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Macrocyclic Oligo-ethers Related to Ethylene Oxide

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An improved preparative method for cyclic oligo-ethers consisting of five or more $-CH_2CH_2$-units has permitted conformational studies of these rings as such and as cation complexes. From IR-spectroscopy it is concluded that the 18-ring hexa-ether adopts a D_{3d} conformation when complexing alkali cations, but an entirely different one when crystallizing alone. The 24-ring octa-ether may have nearly the same conformation in its complex and in the salt-free crystal.

In a preliminary publication[1] we have reported on a modification of the Williamson ether synthesis which has allowed the preparation of macrocyclic oligo-ethers from oligo-ethyleneglycols in an over-all yield improved by a factor of 150 as compared with the method described earlier by Pedersen.[2,3] In this paper we present the synthetic and analytical details, as well as infrared-spectroscopic studies of the ring conformations.

SYNTHESIS AND CHEMICAL PROPERTIES

$$HO-\left(-CH_2CH_2O-\right)_{n-m}-H + TsO-\left(-CH_2-CH_2O-\right)_m-Ts \xrightarrow[KOBu^t/benzene]{} \left[\overline{\left(-CH_2CH_2O-\right)_n}\right] + 2KOTs$$

In the general reaction scheme the glycolditosylate component must be higher than ethyleneglycolditosylate ($m > 1$), which tends to undergo elimination reactions with base. Otherwise, any combination can be used, but medium rings, the cyclic trimer and tetramer, were never obtained, not even under high-dilution conditions. Instead, the expected doubling to the cyclic hexamer and octamer occurs.

In order to be able to isolate these cyclic ethers, their strong tendency to complex alkali cations[2–6] must be recognized and can then be used to advantage in the purification. The ethers themselves are liquids or low-melting solids, while their complexes, particularly with potassium salts, are well

crystalline. The cyclic hexa-ether,* being an 18-membered ring, is the strongest complexing agent for alkali cations, particularly when the cation is potassium or rubidium.[3,6] The nature of the anion seems unimportant, and even potassium fluoride dissolves in chloroform when one equivalent of cyclic hexamer is added. During the synthesis a part of the potassium tosylate formed in the reaction is complexed by the ring (1:1). The excess of potassium tosylate is filtered off and the benzene solution concentrated until the complex crystallizes out in needles, m.p. 164°. This complex is soluble both in organic solvents and in water, and can be extracted completely and unchanged out of water with chloroform. The salt-free cyclic ether is liberated by adsorbing the complex on an alumina column and eluting with a benzene-chloroform mixture (2:1). If more chloroform is used (1:1) the complex is eluted unchanged.

The cyclic ether cannot be liberated from its complex by simple heating. The anion has apparently become such a strong nucleophile that it attacks the ring and destruction occurs. On the other hand, the uncomplexed ethers are perfectly stable and can be distilled and analysed by gas-chromatography.

This analytical method, as well as NMR-spectroscopy in the presence of the paramagnetic tris(dipivalomethanato)europium,[7] both applied to the crude ether mixture, revealed that although the yield of isolated product (Table 2) was highest for the hexamer, the actual yield in the reaction was higher for the heptamer. This seemed the more surprising since the heptamer forms the less stable complex with potassium salts, so that a template effect should have favoured the hexamer. Two competition reactions were then run, one from tetraethyleneglycolditosylate and a mixture of three glycols so as to give cyclic hexa-, hepta-, and octamer, the other from triethyleneglycolditosylate and the same glycol mixture so as to give the cyclic penta-, hexa-, and heptamer. The results (Exp. part) show a significant preference for the formation of the cyclic hepta-ether. The reason is not clear, but it may be that the intermediate hepta-ethyleneglycolmonotosylate folds around a potassium cation through complex formation with its six ether oxygens in such a way that the ends become well oriented for cyclization.

