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Enantioselective Molecular Recognition of Chiral Organic Ammonium Ions and Amino Acids Using Cavitand–Salen-Based Receptors

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Dedicated to Professor Gianfranco Scorrano on the occasion of his 72nd birthday

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Two new receptors, a cavitand–salen (**2**) and a uranyl–cavitand–salen (**3**), for the selective molecular recognition of chiral ammonium ion pairs, where the amino acid is the countercation or counteranion of the ion pair, were designed and synthesized. UV/Vis measurements indicate the formation of 1:1 host–guest complexes with high association constants and good to excellent enantiomeric discriminations. NMR spectroscopic experiments confirmed cation–π interactions between the organic cations and the π-electron-rich cavity, leading to the stability of the complexes, as well as the coordination of the amino acid carboxylate anion to the uranyl metal center. Extraction experiments showed that a racemic mixture of (*R*,*S*)-α-methylbenzyltrimethylammonium iodides undergoes chiral resolution by **2** with high selectivity.

Introduction

Many natural processes such as immunological responses,[1a] the mechanism of drug action,[1b] and the storage and retrieval of genetic information[1c] are regulated by enantiomeric discrimination processes. The development of chiral artificial receptors possessing chiral recognition properties has attracted increasing attention because of their high sensitivity and potential applications in pharmaceuticals,[2,3] analysis,[4,5] biology,[6] catalysis,[7–9] and sensing.[10] Many biological processes involve interactions between ammonium ions and protein receptors, and a selective recognition event controls the cellular response; for example, molecular recognition of amino acids is of crucial importance for the inhibition of biological processes. Therefore, there is great interest in the design of receptors for ammonium ions and amino acids. Important motifs for the recognition of ammonium ions are hydrogen bonds and cation–π interactions, and for this reason π-electron-rich macrocyclic cavities represent very suitable hosts.

Recently, we have devoted our attention to the synthesis of new neutral heteroditopic receptors able to simultaneously bind chiral ammonium cations and their counteranions. In our strategy, the anion is bound by a uranyl dication acting as a Lewis acidic coordination site, whereas the organic cation may be bound by using π-rich frameworks developing cation–π interactions.

In previous papers,[11,12] we have synthesized mononuclear and dinuclear uranyl chiral macrocyclic complexes, incorporating both a salen unit containing two phenyl rings linked to a chiral diimine bridge and the (*R*)-BINOL unit, which behave as efficient ditopic receptors for chiral quaternary ammonium salts. Likewise, a new heteroditopic chiral uranyl–salen complex[13] incorporating two pyrenyl groups was designed and synthesized in our laboratory for the recognition of ammonium salts and tetrabutylammonium and tetramethylammonium amino acids.

In this work we discuss a triquinoxaline-spanned cavitand decorated with a salen chiral framework as an enantioselective molecular receptor for chiral organic ammonium salts and α-amino acid moieties. Cavitands are robust molecules with a bowl shape consisting of four resorcinol rings linked by four methylene bridges.[14] In order to host more sizeable guests, the cavity wall size can be enlarged by insertion of quinoxaline units, which make the cavity deeper and at the same time more conformationally rigid and more lipophilic. The cavity can provide π-electron-rich regions able to develop CH–π and π–π interactions, thus facilitating the recognition of organic cations. The salen framework, because of the presence of two stereogenic carbon atoms in the diimine bridge, generates a chiral pocket that, through imine nitrogen and phenolic oxygen atoms, can coordinate to the uranyl dication, creating, therefore, a Lewis acidic site that can bind the counteranion of an ion pair.

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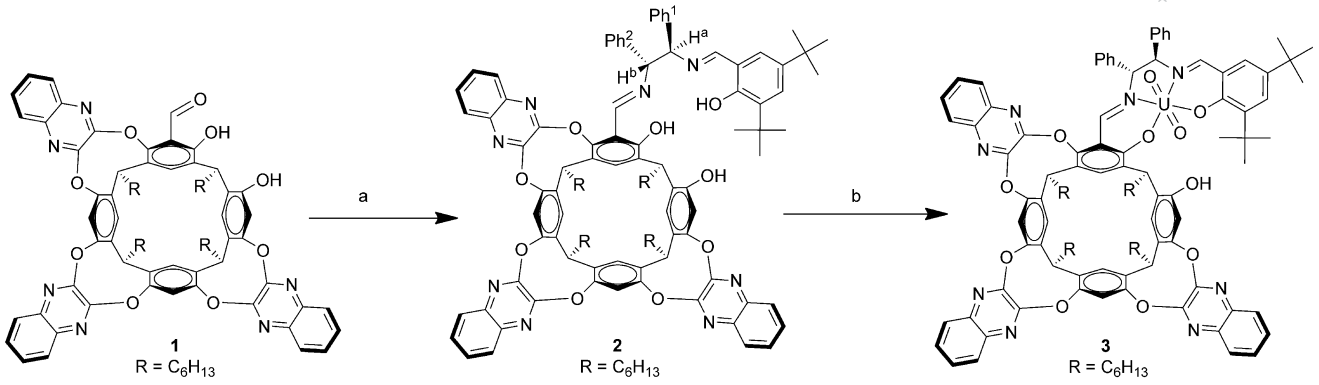


Scheme 1. Synthesis of receptors **2** and **3**. Reagents and conditions: (a) (1*R*,2*R*)-diphenylethylenediamine, 3,5-di-*tert*-butylsalicylaldehyde hydrochloride,[15] Et_3N, EtOH, r.t. (48%); (b) $(AcO)_2UO_2$, EtOH, r.t. (90%).

