SYNTHESIS AND APPLICATION OF CROWN ETHERS

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Abstract

Mono- and bis-benzo-15-crown-5-ether derivatives have been synthesized and determined their potentiometric K^+ selectivity factors. Of bis-crown ether urethanes highly selective ligands were found some of which was used as active ingredient in potassium selective membrane electrode.

Sugar based crown ethers, aza-crowns and cryptands were also prepared and applied as chiral catalyst in enantioselective reactions.

Introduction

Macrocyclic compounds (crown ethers, cryptands etc.) are known to form complexes with various cations offering new possibilities in different field of chemistry, e.g. phase-transfer catalysis, mediation of transport processes through artificial and natural membranes, ion chromatography and electroanalytical chemistry [1,2,3]. Our research program was focussed on the preparation of crown ether derivatives possessing selective complexing ability. These ligands were expected to be employed as biological transport mediators (potential pharmaceuticals) and active ingredients in liquid membrane electrodes (electroanalytical application), respectively. Besides they can be taken into account in special phase-transfer catalysed chemical processes as catalyst.

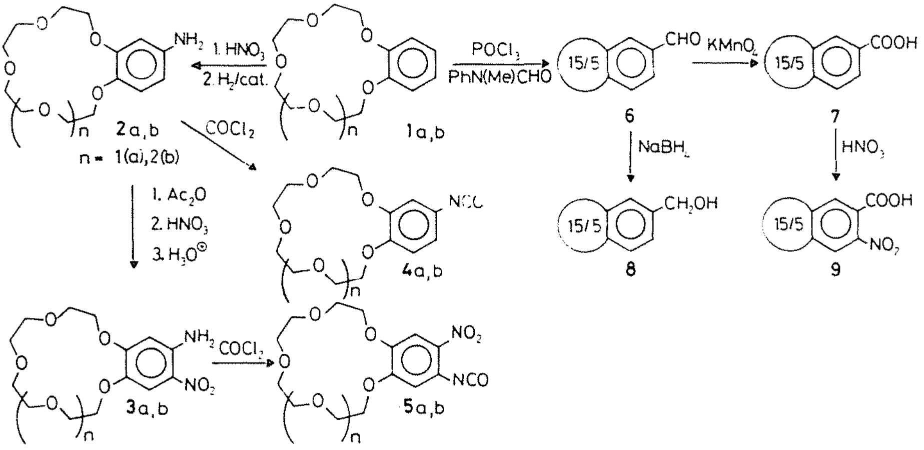
For these purposes two types of crown ethers have been synthesized: benzo-crown ethers and chiral, sugar based crown compounds and cryptands, as well. Now we wish to report on the most important results of both subjects.

Result and discussion

I. Potassium selective benzo-crown ether derivatives

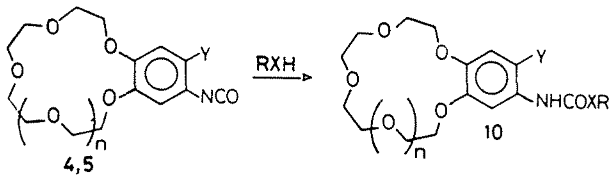
Before starting new research project one of the most important thing is to choose inexpensive and easily accessible starting materials for assuring the continuous work. Moreover they must be suitable for the chemical transformations planned. Benzo-crown ethers were regarded to satisfy these requirements in both respects.

Benzo-15-crown-5 (*1a*) and benzo-18-crown-6 (*1b*) [4] were functionalized on the aromatic ring by different electrophilic reagents according to Scheme 1 [5].



