See: Bell, R. P. *The Proton in Chemistry*; 2nd ed.; Chapman and Hall: London, 1923; p 198. p is the number of dissociable protons that the acidic form of the catalyst has and q is the number of points at which a proton can be attached to the basic form. For a carboxylic acid, $p = 1$, $q = 2$.
(62) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511–527.
(63) See bird, C. W.; Cheeseman, G. W. H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 43.
(64) Cf.: Newkome, G. R.; Paudler, W. W. *Contemporary Heterocyclic Chemistry*; John Wiley: New York, 1982; p 93.
(65) Ostman, B.; Olsson, S. *Ark. Kemi* **1960**, *15*, 275–282.
(66) Bean, G. P.; Wilkinson, T. J. *J. Chem. Soc., Perkin Trans. 2* **1978**, 72. The measured rate constant from Table I of this paper is divided by two to correct for their being two 2-positions in pyrrole.
(67) Bellingham, P.; Johnson, C. D.; Katritzky, A. R. *J. Chem. Soc.* B **1968**, 866.
(68) Marino, G. *Adv. Heterocycl. Chem.* **1971**, *13*, 235–314.
(69) O'Neill, P.; Hegarty, A. F. *J. Chem. Soc., Chem. Commun.* **1987**, 744–748.
(70) Schroeder, D. C.; Corcoran, P. O.; Holden, C. A.; Mulligan, M. C. *J. Org. Chem.* **1962**, *27*, 586–591.

involved filtration in vacuum, evaporation of the tetrahydrofuran, treatment with ether, filtration in vacuum, evaporation of the tetrahydrofuran, treatment with ether, filtration in vacuum, evaporation of the ether, and distillation. Yields were greater than 90%.

3-[(Trimethylsilyl)oxy]benzofuran: bp 65–67 °C (0.01 mm); ^{1}H NMR ($CDCl_3$) δ 0.21 (9 H, s, $Si(CH_3)_3$), 7.21 (1 H, s, C=CH), 7.00–7.70 (4 H, m, aromatic); IR (neat) 3120 (w), 3050 (w), 2960 (w), 1620 (w), 1600 (w), 1585 (s) cm^{-1}; MS *m/e* 206 (89) 73 (100).

3-[(Trimethylsilyl)oxy]benzothiophene: ^{1}H NMR ($CDCl_3$) δ 0.25 (9 H, s, SMe_3), 6.35 (1 H, s, C=CH), 7.20–7.80 (4 H, m, aromatic); IR (neat) 3070 (w), 2960 (w), 1570 (s), 1525 (s); MS *m/e* 222 (8) 73 (39).

3-[(Trimethylsilyl)oxy]furan:[72] bp 64–66 °C (33 mm); ^{1}H NMR (CCl_4) δ 0.20 (9 H, s, $Si(CH_3)_3$), 6.00 (1 H, dd, J = 1.0, 1.8 Hz, H-4), 6.97 (1 H, dd, J = 1.0, 1.8 Hz, H-2), 7.10 (1 H, t, J = 1.8 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ −0.27 (Si-C-3), 106.99 (C-4), 128.39 (C-2), 141.66 (C-5), 143.44 (C-3); MS *m/e* 156 (100), 141 (83), 73 (92).

3-[(Trimethylsilyl)oxy]thlophene:[72] bp 44–45 °C (3 mm); ^{1}H NMR (DMSO-d_6) δ 0.20 (9 H, s, $Si(CH_3)_3$), 6.60 (1 H, dd, J = 1.6, 3.4 Hz, H-2), 6.75 (1 H, dd, J = 1.6, 5.4 Hz, H-4), 7.40 (1 H, dd, J = 3.4, 5.4 Hz, H-5); IR (neat) 2960 (m), 1535 (s) cm^{-1}; MS *m/e* 172 (75), 157 (100), 73 (55); ^{13}C NMR ($CDCl_3$) δ 0.06 (Si-C), 104.33 (C-2), 122.16 (C-5), 123.84 (C-4), 152.71 (C-3).

