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Heteroditopic Chiral Uranyl–Salen Receptor for Molecular Recognition of Amino Acid Ammonium Salts

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A new heteroditopic chiral uranyl–salen complex incorporating two pyrenyl groups was designed and synthesized for the recognition of ammonium salts, tetrabutylammonium (TBA) and tetramethylammonium (TMA) amino acids. UV/Vis measurements indicate the formation of 1:1 host–guest complexes with high association constants and an excellent enantiomeric discrimination between the two enantiomers of phenylalanine–TMA. T-ROESY NMR experiments confirm cation–π and CH–π interactions between the TBA and TMA cations and the two pyrenyl arms, leading to the strong stability of the complexes. This is the first report of a uranyl receptor able to recognize chiral carboxylate guests.

Introduction

Enantiomeric recognition is an essential property of various natural systems, which is reliant on the capacity of a chiral molecular receptor to preferentially form a diastereomeric complex with one of the enantiomers of chiral molecules by exploiting noncovalent weak forces including hydrogen bonding and hydrophobic and electrostatic interactions.[1] The development of synthetic receptors for this appealing aim is an important research area, as it can provide precious information for a better understanding of the interactions between molecules in nature. Furthermore, the study of their recognition properties may also lead to the development of functional molecular devices and materials useful in separation processes,[2] catalysis,[3] biochemical[4,5] and pharmaceutical studies,[6] as well as sensing.[7]

In recent years, there has been great interest in the design, synthesis, and investigation of heteroditopic receptors.[8] Because either of the charged partners of a salt needs a site of recognition, a receptor specifically designed for efficient ion pair complexation should consist of at least two subunits, both of which must be capable of simultaneously binding each partner of the ion pair. In apolar organic solvents, salts typically exist as ion pairs or higher aggregates. Consequently, if the two subunits are appropriately designed, a contact ion pair recognition pathway is preferred, because this avoids the energetically unfavorable separation of the two ions.[9]

Recently, we have studied some chiral uranyl–salen complexes acting as receptors for enantioselective molecular recognition, which are able to recognize anions exploiting the ability of the Lewis acid uranyl center to coordinate equatorially anions.[10] However, so far only few examples of chiral uranyl–salen complexes have been described in the literature.[11]

Here we report the synthesis of a new heteroditopic chiral uranyl–salen derivative bearing two pyrenyl side arms and discuss its ability in the enantioselective molecular recognition of ammonium salts also containing α-amino acid moieties.

Results and Discussion

Target chiral uranyl–salen **1** (Scheme 1) was synthesized in four steps starting from 2-allyloxy-3-chloromethyl-5-*tert*-butylbenzaldehyde (**2**).[11d] 1-Hydroxypyrene was treated with **2** to yield oxypyrenyl derivative **3** (75%), which was then deallylated to give the 3-pyrenyloxymethyl-5-*tert*-butylsalicylaldehyde (**4**; 67%). Condensation of **4** with the (1*R*,2*R*)-(+)-1,2-diphenylethylendiamine yielded salen ligand **5** (78%), which was finally converted into the corresponding salen complex **1** (98%) by uranyl acetate. The proposed structure for this new chiral uranyl–salen complex is consistent with the ^{1}H and ^{13}C NMR spectroscopy data as well as the ESI mass spectrometry data.

Scheme 2 displays the ion pairs employed as guests in the molecular recognition process by complex **1**. Molecular recognition studies were carried out by performing NMR and UV/Vis measurements. We first investigated the binding properties of receptor **1** toward TBACl and TMACl by ^{1}H NMR titration in $CDCl_3$ at 27 °C to understand the role of the cation in the complexation process. During ^{1}H NMR