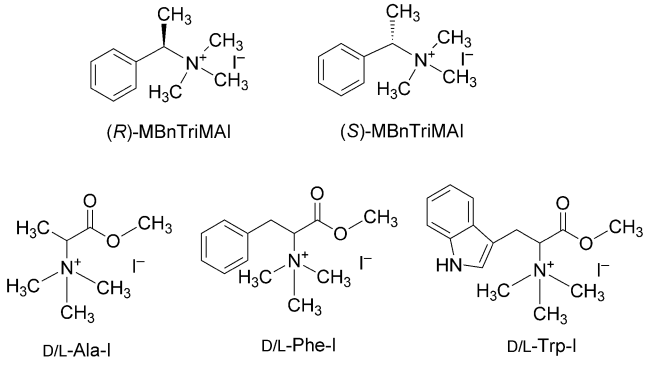
Results and Discussion

Cavitand–Salen Receptor 2

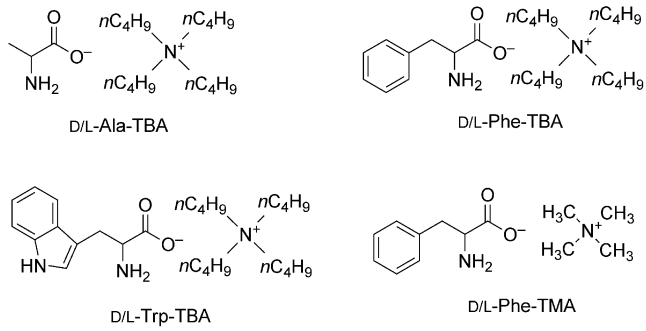
Cavitand–salen receptor **2** (Scheme 1) was synthesized by treating aldehyde **1**[15] with an iminoamino monochloride obtained by reaction of (1*R*,2*R*)-diphenylethylenediamine hydrochloride with 3,5-di-*tert*-butylsalicyladehyde.[16]

The structural characterization of **2** was carried out by MS (ESI) measurements and by ^1H and ^{13}C as well as g-COSY and T-ROESY NMR spectroscopy (see Supporting Information). The disappearance of the aldehyde signal (δ = 10.18 ppm) of **1** and the appearance of two new signals at δ = 8.38 and 8.57 ppm, due to the imine protons of the formed Schiff base, support the presence of the salen framework in the cavitand receptor. The methine CH protons (H^a and H^b) of the salen bridge resonate as an AB system at δ = 4.52 and 4.64 ppm, respectively (^3J = 6.5 Hz). T-ROESY spectra display ROE contacts between phenyl ring 1 of the salen bridge and the quinoxaline wall (see Supporting Information). The bridge methine CH protons of the cavitand display chemical shift values in the range δ = 4–6 ppm and are indicative of a vase conformation of the cavitand itself.[14,17,18] All these data seem consistent with the structure reported in Scheme 1.

Schemes 2 and 3 report the Q^+X^- salts employed as guests in the molecular recognition process.



Scheme 2. Ammonium and amino acid salts used as guests.



Scheme 3. Amino acid ammonium carboxylates used as guests.

We have tested chiral tetramethylammonium iodides, amino acid methyl esters with the amino group transformed into a tetraalkylammonium iodide, and amino acid derivatives as tetraalkylammonium carboxylates. Molecular recognition studies were carried out by performing NMR spectroscopy and UV/Vis measurements. We first investigated the binding properties of receptor **2** towards both (*R*)- and (*S*)-α-methylbenzyltrimethylammonium iodides (MBntriMAI) by ^1H NMR titrations in $CDCl_3$ at 27 °C to understand the role of the cation in the complexation process. Since **2** does not have a preorganized binding site for anions (even if the three OH groups as hydrogen-bond donors might be involved in the recognition of the counteranion) the counteranion will be driven mainly by an ion pair effect.

^1H NMR titrations showed an upfield shift of the signals of the trimethyl group and of the α methyl group for both the (*R*) and (*S*) isomers, but larger changes were observed in the chemical shift values of the (*S*) isomer. By way of contrast, the aromatic protons of the (*R*) isomer did not undergo any appreciable shift, whereas in the case of the (*S*) isomer these protons underwent an upfield shift (Figure 1). We may conclude in both cases that the receptor hosts the ammonium group inside the cavity but that the (*S*) isomer is better accommodated. Molecular mechanics calculations, using the MM2* force field of MacroModel 8.6,[19] appeared to be consistent with these findings (Figure 2).

