Chiral recognition of α-phenylethylamine by sucrose-based macrocyclic receptors†

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Simple chiral aza-crown ethers based on sucrose display high enantioselectivity in complexation of phenylethylammonium chlorides.

Molecular recognition plays a crucial role in biological systems: receptors, antibodies or enzymes, all recognize their specific reaction partners.[1] Synthetic analogs of such receptors are of great interest, since they may be used as enzyme models, ligands for enantioselective reactions or applied for construction of synthetic biochemical sensors.

Chiral crown ethers and their analogs are particularly useful; they can be applied in enantioselective reactions[2] (also as stable complexes with mono- and poly-valent cations) and, moreover, they are capable of differentiation of chiral guests.[3] An especially interesting case represents enantioselective recognition of chiral ammonium cations derived from amines or amino acids. The pioneer works on this topic have been carried out in the 1970s by Cram. He studied the chiral recognition ability for binaphtol based chiral macrocycles using the picrate salts extraction method.[4] Stoddart determined the stability of complexes of D-mannitol based crowns with ammonium cations using NMR spectroscopy.[5] Since then it has become one of the most popular methods of studying host–guest interactions for numerous types of receptors (apart from UV-Vis spectroscopy, photophysical and electrochemical methods).[6,7,8] It also led to the application of several examples of crowns as chiral derivatizing agents for NMR spectroscopy (by Wenzel, Joly and others).[9,10] The main area of application of chiral macrocycles, however, was as chiral modification for HPLC columns, capillary electrophoresis and MS study of molecular recognition in the gaseous phase. The study of enantiomeric recognition of protonated amine derivatives is of high significance due to the presence of such moieties in many biologically active molecules. From all of the chiral scaffolds applied, sugars prove to be the most promising, due to their availability and biocompatibility. Up to date, only monosugars have found a widespread application in the synthesis of crown ether analogs.[11] The disaccharide scaffold is much less pronounced.

In the past several years we have been involved in the transformation of sucrose into fine chemicals.[12] We succeeded in efficient preparation of 2,3,3′,4,4′-penta-*O*-benzylsucrose (**1**) which was applied in the targeted synthesis of the sucrose analogs (at either terminal position: C1′,C6,C6′). Another derivative: 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (**2**) was applied to the preparation of the crown ether analogs by the coupling of their C6 and C6′ (Fig. 1).

The azacoronands **3** and **4** prepared in a few steps from **2** have shown interesting complexing properties. The stability constants of these receptors towards the ammonium cation (NMR titration of NH_4SCN) were—as expected[13]—much higher than the oxygen analogs; for example, the corresponding data for **3** was assigned as 560 M^{-1}, while for the crown **3a** it was only 17 M^{-1}.[14] The receptor containing three nitrogen atoms in the ring (**3**) has shown the highest K_a value, while the K_a value for the receptor **4** (containing two nitrogen atoms) was much lower than for **3** (see Table 1).

This may result either from a too large cavity of this macrocycle or the presence of only two nitrogen atoms in the ring. To find out the reasonable explanation we decided to prepare the macrocycle with the same cavity as **4**, but containing four nitrogen atoms in the ring. The synthesis of such derivatives (compounds **7** and **8**) is outlined in Scheme 1.

The partially protected sucrose **2** was converted into the 6,6′-diamine derivative **5** as described previously.[14] Reaction of this compound either with a proper ditosylate or *N*,*N*′-dibenzyl-ethylenediamine, under the standard conditions, afforded the corresponding macrocycles **7** and **8**, respectively (see ESI for experimental details).†

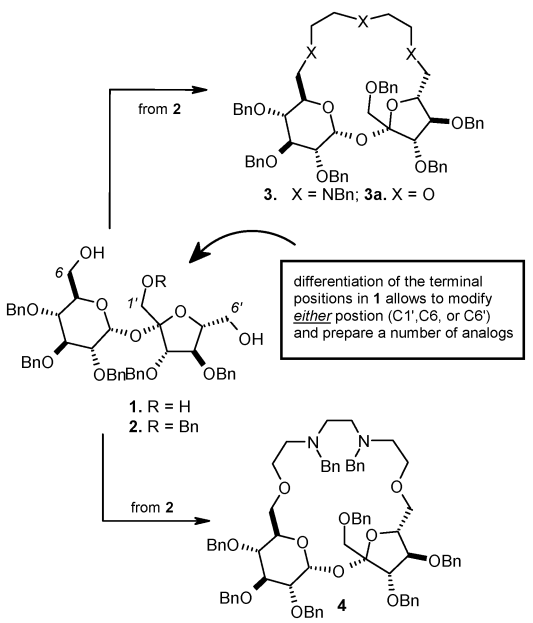

Fig. 1 Synthesis of aza-crowns based on sucrose.

