Pergamon

Tetrahedron Letters 40 (1999) 4997–5000

TETRAHEDRON LETTERS

Chiral Recognition Properties of Spiroacetal Polyethers Using Electrospray Ionisation Mass Spectrometry

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Received 6 April 1999; accepted 6 May 1999

Abstract : Associations between monocyclic or bicyclic polyethers (**1** - **10**) incorporating a chiral spiroacetal moiety and ammonium enantiomeric pairs of phenylglycine methyl ester (**G1**) or phenyl glycinol (**G2**) were studied by Electrospray Ionisation Mass Spectrometry by the enantiomer-labelled method. Several spiro-crowns and spiro-cryptands showed chiral recognition properties.
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Keywords: Spiroacetal, crown ethers, cryptands, recognition, enantiomer-labelled, ESMS

Since the pioneering work of Cram and co-workers[1] on crown ethers incorporating a 1,1'-binaphtyl chiral centre, a great number of optically active macrocycles have been described that will discriminate between enantiomeric forms by specific associations. This important field was recently reviewed for amine compounds recognition.[2]

Host receptors often contain the molecular framework 18-crown-6 (18C6) linked to a chirality source introducing a helical conformation, such as twisted aromatic moities.[3] Alternatively, helicity could be induced by a spiran junction included in an appropriate structure, but to our knowledge this possibility has been scarcely examined.[4] Among numerous possible models, spiroacetals would be valid supporting skeletons for this purpose. Much research has been conducted on their enantioselective synthesis because these moieties are present in many natural compounds.[5] In the course of our investigations in this domain, we recently developed new structures of the spiro-bisdioxane type, conveniently 2- and 8-functionalized.[6] This recently enabled us to synthesize the optically active crown[7] and cryptand-like[8] macrocycles shown in Scheme 1; structures with X = O were C_2-symmetric. The synthesis was initiated from a commercially available 3-carbon chiral synthon and presented some flexibility, for instance a nitrogen could be introduced in the 10 position allowing further functionalization.

The complexing abilities of these new macrocycles were evaluated with representative ligands **4** (X = O, n = 3)[7] and **7** (X = O)[8] in THF. Both formed complexes with alkaline cations, and K^+ was preferred (log β_{11}: 3.24 and 4.80 respectively), but the selectivity scale was different in the alkaline series. Also, cryptand **7** showed a notable complexation with NH_4^+ (log β_{11}: 3.73) suggesting likely the formation of complexes with ammonium guest enantiomers.

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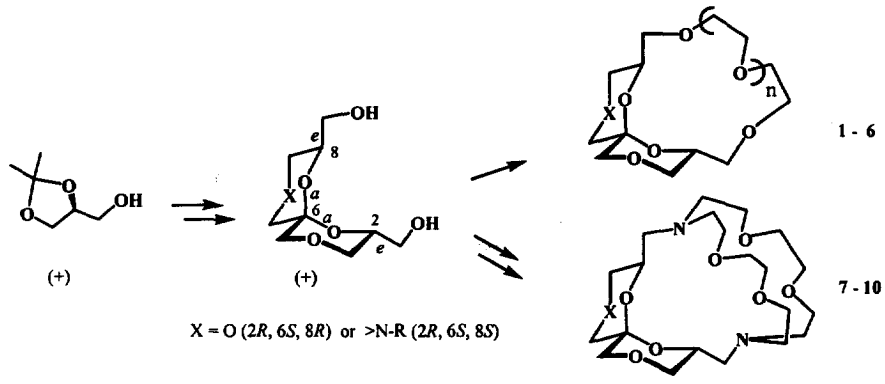
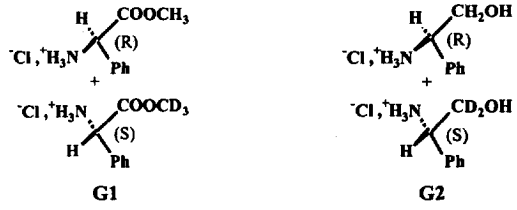
PII: S0040-4039(99)00916-8



Scheme 1

Today electrospray mass spectrometry (ESMS)[9] is widely used for the characterization of synthetical non-covalent complexes.[10] For this kind of compounds, this technique is very attractive since it requires very small amounts of sample (1 pmole) and allows the relative quantization of species present in equilibrium in diluted solution.[11] For studying the formation of our chiral host-guest complexes, we have chosen the ESMS approach developped by Sawada and co-workers.[12] This approach consists in studying by ESMS the solution obtained by mixing the host to be tested and a 1:1 mixture of (+) and (-) guest, with one of the enantiomers isotopically labelled.

Experiments by ESMS[12] with ligands **1** - **10** were performed in methanol for two ammonium guests that frequently appear in the literature: phenylglycine methyl ester **G1** and phenylglycinol **G2** hydrochlorides (Scheme 2). They were prepared by conventional methods from (*R*) or (*S*)-phenylglycine. (*S*)-Labelling was incorporated from CD_3OD or $NaBD_4$, and checked by NMR and MS.