Scheme 1

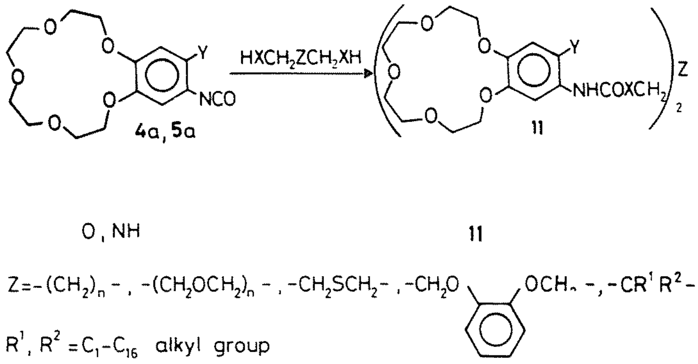
Of these simple crown ether derivatives (*2*—*9*) compounds *4* and *5* containing reactive isocyanate group proved to be very effective in the preparation of a series of urea and urethane derivatives (Scheme 2).



Y = H, NO_2
n = 1,2
X = O, NH
R = alkyl, aralkyl groups, $CH_2CH_2NR^1R^2$, CH_2CH_2OH, $CH_2CH_2OCH_2CH_2NR^1R^2$, $CH_2CH_2OCH_2CH_2OR$ etc.

Scheme 2

The selectivity factors of complexation were determined by potentiometric method incorporating the ligands into *PVC* membrane. It was rather surprising that benzo-15-crown-5 urethanes bearing nitro group on the aromatic ring exhibited relatively high K^+ selectivity (lg $K^{pot}_{K,Na} \sim 2{,}4$—$2{,}6$) [6]. Although the performance characteristics of the electrodes were not satisfactory, these compounds were regarded to be worthy for development. The stoichiometry found for the potassium complexes (crown: $K^+ = 2:1$) indicated a sandwich structure. We realized that by linking two crown ether units with a flexible chain an "inner sandwich complex" was formed and increased stability of this kind of complexes accompanied by enhanced K^+ selectivity was observed. The synthesis was accomplished according to Scheme 3. [7].



Scheme 3

One order of magnitude increase in K^+ selectivity was measured for several ligands some of which showing excellent performance characteristics in *PVC* membrane (Table 1) [6].

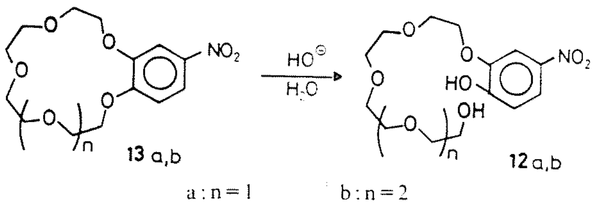
Table I

Selectivity factors of the best ligands

11 ($Y = NO_2$)	Slope value mV/decade	Selectivity factors ($\lg K^{pot}_{K,M}$)				
		Na	NH_4	Rb	Cs	Ca
CH_2SCH_2	−57.7	−3.2	−2.2	−1.2	−2.4	−4.2
$C(CH_3)C_{12}H_{25}$	−58.0	−3.5	−2.2	−0.9	−2.5	−6.1
Valinomycine	−59.0	−4.0	−1.8	+0.4	−0.4	−5.0

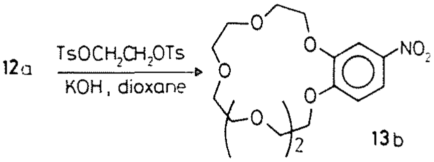
Electrodes prepared from ligands with lipophilic connecting chain work even in biological system (blood, urine) as good as K^+ selective electrodes based valinomycine do with long life-time.

We were interested in elucidating structure-selectivity relationship therefore a great number of derivatives with slightly modified structure have been synthesized. In order to investigate the role of the crown ring in the complexation we prepared ring cleaved analogues by alkaline hydrolytic ring cleavage of nitrobenzo-crown ethers (Scheme 4).



Scheme 4

The site of the nucleophilic attack was unambiguously proved by ^1H and ^{13}C *NMR*. Intermediates *12* were realized to offer new synthetic possibility for building up crown ether ring by the enlargement of the original ring (Scheme 5).