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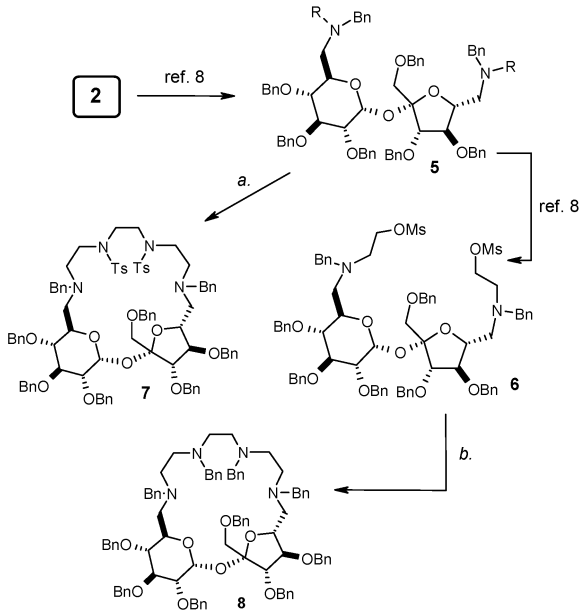
Table 1 Stability constants for complexes of aza-crowns with ammonium cation

Receptor	K_a (NH_4SCN, acetone-d_6)/M^{-1}
3	560 ± 36 (ref. 14)
4	230 ± 18 (ref. 14)
7	112 ± 18 (this work)
8	129 ± 10 (this work)



Scheme 1 Synthesis of aza-crowns **7** and **8**. Conditions: a. **5**, $TsOCH_2CH_2N(Ts)CH_2CH_2N(Ts)CH_2CH_2OTs$, Na_2CO_3, MeCN; b. **6**, $BnN(H)CH_2CH_2N(H)Bn$, Na_2CO_3, MeCN.

These newly prepared aza-crowns were tested for their complexing ability towards simple ammonium cations and the results are collected in Table 1. The association constant for receptor **7** was significantly low, even lower than for macrocycle **4** (with only two N-atoms), which might be associated with the presence of two electron withdrawing (tosyl) groups placed on both ring-nitrogen atoms. Receptor **8**, where all of the nitrogen atoms are protected with benzyl groups, exhibited slightly stronger interaction with the ammonium cation than **7** but again much weaker than the previously tested macrocycles. This is presumably connected with the bigger size of the cavity of these receptors which makes the larger macrocycle less rigid, and consequently formation of the complex requires a much higher loss of free energy. The stability constants of the complexes of crowns **4**, **7** and **8** with the ammonium cation are, therefore, significantly lower than analogous data found for **3**. Thus, the presence of additional nitrogen atoms in the macrocyclic ring does not play a significant role in the binding.

Chiral receptors are especially designed for the enantioselective recognition of chiral guests. Having known that the sucrose based macrocycles do complex the ammonium cation we turned our attention to the problem of discrimination of chiral amines. Both enantiomers of α-phenylethylamine (as hydrochloride salts) were selected for this study.

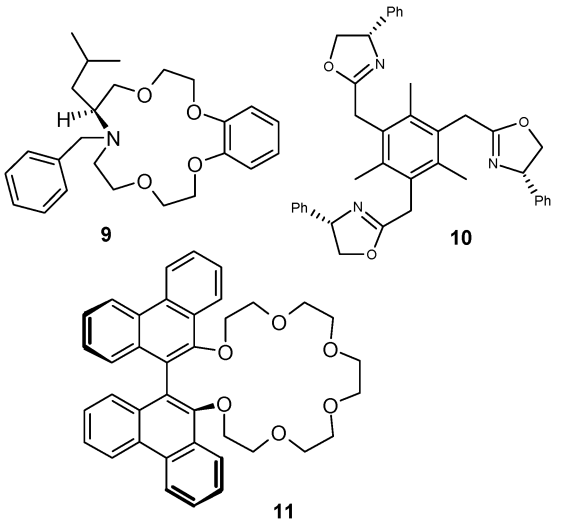


Fig. 2 Enantioselective receptors for phenyethylammonium cations.