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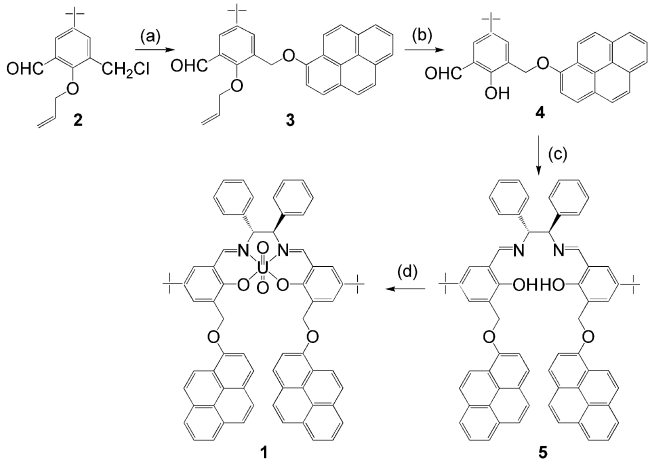
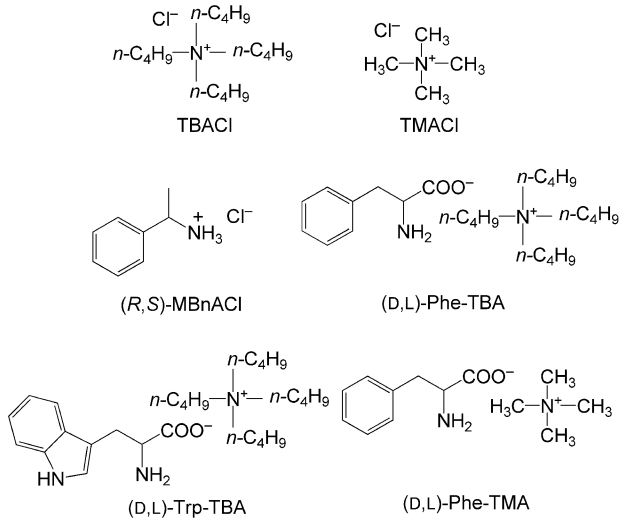


Scheme 1. Synthesis of uranyl–salen complex **1**. Reagents and conditions: (a) 1-Hydroxypyrene, K_2CO_3, CH_3CN, reflux 15 h; (b) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, 80% EtOH, reflux 45 min; (c) (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, EtOH, reflux, 15 h; (d) $UO_2(OAc)_2 \cdot 2H_2O$, MeOH, room temp., 12 h.

titration experiments we followed the upfield shift of the α-CH_2 protons signal of TBACl (2.00×10^{-3} M), upon addition of various aliquots of host **1** (concentration range 0–1.00×10^{-2} M; Figure 1).



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

Likewise, in the case of TMACl we followed the upfield shift of the CH_3 signal. Binding constants (K_a, M^{-1}) of the complexes of receptor **1** with TBACl and TMACl, respectively, and limiting upfield shifts ($-\Delta\delta_\infty$, ppm) were obtained as best-fit parameters by using the program Hyp NMR.[12] Pertinent data are reported in Table 1 together with the Gibbs free energy changes ($-\Delta G°$).[13] Job's plots support the 1:1 stoichiometry of the various host–guest complexes (see the Supporting Information).[14,15]

The large upfield shift of the guest protons suggests that the ammonium cation is strongly interacting with the pyrenyl arms that stabilize it by cation–π and CH–π interactions. Moreover, the signal of the diastereotopic protons

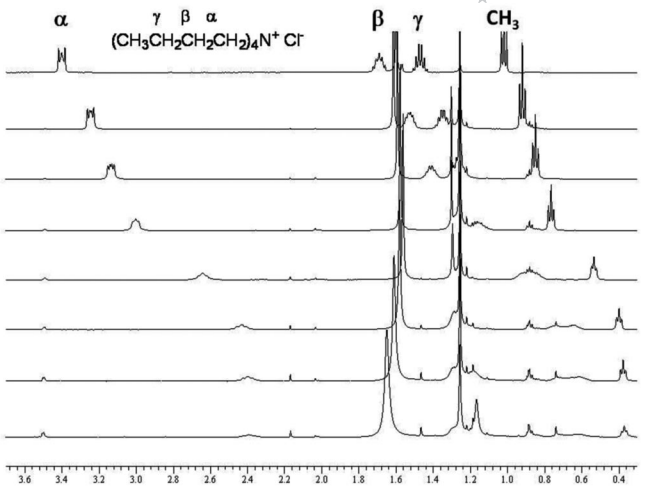


Figure 1. Selected region of the spectrum in a typical ^1H NMR titration of TBACl with receptor **1**. Constant concentration of guest TBACl (2.00×10^{-3} M) with addition of various concentrations (0 to 1.00×10^{-2} M) of host **1**. (a) TBACl; (b) [H]/[G] 1:5; (c) [H]/[G] 1:3; (d) [H]/[G] 1:2; (e) [H]/[G] 1:1; (f) [H]/[G] 1:0.6; (g) [H]/[G] 1:0.4; (h) [H]/[G] 1:0.2.

