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Oxidation of Organic Sulfur Compounds with Hydrogen Peroxide in the Presence of Crown Ethers

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Abstract—Hydrogen peroxide oxidizes methyl phenyl sulfide and benzothiophene in the presence of crown ethers to the corresponding sulfoxides and sulfones. The oxidation is retarded by amino acids. UV and NMR spectroscopies show that, at the initial stage of oxidation, complexation occurs between crown ether, hydrogen peroxide, and sulfide, as well as between crown ether and amino acid.

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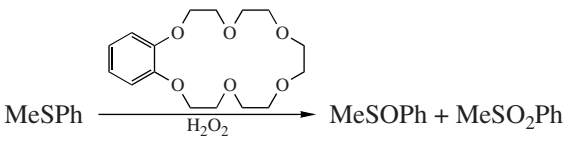
Selective oxidation of sulfides to sulfoxides is an important area in studying oxidation reactions [1–3]. This reaction can be catalyzed by transition metal peroxo complexes with different ligands. In the presence of these complexes, hydrogen peroxide turns out to be many times more efficient than alkyl hydroperoxides. For example, the vanadium catalyst $VO(OR)_3$ form a stronger complex with hydrogen peroxide (peroxovanadate $VO(OR)_2OOH$) than with alkyl hydroperoxide, which is the reason for the choice of hydrogen peroxide as the oxidant [4]. Most methods of peroxide oxidation of sulfides are unsuitable for large-scale use since they involve the formation of environmentally hazardous waste and the use of chlorine-containing solvents [5].

For performing oxidation reactions, catalysts free of transition metals are of interest, for example, 3-cyclodextrines [6–8], which can form complexes with metal cations and organic molecules, and *N*-hydroxyphthalimide in the presence of 1,4-diamino-2,3-dichloroanthraquinone [9–11].

In the present work, we studied whether methyl phenyl sulfide and benzothiohene can be oxidized by hydrogen peroxide in the presence of crown ethers, namely benzo-18-crown-6 (B18C6) and dibenzo-18-crown-6 (DB18C6), in which the cavities are close in size to the cavity of β-cyclodextrine [12].

RESULTS AND DISCUSSION

Our findings are evidence that methyl phenyl sulfide and benzothiophene are rather smoothly oxidized by a 37% aqueous hydrogen peroxide solution in the presence of crown ethers without using transition metal compounds (Scheme 1). GLC analysis of reaction mixtures showed that methyl phenyl sulfide is quantitatively converted within 4 h after the beginning of its oxidation with hydrogen peroxide in the presence of only benzo-18-crown-6 (Table 1).



Scheme 1.

Table 1. Oxidation of methyl phenyl sulfide in the presence of benzo-18-crown-6 (ethanol, 4 h, 40°C)

MeSPh : H_2O_2 ratio	MeSPh : B18C6 ratio	Composition of reaction products, %		
		MeSPh	MeS(O)Ph	$MeSO_2Ph$
1 : 3.6	10 : 1	8	36	56
1 : 3.6	100 : 1	–	91	9
1 : 3.6	500 : 1	4	83	13
1 : 2.4	80 : 1	–	72	28
1 : 2.4	300 : 1	–	49	51

Table 2. Oxidation of methyl phenyl sulfide with hydrogen peroxide at different temperatures (4 h, MeSPh : H_2O_2 = 1 : 3.6)

Crown ether	Temperature, °C	MeSPh : crown ether ratio	Composition of reaction products, %		
			MeSPh	MeS(O)Ph	$MeSO_2Ph$
B18C6	40	10 : 1	8	36	56
B18C6	20	10 : 1	17	19	64
DB18C6	40	100 : 1	90	10	0
DB18C6	20	100 : 1	96	4	0

The course of the oxidation of methyl phenyl sulfide in the presence of crown ethers depends on the reaction temperature (Table 2) and duration, the amount of crown ether, and the amount and the method of addition of the oxidant (hydrogen peroxide), as well as on the presence of an organic ligand capable of complexation with crown ether. An increase in the molar amount of crown ether (Table 1) leads to a decrease in the conversion of sulfide, which can be associated with complexation of crown ether with sulfide. An increase in the amount of hydrogen peroxide by a factor of 1.5 changes only the sulfoxide : sulfone ratio in favor of the latter in the reaction products after the quantitative conversion of the initial sulfide.