Since the main by-products in this cyclic ether synthesis are open-chain polyethers with *t*-butoxy end-groups, it might seem logical to replace potassium *t*-butoxide by other strong bases. With sodium hydride this led, however, to difficulties in the isolation.

The relative strength of the complexes between these cyclic ethers and salts of alkali and alkaline earth metals have been determined by Pedersen.[3] The complexes were, however, never isolated for this simplest series of unsubstituted ethers. We have therefore prepared from the cyclic hexamer not only the complexes of the alkali- and alkaline-earth tosylates whose stoichiometry can be particularly easily determined by NMR-spectroscopy since the anion carries protons, but also of the alkali isothiocyanates and of the potassium halides (Table 3). They all turned out to be 1:1 complexes, except the least stable ones with sodium and calcium tosylate. With lithium tosylate the complex is so

* This compound (1,4,7,10,13,16-hexaoxacyclooctadecane) is called 18-crown-6 by Pedersen.[2] Use of the "crown" nomenclature for constitution should in our opinion be discouraged since it is based on an arbitrary conformation, lacks generality and is unnecessary.

little stable that it dissociates in solution by slight warming to precipitate the salt, which redissolves on cooling. Surprisingly, the thermodynamically less stable alkaline earth complexes showed the slowest exchange rate. Thus, their NMR-spectra at room temperature showed separate lines for ring protons belonging to the complexed ring and those belonging to an excess of cyclic ether, while mixtures of alkali complexes and excess of cyclic ether showed a single line of intermediate chemical shift.

CONFORMATIONAL STUDIES

We have already reported [1] that these macrocyclic oligo-ethers give no low-temperature NMR-spectrum down to $-130°$, and that their observed dipole moments all lie around 3 D, and thus are not very different from the values calculated for free relative orientation of the ether dipoles. Cyclic ethers of ethyleneglycol type seem therefore to be quite flexible, and this is in striking contrast with the zero dipole moment observed [8] for the cyclic tetraether of trimethylene glycol type suggesting exceptional rigidity. Conformational homogeneity and rigidity of such tetra-ethers were also reflected in their

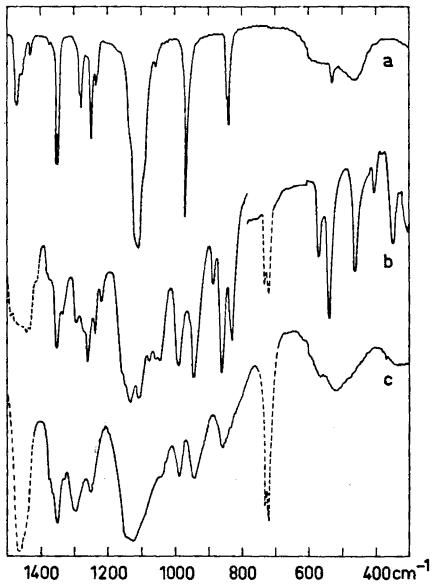

Fig. 1. Infrared spectra of 1,4,7,10,13,16-hexaoxacyclooctadecane as crystalline KBr complex (a), alone as solid at $-60°$ (b), and alone as liquid at 50° (c). Dashed curves indicate bands due to polyethylene film used to protect the KBr windows.

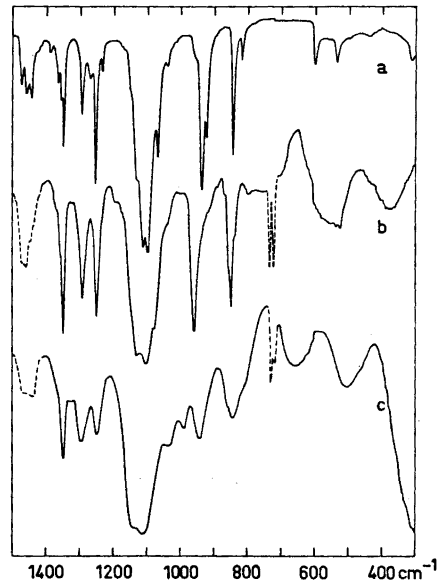

Fig. 2. Infrared spectra of 1,4,7,10,13,16 19,22-octaoxacyclotetracosane as crystalline KBr complex (a), alone as solid at $-60°$ (b), and alone as liquid at 50° (c). Dashed curves indicate bands due to polyethylene film used to protect the KBr windows.

