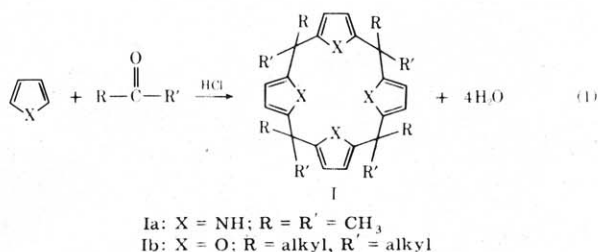


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The experiment described below is designed to acquaint the student with a macromolecular synthesis of a crown ether type compound. The starting materials are readily available and the product, a cyclic polyether, belongs to a class of compounds that has aroused the interest of chemist and biologist alike. The experiment has been successfully carried out many times by sophomore organic students.

Introduction

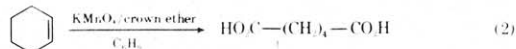
In 1886 Baeyer discovered that pyrrole could be condensed with acetone in the presence of hydrochloric acid as a catalyst to yield a porphyrin-like macrocycle, structure Ia (1).



Subsequent investigations revealed that macrocyclic polyethers (Ib) were formed when furan and various ketones were condensed via a modified Baeyer procedure, (2-5). The practical importance of macrocyclic polyethers was not realized until 1967, when Charles J. Pedersen of DuPont reported that Group IA metal salts could be dissolved in non-polar solvents in the presence of these compounds (6).

Many macrocyclic polyethers have now been synthesized, with the majority containing from four to twenty oxygen atoms separated from one another by two or more carbon atoms (7, 8). The macrocycles contain a hydrophilic cavity into which the cations are selectively drawn, becoming attached to the oxygen atoms by ion-dipole bonds. The hydrophobic exteriors of the complexes afford them solubility in non-polar solvents and the ability to be transported through biological membranes. Stoichiometric 1:1 salt-polyether complexes are quite common. Figure 1.² Group IA and IIA cations, ammonium, alkylammonium and some transition metal ions form such complexes (7). Among the factors affecting the formation and stability of the complexes, the number of oxygens in the ring, and the relative sizes of the cation and the cavity appear to be important (8).

One interesting application of these complexes has been for combining water soluble reagents with water insoluble organic materials. The macrocyclic polyethers act as phase-transfer agents. For example, a benzene solution of potassium permanganate-polyether complex ("purple benzene") quantitatively affords adipic acid from cyclohexene, eqn. (2) (10).



In the absence of a phase-transfer agent these oxidations usually give lower yields of the desired product. Thus, the polyethers catalyze a direct solid to liquid phase-transfer.

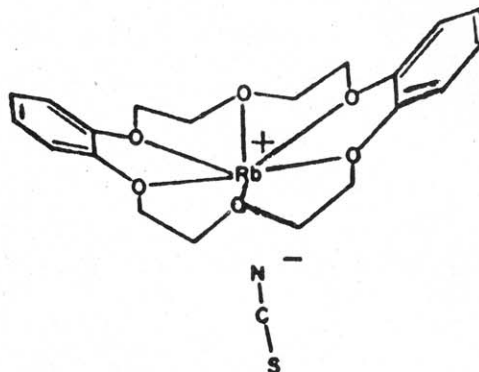
The ability of macrocyclic polyethers to complex with selected metal ions mimics that of certain naturally-occurring macrocyclic antibiotics. Consequently the polyethers serve as convenient models for active ion transport across lipophilic membranes (5).

Cyclic Polyether Preparation

The preparation of the macrocyclic polyethers described below is a one-step synthesis, easily completed, in two two-hour laboratory periods. Enhanced yields of the desired product are obtained when salts of group I, group II (11), or certain transition (12) metals are added to the reaction mixture (Method II). Apparently, the added

"Crown Ether" Synthesis

An organic laboratory experiment



Rubidium thiocyanate dibenzo[18] crown-6 complex (9).

metal cations act as a sort of template to promote ring formation rather than linear condensation.

Experimental (13)

Furan-acetone Macrocycle (1, 1,6,6, 11, 11, 16, 16-Octamethyl-21,22,23,24-tetraoxaquarterene; Ib, R = R' = CH₃).

Method I. To an ice-cold mixture of 95% ethanol (15 ml) and concentrated hydrochloric acid (8 ml) in a 125-ml Erlenmeyer flask add acetone (15 ml, 0.2 mol) and furan (7 ml, 0.1 mol). Allow the stoppered flask to stand at room temperature for at least four days.³ Collect the golden-yellow semi-solid by suction filtration; wash the product with three 10-ml portions of water and press dry it thoroughly. The yield of crude macrocycle is 6-11 g. Crystallization from toluene (~7.5 ml/g of crude product) affords the desired material, a white solid (15%, 4-day reaction; 30%, 2-week reaction); mp 236-238 [lit. (14), 243°C]; ir (KBr) 3096, 1558 (1210 and 1027 C-O-C) (15) 957 and 779 cm⁻¹.

Method II, Template Procedure. To an ice-cold mixture of 95% ethanol (15 ml), concentrated hydrochloric acid (8 ml) and lithium perchlorate (1 g, 0.01 mol) in a 125-ml Erlenmeyer flask add acetone (15 ml, 0.2 mol) and furan (7 ml, 0.1 mol). After allowing the stoppered flask to stand at room temperature for at least four days,³ water (50 ml) and toluene (75 ml) are added with stirring. Removal of the aqueous phase leaves a heterogeneous system which is treated with magnesium sulfate (~1 g) and heated to dissolve the remaining crude product. Hot filtration followed by crystallization affords the desired material (20%, 4-day reaction; 40%, 2-week reaction); mp 236-238°C.

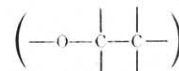
Further Studies

The macrocycles of furan with other ketones can be prepared via Method I: 2-butanone, 20% yield (mp 173-173.5, lit. (14), 173-174°C); 2-pentanone, 30% yield (mp 192.5-195°C); and 3-pentanone [mp 246-246.5, lit. (14), 249°C; nmr (CDCl₃) δ 0.58 (t, 3.1, J = 7.2 Hz,

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² The macrocycle in Figure 1 belongs to a class of compounds which contain repeating



units. Pedersen designated these materials as "crown ethers" since a molecular model of a typical complex resembles a regal crown.

³ Stirring magnetically enhances the yield only a few percent.

CH_3CH_2), 1.88 (q, 2.0, $J = 7.2$ Hz, CH_3CH_2), 5.92 (s, 2.0, $\text{C}_4\text{H}_2\text{O}$). The infrared spectra of these molecules are quite similar to those of the furan-acetone macrocycle.

Heterocycles other than furan might be tried in this synthesis, although our limited efforts in that direction have not been successful. Carbonyl compounds other than simple ketones might also be investigated. The effect of adding various metal cations on the yield of polyether might be studied as well as the role played by the anion (12).

Questions

- 1) Give a possible mechanism for the acid catalyzed formation of the macrocyclic polyether from furan and acetone.
- 2) Would the condensation of furan with 2-butanone yield stereoisomeric macrocyclic polyethers?
- 3) Compound Ib does not form stable complexes; however, the completely saturated analog strongly binds to cations. Offer an explanation.

Acknowledgment

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search and Creative Production for support of a portion of this work.

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