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Pair of Diastereomeric Uranyl Salen Cavitands Displaying Opposite Enantiodiscrimination of α-Amino Acid Ammonium Salts

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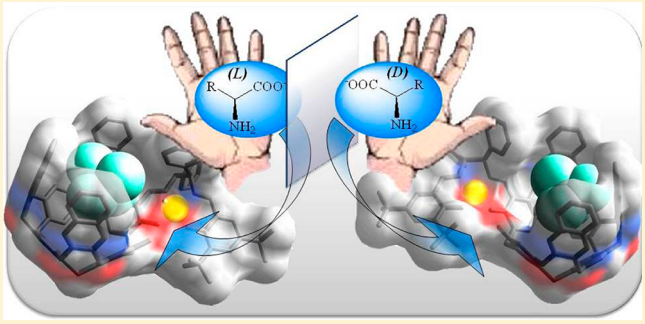
Supporting Information

ABSTRACT: A pair of diastereomeric salen cavitands and their uranyl complexes combine a chiral (*R*,*R*) salen bridge and an inherent chiral tris-bridged quinoxaline cup within the same molecule. Whereas the free ligands show a preference for the same enantiomer of an α-amino acid pair, the corresponding UO_2 complexes display opposite enantiodiscrimination and exceptionally high enantioselectivities (K_D/K_L = 26.4)



Molecular recognition of biological molecules by synthetic receptors is a burgeoning field that merges the principles and applications of supramolecular chemistry.[1] Anions are ubiquitous in the natural world and play numerous roles in biological and chemical features.[2] Among them, chiral carboxylate anions represent interesting subjects in enantiorecognition because of their important presence in enzymes as substrates and cofactors, antibodies and metabolic intermediates,[3] and amino acids. In this context, synthesis of artificial receptors for anions,[4] and in particular chiral recognition of α-amino acids, plays a very important role, and the research in this field is still of increasing interest.

Recently, we reported that triquinoxaline-spanned cavitand, containing a salen chiral framework **2** (Scheme 1), and its uranyl complex **2**-UO_2 are able to perform good to excellent selective molecular recognition of chiral ammonium ion pairs, where the amino acid is the countercation or the counteranion of the ion pair.[5] Here, we correlate the binding abilities of **2** and **2**-UO_2 to those of diastereoisomers **3** and **3**-UO_2, respectively. These diastereomeric receptors hold two distinct elements of chirality: the (*R*,*R*) salen chiral bridge and the inherent chirality of the quinoxaline cavity. In this paper, we demonstrate that, in the "metal free" receptors, the enantioselection is ruled by the bridge configuration, while in the uranyl complexes the enantioselection is tuned by the inherent chirality of the cavitand.

Cavitands **2** and **3** can be obtained by reacting the monoformyl cavitand (±)**1** containing the salicylaldehyde functionality,[6] with an appropriate chiral imino-amino precursor.[7] Because of the inherent chirality of the monoformyl cavitand (±)**1**, the reaction affords two diastereoisomers differing for the cavity configuration. Here, we were able to optimize the purification conditions in order to obtain the diastereoisomer **3** in appreciable amounts. The structural characterization of the diastereoisomer **3** was carried out by MS (ESI) measurements and by ^{1}H and ^{13}C as well as g-COSY and T-ROESY NMR spectroscopy (S3 and S4, see the Supporting Information).[8]

According to Mandolini's chirality descriptor,[9] we can assign the configurations of the **2** and **3** enantiomeric cavities. Envisaging an ideal observer standing inside the resorcarene cavity and applying the sequence rules,[10] *cR* and *cS* configurations, where *c* stands for cavity, are tentatively assigned to receptors **2** and **3**, respectively. Since receptors **2** and **3** differ for the inherent chirality of the cavitand, it seems intriguing to investigate which property, i.e., the chirality of the bridge or the chirality of the cavitand, is responsible for a selective molecular recognition of amino acids. Therefore, we investigated the ability of cavitand **3** to enantiodiscriminate chiral ion pairs. Chart 1 reports the salts employed as guests in the molecular recognition.