A considerable effect on the course of sulfide oxidation is exerted by the presence of an organic ligand in the reaction mixture. Crown ethers are known to form rather stable complexes with molecules containing a free and protonated amino group: amines, amino acids, and their esters [13–15]. We used *L*-alanine as such a ligand, assuming that its interaction with crown ether can considerably influence the chemo- and stereoselectivity of oxidation. Table 3 shows that an increase in the molar content of the ligand (*L*-alanine) in the initial reaction mixture decreases the conversion of sulfide, which can be caused by partial blocking of the catalytic activity of the crown ether due to its complexation with the amino acid. The oxidation of benzothiophene (DB18C6, 45°C, 18 h) quantitatively yields benzothiophene sulfone. The oxidation of dibenzothiophene under the same conditions yields dibenzothiophene sulfone in 11% yield.

Two features of this oxidation are of interest: (1) the reaction proceeds in the presence of crown ether without adding another reagent, and (2) the oxidation is retarded by introducing amino acid into the reaction mixture. To elucidate the catalytic mechanism of crown ethers, we studied their complexation with the other components of the oxidation process—hydrogen peroxide, methyl phenyl sulfide, and amino acid—by UV spectroscopy and NMR. The interaction of macrocyclic ligands with amino acids has been studied [16]. It has been shown that, in aqueous solutions, a complicated receptor containing the benzo-15-crown-5 moiety forms rather stable 1 : 1 complexes with a number of small model peptides containing three to five amino acid residues. The complex formation constants are in the range 10^4–10^5 (no clear preference for a certain type of amino acid sequence was observed).

In our UV spectroscopic studies, a solution of methyl phenyl sulfide (or benzothiophene) in an appropriate solvent was gradually added to a crown ether solution in the same solvent. Figure 1 shows that titration of dibenzo-18-crown-6 with methyl phenyl sulfide is accompanied by a shift of absorption maxima: for methyl phenyl sulfide, from 255 to 258 nm; and for the crown ether, from 238 to 234 nm and from 278 to 276 nm. Upon titration of dibenzo-18-crown-6 with benzothiophene (Fig. 2), the strongest peak in the spectrum of the latter (236 nm) is very close to the peak of the crown ether (238 nm), but at the 1 : 8 molar ratio, the peak of the pure crown ether at 277 nm is sharply shifted to 267 nm due to complex formation. These findings are evidence of the formation of complexes between crown ethers and molecules of organosulfur compounds.

Comparison of the ^1H NMR spectrum of pure benzo-18-crown-6 (in $CDCl_3$) with the spectrum of a mixture obtained by adding hydrogen peroxide shows a downfield shift and broadening of the signals of both the aromatic protons and the protons of the macrocyclic crown ether ring. These spectral changes are clear evidence of complexation of the crown ether molecule with hydrogen peroxide through the formation of

Table 3. Oxidation of methyl phenyl sulfide in the presence of dibenzo-18-crown-6 with additions of the ligand (*L*-alanine, 6 h, 30°C)

MeSPh : DB18C6 : *L*-alanine ratio	Composition of reaction products, %		
	MeSPh	MeS(O)Ph	$MeSO_2Ph$
5 : 1 : 1	40	34	27
10 : 1 : 2	36	29	35
50 : 1 : 1	37	15	48
100 : 1 : 1	26	6	68