Scheme 5

The ring opening reaction of 4-nitrobenzo-crown ethers with other, e.g. N,S-nucleophiles may provide easy accessibility of certain coronands.

II. Crown compounds incorporating sugar units

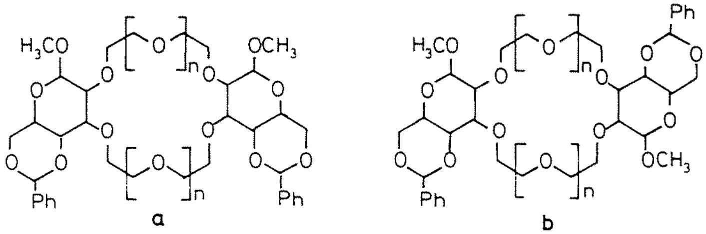
Numerous publications have appeared in the last few years reporting on the synthesis and chiral recognition abilities of chiral crown compounds [8, 9]. Some papers are dealing with crown ethers [10—13] and azacrown compounds [14, 15] incorporating sugar units.

The aim of our work is to synthesize new chiral crown compounds incorporating sugar moieties to find relationship between the structure and complex forming abilities of these molecules and to use them in enantioface differentiating reactions.

Starting from methyl D-glycopyranosides and olygoethyleneglycol derivatives we have elaborated a new method for the synthesis of crown ethers (*14*—*17*) in *THF*-conc. aqueous KOH solution (two phase system) in one pot reaction [16—18] (Fig. 1).

In the reaction *a* and *b* isomers were formed. The structure of isomer *14b* is depicted in Fig. 2 [19].

We observed that crown ethers with various ring size gave different colour reactions with Dragendorff's reagent. This reagent can successfully be used for the detection of crown ethers in thin-layer chromatography [20]. Removal of the benzylidene groups was carried out by hydrochloric acid, acetic



	n	Starting sugar derivative
14	1	Methyl-4,6-O-benzylidene-α-D-glucopyranoside
15	1	Methyl-4,6-O-benzylidene-α-D-galactopyranoside
16	1	Methyl-4,6-O-benzylidene-β-D-galactopyranoside
17	2	Methyl-4,6-O-benzylidene-α-D-glucopyranoside

Fig. 1

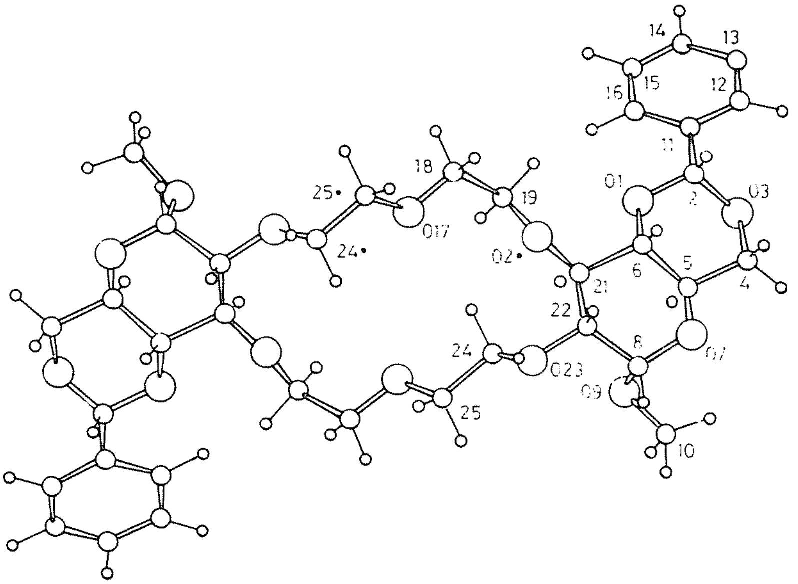
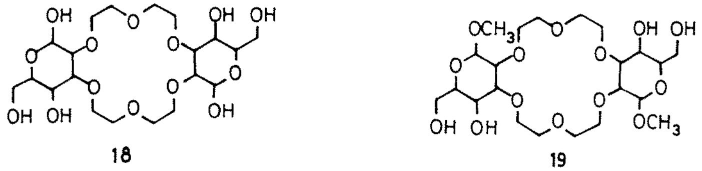