Special Section

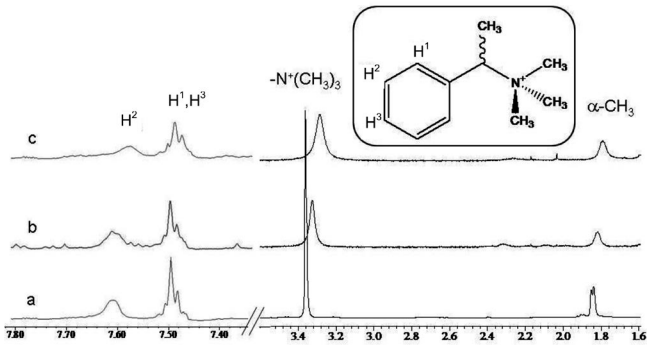


Figure 1. Selected regions of the ^{1}H NMR spectra of (a) (*R*,*S*)-MBntriMAI, (b) **2** + (*R*)-MBntriMAI (3 equiv.), (c) **2** + (*S*)-MBntriMAI (3 equiv.).

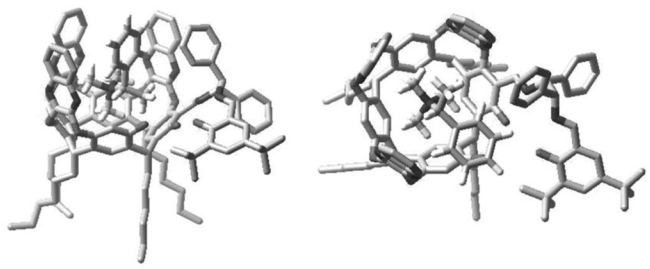


Figure 2. Optimized structures of the (left) **2** ⊂ (*S*)-MBntriMAI and (right) **2** ⊂ (*R*)-MBntriMAI complexes.

Unfortunately, NMR titrations do not allow quantitative determinations to be performed because of the complexity and overlap of many signals as well as the increased relaxation time. Therefore, the binding constants were obtained by UV/Vis titrations. The UV/Vis spectrum of **2** displays an absorbance band at 330 nm (π–π* quinoxaline cavity transition) and at 450 nm (salen framework absorption), which undergo modifications upon the addition of the guest.

Both (*R*)- and (*S*)-MBntriMAI yield complexes with a 1:1 stoichiometry but with different affinities. A representative example of a titration curve is shown in Figure 3 together with the corresponding Job plot.

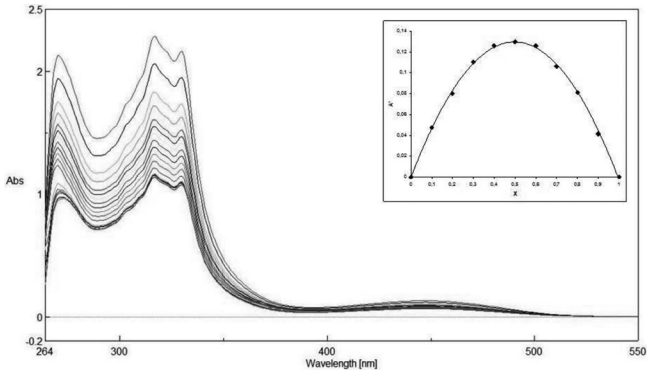


Figure 3. UV/Vis titration of (*S*)-MBntriMAI with **2** in $CHCl_3$ at 27 °C. The inset displays the corresponding Job plot.

As Table 1 reports, the binding constant for the (*S*) enantiomer is higher than the corresponding value of the (*R*) enantiomer (K_S/K_R = 15.9), pointing out that a very efficient chiral discrimination is working. In order to check this finding, a solvent extraction experiment was carried out. To a 1×10^{-3} M aqueous solution of a racemic mixture of (*R*)/(*S*)-MBntriMAI was added an equimolar solution of receptor **2** in chloroform. ^{1}H NMR spectroscopic measurements show that in the $H_2O/CHCl_3$ biphasic system the two salts are present only in water. The biphasic system containing the two salts and the receptor was stirred for 2 h at 22 °C and then, after separation, the specific rotation of the aqueous phase was measured.

Table 1. Binding constants (K_a) and Gibbs free-energy changes ($-\Delta G_0$) for the complexation of (***R***)- and (*S*)-MBntriMAI with **2** in $CHCl_3$ at 27 °C.

Q^+X^-	K_a [M^{-1}][a]	$-\Delta G_0$ [kJ mol^{-1}]	K_S/K_R
(*R*)-MBntriMAI	$(3.18 \pm 0.27) \times 10^4$	25.6	15.9
(*S*)-MBntriMAI	$(5.07 \pm 0.34) \times 10^5$	32.5	

[a] Binding constants for complexes of chiral ammonium salts with host **2** calculated by Hyperquad 2006 (v. 3.1.60).

The outcome reported in Table 2 indicates that **2** is able to extract the (*S*) enantiomer from the water almost quantitatively (88 %*ee*), which is in very good agreement with the determined binding constant values. As the optimized structures of Figure 2 show, the configuration of the stereocenter plays an important role in establishing cation–π as well as CH–π and π–π interactions; for the (*R*) isomer, optimum orientation for interaction with the inner walls of the cavitand cannot be adopted. In this case, for instance, the phenyl ring can protrude through the open wall (salen wall). In the case of the (*S*) isomer, the phenyl ring is positioned between the quinoxaline wall and phenyl ring 1 of the salen wall, and probably the different interactions give a substantial contribution to the observed chiral discrimination. However, a further contribution to chiral selectivity is due also to the different interactions of the host–guest during the approach of the guest to the receptor.[20] Figure 4 displays possible steric interactions between the phenyl ring of the salen bridge (Ph^1 in Scheme 1) and the R group bonded to the stereogenic carbon atom of the guest. We might envisage a larger unfavorable steric interaction for the (*R*) isomer (R = phenyl) than for the (*S*) isomer (R = methyl). Finally, the possible location of the iodide anion near the OH region is counterbalanced by the constraint to maintain an optimal equilibrium distance of the cation–anion of the ion pair, as this can affect differently the binding energy of the two guests and could be responsible for further discrimination.

