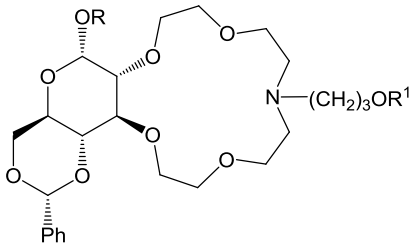
OTKA PD 112166

Report

One aim of the research work was to synthesize new carbohydrate-based crown ethers to acquire further information on the relationship between the structure, activity and enantioselectivity. Previously, it was proved that the most efficient catalysts are monoaza-15-crown-5 type macrocycles annelated to a monosaccharide unit and incorporating a side chain on the nitrogen atom with a three carbon atom spacer. That is the reason why this structure is mainly present in the crown ethers synthesized during the research work.

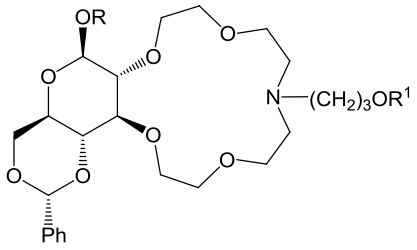
Glucose, which is as a cheap, easily available monosaccharide, was used to prepare a variety of macrocycles. The effect of the substituents on C-1 was studied; therefore replacement of the anomeric hydroxyl group of the glucopyranoside with different alkoxy substituent was carried out. These macrocycles generated significant asymmetric induction as phase transfer catalysts in a few two-phase reactions. It was found that in two liquid – liquid two phase reactions the lariat ethers with α-alkyl substituents (**1**) had approximately the same effect, and the catalysts with β-alkyl groups (**2**) generated, in all case, lower enantioselectivity. In solid - liquid phase reactions the optical purity decreased with the bulkiness of R. The change of the hydroxypropyl side-arm to methoxypropyl substituent resulted in significant decrease of the enantioselectivity.



1

R = Me, Et, *i*Pr, allyl

R^1 = H, CH_3



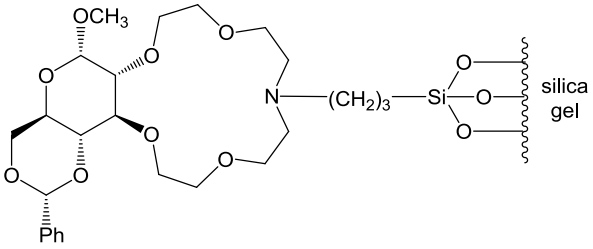
2

R = Me, Et, *i*Pr

R^1 = H, CH_3

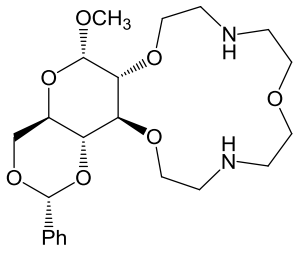
Starting from allyl-α-D-glucopranoside, a monoaza-15-crown-5-type lariat ether was prepared (**1**, R = allyl, R^1 = H). The allyl group would have served as the point of connection to silica gel. Although, the reaction of an allyl group with (3-mercaptopropyl)triethoxysilane is described in the literature, the necessary reaction conditions (UV irradiation, radicals) caused the decomposition of the sugar-based crown ether.

A glucose-based monoaza-15-crown-5 having (3-iodopropyl)trimethoxysilane substituent on the nitrogen was synthesized and was bound to silica gel (**3**). This chiral stationary phase was tested in some model reactions. Longer reaction times were observed due to the increased heterogeneity. The asymmetric induction was quite different in each reaction (0-90% ee). Further optimization is required for the reaction conditions *e.g.* to avoid leakage of the catalyst. Modification of the surface of the chiral silica gel was necessary for the chromatographic separation of racemic ammonium salts. After a few attempts the retention of the salts was too low or too high and there was no enantiomeric separation.



3

Using methyl-4,6-*O*-benzylidene-α-D-glucopyranoside as starting material 15- and 18-membered diaza-crown ethers (**4**, **5**) were prepared. These macrocycles showed decreased complex forming ability towards alkali ions. Applying these compounds in asymmetric reactions low to moderate enantioselectivity was observed.