3-[(Trimethylsilyl)oxy]pyrrole: bp 42–43 °C (0.01 mm); ^{1}H NMR (CCl_4) δ 0.18 (9 H, s, $Si(CH_3)_3$), 6.58 (1 H, td, $J_{3,4}$ = 1.8, $J_{4,5}$ = 3.0, $J_{1,4}$ = 5.6 Hz, H-4), 6.10 (1 H, td, $J_{2,4}$ = 1.8, $J_{2,5}$ = 2.2, $J_{1,2}$ = 4.0 Hz, H-2), 6.32 (1 H, td, $J_{2,5}$ = 2.2, $J_{1,5}$ = 3.0, $J_{1,5}$ = 5.2 Hz, H-5), 7.80 (1 H, br s, NH); IR (neat) 1656 cm^{-1} (s); MS *m/e* 155 (100); ^{13}C NMR ($CDCl_3$) δ −0.11 (Si-C), 101.73 (C-2), 104.34 (C-4), 115.66 (C-5) 142.04 (C-3).

1-Methyl-3-[(trimethylsilyl)oxy]pyrrole: bp 62 °C (3 mm); ^{1}H NMR (CCl_4) δ 0.17 (9 H, s, $Si(CH_3)_3$), 3.50 (3 H, s, CH_3), 5.52 (1 H, t, J = 2.0, H-4), 5.95, (1 H, t, J = 2.0 Hz, H-2), 6.10 (1 H, t, J = 2.0 Hz, H-5); IR (neat), 2960 (s), 1550 (s) cm^{-1}; MS *m/e* 169 (100).

Preparation of Trimethylsilyl Derivatives by Reaction with Chlorotrimethylsilane and Lithium Diisopropylamide (LDA). 1-Indanone[73] and 2(3*H*)-benzothiphenone[74] were prepared by standard methods and converted into their trimethylsilyl derivatives using a method based on that described by Ainsworth and co-workers.[75] *n*-Butyllithium (0.05 mol) in hexane (31.2 mL) was added to diisopropylamine (0.05 mol) in dry tetrahydrofuran (35 mL) at 0 °C under nitrogen. After stirring for 15 min, the solution was cooled to −78 °C and the carbonyl compound (0.05 mol) in dry tetrahydrofuran (20 mL) was added. After 30 min chlorotrimethylsilane (0.25 mol) was added, and the reaction mixture was allowed to come to room temperature over 30 min. The solution was filtered with exclusion of moisture and the excess chlorotrimethylsilane and solvent were evaporated. Dry diethyl ether was added (25 mL) to precipitate any remaining salts which were filtered off, and after evaporation of the ether, the residue was distilled under reduced pressure.

3-[(Trimethylsilyl)oxy]indene:[76,77] bp 49–51 °C (0.01 mm); ^{1}H NMR ($CDCl_3$) δ 0.30 (9 H, s, $Si(CH_3)_3$), 3.16 (2 H, d, J = 2.5 Hz, CH_2), 5.3 (1 H, t, J = 2.5 Hz, C=CH), 7.00–7.40 (4 H, m, aromatic protons); IR (neat) 3050 (w), 2960 (s), 2900 (s), 1605 (s), 743 (s) cm^{-1}; MS *m/e* 204 (68), 73 (100).

2-[(Trimethylsilyl)oxy]benzothiophene: bp 64–65 °C (0.001 mm); ^{1}H NMR ($CDCl_3$) δ 0.33 (9 H, s, $Si(CH_3)_3$), 6.33 (1 H, s, H-3), 7.00–7.70 (4 H, m, aromatic protons); MS *m/e* 222 (100), 73 (100).

Preparation of Trimethylsilyl Derivatives by Reaction with Chlorotrimethylsilane and Zinc Chloride. 2-Indanone,[78] 2(5*H*)-furanone,[79] 2-(5*H*)-pyrrolenone,[44] and 1-methyl-2(5*H*)-pyrrolenone[44] were prepared by standard methods. These compounds were converted into their trimethylsilyl derivatives by the following procedure:[80] anhydrous zinc chloride (0.2 g) was stirred with dry triethylamine (0.11 mol) until it was suspended. The keto compound (0.005 mol) in diethyl ether, tetrahydrofuran, or benzene (20 mL) was added under nitrogen. It was then stirred for several hours at room temperature or, in the case of 2(5*H*)-furanone, at 65 °C. The product was isolated by using a procedure similar to that used when triethylamine was used as the catalyst (see above).