In order to enlarge the scope of our receptor we tested some amino acid derivatives as guests. The amino acids, treated with CH_3I (see Supporting Information), were converted into the corresponding methyl esters, whereas their amino groups were permethylated and converted into tetraalkylammonium iodides. Therefore, the driving force for the

Table 2. Polarimetric measurements at 22 °C of aqueous solutions containing the pure (*R*)- and (*S*)-MBntriMAI salts, respectively, and the salt left after extraction by **2**.

Q^+X^-	$[\alpha]_D^{22}$
(*R*)-MBntriMAI	+54.7
(*S*)-MBntriMAI	–54.7
Aqueous solution (after extraction)	+48.4

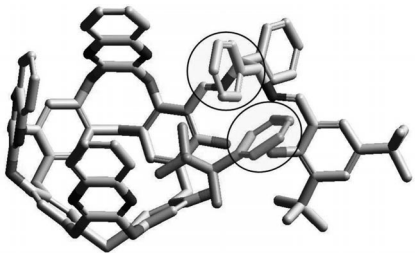


Figure 4. Steric interactions in the recognition of (*R*)-MBntriAI (hydrogen atoms and aliphatic chains of receptor omitted for clarity).

molecular recognition of these guests is the cation–π interaction between the ammonium cation and the π-electron-rich cavity of the receptor. Table 3 reports the pertinent affinity constant values obtained by UV/Vis titrations. A strong chiral discrimination is working for the D- and L-Trp-I pair (K_D/K_L = 14.7) and for the D- and L-Phe-I (K_D/K_L = 0.11) pair, whereas the selectivity is lower for the D- and L-Ala-I pair (K_D/K_L = 3.9). The high binding affinities and the remarkable selectivity are comparable to those observed for the ammonium salts reported in Table 1, probably because there is a good structural analogy between the two series of guests.

Table 3. Binding constants (K_a) and Gibbs free-energy changes ($-\Delta G_0$) for the complexation of tetraalkylammonium iodide amino acids methyl esters with **2** in $CHCl_3$ at 27 °C.

Q^+X^-	K_a [M^{-1}][a]	$-\Delta G_0$ [kJ mol^{-1}]	K_D/K_L
D-Phe-I	$(1.55 \pm 0.39) \times 10^5$	29.6	0.11
L-Phe-I	$(1.59 \pm 0.32) \times 10^6$	35.5	
D-Trp-I	$(1.33 \pm 0.26) \times 10^6$	34.9	14.7
L-Trp-I	$(9.07 \pm 0.62) \times 10^4$	28.2	
D-Ala-I	$(7.08 \pm 0.85) \times 10^5$	33.3	3.9
L-Ala-I	$(1.79 \pm 0.13) \times 10^5$	29.9	

[a] Binding constants for complexes of chiral ammonium salts with host **2** calculated by Hyperquad 2006 (v. 3.1.60).

In fact, both of them are ammonium cations with the nitrogen atom linked to a carbon stereocenter bearing an aromatic residue or an α-carbon atom with an aromatic residue, and in both cases the driving force for the molecular recognition is the affinity of the cation for the π-electron-rich cavity. Figure 5 displays the optimized structures for D- and L-Trp-I.

Further information on the molecular recognition of receptor **2** toward amino acids was collected by converting the amino acids into their tetraalkylammonium carboxylate salts and measuring the pertinent binding constants. In this case, we expected lower selectivity because the amino acid

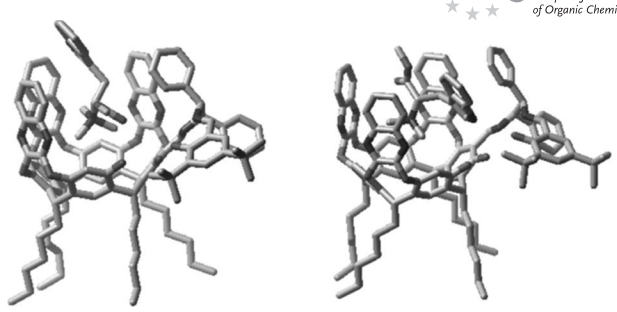


Figure 5. Optimized structures of the (left) **2** ⊂ D-Trp-I and (right) **2** ⊂ L-Trp-I complexes (hydrogen atoms omitted for clarity).

framework is now the counteranion of the ion pair and therefore the main cation–π interactions do not involve the amino acid residue directly, because the organic anion now must be "towed" towards the cavity by the cation through an ion-pair effect. The binding constants reported in Table 4 are nearly one order of magnitude lower than those observed in the previous cases and appear in agreement with the formation of weaker association complexes. The D- and L-Trp-TBA pair (K_D/K_L = 0.80) displays nearly the same affinity, presumably because the carboxylate counteranion gives a scarce contribution to the selectivity.

