

DEUTERIUM EXCHANGE IN A NUMBER OF 3-SUBSTITUTED
SULFOLANES *

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The NaOD-catalyzed isotopic exchange of hydrogen in the 2 position of 3-methoxysulfolane was investigated by PMR spectroscopy, and its pK_a value was estimated to be 24.67. Increased acidity is characteristic for the methylene group of 3-hydroxysulfolane in the 2 position and the methylene group of 3,4-dimethoxysulfolanes in the 2 and 5 positions.

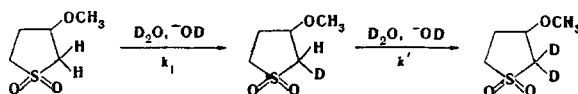
The increased acidity of the hydrogen of the C-H bonds in the α position of sulfones is well known [1]. No such data are available for sulfolane derivatives. The thermodynamic acidity of sulfolane in dimethyl sulfoxide (DMSO) was determined and characterized by $pK_a > 31$ [2]. Attempts to determine the kinetic acidity from the rate constant for isotopic exchange of sulfolane with D_2O in the presence of NaOD was unsuccessful because the process was too slow. [3].

We have previously [4] noted that the introduction of a methoxy group in the 3 position of the sulfolane ring facilitates exchange in the position in weakly alkaline media, whereas the lability of the remaining hydrogen atoms is not changed appreciably.

In the present research we studied the isotopic exchange of hydrogen in 3-methoxy- (I) and 3-hydroxysulfolane (II) and in cis- and trans-3,4-dimethoxysulfolanes (III and IV, respectively).

As seen from Fig. 1, the PMR spectrum of derivative I consists of three groups of signals [4]. Their relative intensities in order of increasing chemical shifts are 2:7:1. The first group of lines - a multiplet centered at 2.33 ppm - belongs to the two hydrogen atoms in the 4 position, the singlet of protons of the methoxy group in the second group of signals at 3.17-3.28 ppm is superimposed on the multiplet of four hydrogen atoms of the methylene groups in the 2 and 5 position, and a quintet of H-3 hydrogen atoms centered at 4.24 ppm is found at weakest field.

The following changes take place in D_2O in the presence of NaOD in the spectrum of I: the intensity of the signals at 3.17-3.28 ppm gradually decreases approaching the final value (5H), and the H-3 quintet at constant intensity after 1 h at 16° is converted into a broadened triplet. The intensity of the water peak (4.58 ppm) increases simultaneously with the changes in the spectrum of I. The observed changes correspond to successive exchange of two hydrogen atoms in the 2 position by deuterium.



Similar transformations occur with 3-hydroxysulfolane (II) in 0.19 M NaOD (Fig. 2): the intensity of the group of signals at 3.15-3.8 ppm affiliated with the four protons of the methyl groups in the 2 and 5

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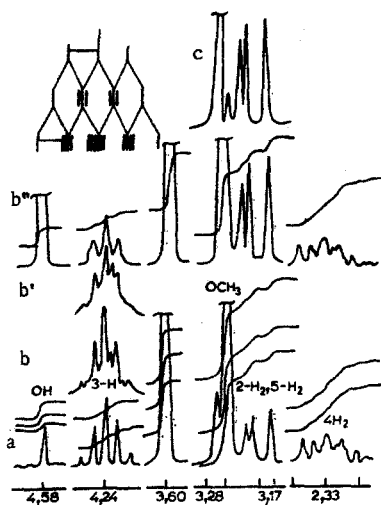


Fig. 1

Fig. 1. PMR spectrum of 3-methoxysulfolane I: a) in D_2O ; b) in 0.062 M NaOD in D_2O at $16^\circ C$ after 10 min; b') after 20 min; b'') after 60 min; c) in 0.2 M NaOD in D_2O at 16° .

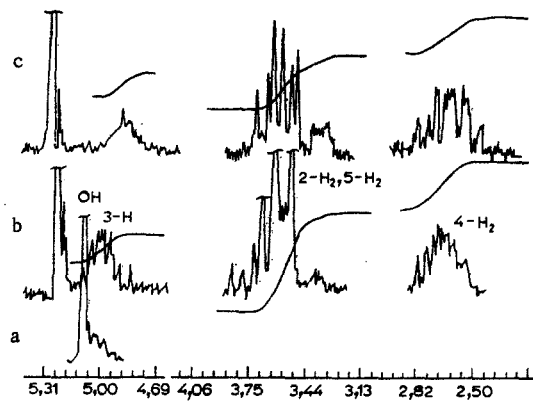


Fig. 2

Fig. 2. PMR spectrum of 3-hydroxysulfolane II in D_2O at $20^\circ C$: a) without added NaOD; b) without added NaOD at 7° for δ 4.69-5.31 ppm; c) in 0.19 M NaOD at 2° for δ 4.69-5.31 ppm.

positions is halved, and the quintet of the hydrogen atom attached to C-3 is converted to a broadened triplet.

