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An Empirical Aromaticity Index (AIRT) Based on "Reversion to Type" in the Hydrolysis of Methyl Ethers, Methyl Thioethers, and Methyl Selenoethers Derived from Some Heterocyclic and Homocyclic Polyenes

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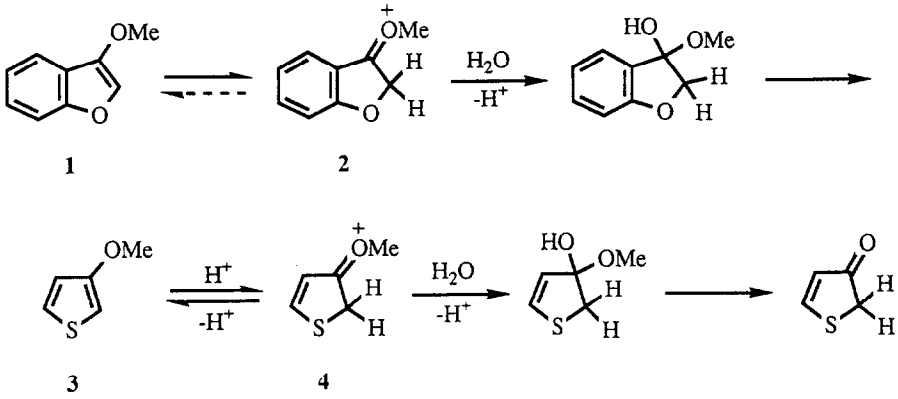
Abstract: *Hydronium ion catalysed hydrolysis and deuterium exchange in CD_3CN-D_2O (9:1 v/v) of the following compounds have been investigated: 1-methoxy-, 3-methoxy-, and 1-methylthio-cyclohepta-1,3,5-triene, 1-methoxy-cyclooctatetraene, 2-methylthio-, 3-methylthio- and 2-methylseleno-benzofuran, 2-methylthio- and 3-methylthio-benzothiophene, and 2-methylthio-N-methyl-indole. The values of log k_{ex}/k_{hyd} for these compounds and those of a previous investigation (ref. 4) have been used to define an aromaticity scale based on "reversion to type" (cf ref. 7).*

INTRODUCTION

Reversible protonation in the hydrolysis of enol ethers, long sought after but not found by Kresge and his co-workers,[1] was demonstrated to occur in the hydrolysis of ketene dithioacetals by Okuyama and his co-workers [2] and in the hydrolysis of seleno enol ethers and ketene diselenoacetals by Hevesi and his co-workers.[3] Subsequently, we showed that reversible protonation occurred in the hydrolysis of heterocyclic *oxygen* enol ethers. It was shown that the tendency to reversibility increased with aromaticity of the heterocyclic ring.[4] Thus, reversibility was not detected in the hydrolysis of 3-methoxybenzofuran (**1**), but in the hydrolysis of 3-methoxythiophene (**3**) $k_{ex}/k_{hyd} = 26 \times 10^4$ in CD_3CN:D_2O (9:1 *v/v*) at 32°C. According to Dewar [5] the furan ring of benzofuran is not aromatic and it was concluded [4] that the tendency for ion **2** to revert to starting material **1** was slight and that hence protonation was not reversible. On the other hand thiophene has a Dewar Resonance Energy (DRE) of 6.5 k cal $mole^{-1}$ [6] and hence the tendency of ion **4** to revert to starting material **3** is strong and protonation is reversible. In 1988 Castells and co-workers proposed that the tendency of the cations formed on protonation to "revert to type" is a better criterion of aromaticity than thermodynamic "extra stability".[7] These workers supported this conclusion with quantum mechanical calculations on the reactions of the cations formed on protonation of benzene and cyclobutadiene. As far as we are aware the only experimental work of relevance to Castells proposal is our work mentioned above on the hydrolysis of

heterocyclic enol ethers,[4] and we now report an extension of this work, with particular reference to the proposed homoaromaticity of cycloheptatriene.

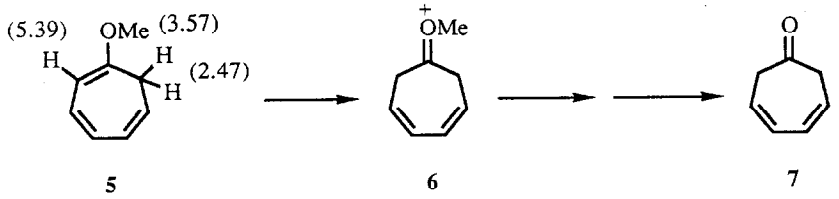


Stabilization of cycloheptatriene by a non-bonding interaction across the ends of the triene systems was originally estimated to be 9 k cal mol^{-1},[8] and such stabilization was termed homoaromaticity by Winstein.[9] However more recent estimates are much smaller (e.g. 3.9 kcal $mole^{-1}$ [10]) and some workers have concluded that the interaction across the ends of the triene system is destabilizing.[11]