2-[(Trimethylsilyl)oxy]indene:[77] bp 55–56 °C (0.01 mm); ^{1}H NMR ($CDCl_3$) δ 0.30 (9 H, s, $Si(CH_3)_3$), 3.30 (2 H, s, CH_2), 5.77 (1 H, s, C=CH), 6.80–7.50 (4 H, m, aromatic protons).

2-[(Trimethylsilyl)oxy]furan:[81] bp 55–56° C (14 mm); ^{1}H NMR δ 0.30 (9 H, s, $Si(CH_3)_3$), 5.00 (1 H, dd, J = 1.2, 3.2 Hz, H-3), 6.12 (1 H, dd, J = 2.2, 3.0 Hz, H-4), 6.71 (1 H, dd, J = 1.2, 2.2 Hz, H-5).

1-(Trimethylsilyl)-2-[(trimethylsilyl)oxy]pyrrole: bp 56.7 °C (0.7 mm); ^{1}H NMR ($CDCl_3$) δ 0.30 (9 H, s, $Si(CH_3)_3$), 0.40 (9 H, s, $Si(CH_3)_3$), 5.30 (1 H, dd, J = 1.7, 3.2 Hz), 6.00 (1 H, t, J = 3.2 Hz, H-4), 6.7 (1 H, dd, J = 1.7, 3.2 Hz, H-5); MS *m/e* 227 (80), 73 (100).

1-Methyl-2-[(trimethylsilyl)oxy]pyrrole:[82] bp 60–65 °C (7.5 mm); ^{1}H NMR ($CDCl_3$) δ 0.27 (9 H, s, $Si(CH_3)_3$) 3.40 (3 H, s, NCH_3), 5.20 (1 H, dd, J = 2.0, 3.4 Hz, H-3), 5.90 (1 H, t, J = 3.4 Hz, H-4), 6.17 (1 H, dd, J = 2.0, 3.4 Hz, H-5); MS *m/e* 169 (59), 73 (100).

2-[(Trimethylsilyl)oxy]thiophene. 3-Thiolen-2-one was prepared as described by Hawkins[41] and trimethylsilylated as described by Dowd and Weber;[83] bp 41–42 °C (3.8 mm); ^{1}H NMR ($CDCl_3$) δ 0.27 (9 H, s, $Si(CH_3)_3$), 6.33 (1 H, dd, J = 1.6, 3.2 Hz, H-3), 6.48 (1 H, dd, J = 1.6, 6.0 Hz, H-5), 6.68 (1 H, dd, J = 3.2, 6.0 Hz, H-4).

1-Indenyl Dimethyl Orthoacetate. This was prepared by the addition of a solution of *trans*-2-bromo-1-indanol[84] in *tert*-butyl alcohol to a solution of ketene dimethyl acetal in *tert*-butyl alcohol[11] and heating under reflux for 15 min. Evaporation of the solvent and recrystallization from light petroleum (40–60 °C) yielded *trans*-2-bromo-1-indanyl dimethyl orthoacetate; yield 90%; ^{1}H NMR ($CDCl_3$) δ 1.50 (3 H, s, CH_3), 3.25 (3 H, s, OCH_3), 3.30 (3 H, s, OCH_3), 4.40 (1 H, dt, BrCH), 5.35 (1 H, d, J = 4.0 Hz, OCH), 3.40 (2 H, m, CH_2). This was dehydrobrominated by treating with a slight excess of potassium *tert*-butoxide in *tert*-butyl alcohol and stirring for 30 min. The *tert*-butyl alcohol was evaporated off; dichloromethane was added, and the mixture was filtered in a dry atmosphere. After evaporation of the dichloromethane and distillation through a short column, 1-indenyl dimethyl orthoacetate was obtained as a colorless oil (bp 74–76 °C/10^{-3} mm) in 64% yield; ^{1}H NMR (CCl_4) δ 1.60 (3 H, s, CH_3), 3.36 (6 H, s, OCH_3), 3.70 (2 H, d, J = 2.5 Hz, CH_2), 5.67 (1 H, t, J = 2.5 Hz, C=CH), 7.00–7.45 (4 H, m, aromatic protons); IR (Nujol) 3060 (w) (γ_{CH}, aromatic), 1600 (s) ($\gamma_{C=C}$, aromatic) cm^{-1}; MS *m/e* M$^+$ 220 (2).