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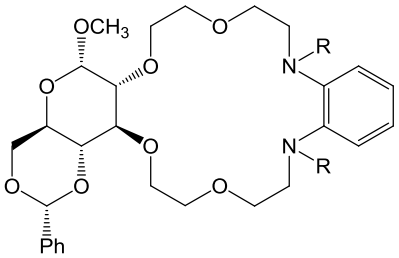
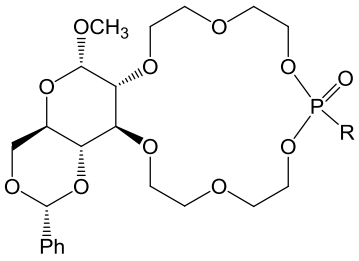


5

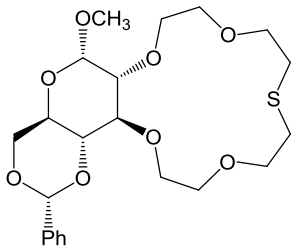
R = H, Me

Similar properties - decreased complexing ability and low asymmetric induction - were detected in the case of glucose-based crown ethers containing phosphorus (**6**) and sulfur atoms (**7**). It can be concluded that changing the monoaza-15-crown-5 structure results in deterioration of the asymmetric catalytic activity.



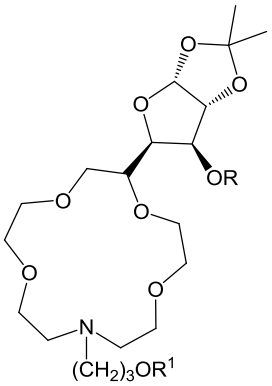
6

R = $NH(CH_2)_2CH_3$, $O(CH_2)_2OCH_3$



7

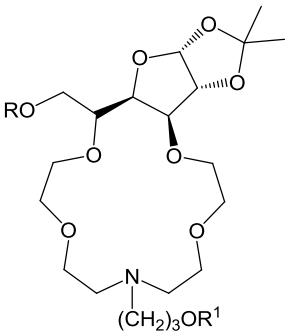
A few α-D-glucofuranoside-based lariat ethers were synthesized derived from D-glucose (**8**, **9**). All these crown ethers were tested in different asymmetric reactions (Darzens condensation, epoxidation, Michael addition, etc.). These compounds resulted in moderate to low asymmetric induction (0-58% ee) as phase transfer catalysts. The complex forming and extracting abilities of all glucofuranoside-based catalysts synthesized were investigated, and lariat ethers containing the sugar moiety bounded to the macro ring with a single covalent bond (**8**) were selective towards Ag^+ cation. This surprising phenomena is outstanding (as far as we know), the selective ionophores described earlier were macrocycles/lariat ethers typically with one or two sulfur atoms.



8

R = Bn, Pr

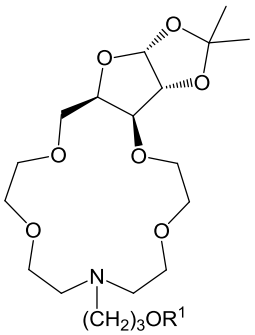
R^1 = H, CH_3



9

R = Tr

R^1 = H, CH_3

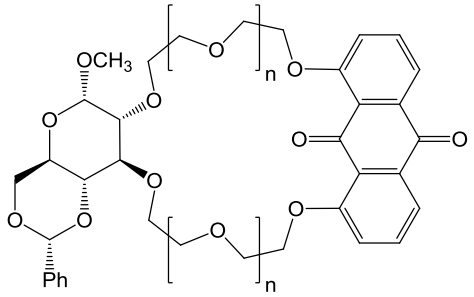


10

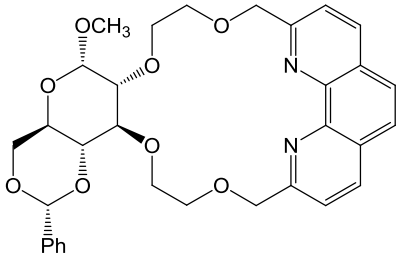
R^1 = H, CH_3

Starting from D-xylose two xylofuranoside-based lariat ethers having similar structure to compounds **9** were synthesized. These macrocycles were tested in asymmetric reactions and generated moderate to low asymmetric induction (0-60% ee) as phase transfer catalysts. Comparing the results obtained there is no significant difference in the asymmetric induction and catalytic activity of **9** and **10**.