RESULTS AND DISCUSSION

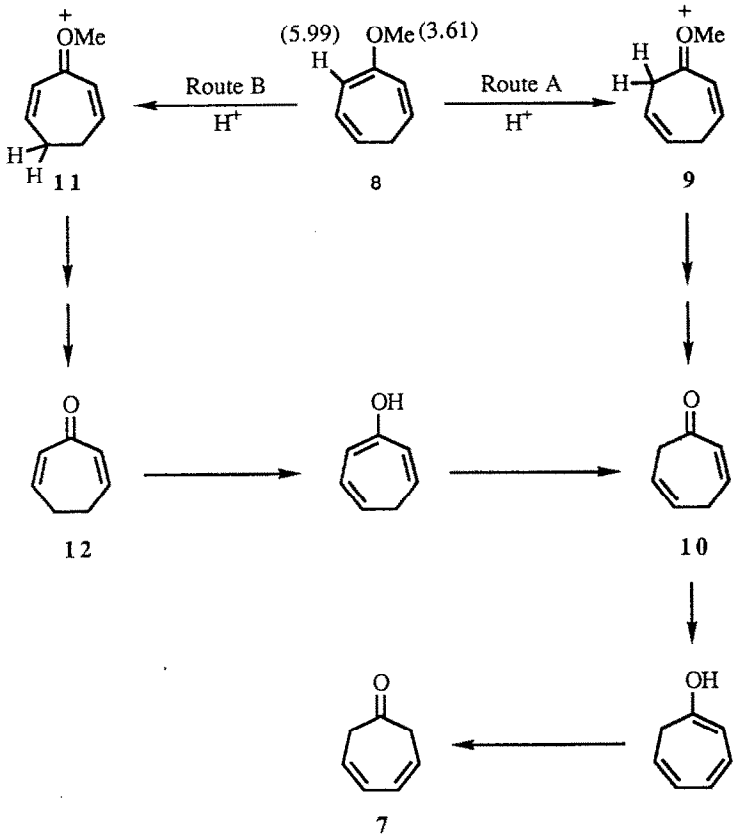
Hydrolysis of Methoxycycloheptatrienes and Methoxycyclooctatetraene

In an attempt to apply the criterion of "reversion to type" to the cycloheptatriene series we have studied the hydrolysis 1-methoxycyclohepta- 1,3,5-triene (**5**) and 3-methoxycyclohepta-1,3,5-triene (**8**). The product of both these reactions, determined by isolation (>95%) and by ^{1}H-NMR spectroscopy of the reaction



The figures in parentheses are the 90MHz ^{1}H NMR chemical shifts (TMS as internal refernence) in CD_3CN:D_2O (9:1 v/v) at 25°C.

solutions, was cyclohepta-3,5-dienone (**7**). This was thought to be derived from the 1-methoxy compound (**5**) by protonation at position 2. Two routes are possible for the formation of (**7**) from the **3-methoxy**-compound (**8**), protonation at carbon 4 (route A) and protonation at carbon 6 (route B, see Scheme 1). Independent experiments (see Experimental section) showed that ketone **12** was not converted into **7** under the reaction conditions, but that ketone **10** underwent rapid tautomerization into **7**.[12] Therefore it was concluded that route A was followed and that the hydrolysis of both **5** and **8** involves protonation at the α-position.

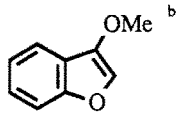
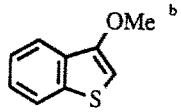


Scheme 1

The figures in parentheses are the 90MHz ^{1}H NMR chemical shifts (TMS as internal reference) in CD_3CN:D_2O (9:1 v/v) at 25°C.

To test whether protonation was reversible the hydrolyses were followed by ^{1}H-NMR spectroscopy in 90% (*v*/*v*) CD_3CN-D_2O (DCl, 50 × 10^{-3} M). Hydrolysis was monitored by disappearance of the methoxy signals of the substrates (**5**, δ 3.57; **8**, δ 3.61) and appearance of the signal of methanol (δ 3.29). Exchange in the hydrolysis of **5** was monitored by the disappearance of the signal of H-2 (δ 6.39) and as the cation **6** is symmetrical, by the disappearance of the signal of H-7 (δ 2.47). Within experimental error the rates of disappearance of these signals were the same as that of hydrolysis and it was concluded that nucleophilic attack by water on cation **6** is much faster than proton abstraction. Exchange of the α-proton of **8** (δ 5.99) in 90% (*v*/*v*) CD_3CN-D_2O (DCl, 5 × 10^{-2} M) was also within experimental error the same as the rate of hydrolysis, and so cation **9** also undergoes nucleophilic attack faster than proton abstraction. A comparison of these results with those previously reported for a series of heterocyclic compounds is given in Table 1.