Table 1. Binding constants (K_a), limiting upfield shifts ($-\Delta\delta_\infty$), and Gibbs free energy changes ($-\Delta G_o$) for the complexation of TBACl and TMACl with receptor **1** in $CDCl_3$ at 27 °C.

Guest	K_a [M^{-1}]	$-\Delta\delta_\infty$ [ppm]	$-\Delta G_o$ [kJ mol^{-1}]
TBACl	$(3.71 \pm 1.53) \times 10^4$	1.02 (N–CH_2)	26.2
TMACl	$(1.32 \pm 0.51) \times 10^3$	1.33 (N–CH_3)	17.9

(H_b and H_c, see Figure 2) of receptor **1**, which undergoes a downfield shift, seems to indicate that the cation is sandwiched between the two pyrenyl arms, whereas as a consequence of the coordination of the chloride anion on the uranyl center, the H_a protons of the diphenylethane bridge move upfield.

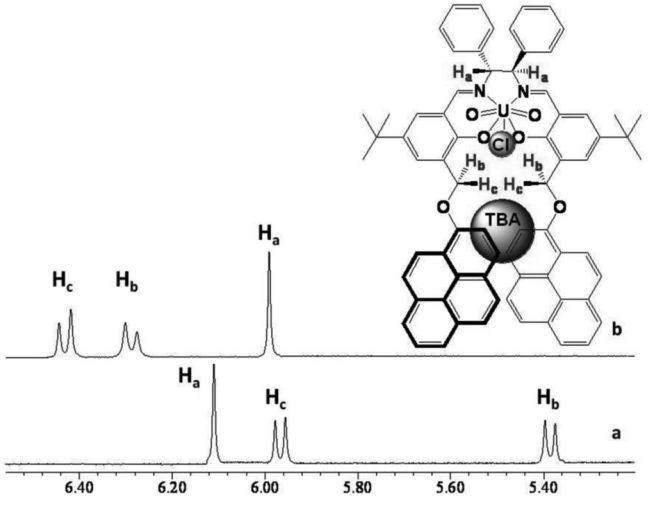


Figure 2. Selected region of the spectra showing the downfield shift of the diastereotopic protons as well as the upfield shift of the H_a protons of receptor **1** after addition of TBACl. (a) Receptor **1** (1.00×10^{-3} M); (b) [Receptor **1**]/[TBACl] 1:3.

Furthermore, T-ROESY experiments reveal ROE contacts between β-CH_2 of TBACl and the pyrenyl moieties, thus confirming the suggested spatial location of the ammonium cation. Similar ROE interactions were also observed between the CH_3 protons of TMACl and the pyrenyl aromatic framework (see the Supporting Information). These results support the conclusion that this new uranyl–salen complex behaves as a heteroditopic receptor in which the metal center is able to coordinate the anion, whereas the two pyrenyl rings act as tweezers toward the ammonium cation stabilizing it through CH–π and cation–π interactions. It is interesting to note that the cation identity affects the binding process. In fact, TBACl displays a higher binding constant than TMACl (K_{TBACl}/K_{TMACl} = 28) probably because of a larger number of and more efficient CH–π interactions involved in the recognition process. On the other hand, the larger TBA cation yields a looser ion pair, whose hosting by the heteroditopic receptor requires a lower separation energy cost.

We also tested the enantiomeric recognition ability of receptor **1** toward (*R*)- and (*S*)-α-methylbenzylammonium chlorides (MBnACl) and some ammonium salts of selected amino acids (Scheme 2) by UV/Vis titrations.[16] UV/Vis titration experiments typically show an increasing absorbance value at 331 nm upon addition of increasing amounts of the guests, and a corresponding decrease in the absorbance at 355, 364, and 384 nm (relative to the π–π* transitions of the pyrenyl moiety; Figure 3).

