



Synthesis of rigid and C_2 -symmetric pyridino-15-crown-5 type macrocycles bearing diamide–diester functions: enantiomeric recognition for chiral primary organoammonium perchlorate salts



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ABSTRACT

Four novel C_2 -symmetric macrocyclic compounds with a pyridine function and possessing amide and ester linkages were prepared. The enantiomeric discrimination abilities of these macrocycles against α -phenylethylammonium and α -(1-naphthyl)ethylammonium perchlorate salts were measured by standard ^1H NMR titration techniques in $\text{DMSO-}d_6$. A binding constant ratio of 31 ($K_{\text{bind}}(\text{S})/K_{\text{bind}}(\text{R})$) for two enantiomers of α -(1-naphthyl)ethylammonium salt with the macrocyclic host (S,S)-**4** bearing phenyl arms was observed, which corresponds to an enantiomeric discrimination of approximately 94%. Molecular dynamic calculations were performed for some of the supramolecular complexes to in order to gain insight into the mode of molecular recognition between the macrocyclic compounds and ammonium salts; these results were consistent with experimental observations, which may be relevant to those in biochemical processes occurring in organisms.

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1. Introduction

Enantiomeric recognition by model systems is essential in our understanding the selectivity of very complex biochemical processes occurring in living organisms, which involves the discrimination of one enantiomer of the guest from the other by a chiral host. Therefore, the design and synthesis of new chiral systems for the selective recognition of small molecules is one of the most challenging topics, which finds broad application, such as enzyme-substrate interactions,¹ asymmetric catalysis,² sensing,³ enantioselective catalysis,⁴ separation science,⁵ development of pharmaceuticals,⁶ biology⁷ and the purification and analysis of enantiomers.⁸ A number of synthetic models have been designed as chiral host molecules to help chemists better understand the basis of the mechanism of host–guest complexation and chiral recognition. The complexation and chiral recognition mechanism are mainly due to non-covalent interactions such as hydrogen bonds, ion-dipole, dipole–dipole interactions, π -stacking, ion– π interactions and hydrophobic interactions, which are also the main driving forces in the maintenance of 3D structures of biological relevance

and their intermolecular interactions. Detailed investigations of chiral recognition phenomena through the elucidation of non-covalent interactions are constantly required for the basis of new approaches in the field of enzyme–substrate interactions, the resolution of enantiomers in chemical processes and asymmetric catalysis. Therefore, the design, synthesis and use of molecules capable of chiral recognition of other molecules are of great interest in these fields.⁹

The study of the recognition of chiral amines and chiral protonated amine compounds is of significance because these compounds are the basic building blocks of biological molecules and therefore, these molecules are frequently used as guests in chiral recognition.¹⁰ Macrocyclic structures have received much attention in the search for artificial receptors, mainly because of their higher degree of preorganization when compared to their acyclic counterparts. A great number of artificial chiral receptors have been synthesized and studied widely.¹⁰ Among these, chiral macrocycles containing pyridine units are dominant structures, due to their ability in chiral discrimination towards organoammonium salts and amino acid derivatives. The pyridine subunits of these macrocycles were reported to be important for tripodal hydrogen bond formation with primary organoammonium salts and π – π interaction with the aromatic moiety of the organoammonium guests.^{10,11} It is also well known that the amide group has a high affinity for cations with

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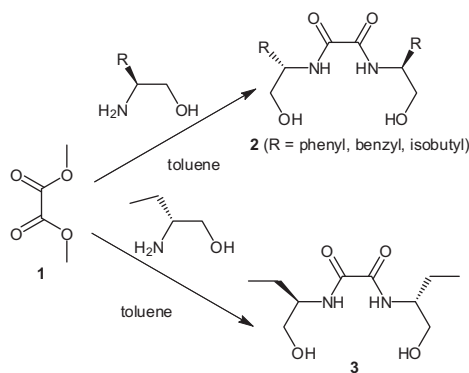
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a high charge density. Many ionophores with amide ligands are currently employed as chemical sensors, quantitatively and reversibly measuring cationic analytes.¹² Cyclic esters (lactones) can be considered as crown ether-like rings and hence are predicted to behave in a similar manner to accommodate organoammonium salts. Pyridine macrocyclic diamides and diesters are widely found in nature and constitute an extensive range of natural products with diverse biological activity.¹³ These natural compounds are complex structures due to the presence of multi-functional groups and their chirality. A number of pyridine-macrocyclic compounds containing diamide–diester groups have been synthesized.^{14,15} However, only a few examples have been reported, that deal with the synthesis and chiral recognition studies of chiral pyridine-macrocyclic containing diamide–diester groups.¹⁵ Herein we report the synthesis of a series of C_2 -symmetric, pyridine and diamide–diester groups containing lactone type macrocycles with different side arms via a high dilution technique, for the recognition of α -chiral primary organoammonium perchlorate salts (*Caution!* The perchlorate salts must be handled with care as they are potential explosives). The enantiomeric recognition properties of these new macrocycles towards primary organoammonium salts were estimated by standard ^1H NMR titration techniques in $\text{DMSO-}d_6$.

