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SYNTHESIS AND COMPLEXING PROPERTIES OF A CHIRAL MACROCYCLIC MOLECULAR RECEPTOR WITH CONVERGENT BINDING SITES

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ABSTRACT. Two novel hosts: 15-crown-5 and N-benzyl-aza-15-crown-5 incorporating a boron-containing D-mannopyranosidic unit form more stable cascade complexes with (S)-amino acid sodium or potassium salts than with the respective (R)-enantiomers. Complexes with sodium salts are more stable than the corresponding complexes with potassium salts as revealed by variable-temperature NMR measurements. Strong non-bonded interaction between the sugar unit and the α-substituents of the amino acids results in enantiomeric differentiation and destabilization of the complex. Complex formation is interpreted in terms of ion-pair inclusion by macrocyclic ring and nitrogen-boron interaction.

1. INTRODUCTION

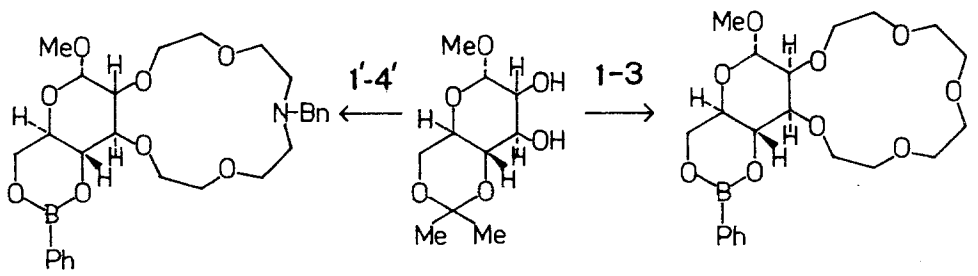
Considerable work has been done in the field of chiral hosts capable of discriminating between enantiomeric guest molecules. A variety of chiral residues either synthetic or derived from natural products [1] (sugars, tartaric acid, amino acids etc.) have been fused to macrocyclic rings. In most cases, chiral primary ammonium cations have been the guest species of choice, although the complexation of chiral carboxylates has been examined to some extent [2].

Amino acids possess two functional groups able to participate in complexation. Appropriate design of the host molecule can lead to a particular host containing two binding sites specific for amino and carboxylic groups.

It is well known that crown ethers form inclusion complexes with ion pairs in aprotic solvents. Phenylboronic cyclic esters form adducts with amines [3], making them good candidates as convergent binding sites for amino groups. Linking these specific binding sites with a chiral residue was the aim of this work as well as an examination

of the complexing properties of the new molecules as enantioselective complexers for amino acid carboxylates by means of VT proton NMR spectroscopy.

Two new chiral macrocyclic compounds containing both a crown ether and a boronic ester were prepared from methyl 4,6-O-isopropylidene-α-D-mannopyranoside |4| as shown in Figure.



B A

1': $(ClCH_2CH_2)_2O$, $Bu_4^nNHSO_4$, NaOH 50%, PTC, 25°, 20h, 75%, |5|

2': $PhCH_2NH_2$, MeCN, refl., Na_2CO_3, 30%, |6|

3': HCl/MeOH, 25°, 2h

4': $PhB(OH)_2$, 75%

1: $TsOCH_2(CH_2OCH_2)_2CH_2OTs$, NaH, DMSO,

2: Dowex-50, MeOH, 2h

3: $PhB(OH)_2$, 90%

2. MATERIALS AND METHODS

The reagents were purchased from Fluka and used without purification except dimethyl sulphoxide and acetonitrile, which were dried and distilled over calcium hydride. Both new compounds A and B gave satisfactory microanalyses and NMR spectra. Selected amino acids: (R)- and (S)-alanine (Ala), (R)- and (S)-phenylglycine (PhGly) and (R)- and (S)- β-phenylalanine (β-PhAla) as their sodium and potassium salts were dried in vacuo over phosphorus pentoxide prior to use and served as guest species. The host/guest ratio was 2:1 in deuteriochloroform solutions. Dissolution of solid salt was accomplished in an ultrasonic bath within 20 to 100 min. The host concentration was ca. 0.1 M. All the variable-temperature spectra were recorded with JEOL-JNM-4H-100 spectrometer at 100 MHz with TMS as internal standard and lock. The anomeric proton served as an NMR probe. The free energy of activation at the coalescence temperature was calculated from the expression |7|:

$$\Delta G_c^{\neq} = 4.575 \times 10^{-3} T_c \, (9.972 + \log T_c/\Delta\nu \,).$$

in kcal mol^{-1}.

