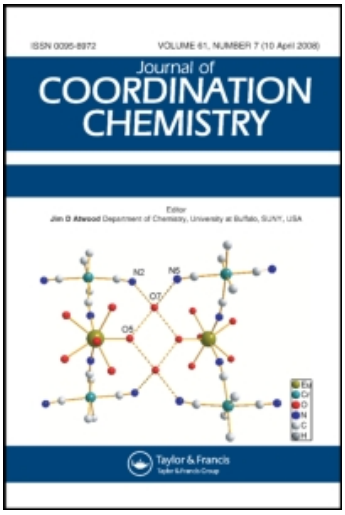

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The Synthesis and Complexing Properties of Chiral Diaza Crown Ethers and Cryptands Incorporating D-Mannopyranoside Units

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THE SYNTHESIS AND COMPLEXING PROPERTIES OF CHIRAL DIAZA CROWN ETHERS AND CRYPTANDS INCORPORATING D-MANNOPYRANOSIDE UNITS

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Several chiral macrocyclic molecular receptors based on D-mannose as a source of chirality, have been synthesized by standard methods. Three types of host molecules have been designed: cryptands, diaza crown ethers with ligating groups, and hosts (or both types) with convergent binding sites. All hosts displayed enantioselectivity upon complexation with primary ammonium cations (**RS**), and alkali metal carboxylates (**SR**) in organic solvents. Hosts featuring convergent binding sites exhibited higher enantioselectivity. The latter was observed by extraction experiments followed by NMR spectroscopy.

INTRODUCTION

There has been considerable interest in the design, synthesis, and complexation properties of chiral macrocyclic molecular receptors capable of performing chiral recognition. Such receptors may incorporate either synthetic or naturally occurring chiral units and have been the subject of review.[1]

We have been interested in the enantioselective properties of chiral diaza crown ethers and cryptands incorporating sugars towards chiral primary ammonium guest cations.[2] Nitrogen-containing chiral macrocyclic molecular receptors were expected to be better models for enantiomeric selection than similar "all-oxygen" chiral crown ethers for which differentiation between enantiomers is not particularly high.[3] The introduction of nitrogen atoms into the macrocyclic ring was expected to increase the binding strength of the complexes and also to establish three classes of host: monofacial receptors (Figure 3A); receptors with ligating side arms (lariats), (Figure 3B), and receptors with convergent binding sites (Figure 3C).

The concept of the ligand design will now be discussed in more detail. The reason for the marriage of aza macrocyclic binding sites and sugars was twofold: it has been demonstrated that aza macrocycles form stronger complexes with primary ammonium cations than "all oxygen" crown ethers,[4] due to stronger N-H ... N hydrogen bonding compared with the N-H ... O hydrogen bonding strength.[5] Furthermore, sugars are a cheap source of chirality and available in many configurations offering a variety of functionalizations. They also contain oxygen atoms that may contribute to the overall binding strength of the receptor.

Using the 4,13-diaza-18-crown-6 macrocycle (**1a**) as a basic binding site for chiral primary ammonium cations, chirality was introduced into the host by the

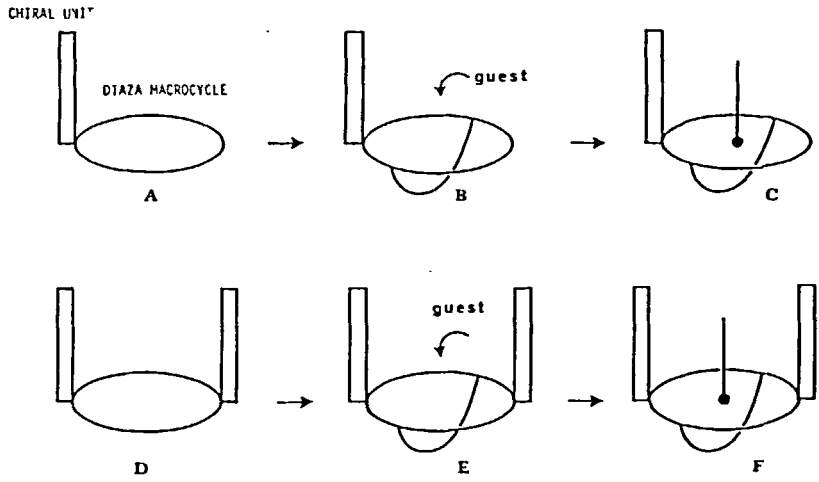


FIGURE 1 Schematic representation of the design concept for "monofacial" molecular receptors.