Molecular recognition studies were carried out by NMR spectroscopy and UV/vis measurements. In particular, NMR experiments gave us important information about the inclusion of the guests inside the cavity of receptor. In fact, the protons of the countercation undergo an upfield shift, consistent with the inclusion of the alkylammonium group inside the π-electron-rich region of the cavity. 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 likely located near the bridge of the salen wall (S5, see the Supporting Information).

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Scheme 1. Synthesis of Diastereomeric Cavitand−Salen Receptors 2 and 3

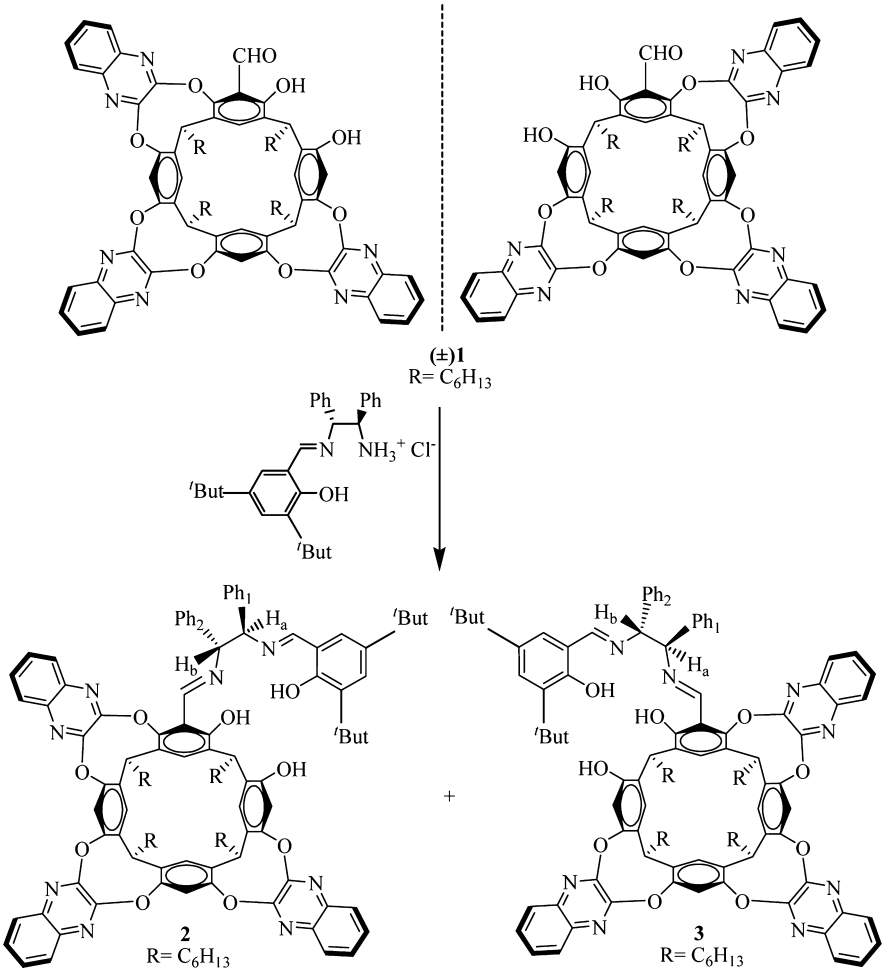

Chart 1. Ammonium and Amino Acid Salts Used as Guests

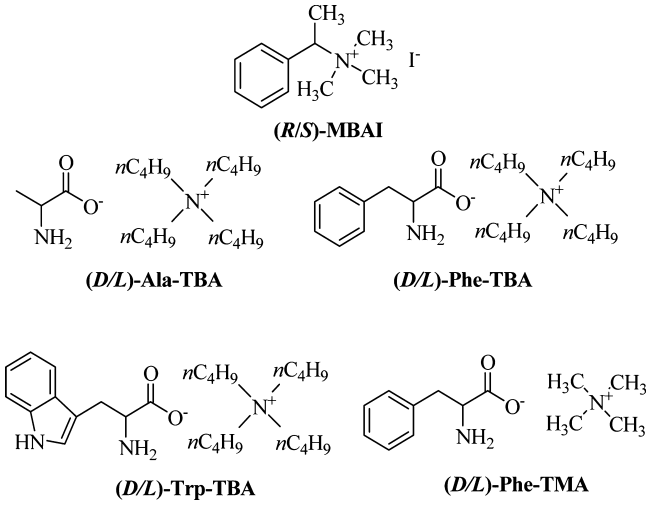

Table 1. Binding Constants (K_a) for Receptor 3 and Relative Enantioselectivities K_L/K_D for the Complexation of L/D Amino Acid Derivatives and (*R*,*S*)-MBAI in $CHCl_3$ at 27 °C