Table 1. Ratio of Rate Constants of Deuterium Exchange (k_{ex}) to Hydrolysis (k_{hyd}) of Some Compounds in CD_3CN-D_2O (9:1 *v*/*v*) at 25°C [a]

Compound	[DCl]/M	k_{hyd}/$M^{-1}s^{-1}$	k_{ex}/$M^{-1}s^{-1}$	k_{ex}/k_{hyd}
5	$5x10^{-3}$	$6.47x10^{-2}$	$<2.15x10^{-4}$	$<3.3x10^{-3}$
8	$5x10^{-2}$	$1.05x10^{-2}$	$<3.6x10^{-5}$	$<3.4x10^{-3}$
13	$5x10^{-3}$	0.215	$<5.57x10^{-4}$	$<2.6x10^{-3}$
14	1	$<2.45x10^{-7}$	$1.68x10^{-4}$	>686
 [b]	0.1	$4.89x10^{-2}$	$<2.45x10^{-3}$	<0.05
15	0.8	$<3.18x10^{-8}$	$1.39x10^{-3}$	>800
 [b]	0.1	$3.5x10^{-4}$	$1.1x10^{-2}$	31
16	0.8	$<1.45x10^{-7}$	$4.38x10^{-4}$	$>3x10^{-3}$

a : Estimated by ^{1}H NMR spectroscopy.
b : At 32°C, ref. 4.

This conclusion was supported by the solvent isotope effects for the hydrolyses of **5** and **8**, measured in H_2O and D_2O at 25°C, which were k_H/k_D = 2.0 and 2.3 (see Table 2) and which are in the normal region for a reaction which involves rate determining protonation.[1(e)]

Table 2. Rate Constants and analytical wavelengths of Acid-Catalysed Hydrolysis and Kinetic Isotope Effects on Hydrolysis of Vinyl Ethers in Aqueous Solution at 25°C[a]

Vinyl Ether	Analytical wavelength	$k_H/10^{-2}$ $M^{-1}s^{-1}$	$k_D/10^{-2}$ $M^{-1}s^{-1}$	k_H/k_D
5	285	14.3	7.2	2.0
8	255	2.2	0.9	2.4
13	211	40.4	11.2	3.6

a: Determined by UV spectroscopy, μ = 1M NaCl.

This behaviour is similar to that found in hydrolysis of 3-methoxybenzofuran[4] and application of the criterion of "reversion to type" indicates that homoaromatic stabilization of the starting materials, if any, must be very small.

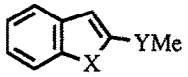
The hydrolysis of methoxycyclooctatetraene **13**, a potentially anti-aromatic enol ether, was also studied, but no exchange could be detected. This is consistent with the solvent isotope effect k_H/k_D = 3.6 which also has the magnitude expected for a reaction with a rate-determining proton transfer.[1(e)]

Hydrolysis of Methylthio- and Methylseleno-ethers

In view of the results of Okuyama[2] it was thought that similar experiments with methyl thio ethers would provide a more sensitive way of applying the criterion of "reversion to type". Three compounds were studied: 1-methylthiocyclohepta-1,3,5-triene(**14**), 3-methylthiobenzofuran(**15**), and3-methylthiobenzothiophene(**16**). With all of these exchange was much faster than hydrolysis (see Table 1). Therefore the methylthio-substituent favours exchange over nucleophilic attack so much that hydrolysis could not be detected.

In the heterocyclic series when the substituent is in the 2-position the tendency for exchange (now at the three position) is less than when it is at the 3-position (see Table 3). In these compounds carbon-2 is formally at the oxidation level of a carboxylic acid, so it is interesting to compare their behaviour with those of the previously studied acyclic ketene O,S acetals and ketene dithioacetals (see Table 4). In all cases the tendency to "revert to type" is much greater with the heterocyclic compounds, even with the derivative of benzofuran. One methylseleno ether was also studied and this shows a much greater value for k_{ex}/k_{hyd} than even an acyclic ketene diselenoacetal.

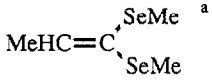
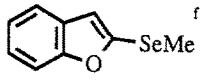
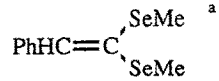
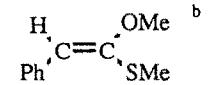
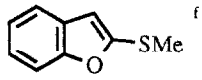
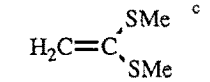
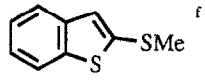
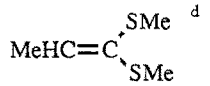
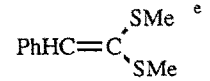
Table 3. Ratio of Rate Constants of Deuterium Exchange (k_{ex}) to Hydrolysis (k_{hyd}) of Some 2-Substituted Benzo-Heterocyclic Compounds in CD_3CN-D_2O (9:1 *v/v*) at 25°C[a]



Compounds	X	Y	[DCl]/M	$k_{hyd}/M^{-1}s^{-1}$	$k_{ex}/M^{-1}s^{-1}$	k_{ex}/k_{hyd}
17	O	S	0.8	6.06×10^{-5}	2.73×10^{-3}	45
18	O	Se	0.8	8.81×10^{-6}	1.21×10^{-3}	137
19	S	S	0.8	1.45×10^{-7}	2.62×10^{-4}	$>1.8\times10^{3}$
20	NMe	S	10^{-3}	2.29×10^{-5}	3.93	$>1.7\times10^{5}$

a: Estimated by ^1H NMR spectroscopy.

