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Inherently Chiral Uranyl-Salophen Macrocycles: Computer-Aided Design and Resolution

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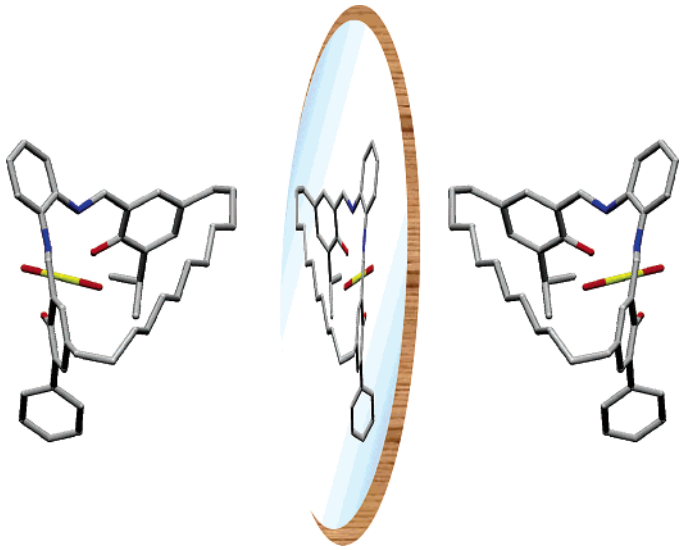

A flipping motion rapidly inverts the bent structure of uranyl-salophen compounds and, consequently, causes fast enantiomerization of nonsymmetrically substituted derivatives. This process has been previously slowed by introducing bulky substituents in the imine bond region. Since the resulting complexes dissociate upon chromatographic treatment, an alternative approach to the design and synthesis of robust, nonflipping uranyl-salophen compounds is here described. Such an approach is based on the idea that the flipping motion would be blocked by connecting the para positions with respect to the phenoxide oxygens by means of polymethylene bridges of suitable length. Analysis of a number of uranyl-salophen compounds by molecular mechanics, while showing that bulky substituents in the imine bond region cause severe distortions of the ligand backbone, suggested that the best chain lengths are those that fit the gap between the phenoxide rings without altering the *natural* geometry of the parent uranyl-salophen compound. Calculations showed that such chains are those composed of 12 and 13 methylene units. Accordingly, chiral uranyl-salophen macrocycles bridged with 12- and 13-methylene chains were synthesized in fairly good yields and resolved by chiral HPLC.

Introduction

The design of synthetic molecular receptors capable of selective recognition of one of the two enantiomers of a target substrate is a main topic in supramolecular chemistry,[1] with many implications in industrial processes and biomedical research.[2] Moreover, enantiomeric recognition at the transition state level is the basis for the development of asymmetric catalysts.[3]

The main point to be satisfied in the design of a chiral receptor is the construction of a dissymmetric spatial arrangement of the interaction sites. Such a request can be in principle more easily met if the chirality of the receptor arises from the geometry of the skeleton rather than from a single stereogenic element. Very few examples of enantioselective receptors and asymmetric

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catalysts based on this concept have been reported so far,[4] although much attention has been devoted in the past decades to chiral structural units devoid of the most usual elements of chirality, such as chiral centers, planes, and axes.

We have recently reported that the inherently chiral[5] uranyl-salophen receptor **1** binds neutral chiral molecules endowed with a donor site (e.g., amines, sulfoxides) with good enantioselectivity.[6] Chirality in nonsymmetrically substituted uranyl-salophen compounds arises from the marked curvature imposed to the coordinated ligand by the large atomic radius of the uranium in UO_2^{2+}. In nonsymmetrical derivatives of the sterically unhindered parent compound **2a**, fast enantiomerization occurs because of the existence of a flipping motion that rapidly inverts the curvature and keeps the two enantiomers in equilibrium (Figure 1). Nevertheless, the flipping could be significantly slowed by introducing bulky substituents in suitable positions (e.g., **3b**).[7] The highest racemization barrier was obtained by replacing the *o*-phenylenediamine ring with its tetramethyl derivative and by introducing a phenyl substituent on one of the imine carbon atoms. The racemization half-life of such compounds is about 17 h at 25 °C.[8]

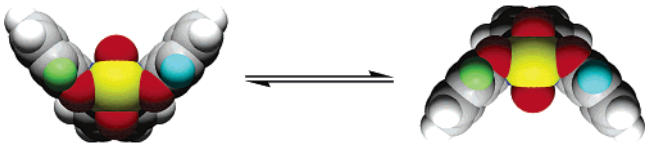

FIGURE 1. Flipping motion of compound **2a.** The calculated structures are observed from the equatorial plane of the uranyl unit. The blue and green hydrogen atoms differentiate the two otherwise indistinguishable conformations.

The behavior of compound **1** illustrates that in this novel class of inherently chiral receptors the use of a tetracoordinated uranyl dication as recognition site allows a rational construction of the receptor, because the complexed guest is bound to the fifth coordination site of the uranium in its equatorial plane. Since synthetic routes to salophen ligands make use of easily available ortho-substituted phenols as starting materials, the binding site can be shaped at will by a proper selection of groups adjacent to the metal center. For example, receptor **1** features a phenyl group, known to act as a secondary binding site in the complexation of a variety of guests,[9] and a methyl group, deputed to introduce more strict shape requirements via repulsive interactions with the bound substrate. Figure 1 clearly shows that, once the flipping motion is blocked, the three interaction sites, namely, the metal center and the two adjacent groups, are arranged in a chiral array.