	cavitand **3**		cavitand **2**[c]
guest	K_a[a] (M^{-1})	K_D/K_L	K_D/K_L
(*R*)-**MBAI**	(3.49 ± 0.68) × 10^3	5.5[b]	15.9[b]
(*S*)-**MBAI**	(1.94 ± 0.16) × 10^4		
D-**Phe-TBA**	(5.04 ± 0.18) × 10^3	1.4	3.5
L-**Phe-TBA**	(3.57 ± 0.09) × 10^3		
D-**Phe-TMA**	(2.49 ± 0.26) × 10^5	0.35	0.72
L-**Phe-TMA**	(7.15 ± 0.33) × 10^5		
D-**Trp-TBA**	(1.27 ± 0.54) × 10^4	3.2	0.80
L-**Trp-TBA**	(3.94 ± 0.28) × 10^3		
D-**Ala-TBA**	(7.77 ± 0.16) × 10^3	2.2	3.0
L-**Ala-TBA**	(3.60 ± 0.11) × 10^3		

[a]Binding constants calculated by Hyperquad 2006 (v. 3.1.60). [b]K_S/K_R. [c]Enantioselectivity values of cavitand **2**[5] reported for comparison.

Since NMR titrations do not allow quantitative determinations to be performed because of the complexity and overlap of many signals, the binding constants were obtained by UV/vis titrations. Table 1 reports the values of binding constants for receptor **3** and the relative enantioselectivities for receptors **3** and **2**.[5] The observed binding affinities appear lower than those previously determined with the diastereomeric receptor **2**, but interesting enough, the selectivity of both receptors works in the direction to prefer in all instances, except **Trp-TBA**, the same enantiomer of the guest pair: (*S*)-**MBAI**, D-**Phe-TBA**, L-**Phe-TMA** and D-**Ala-TBA**, suggesting that the (*R*,*R*) configuration of the salen bridge tunes the recognition event.[11]

The D- and L-**Trp-TBA** pair (K_D/K_L = 0.80) with cavitand **2** displays nearly the same affinity, presumably because the carboxylate counteranion gives a scarce contribution to the

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selectivity. The control of the molecular recognition by the chirality of the bridge might be ascribed to the allocation of the chiral portion of the guest, i.e., the amino acid carboxylate, in proximity of the salen bridge, whereas the cation is accommodated within the π-electron rich cavity, which stabilizes it through CH−π interactions.

By complexation with uranyl acetate, cavitand receptor **3** gave the uranyl cavitand−salen **3-UO$_2$**, able to work as a heteroditopic receptor. The uranyl complex was characterized by MS (ESI) measurements and by ^{1}H NMR spectroscopy (S6, see the Supporting Information). The coordination of UO_2 causes a downfield shift of CH imine proton signals as well as of the H_a and H_b proton signals of the salen bridge (Scheme 1).[12] We have already reported 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.[5,13]

The observed binding affinities and the corresponding enantioselectivies for the selected amino acid salts (Chart 1) with receptor **3-UO$_2$**, determined by UV/vis measurements, are reported in Table 2. Furthermore, for comparison, the enantioselectivities of **2-UO$_2$** are also shown.[5]

Table 2. Binding Constants (K_a) for Receptor 3-UO$_2$ and the Relative Enantioselectivities K_L/K_D for the Complexation of L/D Amino Acid in CHCl$_3$ at 27 °C

	3-UO$_2$		2-UO$_2$[b]
guest	K_a[a] (M^{-1})	K_D/K_L	K_D/K_L
D-Phe-TBA	(3.15 ± 0.12) × 10^5	6.4	0.66
L-Phe-TBA	(4.95 ± 0.27) × 10^4		
D-Phe-TMA	(1.35 ± 0.50) × 10^3	0.27	23.7
L-Phe-TMA	(4.91 ± 0.21) × 10^3		
L-Trp-TBA	(5.57 ± 0.55) × 10^4	26.4	1.0
D-Trp-TBA	(2.11 ± 0.26) × 10^3		
D-Ala-TBA	(2.46 ± 0.20) × 10^3	0.27	6.4
L-Ala-TBA	(9.03 ± 0.75) × 10^3		

[a]Binding constants calculated by Hyperquad 2006 (v. 3.1.60). [b]Enantioselectivity values **2-UO$_2$**[5] reported for comparison.