Two glucose-based fluorescent crown ethers (**11**) containing an anthraquinone unit were prepared using 1,8-dihydroxyanthraquinone. Both the 21-membered and the 15-membered crown compounds showed poor complexing ability towards different cations including chiral ammonium salts. Neither of these macrocycles generated significant asymmetric induction as chiral phase transfer catalysts. The synthesis of fluorescent crown ether **12** was attempted from 2,9-dimethyl-1,10-phenanthroline. This compound was converted to (1,10-phenanthroline-2,9-yl)dimethanol, which was reacted with a glucose-based compound under different conditions, but only formation of a large number of side-products could be observed. Using a dibromo phenanthroline derivative the preparation of macrocycle **12** was not successful either.

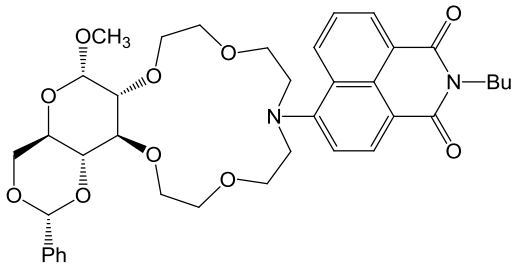


11 n=0,1



12

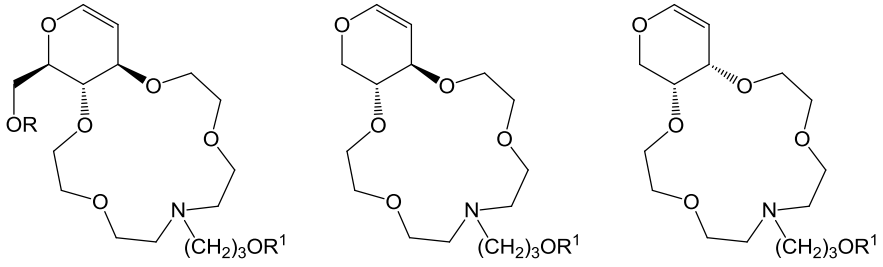
N-Buthyl-5-bromo-1,8-naphthalimide was synthesized using acenaphthene as starting material. The reaction of this fluorescent unit with a glucose-based azacrown ether containing no substituent on the nitrogen atom was attempted several times with different reaction conditions. So far, the desired crown ether **13** could not be obtained.



13

Using glucose, the synthesis of glucal-based crown compounds **14** was attempted. Due to the double bond the glucal structure is sensitive to certain conditions. Introducing protective groups selectively was successful, but after work up procedures decomposition

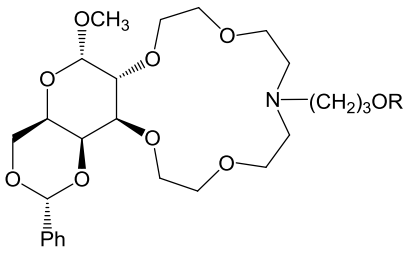
could be observed. This step would provide the key compound bearing two unprotected hydroxyl functions. Further experiments were ceased. Instead, preparation of xylal- (**15**) and arabinal-based (**16**) crown ethers was started from D-arabinose and D-xylose as starting materials. Both monosaccharides contain a double bond in the six-membered sugar ring. Using the crown compounds derived from xylal (**15**) low asymmetric inductions were obtained in Darzens condensation, Michael additions and epoxidation. However, the xylal-based macrocycles proved to be efficient in asymmetric cyclopropane formation (MIRC) reaction (up to 96% ee). Testing the arabinal-based macrocycles **16** has not been finished yet.