Under the same conditions, 3-methyl- and 3-N-dimethylaminosulfolanes do not undergo any changes whatsoever. In the case of *cis*- (III) and *trans*-3,4-dimethoxysulfolane (IV) the hydrogen atoms of the methylene groups in the 2 and 5 positions undergo exchange (Fig. 3).

When sulfolane III is allowed to stand in 0.06-0.09 M NaOD for 2 days, IV is allowed to stand at room temperature for 2-3 h, and I is allowed to stand at $30-38^\circ$ or in 0.2-0.4 M NaOD at 16° , splitting out of methanol is observed in addition to proton exchange. The singlet of a methyl group, which is identified by the addition of pure methanol, appears in the PMR spectra.

In order to determine the rate of exchange of I with D_2O , we used the decrease in the intensity of the signals at 3.17-3.28 ppm (Fig. 1) and the increase in the intensity of the H_2O signal with time (under conditions that exclude the elimination of CH_3OH). The data on H_2O were calculated from a pseudo-first-order kinetic equation taking into account the large excess of D_2O . The kinetic equation of consecutive reactions [5], by means of which one can calculate the k_1 value, was used in the treatment of the data:

$$C_{i(H_2)} = C_0^1 \cdot e^{-k_1 t},$$

$$C_{i(H, D)} = C_0^1 \cdot \frac{k_1}{k' - k_1} (e^{-k_1 t} - e^{-k' t}),$$

$$C_0^1 = C_{i(H_2)} + C_{i(H, D)} + C_{i(D_2)},$$

where C_0^1 is the concentration of starting I, $C_{i(H_2)}$ is the concentration of undeuterated I at time t , and $C_{i(H, D)}$ and $C_{i(D_2)}$ are the same for the monodeuterated and dideuterated products.

Substituting $k' = 1/3k_1$ into the equation for $C_{i(H, D)}$, we obtain

$$C_{i(H, D)} = -\frac{3}{2} C_0^1 (e^{-k_1 t/3} - e^{-k_1 t}).$$

The integral intensities are expressed in the following way in terms of the instantaneous concentrations of the isotopic varieties of I:

TABLE 1. Isotopic Exchange of 3-Methoxysulfolane with D₂O in the 2 Position

T, °C	C ₁ , mole · liter ⁻¹	M _{NaOD}	k ₁ , min ⁻¹	k ₂ , liter · mole ⁻¹ / min	E _a , kcal · mole ⁻¹	ΔS [‡] , eu
16	0,809	0,130	0,05	0,38	19,37	-4,16
			0,092	0,35		
			0,062	0,28		
			0,0175	Av. 0,33		
30	0,809	0,039	0,048	1,23		
			0,062	1,45		
				Av. 1,34		
38	0,857	0,019	0,073	3,84		
			0,011	3,36		
				Av. 3,60		

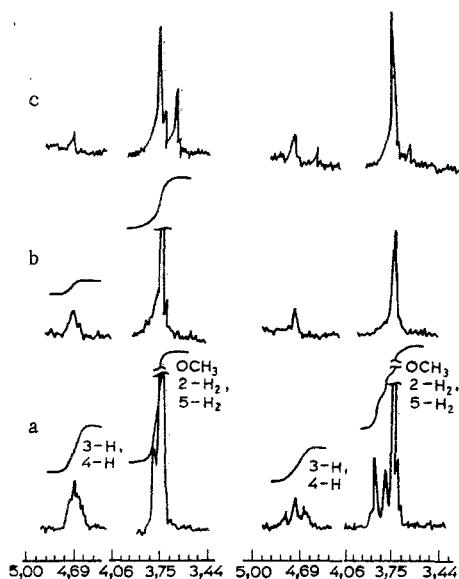


Fig. 3. PMR spectra of cis-3,4-dimethoxysulfolane (III) and trans-3,4-dimethoxysulfolane (IV) in D₂O at 20°C: a) without added NaOD; b) in 0.06 M NaOD after 48 h for III; c) after 3 h for IV.

$$\int_I = 7C_{1(H_2)} + 6C_{1(H,D)} + 5C_{1(D)} \text{ or}$$

$$\int_I = 5C_0^1 + 2C_{1(H_2)} + C_{1(H,D)}$$

Substituting the C₁(H₂) and C₁(H, D) values, we obtain the following dependence of the relative integral intensity on the time:

$$\int_I = 5C_0^1 + \frac{C_0^1}{2}(e^{-k_1 t} + 3e^{-k_2 t/3}).$$

The solution of this equation gives the rate constant for substitution of H by D in sulfolane I (k₁). The k₁ values and bimolecular rate constants for substitution of H by D obtained by division of k₁ by C_{NaOD}, as well as the activation energies and entropies, are given in Table 1. The k₂ values found from the increase in the intensity of the H₂O signal coincide satisfactorily with the values presented in Table 1.