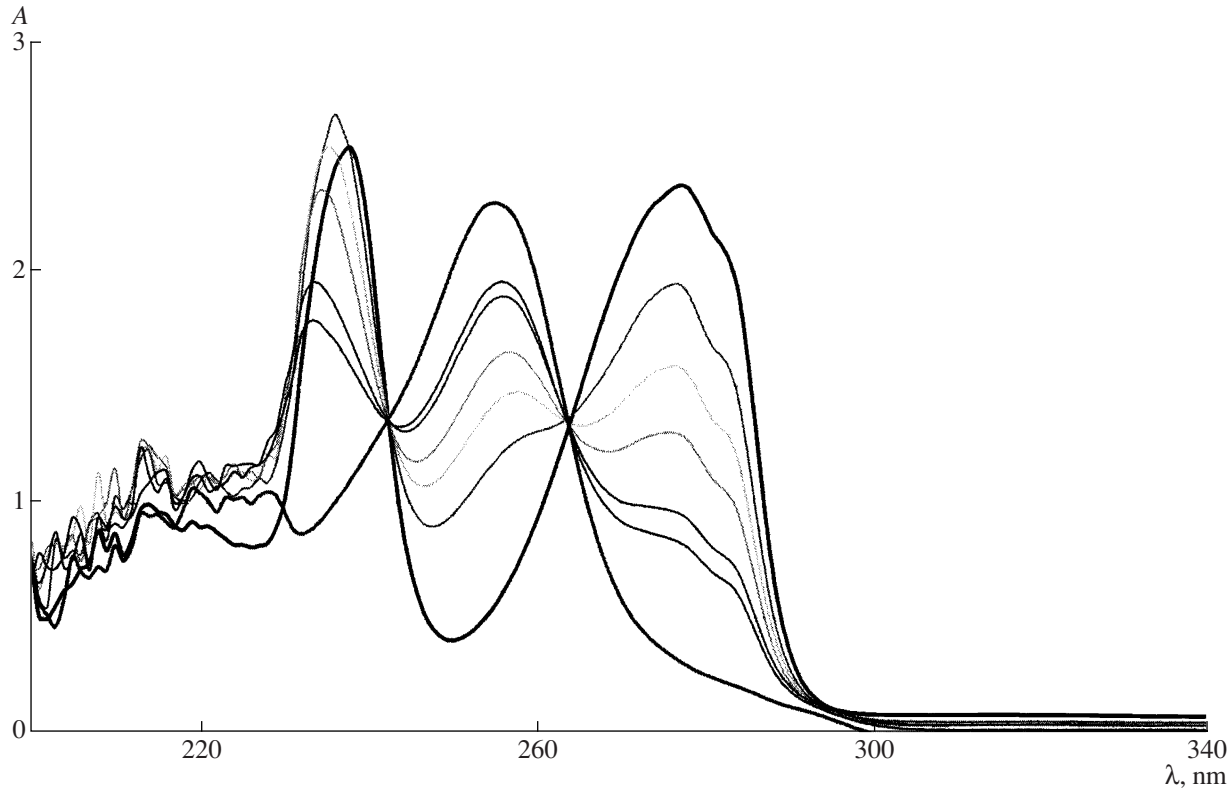


Fig. 1. Titration of dibenzo-18-crown-6 with methyl phenyl sulfide.