Fig. 2

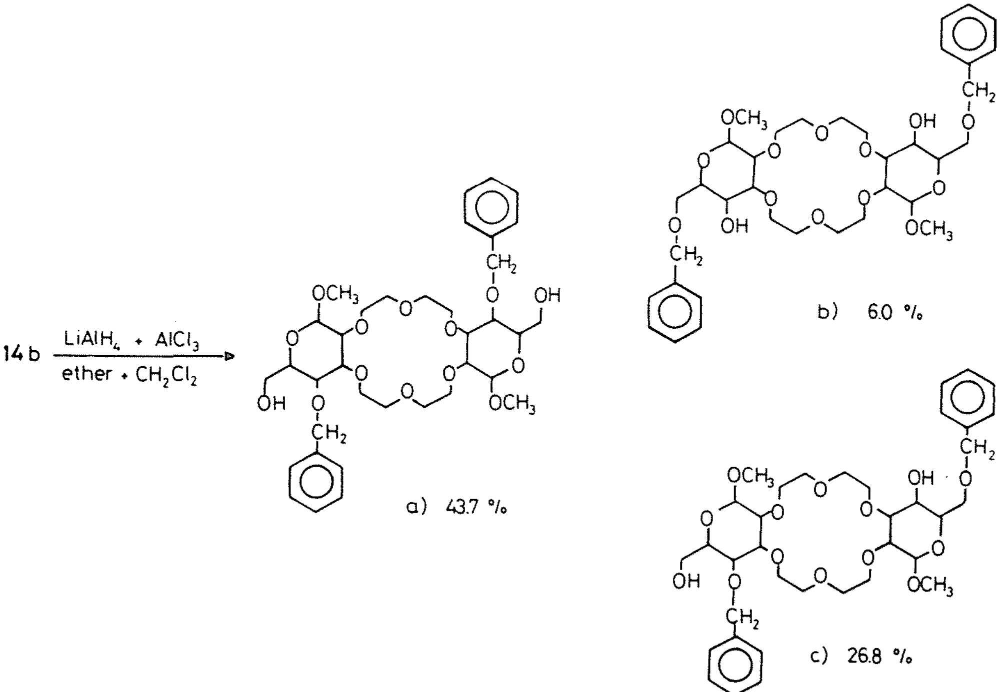
acid when *5* and *6* were formed, respectively (Fig. 3). The cleavage of the acetal ring by $LiAlH_4$—$AlCl_3$ (Scheme 6) and N-bromosuccinimide (Scheme 7) resulted in the formation of different products of benzyl ether and esther type [21].

Beside crown ethers we have synthesized azacrowns and cryptand, too. In the reaction of methyl-2,3-anhydro-4,6-0-benzylidene-α-D-allopyranozide