Table 4. Ratio of rate constants of deuterium exchange (k_{ex}) to hydrolysis (k_{hyd})

Compound	k_{ex}/k_{hyd}	Compound[g]	k_{ex}/k_{hyd}
 [a]	1.2	 [f]	137
 [a]	4		
 [b]	9×10^{-2}	 [f]	45
 [c]	0.32	 [f]	$>1.8\times10^{3}$
 [d]	0.5		
 [e]	13.4		

a : Ref. 3(b), in dioxane-water (6:4 *v/v*) at 30°C.
b : Ref. 13. Estimated from the effect of formate buffer on the hydrolysis rates by steady state approximation.
c : Ref. 2(c), in acetonitrile-water (9:1 *v/v*) at 30°C.
d : Ref. 2(g), in acetonitrile-water (9:1 *v/v*) at 30°C.
e : Ref. 2(d), in CD_3CN-D_2O (9:1 *v/v*) at 31±2°C.
f : All the kinetics were studied in CD_3CN-D_2O (9:1 *v/v*) at 25°C.

Relative Reactivities of Enol Ethers and Enethiol Ethers

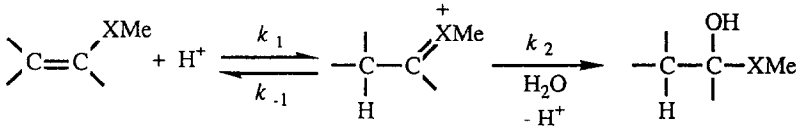
The reversibility of the protonation step in the hydrolysis of the thioethers has a large effect on the ratio of the rate constants for the hydrolysis of enol ethers to those of the corresponding enethiol ethers (Table 5).

Table 5. Ratio of Rate Constants for Acid-Catalysed Hydrolyses of Vinyl Ethers k_H(vinyl ether) to Vinyl Sulfides k_H(vinyl sulfide) at 25°C

Vinyl ether	Vinyl sulfide	k_H(vinyl ether)/ k_H(vinyl sulfide)
$H_2C{=}C(OMe)H$ [a]	$H_2C{=}C(SMe)H$ [a]	34.1
5 [b]	**14** [c]	104

a : Ref. 14, in 1N HCl.
b : In H_2O (μ = 1M NaCl), determined by UV spectroscopy.
c : In CD_3CN-D_2O (9:1 v/v), estimated by ^1H NMR spectroscopy.

The rate determining step in the hydrolysis of both methoxyethene and methylthioethene is protonation of the double bond and the former is hydrolysed 34 times faster than the latter (Table 5).[13] However 1-methoxycyclohepta-1,3,5-triene(**5**) is hydrolysed more than 104 times faster than 1-methylthio-cyclohepta-1,3,5-triene(**14**). This difference in behaviour arises from the methoxy-compound hydrolysing with rate-determining protonation and the methylthio-compound with reversible protonation. When the rate-



determining step is protonation $k_{hyd} = k_1$, but when protonation is reversible $k_{hyd} = k_1 \times k_2/(k_2 + k_{-1})$. Since k_{-1} is greater than k_2, k_{hyd} is less than k_1. So for 1-methoxycyclohepta-1,3,5-triene k_{hyd} is equal to the rate of protonation (k_1) but for 1-methylthiocyclohepta-1,3,5-triene k_{hyd} is less than k_1. Therefore the ratio of the rates of hydrolysis for oxygen and thio compounds is greater than it would be if the rate determining step in both reactions were protonation.

When protonation is reversible the rate constant for exchange is $k_{ex} = k_1 \times k_{-1}/(k_2 + k_{-1})$. With 1-methylthiocyclohepta-1,3,5-triene exchange was found to be much faster the hydrolysis so that $k_{-1} > k_2$ and therefore $k_{ex} = k_1$. The value k_1 estimated in this way is 1.7×10^{-4} M^{-1} s^{-1} which is 385 times less that k_1 ($= k_{hyd} = 6.5 \times 10^{-2}$ M^{-1} s^{-1}) for 1-methoxycyclohepta-1,3,5-triene. The ratio of the rate constants for protonation of methoxy and methylthiocyclo-heptatrienes (385), is therefore about 11 times greater than that found for the methoxy- and methylthio-ethenes (34).