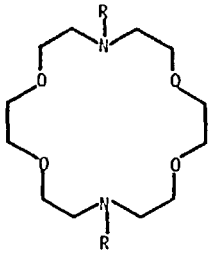
incorporation of a rigid, chiral D-mannopyranosidic unit, shown in its acetal-protected form in **2a** and **2b**. This protection was required at the beginning of the synthetic work to incorporate the diaza crown binding site into the 2,3-O-position of the sugar unit. The effect of fusing the diaza crown with the chiral unit is shown schematically in a Figure 1A: the upper and lower faces of the diaza macrocycle are no longer equivalent and, in principle, the host is capable of chiral recognition in complexation experiments with chiral primary ammonium cations in solution.

Earlier work in this area indicated that sugar-incorporating diaza crown ethers tend to form anisometric complexes with primary ammonium cations,[2] with the more stable complex associated with binding the guest cation at the upper face of the macrocycle containing the sugar unit. An interpretation of this result was based on the fact that the sugar unit provides oxygen atoms capable of forming hydrogen bonds with the primary ammonium cations, thus enhancing the binding strength on the more sterically hindered side of the macrocycle.

However, enantioselectivity is still likely to be weak because *both* faces of the diazamacrocycle can, in principle, still bind the chiral guest and it is only the *upper* face which has the potential for chiral discrimination *via* the chiral sugar unit.

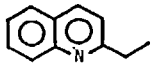
If the binding site on the *lower* face is blocked, then overall chiral recognition would be expected to improve, since this effectively prevents complexation by the *lower* face. This can be achieved by bridging a rigid m-xylyl unit across the two nitrogen atoms of the *lower* face (**3a**), and is shown schematically in Figure 1B and in complexation mode in Figure 1C.

In principle, chiral recognition can be further enhanced by the incorporation of two rigid chiral D-mannopyranosidic "arms" onto the same face of the diaza macrocycle, (**5a**), and shown schematically in Figure 1D. Once again, the further refinement of blocking the *lower* face by a bridging, rigid, m-xylyl unit (**6a**) might be expected to improve chiral recognition and this is shown schematically in Figure 1E, together with its expected complexation mode in Figure 1F.

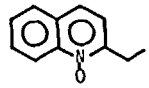


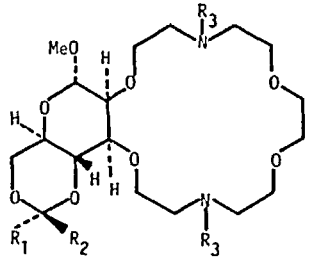
1a: R = Me

1b: R =



1c: R =

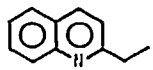




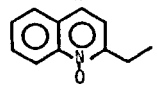
2a: R_1 = Ph, R_2 = H, R_3 = H

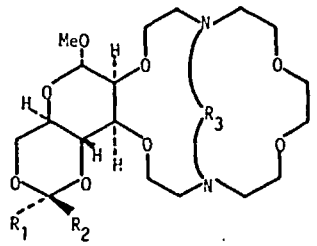
2b: R_1 = Ph, R_2 = Me, R_3 = H

2c: R_1 = Ph, R_2 = Me, R_3 =



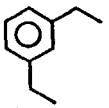
2d: R_1 = Ph, R_2 = Me, R_3 =



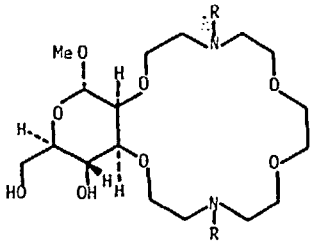


3a: R_1 = Ph, R_2 = Me

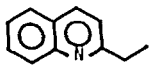
R_3 =



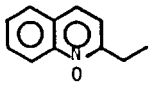
3b: 4,6-O deprotected

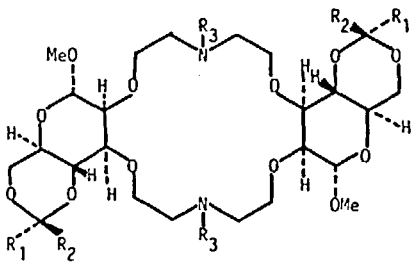


4a: R =



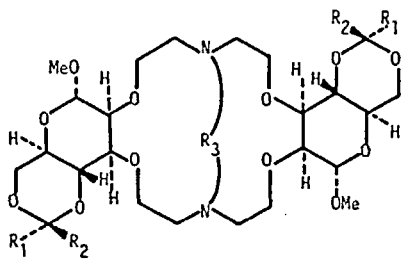
4b: R =



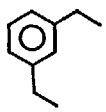


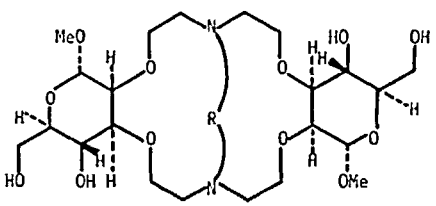
5a: R_1 = R_2 = Me

R_3 = Me

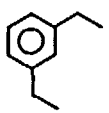


6a: R_1 = R_2 = Me, R_3 =





7a: R =



SCHEME 1

Clearly, now, as the chiral host is developed in complexity, binding inhibition because of steric reasons is a factor which needs to be considered.