Table 4. Binding constants (K_a) and Gibbs free-energy changes ($-\Delta G_0$) for the complexation of amino acid tetrabutylammonium (TBA) or tetramethylammonium (TMA) carboxylates with **2** in $CHCl_3$ at 27 °C.

Q^+X^-	K_a [M^{-1}][a]	$-\Delta G_0$ [kJ mol^{-1}]	K_D/K_L
D-Phe-TBA	$(5.09 \pm 0.75) \times 10^4$	26.8	3.5
L-Phe-TBA	$(1.44 \pm 0.11) \times 10^4$	23.1	
D-Phe-TMA	$(4.03 \pm 0.24) \times 10^4$	26.1	0.72
L-Phe-TMA	$(5.59 \pm 0.11) \times 10^4$	27.1	
D-Trp-TBA	$(3.31 \pm 0.17) \times 10^4$	25.8	0.80
L-Trp-TBA	$(4.19 \pm 0.25) \times 10^4$	26.3	
D-Ala-TBA	$(4.35 \pm 0.34) \times 10^4$	26.5	3.0
L-Ala-TBA	$(1.45 \pm 0.27) \times 10^4$	23.7	

[a] Binding constants for complexes of chiral ammonium salts with host **2** calculated by Hyperquad 2006 (v. 3.1.60).

^{1}H NMR spectroscopic measurements seem to support this interpretation because we observed an upfield shift of the tetrabutyl cation signals (see Supporting Information) and a downfield shift of the CH methine protons of the cavitand, indicative of the hosting of the cation by the cavity (Figure 6). On the other hand, the signals of the two H^a and H^b protons of the chiral salen bridge (Scheme 1) undergo an upfield shift indicating that the carboxylate anion is located near the bridge of the salen wall (probably in proximity to the OH groups, which, due to their hydrogen-donor abilities, might provide a suitable location for the carboxylate anion) and therefore quite outside the cavity. Some selectivity is observed with the D- and L-Phe-TBA (K_D/K_L = 3.5) pair and with the D- and L-Ala-TBA (K_D/K_L = 3.0) pair. Different stabilization by hydrogen bonding of the counteranion (which has two hydrogen-bond acceptor sites, that is, the carboxylate and the amino groups) due to the different configurations of the stereocenter might be also responsible of the selectivity.[21]

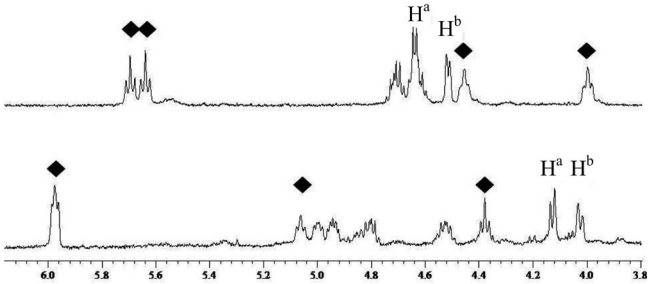


Figure 6. Selected region of the ^{1}H NMR spectra of (top) receptor **2** and (bottom) **2** + D-Ala-TBA (3 equiv.) showing the upfield shift of the H^a and H^b protons of the salen bridge and the downfield shift of the signals (black diamond) relative to the methine protons of the cavitand.

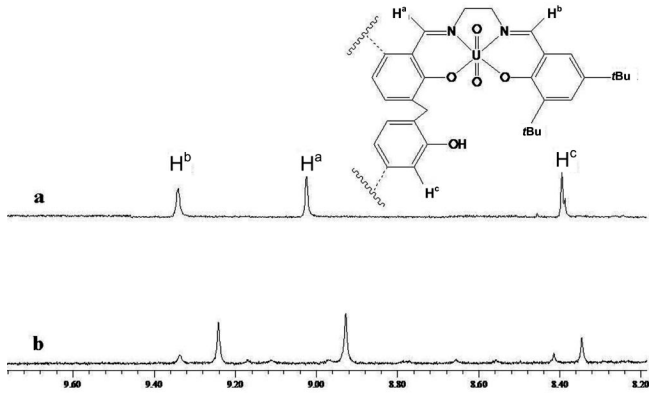


Figure 7. Selected region of the ^{1}H NMR spectra of (a) **3** and (b) **3** + D-Ala-TBA (3 equiv.).

Heteroditopic Uranyl–Cavitand–Salen Receptor 3

By complexation with uranyl acetate, receptor **2** was utilized to prepare uranyl–cavitand–salen **3** (Scheme 1), able to work as a heteroditopic receptor because of the presence of both a Lewis acid uranyl center, which can bind the counteranion of an ion pair, and the electron-rich cavity able to recognize the corresponding countercation. Complex **3** was characterized by MS (ESI) measurements and by ^{1}H NMR spectroscopy. The coordination of UO_2 causes a downfield shift of CH imine proton signals (from δ = 8.38/8.57 to δ = 9.02/9.34 ppm) as well as of the H^a and H^b proton signals of the salen bridge (from δ = 4.52/4.64 to δ = 5.11/5.79 ppm), whose coupling constant ^3J = 8.0 Hz would indicate that the two phenyl rings of the salen bridge form a dihedral angle of about 130°.