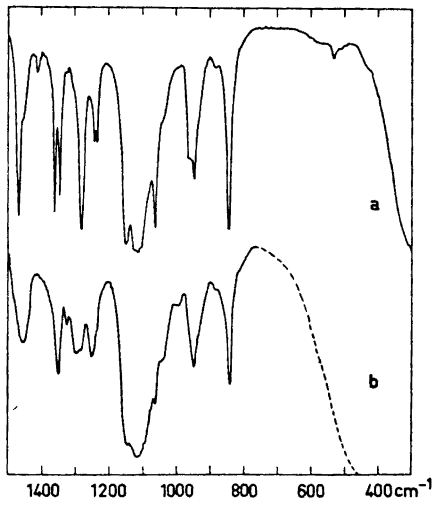

Fig. 3. Infrared spectra of polyethylene glycol (PEG 1540) in the crystalline state at 30° (a) and as molten film at 50° (b).

infrared spectra, which were absolutely identical in solid and solution and consisted of very sharp lines.

The infrared spectrum of the cyclic hexa-ether of ethyleneglycol type in the complexed form, for example when ground and pressed with potassium bromide (Fig. 1), is strikingly similar to the spectrum of crystalline polyethyleneglycol (Fig. 3), which is known [9] to have helically arranged monomer units $-O-CH_2-CH_2-O-$ in the *anti,gauche,anti* conformation (Fig. 6). We therefore conclude that, with a central cation present, the cyclic hexamer adopts the D_3d ring conformation shown in Fig. 4a, which is the only diamond lattice conformation able to accomodate six identical *anti,gauche,anti* monomer units.[10] One "equatorial" lone pair from each ether oxygen is then favourably oriented towards the center. There is some resemblance of this conformation to the crystal conformation of both uncomplexed [11] and complexed [11,12] 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclo-octadeca-2,11-diene, but large parts of these ring conformations are of course imposed by the aromatic systems.

In the absence of a central cation, the orientation of lone pairs as shown in Fig. 4a seems to give repulsion, since the crystalline hexamer alone gives an infrared spectrum which is entirely different (Fig. 1). Instead of two bands in the CH_2-rocking region at $800-1000$ cm^{-1}, five are now visible, suggesting that three types of monomer units are present. A final identification cannot be made on this basis, but the compact, rectangular conformation found to be favoured in the crystal for cyclo-octadecane itself would in fact be able to accommodate two each of two different *anti,gauche,gauche* monomer units and one *anti,anti,anti* monomer unit (Fig. 4b). In the liquid state the infrared bands become very broad (Fig. 1) either because of increased vibrational amplitudes or the admixture of additional conformers. The former possibility is favoured,

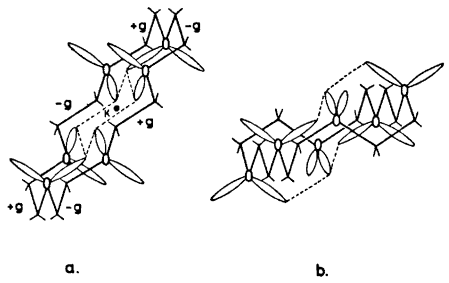

Fig. 4. Proposed conformations of 1,4,7,10,13,16-hexaoxacyclooctadecane in its complexes with potassium salts (a) and in the salt-free crystal (b).