A further type of chiral recognition is potentially possible with these types of host receptor. The introduction of ligating "side arms" at the nitrogen atoms in the 4,13-diaza-18-crown-6 macrocycle leads to stronger binding of alkali metal cations compared to the parent macrocycle.[6] Two types of configuration (*cis* and *trans* geometries) are observed in these systems, and are illustrated schematically in Figure 2.

The increased encapsulation leads to high stability constants. If the ligating "side arms" are incorporated into the chiral D-mannopyranoside-containing diazamacrocycles **2c**, **2d**, then so-called "cascade complexes"[7] may be formed with chiral alkali metal ion carboxylates. The metal ion would be expected to sit in the cavity of the chiral host in the *cis* arrangement and also be "ion paired" with the carboxylate group of the chiral guest species, as shown schematically in Figure 3B.

It should be noted, however, that only the *cis* geometry provides a potential opportunity for the chiral guest to interact closely with the chiral residue of the host and hence show enantioselectivity. In the *trans* case geometry, the upper ligating "side arm" would leave little room (if any) for the approach of the chiral guest species.

The recent X-ray crystal structure determinations of **1b** and **1c** have revealed interesting differences.[8] Whereas in **1b** the two pendant side groups were located far apart from each other, in a *trans* relationship, they were in a *cis* relationship in **1c**. Thus **1c** was expected to be a better host for alkali metal ion carboxylates.

The *cis*-geometry (like in Figure 3B) was expected to occur in **2d**, because the location of two bulky groups in a *cis* arrangement on the same side of the diazacrown as the sugar unit was not expected to happen for steric reasons.

Chiral recognition in this system depends on the chiral group in the host macrocycle closely recognising a particular enantiomer of the chiral carboxylate which is ion-paired to the alkali cation.

Our recent investigations with the "all-oxygen" chiral crown ethers incorporating the D-mannopyranoside unit indicated that removal of the acetal group at the 4,6 position led to enhanced chiral recognition of amino acids in transport experiments across liquid membranes.[10] It is likely that the two hydroxyl groups support a complementary binding through hydrogen bonding with the amino acid.

The acetal groups at the 4,6 position in the sugar unit are easily deprotected (**3b**, **4a**, **4b**, and **7a**) under mild acid conditions, yielding free hydroxyl groups which may serve as additional binding "arms". These sites may contribute to the overall complexation strength through hydrogen bonding to the carboxylic groups of chiral

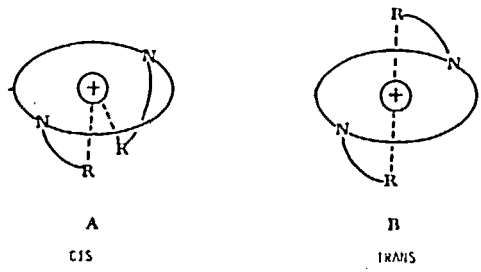


FIGURE 2 Binding modes by hosts containing two ligating "side arms".

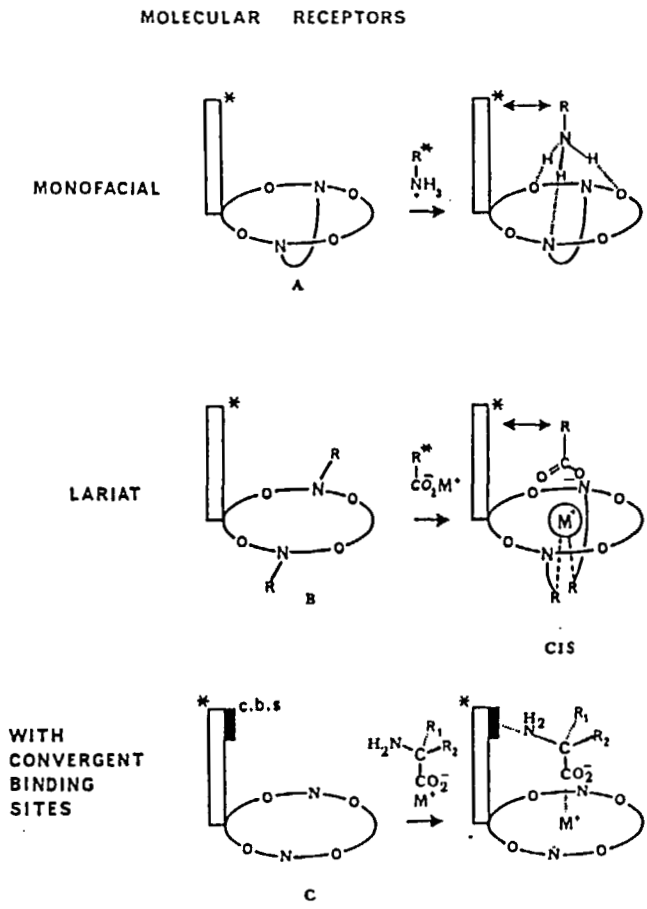


FIGURE 3 Binding modes in three classes of molecular receptors.