We have already reported[13] that amino acid carboxylate ammonium salts can be hosted by UO_2–salen heteroditopic receptors, because the carboxylate anion is able to bind the fifth equatorial coordination site of the uranyl(VI) ion.[22] The coordination of the uranyl center by the carboxylate anion is observed also with receptor **3**, as NMR spectroscopic experiments show. In fact, the observed upfield shift of the imine proton signals and the aromatic proton signal in the *ortho* position to the free OH group of **3** upon NMR titration seems to provide good evidence that the carboxylate anion is able to coordinate the uranyl metal center (Figure 7). At the same time, the α-CH_2 signals of the tetrabutylammonium countercation undergo an upfield shift indicating that it can be accommodated inside the cavity of the receptor (see Supporting Information).

Figure 8 reports the optimized structures of the ternary complexes of **3** with D- and L-Phe-TBA, which appear to be consistent with NMR spectroscopic indications, showing the binding of the cation and the anion inside the cavity and at the uranyl metal center.

The binding constants, determined by UV/Vis measurements, are reported in Table 5 and are more or less comparable in magnitude to the values obtained for the permethylated amino acids but larger than those measured for the same ammonium carboxylates with receptor **2** that does not possess the uranyl center as the binding site for the carboxylate anion.

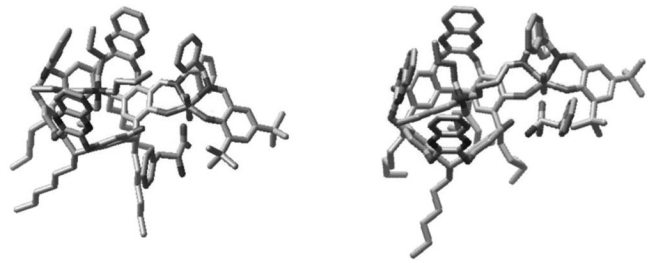


Figure 8. Optimized structures of the (left) **3** ⊂ D-Phe-TBA and (right) **3** ⊂ L-Phe-TBA complexes (hydrogen atoms omitted for clarity).

Table 5. Binding constants (K_a) and Gibbs free-energy changes ($-\Delta G_0$) for the complexation of amino acid tetrabutylammonium (TBA) or tetramethylammonium (TMA) carboxylates with **3** in $CHCl_3$ at 27 °C.

Q^+X^-	K_a [M^{-1}][a]	$-\Delta G_0$ [kJ mol^{-1}]	K_D/K_L
D-Phe-TBA	$(7.15 \pm 0.94) \times 10^5$	33.4	0.66
L-Phe-TBA	$(1.09 \pm 0.15) \times 10^6$	34.4	
D-Phe-TMA	$(2.10 \pm 0.25) \times 10^6$	36.1	23.7
L-Phe-TMA	$(8.85 \pm 0.15) \times 10^4$	28.2	
D-Trp-TBA	$(4.69 \pm 0.51) \times 10^4$	26.7	1.0
L-Trp-TBA	$(4.62 \pm 0.67) \times 10^4$	26.6	
D-Ala-TBA	$(2.05 \pm 0.14) \times 10^5$	30.3	6.4
L-Ala-TBA	$(3.21 \pm 0.31) \times 10^4$	25.7	

[a] Binding constants for complexes of chiral ammonium salts with host **3** calculated by Hyperquad 2006 (v. 3.1.60).

The presence of a preorganized binding site in **3**, which can also accommodate the anion, increases the binding affinity by nearly one order of magnitude. However, the observed chiral discrimination is lower and comparable to that determined with **2**, because also in this case the amino acid is the counteranion, and therefore, it is accommodated in the coordination sphere of the uranyl moiety and not inside the cavity. Both the D- and L-Trp-TBA (K_D/K_L = 1.0) and the D- and L-Phe-TBA (K_D/K_L = 0.66) pairs display nearly the same selectivity, and only the D- and L-Ala-TBA (K_D/K_L = 6.4) pair shows selective recognition. With the smaller amino acid guest, coordination to the metal center appears more susceptible to the different configurations of the carbon atom stereocenter and then the molecular recognition

is more selective. The possibility for the anion to bind the fifth equatorial coordination site of the metal and at the same time to be hydrogen bonded through the amino group to the free OH of the receptor in more or less straightforward and might be responsible, at least partially, for the selectivity. Figure 8 shows that only L-Phe-TBA can be hydrogen bonded to the OH group with the NH_2 group.

A very strong cation effect is observed with the D- and L-Phe-TMA pair. The replacement of TBA with the smaller TMA changes the selectivity dramatically from K_D/K_L = 0.66 to K_D/K_L = 23.7. This effect was already observed with the pyrenyl receptor.[13]

At the moment we do not have a rational explanation for this behavior, but the change from a loose to a tight ion pair and the modification of the conformation of the receptor upon decreasing the size of the guest cation probably have some effect on the coordination and hydrogen bonding of the anion, making the energy binding more sensitive to the configuration of the stereocenter of the guest.

