Design and synthesis of chiral macrocycles as receptors for enantioselective molecular recognition and as catalysts for asymmetric reactions

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The design and the synthesis of chiral macrocycles acting as enantioselective receptors is of great interest in the field of enzyme mimicking enantioselective catalysis as well as in that of racemic resolution and of chiral sensing. Recently particular attention has been devoted to neutral ditopic receptors able to simultaneously bind chiral ammonium cations and their counteranions. In this work we report the synthesis of new chiral macrocycles which can be employed as ligands to obtain neutral chiral ditopic receptors for ion pairs as well as catalysts for asymmetric epoxidation reactions. The two different abilities are modulated both by varying the position of different calix[4]arene scaffolds with respect to the salen-type moiety and varying the transition metal inside the salen unit. The candidates we chose for the first case are calix[4]arene based receptors in 1,3-alternate conformations, linked by different polyether spacers to UO$_2$-salen framework to get ditopic receptor of chiral alkylammonium salts ion pairs. In the second case a salicylaldehyde functionality was incorporated in the calix[4]arene moiety to yield two couples of enantiomeric Mn-salen complexes that have the requisites to act as catalysts in selective oxygen transfer reactions to prochiral olefins.

Complexation between different chemical species and host-guest interaction play a central role in biological process as catalysis or enzymatic inhibition, but also in reproduction, in preservation of genetic information and immune system response. In the past decade the field of biomimetic chemistry has been developed with the purpose both to obtain structures that mimic the enzyme activity and to synthesize artificial systems able to replace the natural systems under conditions of high temperature, extreme pH and so on where the latter can not operate in an efficient way. \(^1\)

Pre-organization and rigidity have a fundamental role in molecular recognition, consequently the use of macrocycles designed and synthesized ad hoc, as the calix-arene scaffolds, provides
unique possibilities to organize several **binding sites** in an array complementary to a potential guest.

The calix-arenes are important building blocks in supramolecular chemistry, since due to the presence of their cavity, they realize **host-guest** complexes with different chemical species\(^2\). Furthermore the binding can be assisted by the substituents on the *upper* or in the *lower rim* and they can be locked in rigid structures. On the other hand, it is known that **salen-type** ligands (salen = N, N’-ethylene-bis-(salicilideneaminato)) form very stable complexes with transition-metal cations. The neutral complexes of the uranyl cation UO\(_2^{2+}\) with salen ligands display a pentagonal bipyramidal coordination geometry, with the oxygen atoms in the axial positions and a solvent molecule (EtOH or H\(_2\)O) located in the fifth equatorial position\(^3\).

Since these neutral complexes are well known to bind strongly hard anions in organic solvents\(^4\), they may act as ditopic receptors. The development of ditopic receptors for ion pairs is a relatively new topic in supramolecular design. The simultaneous complexation of both the partner of ion pairs avoids the unfavorable separation of the two ions. Targeted ion pairs are often alkali metal salts, but few neutral ditopic receptors have been reported for the recognition of quaternary ammonium salts. The literature contains examples of receptors that bind alkylammonium\(^5\) and pyridinium salts.\(^6\) Their complexation has been extensively studied in water\(^7\) and the recognition of quaternary ammonium halides in organic media by means of neutral ditopic receptors is well documented \(^2,8\). However, ditopic receptors for chiral alkylammonium salts are rare\(^9\).

The target of our studies are the chiral quaternary ammonium salts and the ditopic receptors calix[4]arene-salen, in 1,3-alternate conformation, reported below.
Compound 1, 2a and 2b were investigated by $^1$H NMR spectroscopy to have a more detailed description of the conformational properties in solution. The complexing abilities of the hosts 2a and 2b, having the polyether spacers with different length, towards the two enantiomers of alkylammonium salts were studied by $^1$H NMR in CDCl$_3$ solutions at 300 K.

As reference, the flexible salen 1 receptor, which represents a prototype structure for the chiral hosts 2a and 2b, was tested under the same experimental conditions.

In order to better understand the structural and conformational properties of the complex species we perform $^1$H NMR titration at different Host/Guest ratios. The plot of Complexation Induced Shift (CIS) vs. Host/Guest ratios allowed us to determine the stereochemistry and the stability constants of the complexes. This study highlights that the recognition of the anion is ensured by strong binding to the uranyl center at the fifth position in the equatorial plane of the uranium, whereas cation-$\pi$ or $\pi-\pi$ interactions arise between the aromatic units of the macrocycle platforms and the alkylammonium cation.

The reference host 1 complexes both of the enantiomeric ion pairs, but the binding is stronger for the 3S enantiomer ($K_{\text{bind}}(3S)/K_{\text{bind}}(3R) = 3.26$). The chiral salen moiety has a fundamental role in determining the efficiency of complexation and the enantiomeric discrimination.

We are presently pursuing the NMR titration of host 2a and 2b, whose flexibility can be modulated using different polyether spacers, with guest 3R and 3S; these hosts are expected to have greater potential in the selective recognition of chiral alkylammonium salts.

Effective stereochemical communication between substrate and catalyst is essential for attaining high enantioselectivities in asymmetric catalytic reactions.

Enzymatic process achieve this, at least in part, by inducing substrate pre-coordination to catalyst prior to reaction, thereby minimizing the degree of freedom in the critical transition state and maximizing selectivity-determining interaction between the catalyst’s environment and the substrate.$^{10}$

Stereoselective oxidation of prochiral olefins using [Mn-(salen)]-based catalysts represent one of the most elegant and effective technique developed for the formation of carbon-oxygen bond in asymmetric synthesis$^{11}$. These systems do not involve substrate precoordination so they offer the advantage of enhanced generality; the resulting chiral epoxide are usually obtained with enantiomeric excess higher than 90%. Despite the synthetic success of [Mn(salen)] system, the exact mechanism of this complex reaction still remains unclear; among the aspects that have to be considered are the mode of oxygen transfer and the way in
which the chiral information is transferred from the catalyst to the olefin during the enantioselective steps. In this work we present a study aimed at designing new salen catalysts containing a calix[4]arene unit, which potentially might control the alkene approach trajectory by a molecular recognition mechanism.\textsuperscript{12}

Into the calixarene moiety is incorporated a salicylaldehyde functionality (OH and CHO groups \textit{ortho} to each other) in order to build up the “teeth” of the metal binding system, through a Schiff base formation with an appropriate chiral imino-amino counterpart. In order to evaluate the role of the calix[4]arene scaffold on the selectivity we have employed the achiral amine, i.e. \((1R,2S)\)-\textit{cis}-1,2-cyclohexanediamine.

Because of the inherent chirality of the resulting calix[4]arene containing the salicylaldehyde functionality, upon reacting these with imino-amino precursors we would expect the formation of two couples of diastereomeric \textit{salen} ligands.

![One of the four diastereoisomers](image.png)

After chromatographic separation, each \([\text{Mn-(III)-(Salen)}]\)-calix[4]arene complex obtained was tested as catalyst in epoxidation reactions of dihydronaphtalene, of some chromenes and of some standard \textit{cis}-\(\beta\)-alkylstyrenes.

The reactions are usually performed in \(\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}\) at 25 °C using \(\text{NaClO}\) as oxygen donor and 4-phenylpyridine \(N\)-oxide (4-PPNO) as coligand. Enantiomeric excess values for the formation of epoxides (\textit{cis} epoxides in the case of \(\beta\)-alkylstyrenes) were determined by capillary GLC analysis using chiral columns.

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\textsuperscript{1} R. Breslow, \textit{Science}, 1982, 218, 532.