primary ammonium cations derived from amino acids, or alternatively, to the amino group of alkali metal carboxylates derived from amino acids—so-called "cascade complexes". This approach generates a new family of chiral host molecules that can be thought of as receptors containing "convergent binding sites",[9] Figure 3C. The "extra" binding side defines the overall binding "pocket" on the chiral host receptor much more closely and requires a more defined spatial orientation of the chiral guest species which should be reflected in higher enantioselectivity. Though not presented here, the same two-site binding model can also be envisaged for the complexation of chiral primary ammonium cations, Figure 3A, *i.e.*, by removing the acetal protecting group from **2a**, **2b**.

^{1}H-NMR spectroscopy was selected as a tool for the complexation studies. In the sugar units, the anomeric protons and the methyl group in **3a** (R_2) were expected to serve as the NMR probes for variable-temperature host-guest complexation studies, since these are rigidly positioned closely over the active binding site.

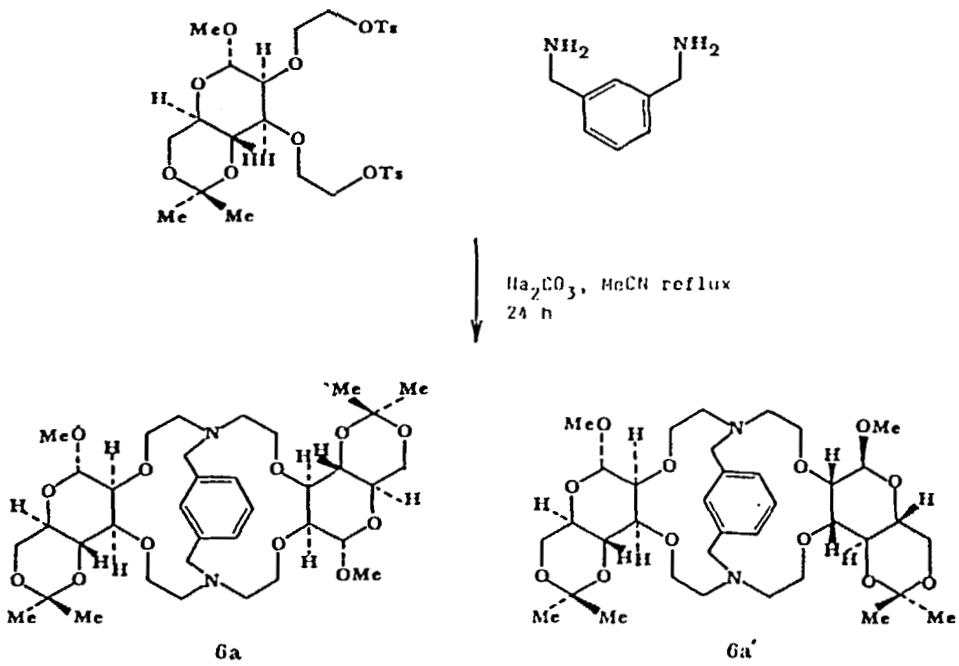


FIGURE 4 One-step macrobicyclization reaction leading to hosts incorporating two rigid chiral units.

RESULTS AND DISCUSSION

Synthesis

The chiral blocks, methyl 4,6-O-(R)-isopropylidene-α-D-mannopyranoside[11] and 4,6-O-(R)-phenylethylidene-α-D-mannopyranoside[12] (the kinetic product of the reaction between α-methoxystyrene and methyl α-D-mannopyranoside) were incorporated into the host structures using routine procedures.[13,14] The synthetic route to host **6a** is shown in Figure 4. This was obtained *via* a template-directed macrobicyclization procedure,[15] and was separated from **6a'** by chromatography. Distinction between the **6a** and **6a'** isomers was made on the basis of ^{1}H-NMR spectra, since **6a** (C_2 symmetry) gives a singlet for the two anomeric protons and two singlets for the isopropylidene methyl groups. The isomer **6a'** displays two separate singlets for the two anomeric protons and four signals for the isopropylidene methyl groups, consistent with the lack of symmetry.