14 **15** **16**

R^1 = H, CH_3 R^1 = H, CH_3 R^1 = H, CH_3

Methyl-4,6-*O*-benzylidene-α-D-galactopyranoside-based chiral macrocycles having 3-hydroxypropyl and 3-methoxypropyl substituent on the nitrogen atom of the crown ring (**17**) were prepared. These lariat ethers were applied in Michael addition of malonates to chalcone derivatives, and excellent enantioselectivity was measured using chiral HPLC (up to 99% ee). The galactopiranoside-based crown ethers **17** generated asymmetric induction up to 85% ee in a MIRC (Michael-initiated ring-closure) reaction resulting in chiral cyclopropane derivatives.

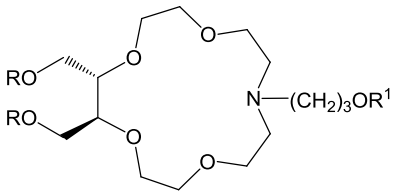


17

R = H, CH_3

Using diethyl-tartarate as starting material, six L-threitol-based chiral crown ethers were synthesized in seven steps. The structures of these macrocycles are similar to each other;

the threitol-based catalysts vary in the side arms on the nitrogen atom of the crown ring and/or in the substituents on the primary OH groups of the threitol moiety. Several asymmetric reactions were carried out in the presence of threitol-based crown ethers, and moderate to excellent enantioselectivity was measured (up to 95% ee).



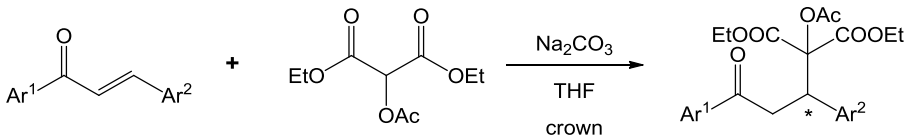
18

R = Bn, Me, *t*Bu

R^1 = H, CH_3

Other aim of the research work was to perform asymmetric reactions applying sugar-based macrocycles as catalysts.

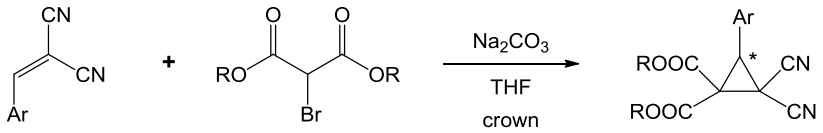
Some substituted diethyl malonate (with Me, Et, Bn, allyl, Br, OAc substituents) were synthesized. All of them were tested in Michael additions with chalcone and mostly moderate enantioselectivity was measured. Except for diethyl acetoxymalonate which gave the best result using glucose-based crown ether **1** (R = Me, R^1 = H) as the catalyst (96% ee). The effect of the substituents of the chalcone on the asymmetric induction were investigated in the reaction of diethyl acetoxymalonate in the presence of lariat ether **1** (R = Me, R^1 = H) and a few chalcone analogs also were used as Michael acceptors (Scheme 1). Moderate to high ee values were observed (30-99% ee). Applying other dialkyl malonates (dimethyl, dibenzyl, diisopropyl) the investigation were extended. Moderate to high asymmetric induction were observed. The absolute configuration of the Michael adduct formed from diethyl acetoxymalonate with chalcone having positive specific rotation proved to be (*S*) on the basis of a joint CD spectral and theoretical study.



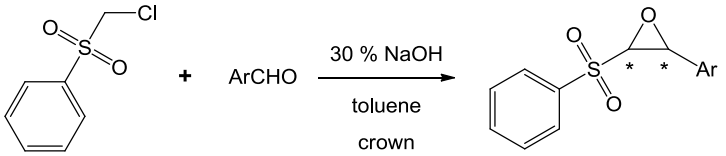
Scheme 1

In order to obtain a deeper mechanistic insight, the reaction of acetoxymalonate with chalcone (Scheme 1, catalyst **17**) was modeled by theoretical calculations. In particular, we addressed the intriguing effect of the substituents, *i.e.* why the enantioselectivity of 99% is decreased to 6% if a NO_2 group is introduced into the phenyl ring in *meta* position. We have performed a combined molecular mechanics (MM) - quantum chemical (QM) calculation series. The calculations nicely correlate with the experimental observations. The calculations predict the *S* configuration to be by 4.1 kcal/mol more stable than the *R*. We could conclude that the theoretical predictions reproduce nicely the experimental 99% and 6% ee values.