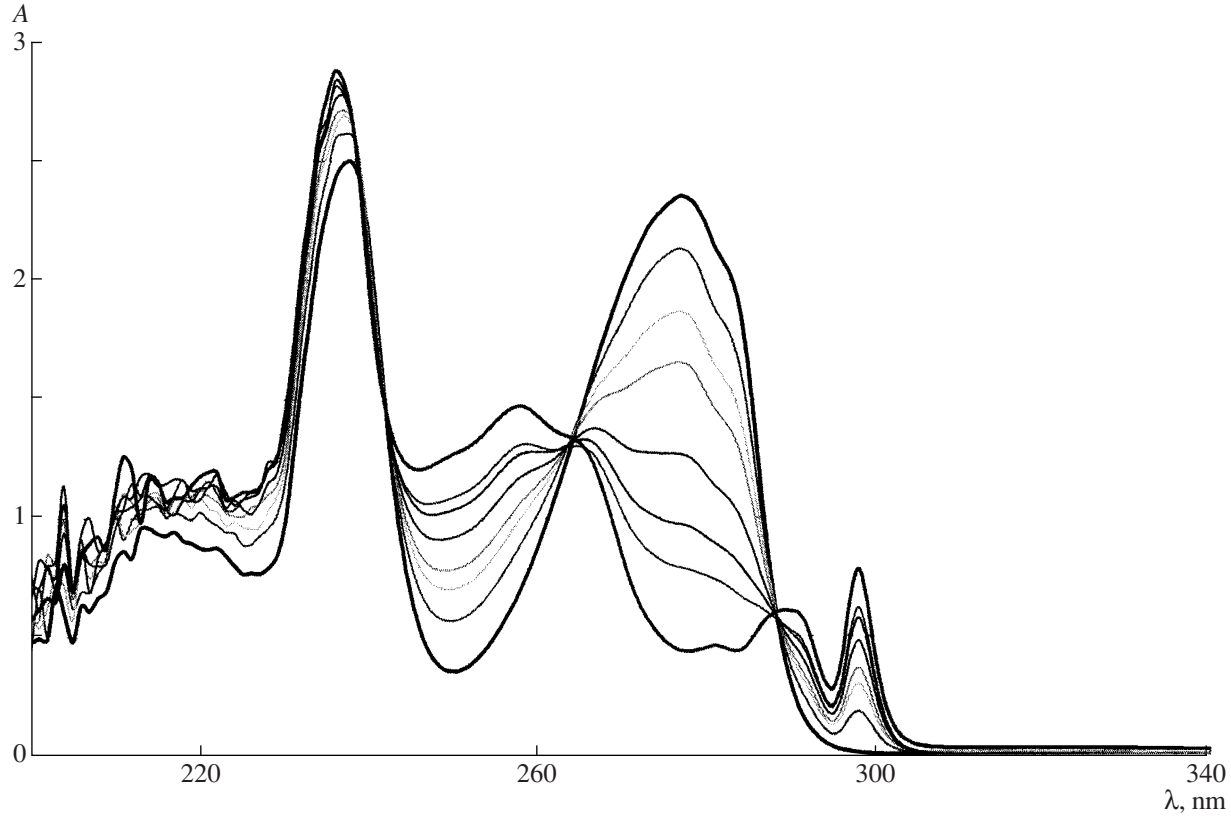


Fig. 2. Titration of dibenzo-18-crown-6 with benzothiophene.

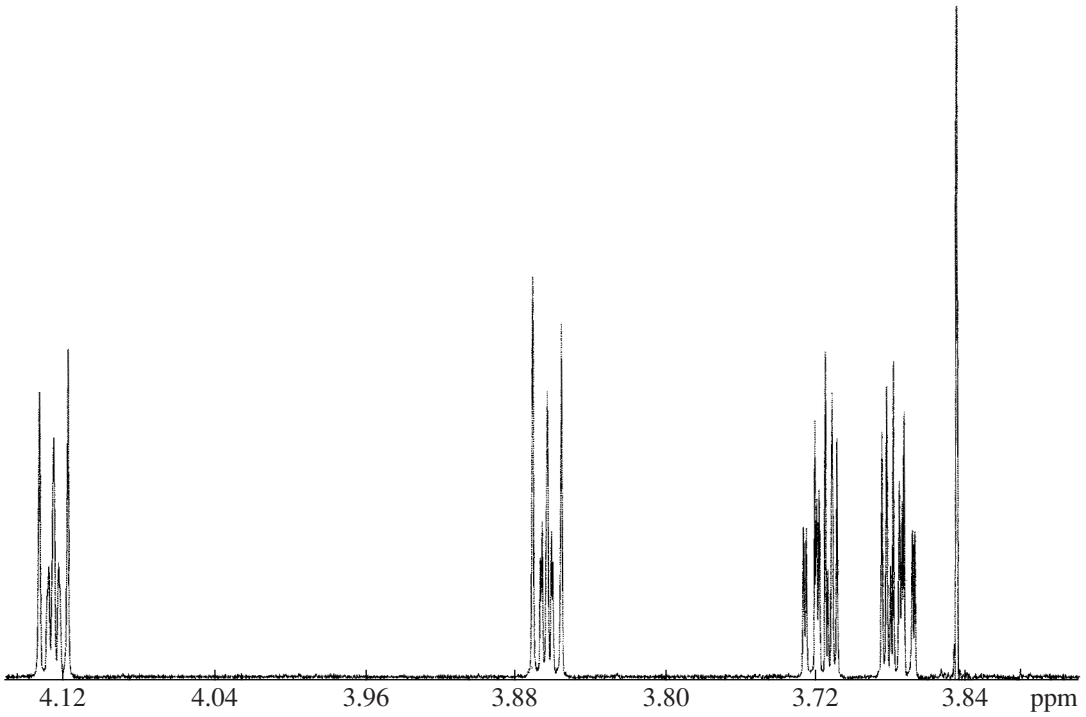
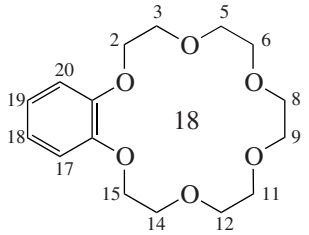