There are numerous examples of chiral receptors which exhibit chiral recognition towards the cations derived from phenylethylamine. Among them the mono-aza-benzo-15-crown-5 derivative **9** investigated by Turgut[15] displays the highest enantioselectivity (the stability constants with the enantiomers of phenylethylamine perchlorates are: $K_R = 9.53 \times 10^3$, $K_S = 4.77 \times 10^3$, $K_R/K_S = 2.00$). Special attention should also be paid to the tris-oxazoline receptor **10** studied by Kim[16] and the biphenantryl-18-crown-6 **11** derivative synthesised by Yamamoto[17] (Fig. 2). Both of these compounds displayed considerably stronger interaction with one enantiomer of phenylethylamine hydrochloride as it was demonstrated by the liquid/liquid extraction experiments (the respective ee values are 42% (*R*) and 45% (*S*)). To date there is no precedent of higher enantioselectivity displayed towards derivatives of phenylethylamine.

The results of the complexation study performed by us on sucrose-based aza-crowns **3**, **4**, **7**, and **8** are presented in Table 2. Macrocycle **7** did not show any affinity either to (*S*)- or (*R*)-α-phenyl-ethylamine.

As proven by our NMR titration experiments, the remaining three receptors all showed the preferential complexation of the (*S*)-amine. The highest value ($K_a = 1244\ M^{-1}$) was noted for the complex of compound **3** (the association constant was determined by NMR titration methodology[18] in deuterated chloroform). The stability constant of the complex of **3** with the (*R*)-amine was significantly lower ($K_a = 837\ M^{-1}$), which assigned the value K_S/K_R at 1.84.

Both remaining receptors: **4** and **8** have remarkably interesting complexing abilities. Although the stability constants with the (*S*)-amine were significantly lower than for **3** ($K_{a4} = 945\ M^{-1}$, $K_{a8} = 264\ M^{-1}$) these macrocycles ***did not complex*** the (*R*)-enantiomer of α-phenylethylamine (see Table 2). We did not observe any shift of the signals of sucrose backbone during titration of the guest into the solution.

The reason for the decreased value of the association constant for compound **8** in comparison to **4** is probably the presence of two additional benzyl groups on the nitrogen atoms which results in a larger steric hindrance preventing the interaction with the guest cation. Compound **7** showed

Table 2 Stability constants for complexes of aza-crowns with phenylethylammonium cation

Receptor	K_a ($S(-)$, $CDCl_3$)/M^{-1}	K_a ($R(+)$, $CDCl_3$)/M^{-1}
3	1244 ± 192	837 ± 104
4	945 ± 221	[a]
7	[a]	[a]
8	264 ± 36	[a]

[a] No signal shift observed in the NMR during titration.

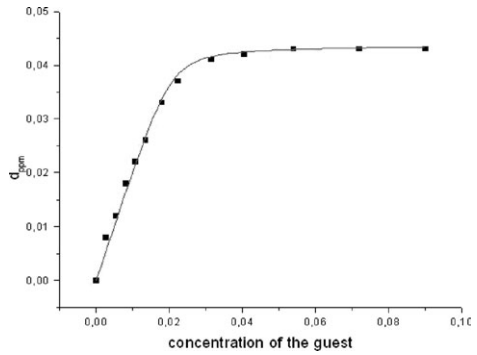


Fig. 3 Titration curve for macrocycle **4** and $S(-)$-phenylethylammonium chloride. The shift of the signal of the anomeric proton of sucrose was followed during the experiment, (for other titration curves see ESI).†

very weak interaction with both enantiomers of the chiral salt, again presumably due to the electron withdrawing influence of the tosylate groups attached to the nitrogen atoms.

The association constants could be determined using the method described by Fielding only with the assumption that the receptors and the chiral salts form 1 : 1 host–guest complexes. To confirm this stoichiometry a Job plot was recorded for the interaction between host **4** and $S(-)$-phenylethylammonium chloride (see ESI for details).† It confirmed the assumed 1 : 1 interaction although the different shapes of the curve's slopes suggest that there are two separate binding modes responsible for the interaction.

A convenient route to the sucrose-based azacoronads was proposed. The stability constants of the complexes of these receptors with α-phenylethylamine were rather moderate (highest value $K_a = 1244\ M^{-1}$), however, we have noted that these macrocycles show remarkably high affinity towards the (*S*)-α-phenylethylamine, Fig. 3.

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