Starting from aromatic aldehydes and malononitrile, several substituted benzylidene malononitriles were prepared. The (Bingel-type or MIRC) reactions of these compounds with bromomalonates were carried out in the presence of chiral lariat ethers (Scheme 2). Applying optimized conditions, enantioselectivity up to 92% was determined based on chiral HPLC analysis. In MIRC reactions a few 2-benzylidene-1,3-diphenyl-1,3-diones were also applied as Michael acceptors, and ee up to 70% were measured. Using 3-bromopentan-2,4-dione instead of bromomalonates resulted in reactions without main products. The desired compound was not formed in the case of 3-benzylidenepentan-2,4-dione. Using arylidene indane-1,3-dione as acceptors enantioselectivity up to 99% was measured in MIRC reactions.



Scheme 2

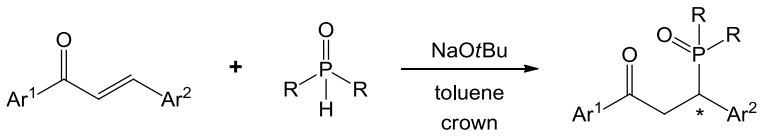


Scheme 3

Applying thioanisole as starting material, chloromethyl phenylsulphone were prepared in two steps. The Darzens reaction of this derivative with benzaldehyde was investigated under phase transfer condition (Scheme 3). So far, the desired chiral epoxy compound could

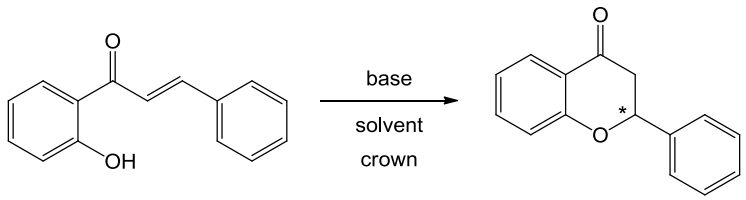
not be isolated, formation of several byproducts was observed. Further attempts and optimization are necessary.

Addition of diethyl and diphenyl phosphite to chalcone (Scheme 4), nitrostyrene and cyclohexanone were investigated. Using combination of different solvents (*e.g.* hexane, toluene, diethyl ether, dichloromethane) with different bases (Na_2CO_3, NaOH, NaO*t*Bu) it was observed that there was reaction in the absence of any crown ether. Thus, in that cases when the desired product was formed, racemic compound was isolated. The same phenomenon was observed using other phosphites.



Scheme 4

2'-Hydroxychalcone was synthesized and used as the starting material for preparation of chiral flavanone. In dichloromethane the formation of the desired flavanone was observed in the presence of NaOH solution, but the reaction resulted in a racemic product. First, glucose-based crown ethers were used, then several others were tested, but only achiral flavanone could be obtained. Then, the reaction was carried out in different solvent in the presence of solid bases. Non-racemic flavanone could be prepared in THF using solid sodium carbonate in the presence of glucose- and galactose-based macrocycles, but the enantiomeric excess was low (<20% ee).

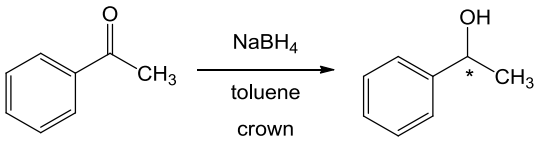


Scheme 5

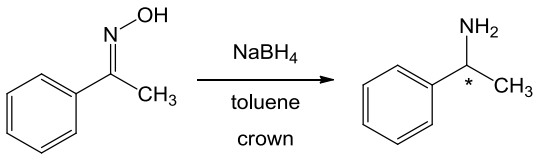
Reductions of prochiral ketones were carried out using carbohydrate-based crown ethers. In the case of acetophenones (Scheme 6) only low enantiomeric excess was measured (<5%). When chalcones were applied as substrates not only the carbonyl group, but the

double bond could be reduced, thus, the reactions resulted in mixtures of products. These compounds were hard to separate, and low enantioselectivity was measured.