Preparation of Furan-2(3*H*)-one. 2-[(Trimethylsilyl)oxy]furan was dissolved in methanol at room temperature. The methanolysis was followed by NMR spectroscopy and on completion the solution was evaporated to yield an oil with a ^{1}H NMR spectrum similar to that reported by Nasman and co-workers:[42] ($CDCl_3$) δ 3.20 (2 H, t, J = 2.4 Hz, H-3), 5.64 (1 H, dt, J = 2.4 Hz, 3.6 Hz, H-4), 6.87 (1 H, dt, J = 2.4, 3.6 Hz, H-5). Our assignments of H-4 and H-5 are the reverse of those given previously.[42]

NMR Spectroscopic Detection of the Unstable Tautomers. The trimethylsilyl derivative (or ortho ester) (ca. 20 mg) was dissolved in the solvent (CD_3CN, CD_3COCD_3, or CD_3SOCD_3, 0.4 mL), and the spectrum was run at the stated temperature in a Varian EM 360, Hitachi-Perkin, or JEOL FX 90Q NMR spectrometer. Deuterium oxide containing a small amount of acid as stated was then added, and the formation and decay of the unstable tautomer was monitored by running the spectrum at convenient time intervals.

Kinetic and Equilibrium Measurements. The kinetics of ketonization of the enolic forms were followed by measuring the appearance of the keto form or disappearance of the enolic form at the wavelengths shown in Table VIII. Stock solutions of the enolic forms were prepared as described in the previous section and 20–25 μL were added to 2.0 mL of the thermally equilibrated reaction solution contained in a cuvette in the thermostated cell holder of a Shimadzu UV 250 spectrophotometer. After initiation of the reaction, absorbance values were collected at predetermined time intervals with an Apple II or Hewlett-Packard HP85 microcomputer operating online through an IEEE interface. Reactions were normally followed to greater than 90% completion and rate constants were calculated by a generalized least-squares method.[85] Rate

(71) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.
(72) Camici, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1986**, *27*, 5155–5158.
(73) House, H. O.; Paragamanian, V.; Ro, R. S.; Wluka, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1452–1457.
(74) Lumma, W. C.; Dutra, G. A.; Voeker, C. A. *J. Org. Chem.* **1970**, *35*, 3442–3444.
(75) Ainsworth, C.; Chen, F.; Kuo, Y. *J. Organomet. Chem.* **1972**, *46*, 59–71. Ainsworth, C.; Kuo, Y. *J. Organomet. Chem.* **1972**, *46*, 73–87.
(76) Parham, W. E.; Roosevelt, C. S. *Tetrahedron Lett.* **1971**, 923–926.
(77) Lenz, B. G.; Regeling, H.; Zwanenberg, B. *Tetrahedron Lett.* **1984**, *25*, 5947–5948.
(78) Horan, J. E.; Schiessler, R. W. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 647–649.
(79) Price, C. C.; Judge, J. M. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 255–258.
(80) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.
(81) Yoshii, E.; Koizumi, T.; Kitatsujz, E.; Kawazoe, T.; Kaneko, T. *Heterocycles* **1976**, *4*, 1663.
(82) Fiorenz, M.; Reginato, G.; Ricci, A.; Taddei, M.; Dembeck, P. *J. Org. Chem.* **1984**, *49*, 551–553.
(83) Dowd, P.; Weber, W. *J. Org. Chem.* **1982**, *47*, 4777–4779.
(84) Dalton, D. R.; Hendrickson, J. B.; Jones, D. *Chem. Commun.* **1966**, 591–592.