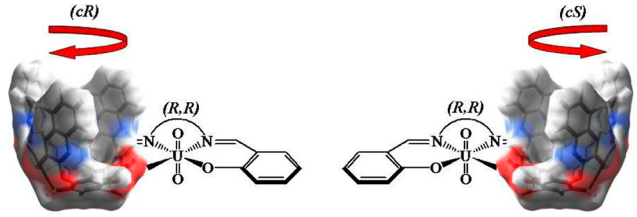
As Table 2 shows, selectivity values of 6.4, 0.27, 26.4, and 0.27 for the D,L-**Phe-TBA**, D,L-**Phe-TMA**, D,L-**Trp-TBA**, and D,L-**Ala-TBA**, respectively, support a very efficient recognition ability of receptor **3-UO$_2$** toward these amino acids salts.

As already anticipated, an inversion of enantiodiscrimination between the two uranyl cavitands, **2-UO$_2$** and **3-UO$_2$**, is operating: the receptors recognize opposite enantiomers of the same amino acid pair, in contrast to the behavior observed with the cavitands **2** and **3**. Since the two uranyl complexes possess the same configuration (*R*,*R*) in the salen bridge but opposite configuration for the cavities (*cS*, *cR*), the enantioselective recognition seems determined now by the inherent chirality of the cavities (Table 3).

At the best of our knowledge, this is the first example of synthetic receptors able to recognize opposite enantiomers of α-amino acid pairs.

In summary, we have optimized a protocol to obtain two diastereomeric salen cavitand-based receptors possessing two chiral subunits, i.e., a salen bridge (*R*,*R*) and an inherent chiral cavity (*cS* and *cR*). The metal-free diastereomeric receptors recognize the same enantiomer of an α-amino acid pair, while uranyl metal complexes are able to recognize opposite enantiomers with high enantioselectivities. The understanding

Table 3. Schematic Representation of Uranyl Salen Cavitand Receptors 2-UO$_2$ and 3-UO$_2$ and the Enantioselectivity Displayed for the Selected Guests



2-UO$_2$ (*cR*,*R*,*R*)	3-UO$_2$ (*cS*,*R*,*R*)
L-Phe-TBA	D-Phe-TBA
D-Phe-TMA	L-Phe-TMA
L-Trp-TBA	D-Trp-TBA
D-Ala-TBA	L-Ala-TBA

of the rules governing the enantiodiscrimination of these cavitand−salen receptors with amino acid guests is the basis for the development of new artificial receptors.