Fig. 3. ^{1}H NMR spectrum of benzo-18-crown-6 (27.2 mM solution in CD_3OD) at 303 K. The region of aliphatic protons is shown.

hydrogen bonds involving the O atoms of the macrocyclic ring and the H atoms aid hydrogen peroxide. The introduction of methyl phenyl sulfide into the system does not lead to significant changes in the NMR spectrum, although it is worth noting that the centers of multiplets are shifted by 0.01–0.02 ppm, which can also point to complexation of crown ether with methyl phenyl sulfide.

To obtain more detailed information on the complexation of macrocyclic ligands with amino acids in methanol solutions, we recorded the ^{1}H NMR spectra of *D*-alanine and benzo-18-crown-6 and their mixtures with various concentration ratios (NMR titration). In titration experiments, the alanine concentration was maintained approximately constant while the crown ether concentration was varied. The ^{1}H NMR spectrum of *D*-alanine is rather simple: the quartet of the methine proton at 3.5638 ppm and the doublet of the methyl group at 1.4497 ppm. Figure 3 shows the aliphatic region of the ^{1}H NMR spectrum of benzo-18-crown-6.

As might be expected, the ^{1}H NMR spectrum of this symmetric molecule shows the signals due to five types of methylene groups. The multiplet at 4.1329 ppm corresponds to two equivalent methylene groups 2-CH_2 and 15-CH_2 (Scheme 2). The multiplet at 3.8700 ppm corresponds to two equivalent methylene groups 3-CH_2 and 14-CH_2.



Numbering of atoms in benzo-18-crown-6

Scheme 2.

The signals have a fairly well resolved multiplet structure (the signal pattern corresponds to the AA'XX' spin system). A characteristic feature of this type of spin system is that both multiplets have virtually the same structure; it is as if they repeat each other. Each multiplet is symmetric with respect to its center (coincides with the chemical shift). The multiplets at 3.7205 ppm (corresponds to two equivalent methylene groups 5-CH_2 and 12-CH_2) and 3.6846 ppm (corresponds to the equivalent methylene groups 6-CH_2 and 11-CH_2) have an analogous structure. These multiplets correspond to the strongly coupled case since they have close chemical shifts. Both multiplets are described by the AA'BB' spin system. An important feature of this part of the spectrum is that the multiplet structure of these signals is symmetric (it is as if the lines in the spectrum are reflected with respect to the center of their spectral density).

As might be expected, the signal due to the equivalent methylene groups 8-CH_2 and 9-CH_2 of benzo-18-