constants for the pH-rate profile were measured in solutions (I = 1.00) whose pHs had been adjusted with low concentrations of HCl (pH < 3.5), NaOAc (<1 × 10^{-3} M, pH 3.5-5.0), KH_2PO_4 (1 × 10^{-3} M, pH 5.0-7.8), $Na_2B_4O_7$ (<5 × 10^{-4} M, pH > 7.8). A constant check was maintained to detect any drift in the pH of the solutions. The values of k^1_{obs} and different pHs were fitted to eq 1 by using a generalized least-squares method.[85]

For aqueous solutions when there was a detectable amount of the enol form present, a equilibrium and the equilibrium constant K_{enol} (= E/K) was determined spectrophotometrically working at a wavelength at which only the keto form absorbed. A stock solution (30 μL) of a tautomeric mixture of known composition (determined by NMR spectroscopy) was injected into buffer (2 mL). The initial and final absorbance (A_0, A_∞), which correspond to the concentration of keto form in the stock solution and to that in the aqueous buffer at equilibrium, were recorded and K_{enol} was calculated from the equation $K_{enol} = (100 - x(A_\infty/A_0))/x(A_\infty/A_0)$ where x is the percentage keto form in the stock solution.

When K_{enol} is less than 0.02, the above technique cannot be used and the values were determined from the ratio of the rate constants for ketonization and enolization. The latter were determined by the iodine-trapping technique.[47] This was unsuccessful with furan-3(2*H*)-one as the disappearance of iodine was not zero order; presumably, there was direct attack of iodine on the double bond of the keto form.

The nonaqueous solutions the equilibrium constants were measured by ^{1}H NMR spectroscopy integrating the signals of the protons at C-2 of the enol and keto form after allowing equilibrium to be attained. Concentrations were normally 0.1-0.3 M and 2-fold dilution did not lead to any measurable change in the proportions of the two forms.

pK_as were determined spectrophotometrically by using a method based on that described by Albert and Serjeant.[86] The following wavelengths were used: 3-hydroxybenzofuran (327 nm), 3-hydroxybenzothiophene (368 nm), 3-hydroxyindole (380 nm), and 3-hydroxy-1-methylindole (417 nm). At these wavelengths the keto forms absorb strongly, the anions weakly, and enolic forms not at all so that

$$pK_a^{keto} = pH + \log [(d - d_i)/(d_m - d)]$$

and

$$pK_a^{enol} = pH + \log K_{enol} + \log [(d - d_i)/(d_m - d)]$$

Measurements were carried out at seven or eight pHs (solutions degassed) and the values were averaged (see Table V and Tables S10-13). These K_as are of course mixed constants.

(85) Wentworth, W. E. *J. Chem.* Educ. **1965**, *42*, 96, 162.
(86) Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and Bases*; Mathuen: London, 1962; p 72.

General-acid-base catalysis was studied in buffer solutions by varying the concentrations of buffer while the ionic strength constant was maintained at 1.00 M with potassium chloride for a series of buffers with different buffer ratios. The values of k_{obs} for reaction in cyanoacetate, chloro acetate, and formate buffers were corrected for small variations in pH by plotting $k_{obs} - k_{H^+}a_{H^+} - k_{HO^-}a_{HO^-}k_{H_2O}$ versus ([A$^-$] + a_{H^+}] for each buffer ratio (r = [HA]/[A$^-$]), where $a_{H^+} = 10^{-pH}$, $a_{HO^-} = K_w/10^{-pH}$, and [A$^-$] and [HA] are the concentrations of basic and acidic forms of the buffer that were added.[10] Plots of the slopes of these lines (k_{cat}) against r were themselves straight lines with slope k_{HA} and intercept k_{A^-}. Except for cyanoacetic acid, the strongest acid used, general-acid catalysis was much weaker than general-base catalysis, so although accurate values of k_{A^-} could be obtained, this was not always possible for k_{HA}.

The proportions of 3- and 4-thiolenone formed in the kinetic product on ketonization of 2-hydroxythiophene were determined at a number of acid concentrations in 90% CH_3CN-H_2O (v/v) by integrating the signals of H-5 of the 4-thiolenone (δ = 6.70) and of the CH_2 group of the 3-thiolenone (δ = 6.40) (Table S14). The percentages of 3-thiolenone formed in the H_3O^+ and H_2O catalyzed reactions were estimated to be 90 ± 5% and 50 ± 5%, respectively.