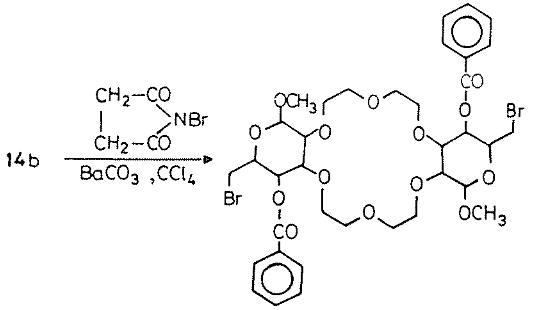


18 **19**

Fig. 3

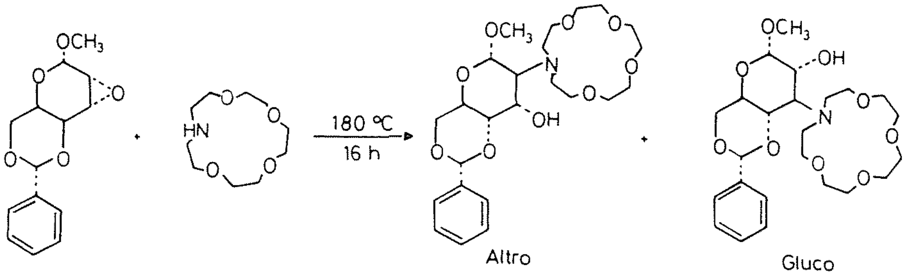


Scheme 6



Scheme 7

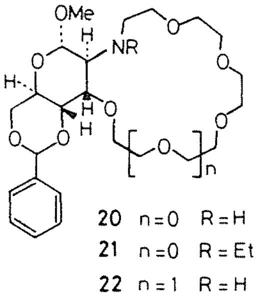
with monoaza-15-crown-5 in accordance with the Fürst-Plattner rule the 2,3-diaxial *altro* addition product is the preponderant (Scheme 8). However, the



Scheme 8

relative proportion of the 2,3-diequatorial *gluco* product was found to be substantially greater: 50% in this reaction [22].

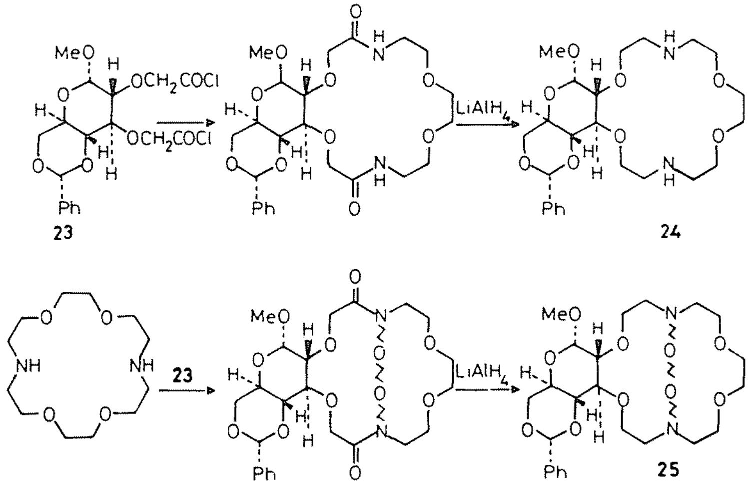
The *20—22* azacrowns were synthesized from the same anhydrosugar (Fig.4).



20 n=0 R=H
21 n=0 R=Et
22 n=1 R=H

Fig. 4

The synthesis of diazacrown and cryptand is shown in Scheme 9; the key molecule is *23* acid chloride [23].



Scheme 9

Having determined the stability constants with various cations (Li^+, Na^+, K^+, NH_4^+) in chloroform we established that 18- and 24-membered crown ethers exhibit relatively high potassium selectivity. The selectivity order is quite opposite with diazacrown (*24*): $NH_4^+ > Na^+ > K^+$. Cryptand (*25*) as it is expected, forms the most stable complexes with each ion.

Investigations have been carried out for using the chiral crowns in stereoselective reactions. The reagent prepared from *18* and $NaBH_4$ reduced acetophenone to *D*-phenylethyl alcohol with 18.5% optical yield.

When the reduction of the acetophenone with $NaBH_4$ has been accomplished in CH_2Cl_2/H_2O two phase system in the presence of catalytic amount of crowns the enantiomer excess in the product was only 2—8%.

In the solid/liquid phase Michael addition of nitromethane to chalcone the optical purity of the resulting 3-phenyl-4-nitrobutyrophenone (3—19%) was dependant on the chiral crwon catalyst used.

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