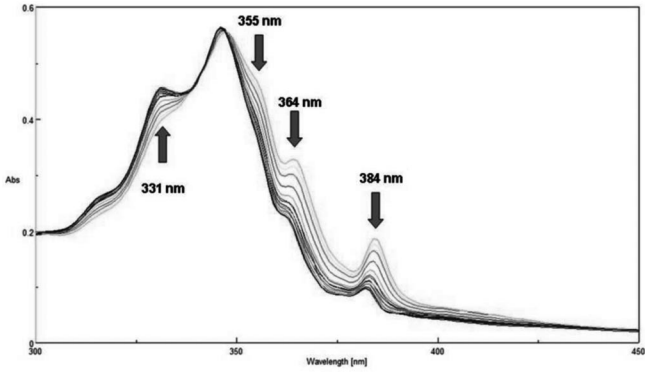


Figure 3. UV/Vis titration between receptor **1** and L-Trp-TMA.

In Table 2 we report pertinent affinity values (K_a), Gibbs free energy changes ($-\Delta G_0$), and enantioselectivities K_S/K_R and K_L/K_D (or $\Delta\Delta G_0$) ratios for the complexation of (*R*)- and (*S*)-α-methylbenzylammonium chlorides and L/D amino acid ammonium salts, respectively, with receptor **1**.

The observed enantioselectivity value (K_S/K_R = 4.4) for the two chiral salts (*S*)-MBnACl and (*R*)-MBnACl is related to the opposite configurations of the benzylic carbon atom stereocenter. In fact, in the (*S*)-MBnACl salt, and differently from the (*R*)-MBnACl, the phenyl group is oriented to develop π–π interactions with the pyrenyl unit, increasing therefore the affinity for receptor **1** (Figure 4).

When the amino acids are taken in consideration as guests, it is interesting to note that pertinent affinities values

Table 2. Binding constants (K_a), Gibbs free energy changes ($-\Delta G_0$), and enantioselectivities K_L/K_D or $\Delta\Delta G_0$ for the complexation of L/D amino acid derivatives and (*R*,*S*)-MBnACl with receptor **1** in $CHCl_3$ at 25 °C.

Guest	K_a [M^{-1}]	K_L/K_D	$-\Delta G_o$ [kJ mol^{-1}]	$\Delta\Delta G_o$[a] [kJ mol^{-1}]
(*R*)-MBnACl	$(5.92 \pm 0.21) \times 10^5$	4.4[b]	32.9	3.7[c]
(*S*)-MBnACl	$(2.59 \pm 0.31) \times 10^6$		36.6	
D-Phe-TBA	$(3.52 \pm 0.16) \times 10^5$	0.61	31.6	1.2
L-Phe-TBA	$(2.14 \pm 0.16) \times 10^5$		30.4	
D-Trp-TBA	$(2.80 \pm 0.22) \times 10^5$	6.7	31.1	4.7
L-Trp-TBA	$(1.88 \pm 0.30) \times 10^6$		35.8	
D-Phe-TMA	$(7.36 \pm 0.12) \times 10^4$	34.0	27.8	8.7
L-Phe-TMA	$(2.50 \pm 0.14) \times 10^6$		36.5	

[a] $\Delta\Delta G_0 = |\Delta G_0(D) - \Delta G_0(L)|$. [b] K_S/K_R. [c] $\Delta\Delta G_0 = |\Delta G_0(R) - \Delta G_0(S)|$.

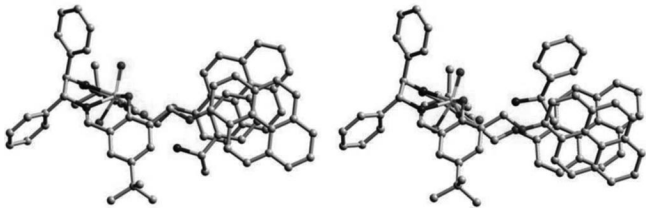


Figure 4. Optimized structures of the 1:1 complexes of **1** with (*S*)-MBnACl (left) and (*R*)-MBnACl (right). Hydrogen atoms are omitted for clarity.

toward receptor **1** are of the same order of magnitude as those observed for α-methylbenzylammonium chlorides. These findings seem to indicate that the carboxylate anion of the amino acid behaves as the hard chloride in binding the uranyl metal center driving the molecular recognition event.[10,17] To the best of our knowledge, this uranyl complex represents the first hitherto reported chiral receptor able to recognize and strongly bind carboxylate anions of amino acids. NMR spectroscopic data support this conclusion. In fact, even in the case of D-Phe-TBA, we observed an upfield shift of the protons of the diphenylethane bridge (H_a, Figure 5), providing good evidence that the carboxylate anion is able to coordinate the uranyl metal center, as the chloride anion does.