Registry No. **1a**, 107637-99-0; **1b**, 520-72-9; **1c**, 480-93-3; **1d**, 107638-00-6; **1e**, 53820-83-0; **3a**, 29212-66-6; **3b**, 17236-59-8; **3c**, 29212-57-5; **3d**, 107638-08-4; **9b**, 496-31-1; **9e**, 615-13-4; **10a**, 20825-71-2; **12a**, 497-23-4; **12c**, 4031-15-6; **12d**, 13950-21-5; 3-acetoxy-1-methylindole, 3260-63-7; benzyl 3-hydroxypyrrole-3-carboxylate, 120475-60-7; 3-[(trimethylsilyl)oxy]benzofuran, 107638-01-7; 3-[(trimethylsilyl)oxy]benzothiophene, 107638-03-9; 3-[(trimethylsilyl)oxy]-furan, 107638-06-2; 3-[(trimethylsilyl)oxy]thiophene, 107638-07-3; 3-[(trimethylsilyl)oxy]pyrrole, 107638-09-5; 1-methyl-3-[(trimethylsilyl)-oxy]pyrrole, 107638-10-8; 1-indanone, 83-33-0; 3-[(trimethylsilyl)oxy]-indene, 31928-64-0; 2-[(trimethylsilyl)oxy]benzothiophene, 107638-11-9; 2-[(trimethylsilyl)oxy]indene, 95683-63-9; 2-[(trimethylsilyl)oxy]furan, 61550-02-5; 1-(trimethylsilyl)-2-[(trimethylsilyl)oxy]pyrrole, 120475-58-3; 1-methyl-2-[(trimethylsilyl)oxy]pyrrole, 87884-52-4; 2-[(trimethylsilyl)oxy]thiophene, 83043-44-1; *trans*-2-bromo-1-indanol, 10368-44-2; *trans*-2-bromo-1-indanyl dimethyl orthoacetate, 120475-59-4.

Supplementary Material Available: Tables of first-order rate constants for the ketonization of hydroxy heterocycles in water (Tables S1-8), of the solvent effect on K_{enol} for 3-hydroxyindole (Table S9), of pK_a measurements (Tables S10-13), and of the percentage of 3-thiolen-2-one formed from 2-hydroxythiophene in acetonitrile-water mixtures at different acid concentrations (Table S14) (15 pages). Ordering information is given on any current masthead page.

Experimental and Theoretical Studies of Substituent Effects on an Orbital Symmetry Forbidden Electrocyclization

David C. Spellmeyer,[1a] K. N. Houk,*[,1a] Nelson G. Rondan,[1b] R. D. Miller,*[,1c] Lothar Franz,[1c] and G. N. Fickes[1c,d]

Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90024, the IBM Almaden Research Center, San Jose, California 95120, and the Department of Chemistry, University of Nevada, Reno, Nevada 89557. *Received August 8, 1988. Revised Manuscript Received January 12, 1989*

Abstract: The disrotatory electrocyclizations of several transient bridged *o*-xylylenes to form benzocyclobutenes has been investigated experimentally. Electron-withdrawing groups at the *o*-xylyene termini have large effects on the activation energy for this orbital symmetry forbidden reaction, while electron-donating groups have smaller effects. Ab initio quantum mechanical calculations on models of the transition structures of disrotatory electrocyclizations of butadienes reproduce these trends and have been used to develop a qualitative hypothesis to explain the unusual substituent effects found in the experimental study.

How do substituents influence the rates of orbital symmetry forbidden reactions? Little information is available to answer this question, because of the scarcity of examples of forbidden reactions. This question is related to the more general subject of substituent effects on allowed and forbidden pericyclic reactions. These are not known in general, except for cycloadditions such as the Diels-Alder reaction. Nevertheless, it is interesting and important to know these for many reasons. Carpenter predicted that the substituent effects on forbidden processes will be larger

(1) (a) U.C.L.A. (b) Present address: Dow Chemical Co., Midland, Michigan. (c) IBM. (d) University of Nevada.

0002-7863/89/1511-5356$01.50/0