Using oximes instead of ketones as substrates of the reduction (Scheme 7) byproducts could be observed and the asymmetric induction was still low.

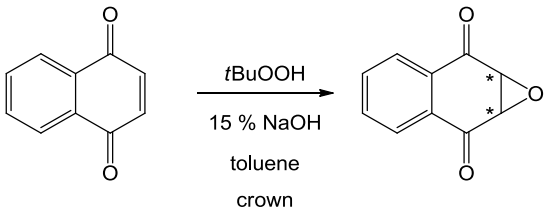


Scheme 6



Scheme 7

Earlier, epoxidation of chalcones were carried using chiral crown ethers, and the products were obtained with good yield and enantioselectivity (up to 90% ee). Naphthoquinone was tested as substrate in order to optimize the reaction conditions (Scheme 8).



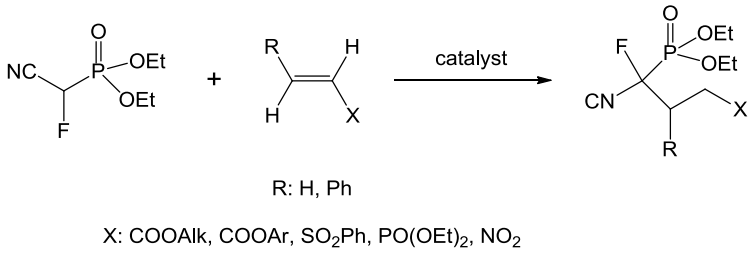
Scheme 8

The reaction was very fast, it required less than one minute at 25 °C. But not only the desired product was formed, a large number of byproducts were present in the mixture. When the temperature was decreased, the result was the same. The epoxy compound derived from naphthoquinone could not be detected from the crude product. Further attempts were ceased, and the substituted naphthoquinones were not tested in epoxidations.

A few aza-Michael reactions were tested applying sugar-based crown ethers in a two phase system. As Michael donors, imidazole, indole, acetanilide, tosylamide were used. As Michal acceptor benzylidene tosylamide was tested. Application of different solvents and different bases, until now, neither of the reactions gave the desired product.

Starting from pyruvic acid, β,γ-unsaturated α-carbonyl compounds were prepared. These derivatives were subjected to asymmetric epoxidation, Michael addition and cyclopropanation. In these reactions the conversion was complete, but surprisingly only a very small amount of product could be isolated (except in case of cyclopropanation). It turned out that decarbonylation occurred during the work up procedure. Only the cyclopropane derivatives proved to be stable enough. Optimization of the conditions and the determination of the enantiomeric excess are in progress.

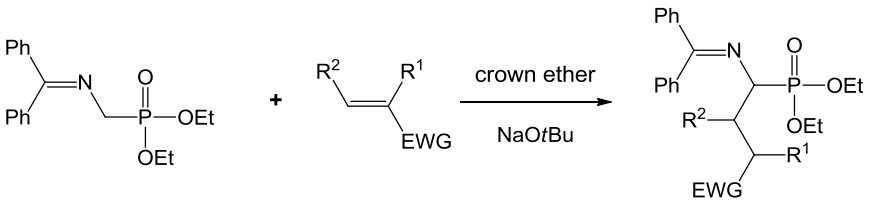
The Michael addition of diethyl (cyanofluoromethyl)phosphonate was investigated in the presence of sugar-based crown compounds (Scheme 9). With different Michael acceptors enantioselectivity up to 88% was observed.



Scheme 9

Michael addition of 2-nitropropane and diethyl benzylidenemalonate was carried out applying monosaccharide-based crown ethers as catalysts. The addition was very slow under optimized conditions, and after the work up procedure, the pure product was almost racemic (ee <10%).