On the other hand, a strong downfield shift of the signals for the diastereotopic protons of receptor **1** (H_b and H_c) is observed, confirming therefore the presence of the cation nearby the π-electron rich pyrene framework. A ROESY experiment displays also in this case a ROE contact between the CH_3 protons of the TBA cation and the pyrenyl arms, therefore supporting the spatial location of the cation (see the Supporting Information).

As Table 2 shows, selectivity values of 0.61, 6.7, and 34.0 for the L,D-Phe-TBA, L,D-Trp-TBA, and L,D-Phe-TMA, respectively, support a very efficient recognition ability of receptor **1** toward these amino acids salts.[18] The observed selectivity shows a quite complex dependence on the configuration of the anion (amino acid carboxylate) and cation identities. The possibility to develop interactions among the aromatic moieties of the amino acid anions [which occupy the fifth equatorial coordination site of the uranyl(VI)

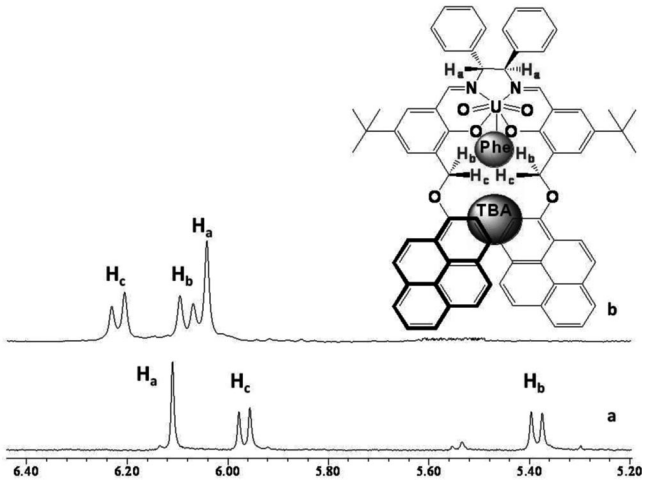


Figure 5. Selected region of the spectra showing the downfield shift of the diastereotopic protons as well as the upfield shift of the H_a protons of receptor **1** after addition of D-Phe-TBA. (a) Receptor **1** (1.00×10^{-3} M); (b) [Receptor **1**]/[D-Phe-TBA] 1:3.

ion][19] and the pyrenyl moiety might be conflicting or reinforcing with the recognition process of the cation, which might also depend on the bulkiness of the cation itself.

Conclusions

We have synthesized a new chiral uranyl–salen receptor bearing two pyrenyl arms and evaluated the enantiomeric recognition properties of this complex toward ammonium salts containing α-amino acid moieties by ^{1}H NMR and UV/Vis titrations. This receptor is readily prepared by a short synthetic sequence and displays a very high selectivity toward an L,D pair of amino acid salts, in particular for the two enantiomers of Phe-TMA. T-ROESY experiments have shown that the two pyrenyl groups play a key role in the complexation phenomena interacting through CH–π and cation–π with the ammonium cations, leading to high binding affinities. The identity of the cation, TMA versus TBA, and the configuration of the amino acid are crucial in determining the enantiomeric selectivity for the L and D pair.

Supporting Information (see footnote on the first page of this article): General experimental methods, characterization of all compounds, DOSY experiments, Job Plots, and UV/Vis and ^{1}H NMR titrations.

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[18] (D)- and (L)-Trp-TMA salts were also prepared according to a general procedure (see the Supporting Information), but their use was precluded by their scanty solubility in chlorinated solvents.
[19] A pentagonal bipyramidal coordination geometry for the uranyl(VI) ion with two axial oxo 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.[11d,17]

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