VARIABLE TEMPERATURE ^{1}H NMR SPECTROSCOPIC STUDIES OF INCLUSION COMPLEXES

Enantiomeric discrimination of chiral guest molecules by chiral hosts can be conveniently followed by variable temperature (VT) NMR spectroscopy using the methods described in the literature.[16]

The process that can be observed by NMR spectroscopy is the following:

$$H^* + GH \rightleftarrows GH^* + G$$

Where *H* and *G* refers to host and guest species, respectively. When the exchange process is slow on the NMR time scale, we can observe separate signals for the complexed and uncomplexed host molecules, provided that the host molecule contains groups of protons giving well resolved signals in its ^{1}H NMR spectra and furthermore, that the positions of these signals should be different in the free host molecule and in the complex to ensure the exchange process can be observed.

Accordingly, the chiral primary ammonium salts were mixed with the chiral hosts in a 1:2 ratio, dissolved in CD_2Cl_2, and VT ^{1}H NMR spectra were recorded after dissolution of the substrates.

The chiral carboxylates were mixed with the chiral hosts in CD_3OD, since the solubility of the complexes formed was low in other solvents.

In case of cascade complexes with chiral carboxylates only the binding mode shown schematically in Figure 3B would lead to meaningful chiral discrimination.

As NMR probes two singlets where chosen: the anomeric proton (H-1) and the methyl group in the 4,6-O-acetal protecting group. In the case where the protection group was removed, the H-1 proton was the only available signal as an NMR probe.

Extraction Experiments

To complement the VT NMR studies we decided to run enantioselective extraction experiments involving the chiral hosts and either chiral primary ammonium cations or chiral carboxylates. The water phase contained the guest species and the $CDCl_3$ phase contained the host compounds. Full details are given in the experimental section. The population of **R** and **S** isomers was estimated on the basis of integrating a well resolved signal in the ^{1}H-NMR spectrum for the guest species as described in the preceding section.

DISCUSSION

Complexation Studies by ^{1}H-NMR

The VT ^{1}H-NMR studies of complexes with chiral primary ammonium cations showed unexpectedly, coalescence of the signals for the anomeric proton or the methyl group in the acetal function in only a few cases.

Table 1 shows the results for the complexation of phenylglycine hydrochloride with the ligands **3a** and **3b**. The higher coalescence temperature for the complex involving host **3b** (deprotected) reflects additional binding probably related to hydrogen bonding between the two hydroxyl groups in the 4,6 position in the ligand and the guest cation.

The hosts **6a** and **7a** did not display any conclusive results at the low temperature limit for complexation.

Similarly, complexation studies with chiral alkali metal carboxylates of amino acids were disappointing. The ligands **2c**, **2d**, **4a**, and **4b** were designed to form so-called cascade complexes with alkali metal ion chiral carboxylates. Generally, these

TABLE I

VT ^{1}H-NMR spectroscopic studies of complexes with chiral primary ammonium cations in CD_2Cl_2 solution. Host:guest ratio, 2:1.

Host	Guest	Coalescence temperature T_c (K)	$\Delta\nu$ (Hz)	$\Delta G_c^{\ddagger}$ (Kcal mol^{-1})
3a	(S)-PhGlyMeHCl[a]	196.3	10	10.1
	(R)-PhGlyMeHCl	212.2	12	10.9
3b	(S)-PhGlyMeHCl	266.4	8	14.0
	(R)-PhGlyMeHCl	—	—	—

[a] PhGlyMeHCl = $PhCH(NH_2)CO_2Me.HCl$.

TABLE II

VT ^{1}H-NMR spectroscopic studies of complexes with chiral alkali metal carboxylates of amino acids in MeOH-d_4 solution. Host:guest ratio, 2:1.

Host	Guest	Coalescence temperature T_c (K)	$\Delta\nu$ (Hz)	$\Delta G_c^{\ddagger}$ (Kcal mol^{-1})
2d	(S)-PhGlyNa[a]	238.6	44	11.7
	(R)-PhGlyNa	238.8	43	11.7

[a] PhGlyNa = $PhCH(NH_2)CO_2Na$.

complexes were not soluble in CD_2Cl_2 and so their low-temperature spectra were recorded in CD_3OD at the risk of lower complex stability, due to the higher polarity of CD_3OD.

Only in the case of ligand **2d**, was unequivocable coalescence observed (Table II), but calculations of the free energy of activation for the exchange process revealed no differences in binding strength for **R** or **S** sodium phenylglycinate.

Complexation Studies by Extraction

For the extraction experiments, α-phenylalanine was selected as a guest, since it possesses a methyl group that gives a well separated singlet in the ^{1}H NMR spectrum that can be used as a convenient probe. The hosts' discrimination between the **R** and **S** enantiomers on complexation was assessed by extraction of the pure enantiomer alone under similar conditions as a comparison. Extraction experiments involving all the host molecules and the model guest-(racemic) α-phenylalanine in the form of its perchlorate salt, complemented the VT NMR studies. The results are shown in Tables III and IV.