The observation that in most cases the host–guest exchange of the ammonium ion is fast on the NMR timescale, whereas the receptor seems to be in slow exchange with the complex (cation protons appear as a time-averaged signal, but the imine protons of the free and complexed receptor appear as separate signals) deserves some comment. Mandolini[23] observed a similar situation in the ion pair recognition of quaternary ammonium ions by uranyl–salophen receptors. The rationale offered is based on the assumption that the recognition mechanism involves a slow equilibrium between the receptor and the ion pair, which equilibrates the receptor between its free and complexed form, and a second fast equilibrium between the ternary complex formed and a second external ion pair (ion-quartet mechanism), which implies a fast cation exchange between the ion pair complexed and the external ion pair. Also, our data seem to support this mechanism and the fast cation exchange observed with receptors **2** and **3** is favored by the presence of a mobile fourth wall (salen wall) in the cavitand.

Conclusions

We have designed and synthesized cavitand–salen (**2**) and cavitand–salen–uranyl (**3**) receptors for the molecular recognition of chiral ammonium ion pairs, where the amino acid is the countercation or the counteranion of the ion pair. UV/Vis measurements and Job plots indicate the formation of 1:1 host–guest complexes. Larger selectivity values are observed for ion pairs whose quaternary ammonium cation is an amino acid, due to different π–π and CH–π interactions, whereas the selectivity is substantially lower when an amino acid carboxylate is the anion of the ion pair. When the guest is an amino acid carboxylate ammonium salt, the presence of a preorganized binding site in the receptor, which can also accommodate the anion, increases the affinity but not the selectivity, even if a very high value of selectivity is observed for the D- and L-Phe pair when changing the cation from TBA to TMA. Work is in progress in our laboratory to improve our knowledge on the rules governing the interactions of these cavitand–salen receptors with amino acid guests in order to design responsive host–guest systems, because of their potential applications in separation and in drug design.

Experimental Section

General Experimental Methods: NMR experiments were carried out at 27 °C with a Varian UNITY Inova 500 MHz spectrometer (^{1}H at 499.88 MHz, ^{13}C NMR at 125.7 MHz) equipped with pulse field gradient module (Z axis) and a tunable 5 mm Varian inverse detection probe (ID-PFG). Unless otherwise stated, NMR spectra were obtained in $CDCl_3$ solutions. The chemical shifts were referenced by using the residual solvent signal as the internal standard. ^{1}H NMR peak assignments follow from 2D-COSY experiments. Mass spectra (ESI) were acquired with an ESI-MS Thermo-Finnigan LCQ-DECA using MeOH (positive ion mode). A JASCO V-560 UV/Vis spectrophotometer equipped with a 1 cm path-length cell was used for the measurements of Job plots and for the UV/Vis titrations. D-/L-Phenylalanine, D-/L-tryptophan, D-/L-alanine, and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine were commercially available reagent-grade materials (Aldrich). Monoiminoamino-(1*R*,2*R*)-diphenyl-3,5-di-*tert*-butylsalicylaldehyde and (*R*)-/(*S*)-MBnTMAI were obtained as previously reported.[16] All chemicals were reagent grade and were used without further purification.

Receptor 2: In a round bottom flask, to a solution of monoformyl cavitand **1**[15] (0.183 mmol) in absolute EtOH (20 mL) was added monoimineamine-(1*R*,2*R*)-diphenyl-3,5-di-*tert*-butylsalicylaldehyde[16] (0.183 mmol) and triethylamine (0.366 mmol). The reaction was stirred for 48 h at room temperature and monitored by TLC (hexane/EtOAc, 80:20). The reaction was quenched by evaporation of the solvent under reduced pressure, and receptor **2** was purified by flash chromatography (hexane/EtOAc, 80:20). Yield: 48%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 15.79 (s, 1 H, OH), 13.05 (s, 1 H, OH), 9.55 (s, 1 H, OH), 8.56 (s, 1 H, CH=N), 8.38 (s, 1 H, Ar), 8.15 (s, 1 H, CH=N), 8.00 (d, J = 8.5 Hz, 1 H, Ar), 7.95 (d, J = 8.5 Hz, 1 H, Ar), 7.87 (d, J = 8.5 Hz, 1 H Ar), 7.80–7.83 (m, 2 H, Ar), 7.75 (d, J = 8.5 Hz, 1 H Ar), 7.71 (s, 1 H, Ar), 7.50–7.63 (m, 6 H, Ar), 7.48 (s, 1 H, Ar), 7.36 (s, 1 H, Ar), 7.21–7.24 (m, 3 H, ArH), 7.18 (s, 2 H, Ar), 7.11–7.15 (m, 2 H, Ar), 7.03–7.09 (m, 3 H, Ar), 6.94–6.98 (m, 4 H, Ar), 6.66 (s, 1 H, Ar), 5.68 (t, J = 8.0 Hz, 1 H, CH methine), 5.63 (t, J = 8.0 Hz, 1 H, CH methine), 4.62–4.71 [m, 2 H, $CH_2(CH_2)_3CH_3$ and 1 H, CH methine], 4.52 (d, J = 6.5 Hz, 1 H, CH chiral bridge), 4.46 (t, J = 8.0 Hz, 1 H, CH methine), 4.00 (t, J = 8.0 Hz, 1 H, CH methine), 2.00–2.40 [m, 6 H, $CH_2(CH_2)_3CH_3$ and 2 H, $CH_2(CH_2)_3CH_3$], 1.36–1.57 [m, 22 H, $CH_2(CH_2)_3CH_3$], 1.27 (s, 9 H, *t*Bu), 1.22–1.31 (m, 12 H), 0.92 [t, J = 7.0 Hz, 3 H, $CH_2(CH_2)_3CH_3$], 0.89 [t, J = 7.0 Hz, 3 H, $CH_2(CH_2)_3$-CH_3], 0.74 [t, J = 7.0 Hz, 3 H, $CH_2(CH_2)_3CH_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 165.1, 162.2, 157.9, 157.7, 154.6, 153.6, 152.6, 152.4, 152.2, 152.1, 151.9, 148.8, 147.5, 147.0, 139.95, 139.91, 139.7, 139.6, 138.4, 138.3, 137.39, 137.31, 136.3, 136.2, 135.2, 134.0, 130.1, 129.6, 129.1, 128.8, 128.6, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 126.9, 126.7, 126.4, 126.1, 124.4, 122.9, 122.8, 118.6, 118.0, 117.8, 117.3, 116.3, 111.5, 106.8, 78.4, 76.2, 63.6, 34.9, 34.8, 34.6, 34.2, 34.1, 33.6, 33.4, 33.3, 33.2, 32.8, 32.3, 31.9, 31.6, 31.99, 31.38, 31.0, 29.5, 29.4, 29.3, 29.2, 29.0, 28.0, 27.9, 27.6, 22.7, 22.6, 22.4, 14.07, 14.06, 13.8 ppm. MS (ESI): m/z = 1686 $[M + H + C_2H_5OH]^+$. $C_{106}H_{112}N_8$ (1498.10): calcd. C 77.53, H 6.87, N 6.82; found C 77.47, H 6.82, N 6.77.