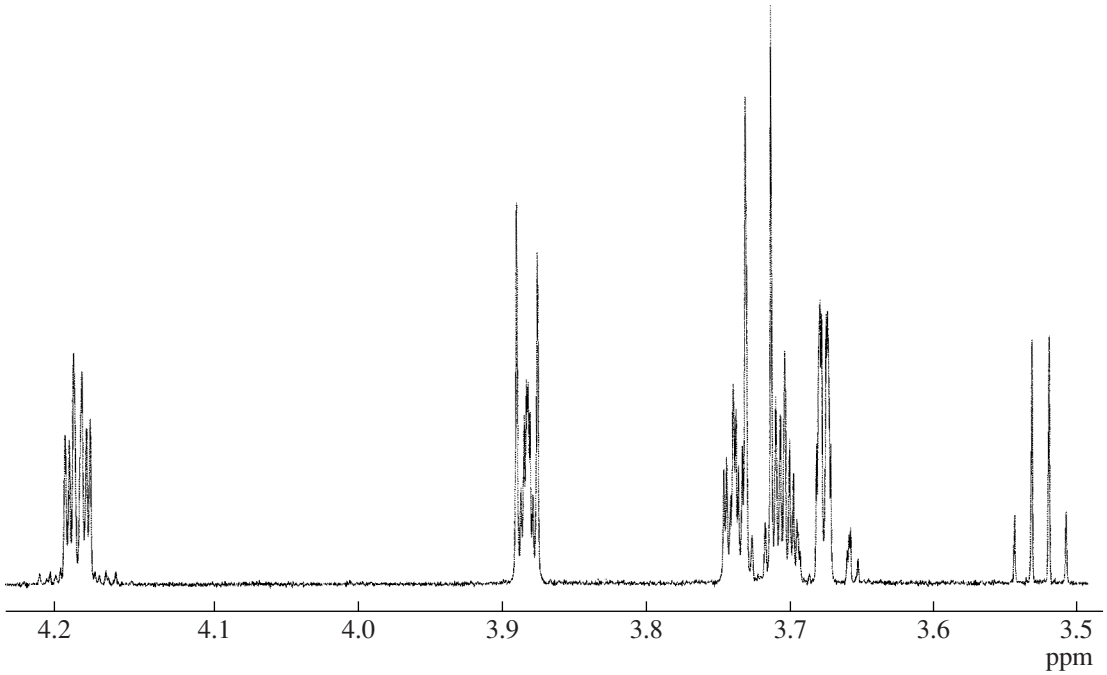


Fig. 4. ^{1}H NMR spectrum of a mixed solution of benzo-18-crown-6 (6.6 mM solution in CD_3OD) and *D*-alanine at 303 K. The region of aliphatic protons is shown.

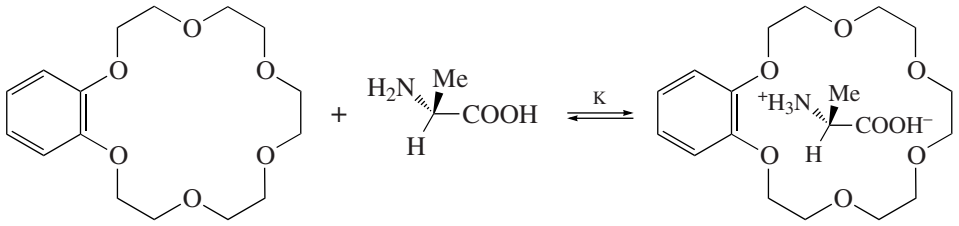
crown-6 at 3.6520 ppm is a singlet. A somewhat unexpected pattern is observed for mixed solutions containing *D*-alanine and benzo-18-crown-6. It is evident that the far spin coupling of the 8-CH_2 and 9-CH_2 protons to distant protons (for example, of the 5-CH_2 and 6-CH_2 protons) in this macrocycle can be neglected.

Fragmentary data are available concerning complexation of protonated amines, amino acids, and peptides in the zwitterionic form [16, 17]. Some amino acids containing a protonated amino group R–NH_3^+ form very strong complexes with crown ethers, the stability constant of a complex in an aqueous solution being on the order of 10^6 M^{-1} [18]. It is of interest to estimate the stability parameters of such complexes in a neutral methanol solution. The ^{1}H NMR spectrum of a mixed solution in methanol-d_4 containing both the amino acid *D*-alanine and benzo-18-crown-6 is shown in Fig. 4. The chemical shifts and multiplicity of the crown ether signals depend on the mixture composition (Table 4). Figure 4 shows that the multiplet pattern of the crown ether changes considerably when approximately one equivalent of the amino acid is added. First

Table 4. Oxidation of methyl phenyl sulfide in the presence of dibenzo-18-crown-6 with additions of the ligand (*L*-alanine, 6 h, 30°C). Chemical shifts of the aliphatic protons of benzo-18-crown-6 and *D*-alanine in mixed solutions in CD_3OD (303 K). Concentrations of solutions of the crown ether (*C*(B18C6)) and *D*-alanine (*C*(*D*-Ala)) are in mmol/L