For the hosts **3a** and **6a**, the **R** enantiomer was preferentially extracted, although it should be noted that in the case of **6a** the ratio of **R:S** was lower than for host **3a**, indicating that despite the incorporation of greater chirality in **6a** (two chiral

TABLE III
Enantioselective extraction experiments with primary ammonium salts.[a]

Host	Guest	R:S
3a	± PhAla[b]	64:36
3b	± PhAlaK	75:25
6a	± PhAla	58:42
7a	± PhAla	73:27

[a] R/S population estimated by integration of the CH_3 signals of the amino acid.
[b] PhAla:$PhCCH_3(NH_2)CO_2Me.HClO_4$.

TABLE IV
Enantioselective extraction experiments with chiral alkali metal carboxylates of α-phenylalanine.[a]

Host	Guest	R:S
2c	± PhAlaNa[b]	50:50
	± PhAlaK	50:50
2d	± PhAlaNa	39:61
	± PhAlaK	28:72
4a	± PhAlaNa	41:59
	± PhAlaK	33:67
4b	± PhAlaNa	33:67
	± PhAlaK	21:79

[a] R/S population estimated by integration of the CH_3 signals of the amino acid.
[b] PhAlaNa(K):$PhCCH_3(NH_2)CO_2Na(K)$.

carbohydrate units) the binding cavity was probably too sterically hindered for efficient complexation.

Interestingly, the ratio R:S for the hosts **3b** and **7a**—related to **3a** and **6a** by simple deprotection—is now much higher and this may be attributed to convergent binding involving the two, or four free hydroxyl groups. Generally, deprotected ligands displayed better chiral recognition. It is interesting to note that all cases where chiral recognition was shown towards primary ammonium cation, this was always in favour of the **R** enantiomer.

The so-called cascade complexation studies with chiral alkali metal carboxylates of amino acids—unsuccessful by ^1H NMR because of poor solubility—were more amenable to study by extraction and the results are shown in Table IV.

The host **2c** did not show any chiral recognition. Solid state studies[8] show that the methylquinoline-derived ligating groups are located on opposite sides of the diazamacrocyclic ring (Figure 2B) in *trans* relationship. Such a conformation at the

binding site on complexation would throw the amino acid carboxylate anion out of close proximity to the chiral unit and hence little chiral recognition would be evident. It should be noted, however, that on deprotection to give **4a**, distinct enantioselectivity was shown probably due to a convergent binding site now involving the free hydroxyl groups.

The host **2d** appeared to be much more efficient in enantioselection than **2c**. This is probably due to the fact that the binding site in **2d** has a cryptand-like structure in the solid state.[8] Both methylquinoline N-oxide-derived ligating groups are located on the opposite side of the sugar unit in a *cis* arrangement, creating a "nest" for the alkali metal ion, which is ion-paired with the carboylate anion. This time, the latter is not prevented sterically from interacting with the chiral unit of the host. Again, the deprotected ligand **4b** was more efficient in enantioselectivity than **4a**.

In all cases, the potassium salts were extracted with higher enantioselectivity than the respective sodium salts. It is also interesting to note that where chiral recognition was shown towards chiral alkali metal carboxylates, the S enantiomer was always preferentially extracted.

CONCLUSIONS

In this paper, it has been shown that chiral diaza crown ethers and cryptands incorporating rigid sugar units are able to show enantio-selectivity towards chiral primary ammonium guest cations and chiral alkali metal ion carboxylates. Hosts have been presented with the incorporated sugar units being in their acetal-protected forms or deprotected forms. Enantioselectivity towards the **R** enantiomer was observed in the case of primary ammonium cations, whereas S enantioselectivity was found for chiral alkali metal ion carboxylates. Enantioselection in the latter case may be regulated to some extent by the nature of metal ion involved. The introduction of two rigid, chiral sugar units into the macrocyclic framework did not lead to more efficient chiral recognition. It is likely that the binding site was too sterically crowded by chiral units to allow efficient accommodation guest molecules. Free hydroxyl groups in the chiral sugar units, available when the latter are deprotected, provided additional binding as convergent binding sites. Deprotected hosts always exhibited better chiral recognition. Work is continuing towards the preparation of crystalline samples of the complexes to allow X-ray structural determination to be carried out.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

General

All reagents were purchased from Fluka or Aldrich and used without further purification. ^{1}H NMR spectra were recorded on Bruker WH400 or Varian Gemini 200 instruments. The exact temperature measurements inside the NMR probe during VT experiments were made using a Comark thermocouple in an NMR tube containing CH_2Cl_2. Mass spectra were recorded on a Kratos MS8ORF spectrometer equipped with a FAB facility, 8keV, xenon primary atom beam, 3-nitrobenzyl alcohol

matrix. Microanalyses were obtained at the Institute of Organic Chemistry of the Polish Academy of Sciences, Warsaw, Poland.