EXPERIMENTAL SECTION

Synthesis of Cavitand−Salen 3. In a round-bottom flask, to a solution of monoformyl cavitand (±)**1** (0.274 mmol) in 30 mL of abs EtOH were added monoimine−amine−(1*R*,2*R*)-diphenyl 3,5-di-*tert*-butylsalicylaldehyde[7] (0.274 mmol) and triethylamine (0.549 mmol). The reaction was stirred for 48 h at room temperature and monitored by TLC (hexane/EtOAc 60:40, R_f = 0.7). The reaction was quenched by evaporation of the solvent under reduced pressure, and the receptor **3** was purified by flash chromatography (hexane/EtOAc 90:10) (40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 15.91 (s, 1H), 13.23 (s, 1H), 9.93 (s, 1H), 8.44 (s, 2H), 8.31 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.69 (m, 2H), 7.63 (m, 4H), 7.55 (m, 5H), 7.50 (m, 5H), 7.43 (s, 1H), 7.36 (s, 1H), 7.27 (s, 1H), 7.22 (s, 1H), 7.06−7,17 (m, 11H), 7.03 (s, 1H), 6.97 (m, 4H), 6.80 (m, 2H), 5.50−5.56 (m, 2H), 4.71 (d, *J* = 7.5 Hz, 1H), 4.62−4.69 (m, 2H), 4.60 (d, *J* = 7.5 Hz, 1H), 4.42 (t, *J* = 8.0 Hz, 1H), 3.95 (t, *J* = 8.0 Hz, 1H), 2.00−2.40 (m, 8H), 1.57 (t, *J* = 6.5 Hz, 3H), 1.48 (m, 16H), 1.36 (m, 8H), 1.26 (m, 16H), 1.06 (m, 8H), 0.92 (t, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.74 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.88, 162.3, 157.92, 154.62, 152.99, 152.56, 152.4, 152.3, 152.2, 152.1, 151.7, 148.9, 147.5, 146.8, 140.3, 140.0, 139.7, 139.5, 138.9, 138.3, 137.6, 137.1, 136.1, 135.0, 133.9, 130.4, 129.3, 129.0, 128.9, 128.3, 128.1, 127.9, 127.8, 127.7, 127.5, 127.4, 126.9, 126.7, 126.4, 124.5, 123.1, 122.7, 118.8, 117.9, 117.7, 111.6, 106.6, 79.4, 75.6, 63.5, 34.9, 34.7, 34.3, 33.5, 33.1, 33.0, 32.3, 31.9, 31.6, 29.5, 29.48, 29.40, 29.3, 29.0, 28.0, 27.99, 27.91, 27.6, 22.7, 22.6, 22.4, 14.0, 13.8 ppm; ESI-MS *m*/*z* 1688 [M + H + (C_2H_5OH)]$^+$ for $C_{106}H_{112}N_8O_9$. Anal. Calcd for $C_{106}H_{112}N_8O_9$: C, 77.53; H, 6.87; N, 6.82; O, 8.77. Found: C, 77.50; H, 6.83; N, 6.81.

Synthesis of Uranyl Receptor 3-UO$_2$. To a solution of **3** (0.124 mmol) dissolved in 10 mL of absolute ethanol was added uranyl acetate (0.179 mmol). The reaction was stirred overnight at room temperature, and the solid was filtered and dried to yield **3-UO$_2$** as a red powder (95%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 9,40 (s, 1H), 9,16 (s, 1H), 8.43 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.80 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.65 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.47−7.57 (m, 3H), 7.43 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 7.29 (s, 1H), 7.18−7.28 (m, 10H), 7.16 (s, 1H), 6.82−6.90 (m, 3H), 6.10 (s, 1H), 5.73 (t, *J* = 7.5 Hz, 2H), 5,65 (s, 1H), 5.12 (t, *J* = 7.5 Hz, 1H), 4.55−4.69 (m, 2H), 4.03 (t, *J* = 7.5 Hz, 1H), 2.24−2.43 (m, 6H), 1.73 (s, 9H), 1.33−1.61 (m, 24H), 1.31(s, 9H), 1.24−1.29 (m, 8H), 0,95 (t, *J* = 6.5 Hz, 6H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.67 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.88, 165.3, 161.92, 156.99, 156.56, 156.05, 155.68, 152.83, 150.80, 143.67, 143.54, 142.90, 142.35, 141.61, 141.15, 140.24, 140.08, 139.04, 137.87, 134.41, 134.12, 133.35, 133.06,

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132.77, 132.55, 132.36, 132.11, 132.03, 131.90, 131.79, 131.72, 131.53, 131.38, 130.94, 130.76, 130.39, 128.51, 127.15, 126.75, 122.81, 121.78, 115.68, 110.62, 90.03, 63.57, 34.96, 34.69, 34.31, 33.48, 32.97, 32.63, 32.30, 31.96, 31.88, 31.65, 31.40, 31.21, 31.19, 30.12, 29.47, 29.39, 29.04, 28.05, 27.98, 27.90, 27.67, 22.63, 22.46, 14.06, 13.85 ppm; ESI-MS *m/z* 1955.2 $[M + H + (C_2H_5OH)]^+$ for $C_{106}H_{110}N_8O_{11}U$, 1977 for $[M + Na + (C_2H_5OH)]^+$. Anal. Calcd for $C_{106}H_{110}N_8O_{11}U$: C, 66.65; H, 5.80; N, 5.87. Found: C, 66.63; H, 5.75; N, 5.84.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H, ^{13}C, g-COSY, T-ROESY spectra, MS (ESI), UV/vis titrations, and Job's plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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