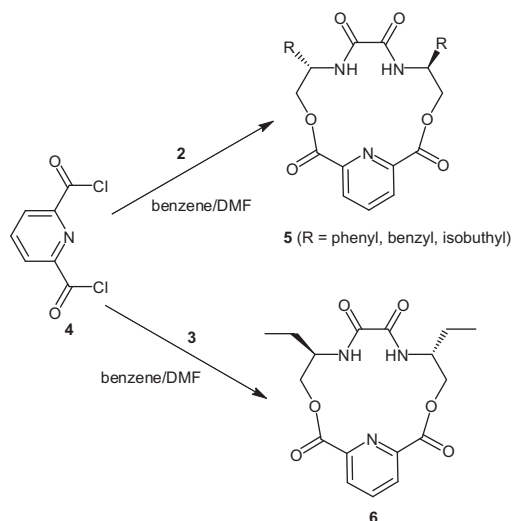
2. Result and discussion

2.1. Synthesis

The procedure for the synthesis of rigid C_2 -symmetric pyridino-15-crown-5 type macrocycles (*S,S*)-**4**, (*S,S*)-**5**, and (*R,R*)-**6** containing diamide–diester functions, derived from bis(aminoalcohol) oxalamides (*S,S*)-**2**, and (*R,R*)-**3** is outlined in Schemes 1 and 2. Chiral bis(amino alcohol)oxalamides were synthesized according to the procedures previously reported, by reacting *L*-phenylglycinol, *L*-phenylalaninol, *L*-leucinol and (*R*)-2-amino-1-butanol with dimethyloxalate in methanol at room temperature, with almost quantitative yield.¹⁶ Pyridino-15-crown-5 type macrocycles were synthesized from the corresponding chiral bis(amino alcohol)oxalamides. A high dilution technique was employed for the cyclization step to afford the macrocycles with high yields. The procedure involves short synthetic sequences and allows high modularity by simply changing the amino alcohol moiety. The functionality of the pyridine, amides and esters ensures a high rigidity, which may play a crucial role in the binding and recognition of small chiral molecules. The structures proposed for these new chiral bis(amino alcohol)oxalamides and macrocycles are consistent with the data obtained from ^1H , ^{13}C NMR, IR spectroscopy and elemental analysis. All of ^1H and ^{13}C NMR signals were assigned based on DEPT and ^1H – ^{13}C correlation experiments.



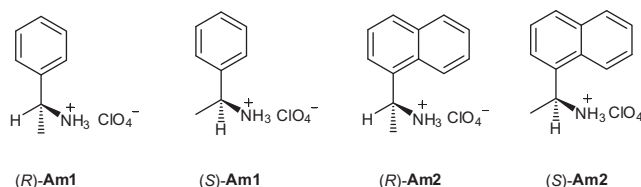
Scheme 1. Synthesis of bis(aminoalcohol)oxalamides.



Scheme 2. Synthesis of pyridino-15-crown-5 type macrocycles.

2.2. Enantiomeric recognition studies: selective cation binding

The enantiomeric recognition can be characterized by various spectroscopic methods, such as NMR, ultraviolet–visible (UV–vis), fluorescence and infrared (IR), which are powerful tools for the examination of the recognition ability of new chiral macrocycles.¹⁷ Standard ^1H NMR titration experiments were applied in order to investigate the stability of the complexes of the pyridino-15-crown-5 types macrocycles **5** and **6** with perchlorate salts of enantiomers of **Am1** and **Am2**, since it is one of the most effective tools in studying host–guest supramolecular chemistry.¹⁸ These cations are commonly used as standard guests for the chiral recognition of primary organic ammonium ions and in most cases give the best results. Upon the addition of guest molecules to the macrocycles, the signals in the ^1H NMR spectra shifted upfield or downfield depending on the non-covalent interactions between host and guest molecules. Increasing the concentration of organic ammonium cations (guest), which were used as perchlorate salts (Scheme 3) from 0.1 to 6 equiv in the presence of a constant host concentration (1×10^{-3} M), was carried out for ^1H NMR titration measurements. The addition of increasing amounts of ammonium salts to the diamide–diester pyridine-macrocycles caused considerable and reproducible upfield or downfield shifts ($\Delta\delta$) in the protons of the NH (amide), the N–CH groups of the diamide–diester pyridine-macrocycles, as well as in the CH and CH_3 protons of the ammonium salts. The NH (amide) protons of diamide–diester pyridine-macrocycles and CH protons of the ammonium salts were greatly affected and displayed significant upfield shifts. The association constants of the complex formation between the host and the guest were calculated according to a modified Benesi–Hildebrand equation where $[\text{H}]_0$ and $[\text{G}]_0$ refer to the total concentration of the macrocycles and organic ammonium salts, respectively.¹⁹ A key feature of this method is that by working with a large excess of component H the concentration of uncomplexed H, can be set equal to the initial concentration, $[\text{H}] = [\text{H}]_0$. Relationships between



Scheme 3. Primary ammonium perchlorate salts used as guests.

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