An Aromaticity Index based on "Reversion to Type" (AIRT)

On the basis of our results it is possible to define an Aromaticity Index based on "Reversion to Type".[7] This is defined as the logarithm of k_{ex}/k_{hyd} for the corresponding methyl ether. In addition secondary indexes

$$\text{AIRT} = \log \frac{k_{ex}}{k_{hyd}}$$

may be define on the basis of k_{ex}/k_{hyd} for the corresponding methyl thio ether and k_{ex}/k_{hyd} for the corresponding methyl seleno ethers. All reactions were studied in CD_3CN:D_2O (9:1 *v/v*) at 25°C.

$$\text{AIRT}' = \log \frac{k_{ex}^{MeS}}{k_{hyd}^{MeS}}$$

$$\text{AIRT}'' = \log \frac{k_{ex}^{MeSe}}{k_{hyd}^{MeSe}}$$

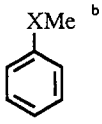
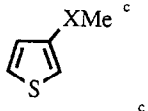
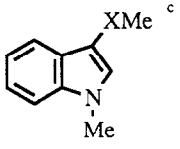
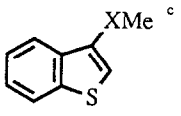
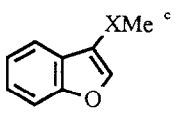
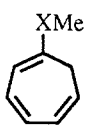
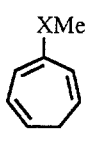
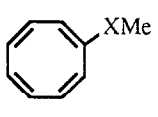
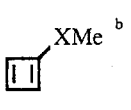
These should be related to one another by equation of the form

$$\text{AIRT} = \text{AIRT}' + \text{CONST}' \quad (1)$$

$$\text{AIRT} = \text{AIRT}'' + \text{CONST}'' \quad (2)$$

Limits of the value of CONST' may be obtained by comparing the results for the benzothiophene, benzofuran and 1-substituted cycloheptatriene compounds in Table 6 which yield the values < -1.3, < -4.2, and < -5.3 respectively. It therefore seems that CONST' must be less than -5.3.

Table 6. AIRT and AIRT' Values

Compound	AIRT [a] X=O	AIRT' [a] X=S	DRE kcal mol^{-1}
	ca. 9 [b]	-	22.6 [d]
	4.4 [c]	-	6.5 [e]
	3.1 [c]	-	23.8 [f]
	1.5 [c]	>2.8	24.8 [e]
	<-1.3 [c]	2.9	20.3 [g]
	<-2.5	>2.8	-
	<-2.5	-	-
	<-2.6	-	-
	ca. -24 [b]	-	-

a: Log k_{ex}/k_{hyd} values for the hydronium catalysed hydrolysis in $CD_3CN:D_2O$ (9:1 *v/v*) at 25 °C.
b: Estimated from the quantum mechanical calculation on the parent hydrocarbons in ref. 7.
c: Results from ref. 4.
d: Ref. 15.
e: Ref. 6.
f: Dewar resonance energy of indole, ref. 5.
g: ref. 5.

Yet a further series can be obtained from the results for the 2-substituted heterocyclic compounds, defined in the same way as above and designated AIRT(2), AIRT'(2), and AIRT"(2) for the 2-methoxy-, 2-methylthio-, and 2-methylseleno- series respectively. These will be related to the primary values by the following equations:

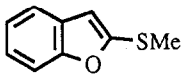
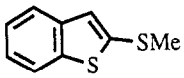
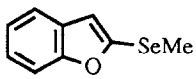
$$\text{AIRT} = \text{AIRT(2)} + \text{CONST(2)} \tag{3}$$

$$\text{AIRT} = \text{AIRT'(2)} + \text{CONST'(2)} \tag{4}$$

$$\text{AIRT} = \text{AIRT"(2)} + \text{CONST"(2)} \tag{5}$$

Some AIRT'(2) values are given in Table 7. A comparison of these results with those of the corresponding 3-methoxy compounds in Table 6 yield values of < -3, < -1.8 and < -2.1 which suggest that CONST'(2) must be less than -3.

Table 7. AIRT'(2) Values [a]

Compound	AIRT'(2)
	1.7
	>3.3
	>5.2

a: Log k_{ex}/k_{hyd} values for the hydronium catalysed hydrolysis in $CD_3CN:D_2O$ (9:1 *v/v*) at 25°C.

Comparison of the results for the derivatives of cycloheptatriene and benzofuran in Table 6 shows that their AIRT and AIRT' values are similar and thus on the basis of this criterion the homoaromaticity of cycloheptatriene is no more than that of the furan ring of benzofuran. Dewar considered that as the Dewar Resonance Energy of benzofuran was almost the same as that of benzene the furan ring of the latter was not aromatic.[5]

Although our results are far from complete they indicate how a useful empirical index of aromaticity would be constructed on the basis of "reversion to type".

EXPERIMENTAL

All b.p.s and m.p.s are uncorrected. ^{1}H NMR spectra at 90 MHz and ^{13}C NMR spectra at 22.5MHz were measured with a JEOL FX-90Q instrument. ^{1}H NMR spectra at 270 MHz and ^{13}C NMR at 67.8 MHz were recorded with a JEOL GSX-270 spectrometer. Chemical shifts were measured downfield from internal tetramethylsilane and were quoted in δ. Infrared spectra were recorded on a Perkin-Elmer 157G spectrometer and were calibrated against a polystyrene absorption peak at 1601 cm^{-1}. Ordinary mass spectra were run on a Hitachi RMS-4 mass spectrometer. High resolution mass spectra were recorded on a VG 7070F MICRO-MASS mass spectrometer. Microanalyses were performed at the Butterworth Laboratories Ltd., UK.