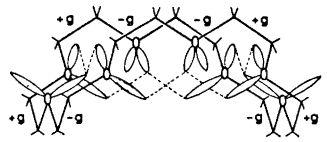

Fig. 5. Proposed conformation of 1,4,7,10,13,16,19,22-octaoxacyclotetracosane in its complexes with potassium salts as well as in the salt-free crystal.

since any conceivable diamond lattice conformation[10] should have zero dipole moment if it were rigid. The very similar values of the melting entropy observed (Table 2) for this compound and for cyclo-octadecane [10] and its 1,1,10,10-tetramethyl derivative [10] suggest on the other hand that the ether behaves much like the hydrocarbon and is a conformer mixture.

Also the cyclic octamer is able to arrange eight identical *anti,gauche,anti* monomer units on a diamond lattice 24-ring conformation of D_2d symmetry (Fig. 5). Since the infrared spectrum of its potassium bromide complex (Fig. 2) is also rather similar to the spectrum of the crystalline polymer (Fig. 3), we believe that the octamer has a complex conformation close to the one shown in Fig. 5. In this case, however, the salt-free cyclic ether has in the crystalline state an infrared spectrum which is not very different, so that essentially the same conformation may be present. Conformational homogeneity is also supported by the very slight increase of melting entropy when compared with the smaller 18-ring (Table 2).

It is tempting to propose that one reason for the stronger complexing ability of the 18-ring with cations of various sizes,[6] is that it has a good diamond lattice conformation for complexing which becomes unstable when the cation is absent, since all six oxygen atoms have one "inner" lone-pair squeezed in between two neighbouring lone-pairs (Fig. 4a). The 24-ring has got a diamond-lattice conformation which is less tight for complexing, but without the cation it also becomes relatively less unstable since only four of the oxygen atoms

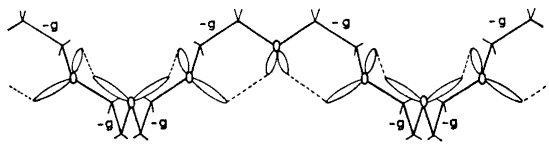

Fig. 6. The conformation of polyethylene-glycol in the crystalline state.

have "inner" lone pairs squeezed between two neighbouring lone pairs (Fig. 5); the remaining four have the same surroundings as in the stable helical polymer. The driving force for complexing is therefore reduced. A support for this view comes from the observation that the conformationally stable 16-ring tetraether [8] shows little complexing power even for lithium salts.

The cyclic penta- and hepta-ethers are 15- and 21-membered rings, and can have no diamond-lattice conformation. It may be significant that these are not crystalline.

EXPERIMENTAL

General preparative procedure for oligoethyleneglycol ditosylates. The glycol (0.1 mol) was dissolved in pyridine (80 ml) and *p*-toluenesulphonyl chloride (38.5 g = 0.2 mol) added portion-wise over 2 h as powder to the stirred and ice-cooled solution. Stirring and cooling was then continued for another 4 h. The mixture was left overnight, then poured on ice (100 g) and further diluted with water (50 ml). Precipitated ditosylate was filtered off and washed on the filter with water (160 ml). Recrystallization from ethanol (200 ml) gave the pure ditosylate. Yields and data for individual compounds are presented in Table 1.

Since tetraethyleneglycolditosylate is liquid, it was isolated in a different manner. After the reaction mixture had been poured on ice, the solution was made acidic with hydrochloric acid (18 %) and extracted with chloroform. The organic layer was washed with sodium carbonate and then with water and dried over magnesium sulphate. After evaporation of chloroform at reduced pressure an oil was left which analysed correctly (Table 1).

Table 1. Data for oligoethyleneglycol ditosylates.