C(B18C6)	*C*(*D*-Ala)	Crown ether fragments						*D*-alanine fragments	
		2-CH_2	3-CH_2	5-CH_2	6-CH_2	8-CH_2	9-CH_2	CH	CH_3
–	7.9	–	–	–	–	–	–	3.5638	1.4497
3.7	8.3	4.2029	3.8856	3.7359	3.7024	3.6860	3.6684	3.5456	1.4200
6.6	8.0	4.1940	3.8824	3.7361	3.7074	3.6854	3.6699	3.5256	1.3860
8.9	9.4	4.1893	3.8815	3.7380	3.7082	3.6866	3.6686	3.5184	1.3655
15.1	10.1	4.1799	3.8791	3.7371	3.7051	3.6823	3.6695	3.4905	1.3258
27.3	11.2	4.1665	3.8758	3.7327	3.6997	3.6752	3.6636	3.4679	1.2876
52.7	12.5	4.1527	3.8721	3.7284	3.6928	3.6681	3.6568	3.4527	1.2608
27.2	–	4.1329	3.8700	3.7205	3.6846	3.6520	3.6520	–	–

of all, the multiplet structure of the signals of the 8-CH_2 and 9-CH_2 protons remote from the benzene ring transforms into a complicated multiplet. The multiplet structure of the other four signals of methylene groups also changes: the symmetric multiplets corresponding to the AA'XX' (pairs of the equivalent methylene groups 2- and 3-CH_2 and 14- and 15-CH_2) and AA'BB' (pairs of the equivalent methylene groups 5- and 6-CH_2 and 11- and 12-CH_2) spin systems transform to asymmetric multiplets in the spectrum of the mixture. These effects can be interpreted in terms of formation of a rather strong complex of benzo-18-crown-6 and *D*-alanine. It is worth noting that the lines in the NMR spectrum are rather narrow (Fig. 4); therefore, we may conclude that complex formation (Scheme 3) is rapid on the NMR time scale.



Scheme 3.

Analysis of the titration curves allows us to estimate the stability constants of the complex of benzo-18-crown-6 with *D*-alanine at about 200 M^{-1}, which is considerably lower than the constant for analogous complexes in water. In conclusion, it should be stated that the structure of the crown ether in the rather stable complex with *D*-alanine becomes chiral (since the methylene protons in the complex become diastereotopic). Our NMR and UV spectroscopic data allow us to assume that, at the early stage of the oxidation reaction, the crown ether, hydrogen peroxide, and sulfide are gradually bound in a common complex.

EXPERIMENTAL

Commercial methyl phenyl sulfide, benzothiophene, dibenzothiophene, benzo-18-crown-6, dibenzo-18-crown-6, and 37% hydrogen peroxide were used as purchased. The ^1H NMR spectra were recorded on a Bruker Avance-600 spectrometer operating at 600.13 MHz. Chemical shifts were reported on the δ scale (ppm) from HMDS (0.05 ppm).

Gas–liquid chromatographic (GLC) analysis was carried out on a Tsvet 500 chromatograph with a flame ionization detector on a column (L = 25 m, d = 0.0025 m) with an SE-30 stationary phase using temperature programming in the range from 180 to 230°C and nitrogen as the carrier gas.

Gas chromatography/mass spectrometry analysis was carried out on a Finnigan MAT 112S mass spectrometer (EI, 70 eV). Gas chromatographic separation was carried out on a quartz capillary column (L = 50 m, d = 0.25 mm) with a DB-1 nonpolar liquid phase with temperature programming from 40°C (5 min) to 250°C at a rate of 5 K/min.

Oxidation in the Presence of Crown Ethers

Crown ether (0.25 mmol) was added to 15 mL of C_2H_5OH, the resulting solution was stirred for 15 min at 40°C, and then methyl phenyl sulfide (1.25 mmol) and 37% hydrogen peroxide (1 mL) were added. The reaction mixture was stirred for the necessary period of time. The composition of the reaction mixture was monitored by TLC (acetone–hexane (4 : 1) as the eluent). After the end of the reaction, a hydrogen peroxide excess was neutralized by adding triphenylphosphine, and the reaction products were analyzed by GLC.

Oxidation in the Presence of Crown Ethers with Addition of the Ligand L-Alanine

Crown ether (0.25 mmol) and the ligand (0.25 mmol) were added to 15 mL of C_2H_5OH, the resulting solution was stirred for 15 min at 40°C, and then methyl phenyl sulfide (1.25 mmol) and 37% hydrogen peroxide (1 mL) were added.

The reaction mixture was stirred for the necessary period of time. The composition of the reaction mixture was monitored by TLC (acetone–hexane (4 : 1) as the eluent). After the end of the reaction, a hydrogen peroxide excess was neutralized by adding triphenylphosphine, and the reaction products were analyzed by GLC.

ACKNOWLEDGMENTS

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