Kinetics of Hydrolysis

The aqueous solutions were made up with deionized and degassed water and ionic strength was maintained at 1M by potassium chloride. Solutions of different acid concentrations were prepared by mixing appropriate volumes of 1M standard hydrochloric acid (E. Merck) and 1M potassium chloride solution. The chemicals used were "Analar" grade.

A stock solution was prepared by dissolving 2 to 5 μl of the enol ether in 2 ml spectroscopic grade acetonitrile (Aldrich). This solution (20μl) was injected into 2.0 ml of aqueous solution in a 10mm quartz cell which was thermostatted in the cell compartment of a Shimadzu UV-250 spectrophotometer. The decay of the enol ether or the growth of the keto form was monitored by an APPLE IIe microcomputer operating on-line via an IEEE interface. Normally the hydrolyses were followed to more than 90% completion and 80 absorbance values were collected at convenient time intervals and the observed first order rate constants were calculated by a general-least-squares method from the following equations:

$$\ln (A_o - A_t) = k_{obs} t + \ln (A_o - A_\infty)$$

or

$$k_{obs} = \frac{1}{t} \ln \frac{A_o - A_\infty}{A_o - A_t}$$

The second-order rate constants for hydrolysis, k_H, were obtained from plots of k_{obs} against acid concentration using a linear least squares method.

Kinetics of Exchange

The enol ether (10-25μl) was dissolved in CD_3CN (540μl) and the ^1H NMR spectrum was measured. DCl of appropriate concentration (60μl) was added and the ^1H NMR spectrum collected at convenient time intervals with solution being kept at temperature and sealed under nitrogen atmosphere. The relative rates of exchange to hydrolysis were estimated from times required for equivalent amounts of decay of a ring proton and the methylthio or methyl seleno groups.

***3-Methylthiobenzofuran* (15)**

This was prepared by the method used by Hartke and his coworkers for the synthesis of 2-methylthioindene.[16] The yield was 95%. B.p. 55-57°C/3mmHg. ^1H NMR (90MHz, $CDCl_3$): δ_H2.36 (s, 3H, SMe), 7.54 (s, 1H, H-2), 7.20-7.69 (m, 4H, H-4,5,6,7); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C 18.04 (q, SMe), 111.73 (d), 114.96 (s), 119.78 (d), 122.95 (d), 124.84 (d), 128.12 (s), 144.64 (d), 155.42 (s); MS (*m/e*): 149 (82%), 164 (100%, M^+); Anal. Calcd. for C_9H_8OS: C, 65.85; H, 4.91. Found: C, 65.97; H, 5.00.

***3-Methylthiobenzothiophene* (16)** [17]

The procedure was the same as 3-methylthiobenzofuran. The yield was 90%. B.p. 119-121°C/0.5mmHg (Lit.[17] b.p.151°C/1mmHg). ^1H NMR (90MHz, $CDCl_3$): δ_H2.39 (s, 3H, SMe), 7.04 (s, ^1H, H-2), 7.25-7.88 (m, 4H); ^1H NMR (Lit.[17], $CDCl_3$): δ_H2.5 (s), 7.35 (s); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C16.96 (q), 121.51 (d), 122.08 (d), 122.78 (d), 124.19 (d), 124.73 (d), 129.20 (s), 138.11 (s), 139.82 (s); MS (*m/e*): 165 (85%), 180 (100%, M^+).

***2-Methylthiobenzofuran* (17)**

A solution of 2-bromobenzofuran (2g, 10ml) in diethyl ether (5ml) was added at once to a stirred solution of n-butyllithium (14mmol) in anhydrous diethyl ether (50ml), cooled to -70°C in a Dry Ice-acetone bath.[18] The mixture was stirred for 2 min and then a solution of dimethyl disulfide[19] (1.31g, 14mmol) in diethyl ether (5ml) was added. The resulting mixture was kept stirring for 3 hours and then the temperature of the mixture was allowed to rise to room temperature slowly. Water (100ml) was added and the organic layer was separated, dried and concentrated. The residue was distilled under vacuum to give pure product (1.47g, 90%) at b.p. 66-68°C/4mmHg. ^1H NMR (90MHz, $CDCl_3$): δ_H2.51 (s, 3H, SMe), 6.65 (d, J=0.66Hz, 1H, H-3), 7.13-7.51 (m, 4H, H-5,6,7,8); ^{13}C NMR(22.5MHz, $CDCl_3$): δ_C17.01 (q, SMe), 107.83 (d), 110.73 (d), 120.08 (d), 122.87 (d), 123.92 (d), 128.77 (s), 152.34 (s), 156.23 (s); MS (*m/e*): 149 (95%), 164 (100%, M^+); Anal. Calcd. for C_9H_8OS: C, 65.85; H, 4.91. Found: C, 65.97; H, 5.00.