Ditosylate of	Yield %	M.p. °C	Found C	Found H	Found S	Analysis Formula	Calc. C	Calc. H	Calc. S
Diethylene-glycol	70	98	51.83	5.53	15.34	$C_{18}H_{22}O_7S_2$	52.16	5.35	15.47
Triethylene-glycol	75	78	52.23	5.73	14.01	$C_{20}H_{26}O_8S_2$	52.17	6.08	13.91
Tetraethylene-glycol	67	oil	52.80	6.05	12.49	$C_{22}H_{30}O_9S_2$	52.57	6.02	12.76

General preparative procedure for cyclic oligo-ethers. Potassium (9.8 g = 0.25 mol) was added to *t*-butanol (200 ml) and the resulting solution of *t*-butoxide diluted with benzene (200 ml). To this stirred and heated solution was dropped over 5 h a mixture of the glycol (0.1 mol) and the ditosylate (0.1 mol) dissolved in benzene (2000 ml). Precipitated potassium tosylate was filtered off and washed with warm chloroform, and all solvents evaporated in a rotary evaporator. The cyclic polyether was isolated in one of the following two ways:

Method A. The potassium tosylate complex of the cyclic ether crystallized during evaporation and was filtered off. To liberate the cyclic ether, the complex was adsorbed on an alumina column (3.5 × 22 cm) packed in benzene, and the ether eluted with a mixture of chloroform and benzene (1:2). (More chloroform in the mixture elutes the complex).

Table 2. Data for cyclic oligo-ethers.

Cyclic ether	Glycol used	Glycol ditosylate used	Isolation procedure	Preparative yield, %	M.p. °C	Found C	Found H	Analysis Formula	Calc. C	Calc. H
Pentaether	Triethylene	Diethylene	B	20[a]	liq.	53.80[b]	9.21	$C_{10}H_{20}O_5$	54.53	9.15
Hexaether	,,	Triethylene	A	33	39[c]	54.64	8.91	$C_{12}H_{24}O_6$	,,	,,
Heptaether	,,	Tetraethylene	B	26[a]	liq.	54.31	9.03	$C_{14}H_{28}O_7$	,,	,,
Octaether	Tetraethylene	,,	B	15[a]	19[d]	54.26	9.15	$C_{16}H_{32}O_8$	,,	,,

[a] Actual yield shown by gas-chromatography to be substantially higher. [b] Hygroscopic. [c] $\Delta H_m = 8.13$ kcal/mol; $\Delta S_m = 26.1$ e.u. [d] $\Delta H_m = 8.24$ kcal/mol; $\Delta S_m = 28.2$ e.u.

Method B. The semi-solid residue left after evaporation was adsorbed on an alumina column (2 × 50 cm) packed in benzene, and eluted first with benzene and then with chloroform. All solvents were evaporated in a rotary evaporator and a salt-free oil was left. This oil was adsorbed on an alumina column (2 × 50 cm) packed in hexane. Elution with hexane removed open-chain polyethers with *t*-butoxy end-groups. The pure cyclic ether was finally eluted with a mixture of chloroform and benzene (1:1). Yields and data for individual compounds are presented in Table 2.

Warning! The cyclic ethers attack KBr and other alkali halide materials used for IR-spectroscopy.

Competition reactions. The high analytical yield of heptamer was checked by running the above synthesis with one ditosylate component and three different diol components in a competitive reaction. The reaction mixture was analysed by gas chromatography of the uncomplexed cyclic products. A first experiment was run with 0.18 mol of tetraethyleneglycolditosylate and 0.06 mol each of diethyleneglycol, triethyleneglycol, and tetraethyleneglycol. A second experiment was run with 0.18 mol of triethyleneglycolditosylate and 0.06 mol each of the same diol components. The results showed a significant preference for the formation of heptamer:

	$n=5$	$n=6$	$n=7$	$n=8$
First run		29 %	44 %	27 %
Second run	30 %	31 %	39 %	

Infrared spectroscopy. The infrared spectra of the uncomplexed ethers were run on films between KBr-discs protected with polyethylene films. To obtain the infrared spectra of the crystalline hexamer and octamer, a RIIC low-temperature cell was used, cooled with methanol/dry-ice mixture.