Synthesis

All the compounds described, except host **6a**, were prepared according to known procedures.[13,14] The diaza crown ether **2b** incorporating the D-mannopyranoside unit, was used as the basic building block. Reaction with 2-chloromethylquinoline, 2-chloromethylquinoline-1-oxide and 1,3-bis(bromomethyl)benzene in acetonitrile at 80°C in the presence of finely powdered and dried Na_2CO_3 gave compounds **2c**, **2d**, and **3a**, respectively. The ligands were isolated by chromatography on alumina (Merck 90) using 5% MeOH (v/v) in $CHCl_3$ as eluent.

Ligand **6a** was obtained by the reported template-directed macrobicyclization procedure,[15] and isolated by chromatography on alumina (2% MeOH in $CHCl_3$ as eluent).

Deprotection of all ligands was achieved in 1% HCl in MeOH at room temperature followed by neutralization with solid Na_2CO_3, evaporation of the solvent and short chromatographic filtration.

Analytical Data

Ligand 2c:

^{1}H NMR ($CDCl_3$, ref TMS, 400 MHz) δ: 1.58 (s, 3H, CH_3), 2.77 (t, 4H, J = 6 Hz, 2 × NCH_2), 2.79 (t, 4H, J = 6 Hz, 2 × NCH_3), 3.33 (s, 3H, OCH_3), 3.49–3.65 (m, 18H, 6 × OCH_2, and sugar protons), 3.98 (s, 2H, CH_2-quin), 4.00 (s, 2H, CH_2-quin), 5.05 (s, 1H, H-1), 7.16 (tt, 1H, Ph), 7.23 (tt, 4H, Ph), 7.48–7.58 (m, 2H, quin), 7.66–7.80 (m, 6H, quin), 8.03–8.11 (m, 4H, quin).

Elem. anal. calcd for $C_{45}H_{54}N_4O_8$: C: 69.39; H: 6.99; N: 7.19
found: C: 69.31; H: 6.91; N: 7.10

FAB(+)MS: 666, 779($M+H^+$), 801 ($M+Na^+$).

Ligand 2d:

^{1}H NMR ($CDCl_3$, ref TMS, 400 MHz) δ: 1.57 (s, 3H, CH_3), 2.80 (t, 4H, J = 6 Hz, 2 × NCH_2), 2.84 (t, 4H, J = 6 Hz, 2 × NCH_2), 3.34 (s, 3H, OCH_3), 3.49–3.65 (m, 18H, 6 × OCH_2, and sugar protons), 4.20 (bd, 2H, CH_2-quin-O), 4.21 (bd, 2H, CH_2-quin-O), 5.06 (s, 1H, H-1), 7.07 (tt, 1H, Ph), 7.16 (tt, 4H, Ph), 7.46–7.94 (m, 10H, quin-O), 8.75 (m, 2H, quin-O).

Elem. anal. calcd for $C_{45}H_{54}N_4O_{10}$: C: 66.65; H: 6.71; N: 6.91
found: C: 66.57; H: 6.96; N: 6.82

FAB(+)MS: 654, 811 ($M+H^+$), 833 ($M+Na^+$).

Ligand 3a:

^{1}H NMR ($CDCl_3$, ref TMS, 400 MHz) δ: 1.60 (s, 3H, CH_3), 2.40–2.78 (m, 8H, 4 × NCH_2), 3.32–3.86 (m, 18H, 4 × OCH_2, and sugar protons), 3.42 (s, 3H, OCH_3), 4.20–4.35 (m, 4H, CH_2-m-xyl-CH_2), 5.07 (s, 1H, H-1), 6.93–7.55 (m, 9H, Ph, m-xyl).

Elem. anal. calcd for $C_{33}H_{46}N_2O_8$: C: 66.20; H: 7.74; N: 4.68
found: C: 66.25; H: 7.69; N: 4.63

FAB(+)MS: 599 ($M+H^+$), 621 ($M+Na^+$).

Ligand 6a:
^{1}H NMR ($CDCl_3$, ref TMS, 400 MHz) δ: 1.45 (s, 6H, $2\times CH_3$), 1.56 (s, 6H, $2\times CH_3$), 2.61–3.02 (m, 8H, $4\times NCH_2$), 3.30–3.89 (m, 2OH, $4\times OCH_2$, and sugar protons), 4.08 (dd, 4H, J = 10 Hz, CH_2-m-xyl-CH_2), 3.38 (s, 6H, $2\times OCH_3$), 4.66 (s, 2H, H-1), 7.19–7.35 (m, 4H, m-xyl).