***2-Methyselenobenzofuran* (18)**

The procedure was the same as that of 2-methylthiobenzofuran except that dimethyl diselenide[20] was

used instead of dimethyl disulfide. The yield was 85%. B.p. 75-77°C/1mmHg. ^{1}H NMR (90MHz, $CDCl_3$): δ_H2.40 (s, 3H, SeMe), 6.78 (d, J=0.88Hz, 1H, H-3), 7.14-7.54 (m, 4H, H-5,6,7,8); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C7.96 (q, SeMe), 110.78 (d), 111.49 (d), 120.02 (d), 122.81 (d), 123.92 (d), 128.88 (s), 145.08 (s), 157.10 (s); MS (*m/e*): 212 (96%), 227 (100%, M^+); HRMS for C_9H_8OSe: calcd. 211.9785, found 211.9730.

***2-Methylthiobenzothiophene* (19)** [17]

The procedure was the same as that of 2-methylthiobenzofuran except that the starting material was benzothiophene. The yield was 70%. B.p. 133-135°C/0.5mmHg (Lit.[17] b.p. 147°C/1mmHg). ^{1}H NMR (90MHz, $CDCl_3$): δ_H2.51 (s, 3H, SMe), 7.71 (d, J=0.66Hz, 1H, H-3), 7.14-7.72 (m, 4H, H-5,6,7,8). ^{1}H NMR (Lit.[17], $CDCl_3$): δ_H2.50 (s); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C20.04 (q, SMe), 121.70 (d), 122.59 (d), 123.89 (d), 124.38 (d), 124.60 (d), 139.60 (s), 139.88 (s), 140.72 (s); MS (*m/e*): 165 (90%), 180 (100%, M^+).

***2-Methylthio-N-methylindole* (20)** [21]

The procedure was the same as above except that N-methylindole[22] was used as starting material. The yield was 86%. B.p. 80-82°C(3mmHg). ^{1}H NMR (270MHz, $CDCl_3$): δ_H2.42 (s, 3H, SMe), 3.75 (s, 3H, NMe), 6.56 (s, 1H, H-3), 7.12-7.55 (m, 4H, H-5,6,7,8); ^{1}H NMR (Lit.[21], $CDCl_3$): δ_H2.42 (s, 3H), 3.76 (s, 3H), 6.58 (s, 1H), 7.10-7.60 (m, 4H); ^{13}C NMR (67.8MHz, $CDCl_3$): δ_C19.10 (q, SMe), 29.77 (q, NMe), 104.77 (d), 109.14 (d), 119.66 (d), 119.86 (d), 121.69 (s), 134.14 (s), 138.13 (s); MS (*m/e*): 162 (98%), 177 (100%, M^+).

***3-Methoxycyclohepta-1,3,5-triene* (8)** [23]

This was prepared by the procedure of Weth and Dreiding.[24] The yield was 75%. B.p. 60-62°C/6mmHg (Lit.[23] b.p.74-75°C/15mmHg). ^{1}H NMR (90MHz, $CDCl_3$): δ_H2.29 (t, J=6.78Hz, 2H, H-7), 3.63 (s, 3H, OMe), 5.14-6,56 (m, 5H); ^{1}H NMR (Lit.[23], $CDCl_3$): δ_H2.23 (t, 2H, H-7), 3.57 (s, 3H, OMe); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C27.54 (t, C-7), 54.55 (q, OMe), 104.01 (d), 116.28 (d), 123.52 (d), 124.14(d), 125.09 (d), 160.03 (s, C-3).

***1-Methoxycyclohepta-1,3,5-triene* (5)** [25]

The procedure was the same as above except that the reaction time was 48 hours. The yield was 60%. B.p.57-59 °C/7mmHg (Lit.[25] b.p. 77-78°C/30mmHg). ^{1}H NMR (90MHz, $CDCl_3$): δ_H2.51 (d, J=7Hz, 2H, H-7), 3.58 (s, 3H, OMe). 5.20-5.65 (m, 5H, H-2,3,4,5,6); ^{1}H NMR (Lit.[25], $CDCl_3$): δ_H2.45 (d, 2H, H-7), 3.53 (s, 3H, OMe), 5.24 (m, 2H), 6.36 (m, 3H); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C32.99 (t, C-7), 55.96 (q, OMe), 96.37 (d), 117.72 (d), 124.41 (d), 127.63 (d), 128.82 (d), 151.85 (s, C-1).