Enantioselective Michael addition of an N-protected aminomethylenephosphonate to acrylic acid derivatives and β-nitrostyrene were carried out using monoaza-15-crown-5 type macrocycles as chiral catalysts (Scheme 10). Michael adducts were formed with good to excellent enantio- and diastereoselectivities.

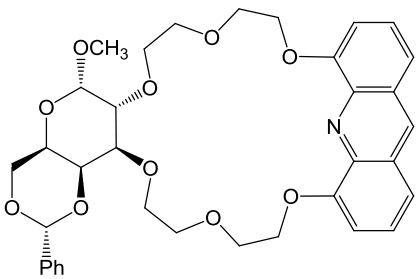


R^1 : H, Me
R^2 : H, Ph
EWG : CN, COOMe, COOEt, COOtBu, NO_2

Scheme 10

Theoretical modeling of stereoselectivity in the catalytic formation of the adducts rationalized the absolute configuration of the predominant adducts. The pronounced influence of the side arm of two crown ethers was also rationalized by the calculations. A mechanism was proposed where the strength of interaction between the lariat and the sodium cation is correlated with stereoselectivity. This mechanism provides explanation also for the decline in stereoselectivity when Na^+ is replaced by K^+.

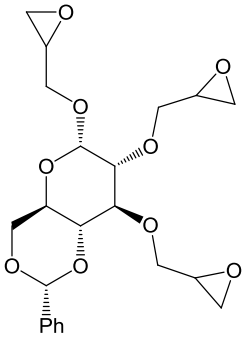
Previously, a glucose-based fluorescent crown ether containing an acridine unit was synthesized. This derivative formed stable complexes with metal ions; the highest stability constant was obtained for the Ca^{2+} complex. The coordination of metal ions by this macrocycle was accompanied by marked fluorescence enhancement, whereas the binding of ammonium ions by the same species resulted in significant fluorescence quenching. This crown ether showed a promising performance as a chiral fluorescent sensor molecule; its chiral discrimination ability was similar to that of various other crown ethers with C or P stereogenic centers. Due to the incorporation of the rigid acridine unit in the crown ring, the stability values for the complexes of this crown compound with the ammonium ions were higher than most of the values reported for more flexible crowns. Considering these results, a similar macrocycle (**19**) was synthesized starting from galactose.



19

Fluorescent measurements were carried out using crown ether **19**. Its chiral discrimination ability towards quaternary ammonium ions was determined. In the case of the enantiomers of the (1-naphthylethylamine)hydrochloride salt there is a larger selectivity, but it has to be confirmed using a different method.

Beside the research work with crown ethers, as a side project flame retarded bioepoxy resins and carbon fiber reinforced composites were prepared from a novel glucofuranoside-based trifunctional epoxy monomer (**20**) cured with aromatic amine hardener. 4% Phosphorus-containing samples were prepared using liquid resorcinol bis(diphenyl phosphate) and solid ammonium polyphosphate. Their combination resulted in V-0 UL-94 rated bioepoxy matrix and composite specimens.



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Based on the research work, 9 articles were published and 11 oral presentations were held. Two other manuscripts have been submitted to New Journal of Chemistry and Research on Chemical Intermediates. Another one manuscript is almost finished and will be submitted in September.

List of oral presentations:

1. Nemcsok T., **Rapi Zs**., Bakó P: Synthesis of chiral crown ethers derived from monosaccharides and application as enantioselective catalysts.
   2014. November 3-5. XXXVII. Kémiai Előadói Napok, Szeged, Hungary.

2. **Rapi Zs.**, Bakó P., Botyánszki A., Démuth B., Nemcsok T., Sóti P., Szabó T., Vigh T: Synthesis and application of sugar-based crown ethers.
   2014. November 6-9. XX. International Conference on Chemistry, Cluj Napoca, Romania.

3. **Rapi Zs.**, Bakó P., Nemcsok T., Pálvölgyi Á., Kánya N. Asymmetric syntheses catalyzed by chiral crown ethers.
2015. September 24-26. XXI. International Conference on Chemistry, Sumuleu Ciuc,, Romania.

4. Nemcsok T., **Rapi Zs.**, Bakó P: Synthesis of chiral crown ethers and their application as enantioselective catalysts.
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