3. RESULTS

The ^{1}H NMR spectra of solutions containing the free ligand and the complex in a 1:1 ratio showed one signal for the anomeric proton at ambient temperature, indicating fast exchange between nonequivalent sites. Cooling the samples resulted in line broadening and finally splitting of the anomeric proton signal into two components attributed to the 1:1 complex and the free ligand. Generally, higher coalescence temperatures were observed for the samples containing (S)-enantiomers. The complexes with the potassium were less stable than those with the sodium carboxylates. Thermodynamic data are collected in the Table.

Table I. Kinetic stabilities of inclusion complexes involving the hosts A and B and alkali metal carboxylates of the amino acids

Amino acid salt	HOST A			HOST B		
	Tc[a]	$\Delta\nu$[b]	$\Delta G_c^{\neq}$[c]	Tc	$\Delta\nu$	$\Delta G_c^{\neq}$
(R)-Ala$^-$Na$^+$ [d]	228	11	11.8	225	10	11.6
(S)-Ala$^-$Na$^+$	245	15	12.5	240	15	12.3
(R)-Ala$^-$K$^+$	218	10	11.3	212	9	11.0
(S)-Ala$^-$K$^+$	226	16	11.5	220	13	11.3
(R)-PhGly$^-$Na$^+$ [e]	214	9	11.1	210	10	10.9
(S)-PhGly$^-$Na$^+$	225	13	11.5	222	17	11.3
(R)-PhGly$^-$K$^+$	-	-	-	207	9	10.7
(S)-PhGly$^-$K$^+$	231	12	11.9	220	14	11.2
(R)-β-PhAla$^-$Na$^-$ [f]	225	14	11.5	222	16	11.3
(S)-β-PhAla$^-$Na$^+$	240	21	12.1	232	22	11.6
(R)-β-PhAla$^-$K$^+$	215	12	11.0	209	11	10.8
(S)-β-PhAla$^-$K$^+$	227	18	11.5	223	16	11.3

[a] Coalescence temperature (°K). [b] $\Delta\nu$ is the frequency separation (in Hz) of the two signals in the slow exchange limit. [c] Free energy of activation in kcal mol^{-1} (see Ref. |7|). [d] Ala$^-$Na$^+$; $CH_3CH(NH_2)CO_2^-Na^+$. [e] PhGly$^-$Na$^+$; $PhCH(NH_2)CO_2^-Na^+$. β-PhAla$^-$Na$^+$; $PhCH_2CH(NH_2)CO_2^-Na^+$.

4. DISCUSSION

It was assumed that the amino acid carboxylates form complexes with A and B in a cascade mode, i.e. the alkali cation is held in the cavity of the macrocycle and ion-paired with carboxylate group, and the amino group is linked to the boron site. This model of complexation would lead to highly defined complexes in which remarkable differentiation between enantiomers is achieved through non-bonded interactions between substituents at the α-carbon atom of the guest and the chiral unit. On the other hand, if these steric interactions are too strong, they will lead to destabilization of the complex. In fact, the observed coalescence temperatures are not very much higher than those reported for the inclusion complexes with primary ammonium cations |8|. Probably, steric interactions contribute significantly to destabilization of the complexes.

This interpretation can be supported by an observed slow dissolution of the solid salts in the guest solutions.

Potassium carboxylates form weaker complexes, probably due to weaker complexation of the potassium cation which is too large to fit into the cavity of the 15-membered macrocyclic ring. There is also a very small difference between hosts A and B in their strength of complexation.

The (S)-enantiomers form stronger complexes with hosts A and B. Although some enantioselectivity was achieved, it is difficult to draw a final conclusion about the stereochemical nature of these complexes. An attempts are made to obtain a good crystals for an X-ray analysis.

5. ACKNOWLEDGEMENT

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