Uranyl Receptor 3: To a solution of **2** (0.089 mmol) dissolved in absolute ethanol (10 mL) was added uranyl acetate (0.128 mmol). The reaction was stirred overnight at room temperature, and the resulting solid was filtered and dried to yield **3** as a red powder (90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.34 (s, 1 H, CH=N), 9.02 (s, 1 H, CH=N), 8.39 (s, 1 H, Ar), 8.00 (d, J = 8.0 Hz, 1 H, Ar), 7.92 (d, J = 8.0 Hz, 1 H, Ar), 7.82 (d, J = 8.0 Hz, 2 H, Ar), 7.75 (s, 1 H, Ar), 7.72 (s, 1 H, Ar), 7.67 (d, J = 8.0 Hz, 1 H, Ar), 7.51–7.63 (m, 7 H, Ar), 7.48 (s, 1 H, Ar), 7.42 (s, 1 H, Ar), 7.39 (s, 1 H, Ar), 7.33 (s, 1 H, Ar), 7.32 (s, 1 H, Ar), 7.16–7.21 (m, 7 H, Ar), 7.09 (s, 1 H, Ar), 7.08 (s, 1 H, Ar), 7.04 (m, 3 H, Ar), 6.80 (s, 1 H, OH), 5.79 (d, J = 8.0 Hz, 1 H, CH chiral bridge), 5.65–5.70 [m, 3 H, CH methine and $CH_2(CH_2)_3CH_3$], 5.11 (d, J = 8.0 Hz, 1 H, CH chiral bridge), 4.64 (t, J = 7.5 Hz, 2 H, CH methine), 4.03 (t, J = 7.5 Hz, 1 H, CH methine), 2.23–2.45 [m, 8 H, $CH_2(CH_2)_3$-CH_3], 1.68 (s, 9 H, CH_3 *t*Bu), 1.33–1.63 [m, 24 H, $CH_2(CH_2)_3CH_3$], 1.27 (s, 9 H, CH_3 *t*Bu), 0.94 [t, J = 6.5 Hz, 6 H, $CH_2(CH_2)_3CH_3$], 0.79 [t, J = 6.5 Hz, 3 H, $CH_2(CH_2)_3CH_3$], 0.65 [t, J = 6.5 Hz, 3 H, $CH_2(CH_2)_3CH_3$] ppm. MS (ESI): *m*/*z* = 1955.4 [M + H + $_2H_5OH]^+$, 1978.8 [M + Na + $C_2H_5OH]^+$. $C_{106}H_{110}N_8O_{11}U$ (1910.11): calcd. C 66.65, H 5.80, N 5.87; found C 66.61, H 5.77, N 5.81.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{13}C, g-COSY, T-ROESY, and 2D-DOSY NMR spectra, MS (ESI), UV/Vis titration curves, and Job Plots.

Acknowledgments

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[21] The optimized structure for complex **2** ⊂ D-Phe-TBA (see Supporting Information) appears to be consistent with the NMR spectroscopic data and seems to support these observations.
[22] A pentagonal bipyramidal coordination geometry for the uranyl(VI) ion with two axial oxido groups and with the fifth equatorial site available for complexation with anionic monodentate ligands X^- has been previously indicated in these uranyl chiral macrocyclic complexes.[11–13]
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