Elem. anal. calcd for $C_{36}H_{56}N_2O_{12}$: C: 61.00; H: 7.96; N: 3.95
found: C: 59.87; H: 7.93; N: 3.87

FAB(+)MS: 709 ($M+H^+$), 731 ($M+Na^+$), 747 ($M+K^+$).

Deprotected ligands:
Ligand 3b:
^{1}H NMR ($CDCl_3$, ref TMS, 200 MHz) δ: 2.42–2.76 (m, 8H, $4\times NCH_2$), 3.30–3.84 (m, 18H, $4\times OCH_2$, and sugar protons), 3.40 (s, 3H, OCH_3), 4.20–4.33 (m, 4H, CH_2-m-xyl-CH_2), 4.61 (s, 1H, H-1), 7.35 (m, 4H, m-xyl).
MS (EI): 497 ($M+H^+$), 519 ($M+Na^+$).

Ligand 4a:
^{1}H NMR ($CDCl_3$, ref TMS, 200 MHz) δ: 2.75 (t, 4H, J = 6 Hz, $2\times NCH_2$), 2.79 (t, 4H, J = 6 Hz, $2\times NCH_2$), 3.30 (s, 3H, OCH_3), 3.48–3.66 (m, 18H, $6\times OCH_2$, and sugar protons), 3.95 (s, 2H, CH_2-quin), 4.89 (s, 1H, H-1), 7.46–7.57 (m, 2H, quin), 7.65–7.78 (m, 6H, quin), 8.01–8.10 (m, 4H, quin).
MS (EI): 564, 677 ($M+H^+$), 699 ($M+Na^+$).

Ligand 4b:
^{1}H NMR ($CDCl_3$, ref TMS, 200 MHz) δ: 2.80 (t, 4H, J = 6 Hz, $2\times NCH_2$), 2.85 (t, 4H, J = 6 Hz, $2\times NCH_2$), 3.35 (s, 3H, OCH_3), 3.48–3.66 (m, 18H, $6\times OCH_2$, and sugar protons), 4.20 (bd, 2H, CH_2-quin-O), 4.23 (bd, 2H, CH_2-quin-O), 4.92 (s, 1H, H-1), 7.44–7.95 (m, 10H, quin-O), 8.77 (m, 2H, quin-O).
MS (EI): 522, 709 ($M+H^+$), 731 ($M+Na^+$).

Ligand 7a:
^{1}H NMR ($CDCl_3$, ref TMS, 200 MHz) δ: 2.60–3.01 (m, 8H, $4\times NCH_2$), 3.32–3.87 (m, 20H, $4\times OCH_2$, and sugar protons), 4.06 (dd, 4H, J = 10 Hz, CH_2-m-xyl-CH_2), 3.36 (s, 6H, $2\times OCH_3$), 4.64 (s, 2H, H-1), 7.20–7.33 (m, 4H, m-xyl).
MS (EI): 629 ($M+H^+$), 651 ($M+Na^+$).

All protected and deprotected compounds were viscous oils.

VT NMR and Extraction Experiments

The chiral hosts were used in amounts typically around 10–20 mg, and the calculated amounts of amino acid methyl esters in the form of their ammonium salts were added as solids to the solution of the hosts in CD_2Cl_2. Dissolution was instantaneous.

Stock solutions of the sodium or potassium salts of the chiral carboxylates derived from amino acids were freshly prepared in MeOH and the calculated amounts were evaporated to dryness at high vacuum to avoid possible racemization. Solutions of

the chiral hosts in CD_3OD were added to the solid salts and subjected to ultrasound for 10 min. for complete solubilization.

The free energy of activation for the exchange process was calculated from the expression[17]:

$$\Delta G_c^{\ddagger} = 4.575 \times 10^{-3} T_c(9.972 + \log T_c/\Delta v) \text{ in kcal mol}^{-1}$$

Extraction experiments were performed with racemic α-phenylalanine in the form of its methyl ester perchlorate in extraction experiments with primary ammonium salts. For extraction studies with chiral alkali metal carboxylates of α-phenylalanine, the potassium or sodium salts were used. A three-fold excess of the perchlorate was used in the water phase, and a twenty-fold excess of the sodium or potassium salt was needed. The alkali metal satls were prepared prior to use to avoid racemization.

To establish which enantiomer was preferentially extracted, additional extractions with pure **R** enantiomer were done. The solutions containing the guest species in water and the hosts in $CDCl_3$ were shaken vigorously together for 1 h and left to separate until clear phases were formed. A sample from the organic phase was taken, evaporated to dryness and its ^1H NMR spectrum recorded. The **R**:**S** populations were estimated from the integrals, taking the methyl group of the guest molecules as a diagnostic signal.

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