A comparison of the k₂ values for exchange of I at 24°C with the values in [3] showed that 3-methoxysulfolane is deuterated in the 2 position faster by a factor of six than dimethyl sulfone and faster by a factor of > 300 than diethyl sulfone.

The rate constants found for the deuteration of I make it possible to approximately evaluate the pK_a value of its C-H acidity by means of the equation

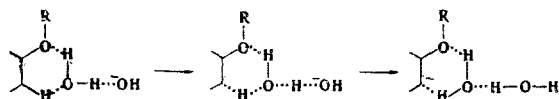
$$pK_a = -\lg K_a^1 = -\lg \frac{k''_1}{k''_{-1}}$$

of $0.5 \cdot 10^{-7}$ (the D₂O ion product at 25° is $K_a^{D_2O} = 0.195 \cdot 10^{-14}$). (The k''₁ value is not difficult to calculate with a knowledge of the k₂ value and the OD⁻ concentration. In our case it is $\sim 7.04 \cdot 10^{-10} \text{ sec}^{-1}$.) The k''₋₁ term is the rate constant for recombination of the carbanion with the proton. In an approximate calculation we assumed that it is equal to the k''₋₁ value of dimethyl sulfone ($3.3 \cdot 10^{15}$ [7]), inasmuch as the rates of deuteration of I and dimethyl sulfone under conditions differ from one another by less than one order of magnitude. Thus

$$pK_a^1 = -\lg \frac{7.04 \cdot 10^{-10}}{3.3 \cdot 10^{15}} = 24.67.$$

According to the data in [8], the pK_a values of sulfones increase by a factor of approximately two logarithmic units on passing from water to DMSO, and the pK_a value for I in DMSO can therefore be assumed to be ~ 27 . It follows from a comparison with the pK_a value of sulfolane that the introduction of a methoxy group in the 3 position of the sulfolane ring increases the acidity of the hydrogen in the 2 position by a factor of more than four orders of magnitude.

It is known [9] that the acidity of sulfones is determined to a considerable degree by structural, electrostatic, and solvation factors. The decrease in the acidity on passing from dimethyl sulfone to sulfolane can be explained by the fact that the flexible structure of the carbanion of diethyl sulfone reduces electrostatic repulsion to a minimum and makes the carbanion more stable. The sharp increase in the acidity of the sulfolane ring that we observed on introduction of oxygen-containing substituents cannot be explained only by the inductive effect of the oxygen atoms of the OH and OCH₃ groups in the β position, especially since the lability of the hydrogen attached to the carbon atom bonded to the substituent does not change under our conditions. The essential factor here is apparently the ability of the oxygen atom to give strong hydrogen bonds, which is important for proton exchange reactions [10]. It might be supposed that sulfolane I forms cyclic hydrates, the formation of which favors the spatial orientation of the oxygen atoms and of the proton being detached.



The transition from the starting state to the carbanion may be realized by energetically advantageous redistribution of the bonds in the hydrates without substantial disruption of their form and composition. The small change in the entropy during the reaction ($\Delta S^\ddagger = -4.07$ eu) constitutes evidence in favor of the proposed scheme.

EXPERIMENTAL METHOD

The PMR spectra were recorded with a Tesla BS-487 s spectrometer (80 MHz). The samples were thermostated with an accuracy of $\pm 0.5^\circ$. The solvent was D₂O with added dioxane (0.35 mole/liter) for I. Acetonitrile served as the internal standard in the kinetic investigations of the isotope exchange, whereas hexamethyldisiloxane (HMDS) served as the external standard. The chemical shifts were determined relative to CH₃CN and were converted relative to HMDS.

Method Used for the Kinetic Measurements. The experiments on the isotope exchange of I were carried out in the spectrometer ampul at a fixed temperature. A solution of I in D₂O (1.62 M) with added 0.7 M dioxane and 1.92 M acetonitrile was prepared. Equal volumes of the solution of I and the titration solution of NaOD in D₂O were mixed, and the intensities of the peaks under investigation were found every 5 min for 1 h. In a control experiment the spectrum of a solution of I diluted with D₂O was recorded. The NaOD concentration in the mixture was determined by titration of a sample prior to and after the experiment.

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