The infrared spectra of the complexed ethers were recorded as KBr-pellets. The pentamer and the hexamer were ground and pressed with potassium bromide, but for the heptamer and octamer this procedure did not give a pellet of satisfactory quality. Instead in these cases the CsI-complex was ground with potassium bromide and pressed.

Preparation of CsI complex. To a solution of the cyclic ether in methylene dichloride was added an excess of cesium iodide and the mixture left overnight. The solution was then filtered and left to evaporate in an open beaker. The complex crystallized at near dryness. With cyclic hepta-ether white crystals of a 1:1 complex were formed, m.p. 124° (dec.) (Found: C 29.67; H 5.19. Calc. for $C_{14}H_{28}O_7CsI$: C 29.57; H 4.93). With cyclic octa-ether yellowish crystals, also of a 1:1 complex, were obtained, m.p. 115° (dec.) (Found: C 31.82; H 5.50. Calc. for $C_{16}H_{32}O_8CsI$: C 31.37; H 5.23.)

Preparation of cyclic hexaether complexes. These complexes were prepared as described above from mixtures of the cyclic hexaether and various salts: *p*-toluenesulphonates, isothiocyanates and halides. The properties of the complexes are given in Table 3.

Table 3. Data for cation complexes with 1,4,7,10,13,16-hexaoxacyclooctadecane.

Salt	Ratio hexaether to salt	M.p. °C	Found C	H	S	N	Analysis Formula	Calc. C	H	S	N
Na tosylate	3:2	ca. 40 dec.	48.60	7.89	4.65		$C_{50}H_{86}O_{24}S_2Na_2$	50.83	7.34	5.43	
K ,,	1:1	164	47.95	6.47	6.88		$C_{19}H_{31}O_9SK$	48.10	6.54	6.75	
Rb ,,	1:1	153	44.07	6.20	6.32		$C_{19}H_{31}O_9SRb$	43.80	5.99	6.15	
Cs ,,	1:1	130	40.51	5.47	5.64		$C_{19}H_{31}O_9SCs$	40.15	5.50	5.64	
Ca ,,	2:1	dec.	47.91	6.61	7.08		$C_{38}H_{62}O_{18}S_2Ca$	50.10	6.86	7.04	
Sr ,,	1:1	,,	43.78	5.69	9.20		$C_{26}H_{38}O_{12}S_2Sr$	44.97	5.52	9.24	
Ba ,,	1:1	,,	41.83	5.22	8.62		$C_{26}H_{38}O_{12}S_2Ba$	41.97	5.15	8.62	
$NaNCS.H_2O$	1:1	142	43.03	7.15		3.92	$C_{13}H_{26}O_7SNNa$	42.97	7.16		3.85
KNCS	1:1	190	42.90	6.26		3.97	$C_{13}H_{24}O_6SNK$	43.12	6.65		3.87
$RbNCS.H_2O$	1:1	193	38.60	5.88		3.62	$C_{13}H_{26}O_7SNRb$	38.85	6.47		3.48
$CsNCS.H_2O$	1:1	200	34.69	5.35		3.10	$C_{13}H_{26}O_7SNCs$	34.74	5.79		3.11
KF	1:1[a]	57	45.06	8.37			$C_{12}H_{24}O_6KF$	44.72	7.45		
$KCl.H_2O$	1:1[a]	98	40.14	7.42			$C_{12}H_{26}O_7KCl$	40.38	7.29		
KBr	1:1[a]	196	37.32	7.83			$C_{12}H_{24}O_6KBr$	37.59	6.27		
KI	1:1[a]	>260	33.75	6.04			$C_{12}H_{24}O_6KI$	33.48	5.58		

[a] Hygroscopic.

Added in proof: Professor J. Dunitz has very recently shown by X-ray crystallography that the uncomplexed 1,4,7,10,13,16-hexaoxacyclooctadecane (Fig. 4b) has a less symmetrical conformation than the one we have proposed.[13]

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