1-Methylthiocyclohepta-1,3,5-triene (14) [26]

The procedure was the same as above. A solution of 7-methylthio-1,3,5-cycloheptatriene (2g, 14.6mmol, perpared by the method of Doering and Knox[27]) and hydroquinone (0.1g, mmol, acted as polymerization inhibitor) in benzene (10ml) was sealed in a thick-wall glass tube. The sealed tube was heated at 185°C and the progress of the reaction was monitored at regular time intervals by ^{1}H NMR spectroscopy. After more the 100 hours the reaction was almost complete. The product (1.4g, 70% yield) was purified by column chromatography on silica gel (diethyl ether:pet. ether = 1:4). ^{1}H NMR (270MHz, CD_3CN): δ_H2.30 (s, 3H, SMe), 2.55 (d, 2H, $J_{6,7}$=6.84Hz, H-7), 5.28 (dt, 1H, $J_{5,6}$=9.28Hz, H-6), 5.85 (d, 1H, $J_{2,3}$=5.86Hz, H-2), 6.14 (dd, 1H, $J_{4,5}$=5.37Hz, H-5), 6.36 (dd, 1H, $J_{3,4}$=11.23Hz, H-4), 6.50 (dd, 1H, H-3); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C15.82 (q, SMe), 34.26 (t, C-7), 117.26 (d), 120.02 (d), 127.19 (d), 127.55 (d), 130.18 (d), 131.40 (s, C-1); MS (*m/e*): 138 (100%, M^+); HRMS for $C_8H_{10}S$: calcd. 138.0503, found 138.0571.

1-Methoxycyclooctatetraene (13) [28]

This was prepared by procedure of Oth and his co-workers[28]. B.p. 66-70°C/3mmHg (Lit.[28] b.p. 46-48°C/0.4mmHg). The crude product was further purified by column chromatography on silica gel (diethyl ether:pet. ether = 1:3). Overall yield was 55%. ^{1}H NMR (90MHz, $CDCl_3$): δ_H3.59 (s, 3H, OMe), 4.89 (bs, 1H, H-2), 5.76-5.87 (bs, 6H, H-3,4,5,6,7); ^{1}H NMR (Lit.[28], $CDCl_3$): δ_H3.52 (s), 4.88 (bs), 5.80 (bs); ^{13}C NMR (22.5MHz, $CDCl_3$): δ_C55.07 (q, OMe), 99.98, 128.74-133.48(broad signal), 155.56(s, C-1).

Isomerization of 2,6-Cycloheptadienone (12)

A solution of 2,6-cycloheptadienone[29] (1g) in 20ml of CD_3CN:D_2O (9:1 *v/v*) containing $5x10^{-2}$ M HCl was stirred vigorously at room temperature for more than 24 hours. 30ml of water was added and the resulting mixture was extracted with diethyl ether (3x15ml). The organic layer was dried and concentrated. TLC and ^{1}H NMR experiments on the crude product indicated that there was no detectable isomerization product. 0.98g of starting substrate 12 was recovered by column chromatograph on silica gel. Therefore, it was concluded that 12 did not isomerize to 3,5-cycloheptadienone 7 under the experimental conditions.

Isolation of Hydrolysed Product of 2-Methylthiobenzofuran

To a stirred solution of 0.1g (0.6 mmol) of 2-methylthiobenzofuran in 5ml of acetonitrile was added 0.5ml of concentrated HCl solution. Stirring was continued for 2 days. 20ml of water was added. The resulted mixture was extracted with diethyl ether (3 x 10ml). The combined organic phase was concentrated in vacuum. The residue was purified by column chromatography on silica gel to give two products.

The first product was a yellow oil which was identified to be *S*-methyl 2-(*o*-hydroxyphenyl) thioethanoate. The yield was 60mg (54%). ^{1}H NMR (270MHz, CD_3CN): δ_H2.22 (s, 3H, SMe), 3.81 (s, 2H), 6.81-6.89 (m, 2H), 7.12-7.18 (m, 2H), 7.26 (bs, 1H, OH); ^{13}C NMR (67.8MHz, CD_3CN): δ_C11.98 (q,

SMe), 45.38 (t), 116.11 (d), 120.96 (d), 121.87 (s), 129.85 (d), 132.68 (d), 156.12 (s), 199.48 (s, C=O); IR (neat, cm^{-1}): 3600-3200 (b, OH), 1661 (s, C=O); MS (*m/e*): 135 (100%), 182 (78%, M^+); HRMS for $C_9H_{10}O_2S$: calcd. 182.0491, found 182.0469.

The second product was a white solid which was identified to be *o*-hydroxyphenylacetic acid. The yield was 35mg (37%). M.p. 145-147°C (Lit.[30], m.p. 147°C). ^1H NMR (270MHz, CD_3CN): δ_H3.59 (s, 2H), 6.79-6.85 (m, 2H), 7.09-7.15 (m, 2H), 7.74 (bs, 2H, OHs); ^{13}C NMR (67.8MHz, CD_3CN): δ_C36.17 (t), 116.04 (d), 120.93 (d), 122.30 (s), 129.47 (d), 132.26 (d), 155.86 (s), 175.15 (s); IR (nujol, cm^{-1}): 3600-3200 (b, OH), 1705 (s, C=O); MS (*m/e*): 152 (100%, M^+).

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