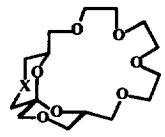
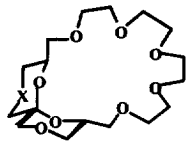
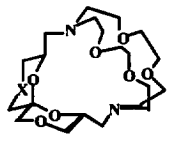


Scheme 2

The results obtained are presented in Table 1. ESMS intensities ratio of the peak (*R*)/(*S*) (unlabelled/labelled) are stated for the inclusion complexes. Some experiments were also carried out with (*R*)-[$^2H_3$] labelling for **G1**, in which case intensities ratio unlabelled/labelled obtained were correctly inverted, within the limit of experimental error. This confirmed the reliability of the method, and also of the chiral discrimination between (*R*) and (*S*) guests for several ligands. Ratios were in the range of those published for other different chiral ligands in methanol.[12]

From this first investigation various degrees of chiral recognition properties emerged for the new ligands synthesized. The highest ratios were recorded for C_2 symmetric spiro-crown **4** with (*R*)-phenyl glycinol and spiro-cryptands **7** to **10** with (*R*)-phenylglycine methyl ester. N-functionalization which created asymmetric structures did not markedly change the complexation for bicyclic systems while monocyclic polyethers were sensitive to the N-branched function. Given that, as the synthesis of the free secondary amine precursor proved straightforward,[7] this result was a strong incentive to continuing work in this field with new N-substitution.

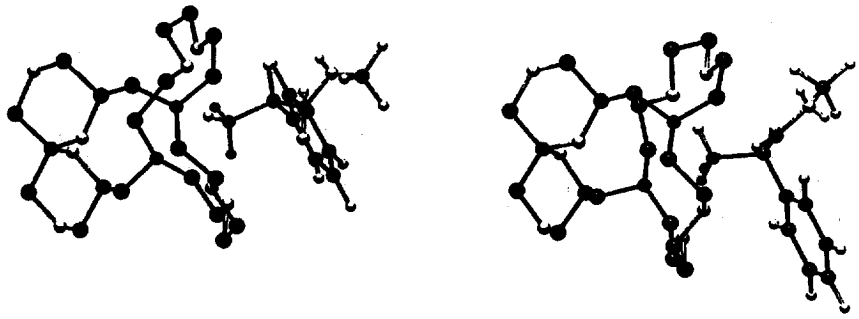
Table 1 : ESMS intensities ratio (*R*)/(*S*) for the diastereomeric complexes between ligands **1-10** and ammonium enantiomeric pairs **G1** and **G2** with respectively (*S*)-[$^2H_3$] and (*S*)-[$^2H_2$] labelling

Ligands	N°	X =	G1	G2
	**1**	-O-	1.06**	1.00
	2	>N-CH_2COOEt	1.16 (0.85)*	1.07
	3	>N-CH_2COOH	1.14	1.23
	**4**	-O-	1.00	1.41
	5	>N-C(O)-C_6H_5	0.95	1.24
	6	>N-CH_2-C_6H_5	0.82	1.15
	**7**	-O-	1.47	1.07
	8	>N-C(O)-C_6H_5	1.43	1.00
	9	>N-CH_2-C_6H_5	1.58 (0.60)*	1.04
	10	>N-CH_2-COOEt	1.58	1.05

* Values unlabelled/labelled obtained for a cross-chiral labelling of the enantiomer (*R*)-[$^2H_3$]

** Reference achiral compounds 18C6 and [2.2.2] cryptand gave ≈ 1.00 in the same conditions.

In the complexation process the ammonium group of the guest molecule must interact by hydrogen bondings with donor atoms in a tripod or tetrapod fashion.[1,2] For bicyclic systems such as **7 - 10** interactions probably took place in the diaza-crown part of the structure which offers six donor atoms evenly distributed in the ring; hydrogens in the spiroacetal skeleton sterically hindered access to corresponding oxygens. Computer simulated complexes with cryptand **7** and **G1**(*R*) and (*S*)[14] are shown in Scheme 3 (H-bondings are omitted for clarity).



complex **7** - **G1**(*R*) complex **7** - **G1**(*S*)

Scheme 3

Strains on the two nitrogens of the diaza-crown system are asymmetrical. Scheme 3 shows that this can induce different conformations for **7 - G1(*R*)** and **7 - G1(*S*)**. Determination of the thermodynamic parameters for this new type of host-guest equilibrium will provide a better understanding of the discrimination efficiency. This will accordingly be the subject of further work.

AVD, EL and HN thank the TMR-Project EU Nr. ERBFMRXCT980226 on Nanometer Size Metallic Complexes for the financial support of the ESMS work.

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13. Positive ES mass spectra were obtained on a ES triple quadrupole mass spectrometer Quattro II with a m/Z range extended to 8000 (Micromass, Altrincham, UK). The ES source was heated to 60°C. The sampling cone voltage (Vc) was at 20 Volts to avoid any fragmentation processes. Sample solutions were introduced into the mass spectrometer source with a syringe pump (Harvard type 55 1111: Harvard Apparatus Inc., South Natick, MA, USA) with a flow rate of 5 $\mu l.min^{-1}$. Calibration was performed using protonated horse myoglobin. Scanning was performed from m/Z 100 to 1000 in 10s, and several scans were summed to obtain the final spectrum.
14. Conformational searches were conducted using the MacroModel/BATCHNIN 5.0 computational chemistry programm package (a) and using AMBER* force field (b). (a) Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Canfield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comput. Chem.* **1990**, *11*, 440-467. (b) MacroModel implementation of AMBER.