Unfortunately, there are major drawbacks in the strategy of slowing down the flipping motion by introducing steric bulk in the imine bond region. First of all, this strategy cannot be pushed further, as shown by the fact that all our attempts at introducing either bulkier substituents or substituents also on the second imine carbon atom were unsuccessful.[10] Second, sterically crowded uranyl-salophen complexes, including **1**, dissociate upon chromatographic treatment to give the free ligands in a pure form,[11] thus precluding enantiomeric resolution via chiral HPLC. Given that the strategy based on the introduction of bulky groups turned out to be a dead end, we carried out a computational study of the hindered complexes. A careful analysis of calculated geometries pointed to excessive ligand distortion as a reasonable explanation for the above-mentioned problems. So, we reasoned that the flipping motion could be blocked by connecting the para positions of the phenoxide rings by means of chains of appropriate length (see Figure 1). Of course, whereas short chains would induce severe strain energies, too-long chains would lead to curvature inversion through conformational changes of the jump-rope type. As a first approach to nonflipping uranyl-salophen compounds stable under chromato-

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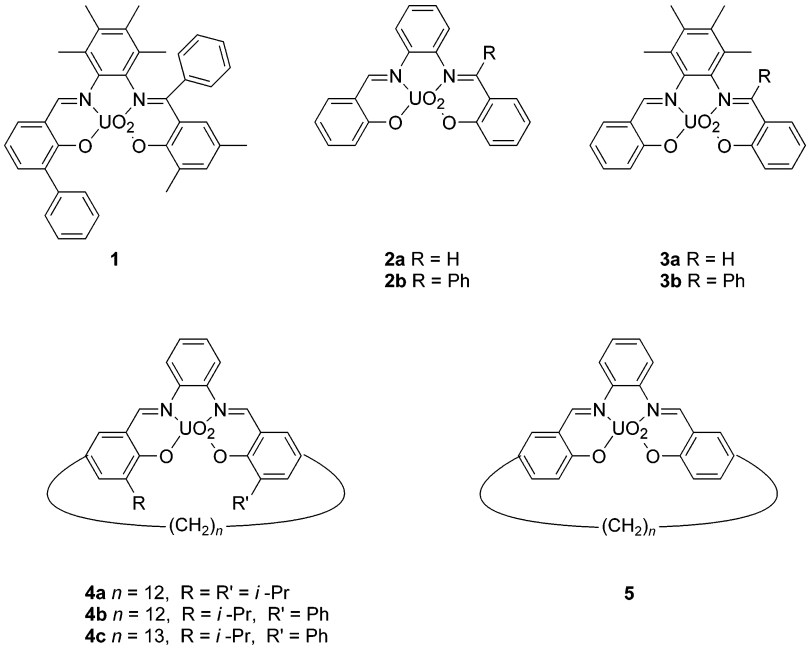
CHART 1



graphic conditions, we report here on a computer-aided design and synthesis of three novel macrocyclic compounds, namely, the symmetric uranyl-salophen compound **4a**, and the chiral analogues **4b** and **4c** (Chart 1). In line with expectations, the new complexes proved to be resistant to chromatographic treatment so that the enantiomers of **4b** and **4c** could be resolved by HPLC on a chiral stationary phase.

Computational Procedure

The structures of uranyl-salophen complexes were calculated utilizing the force field MM3 as implemented in Macromodel version 6.0. The parameters introduced for uranium, uranyl oxygens, and phenoxide oxygens have been previously published.[7] Partial atomic charges were computed using the electrostatic potential (ESP) from the wave function obtained by an AM1 calculation in SPARTAN version 5.0.1. Charges of +2 on the uranium and 0 on the oxygens were used for the uranyl dication. These parameters gave good agreement with the structure of the uranyl pentahydrate cation, as well as with several X-ray structures of salophen-uranyl complexes.[12]

Calculation Results

Analysis of calculated structures of uranyl-salophen complexes led us to observe that compounds with steric hindrance in the imine bonds region, such as **1** and **2b**, are much more distorted than unhindered ones. It seems likely that such an increased distortion of the ligand backbone can be held responsible for a decrease in thermodynamic stability of the complexes that accounts for their chromatographic lability as well as for our unsuccessful attempts at the synthesis of more hindered compounds.[10] To test this hypothesis and exploit it for the rational design of stable noninterconverting structures, the deviation from planarity of the ligand should be quantified. To this purpose we define two parameters, δ and δ', as in eqs 1 and 2, where α, β, γ, α', β', and γ' are the torsion angles defined in Figure 2.

$$\delta = (180 - \alpha) + (180 - \beta) + (180 - \gamma) \qquad (1)$$

$$\delta' = (\alpha' - 180) + (\beta' - 180) + (\gamma' - 180) \qquad (2)$$

These parameters are related to the left- and right-hand sides, respectively, of a uranyl-salophen compound watched by an observer facing its concave face with the *o*-phenylenediamine ring directed up, as in Figure 2.

The two parameters δ and δ' will be 0° for a perfectly planar structure, such as that observed in the Mg^{2+} complex of the parent salophen ligand,[13] and 90° when the planes of the phenoxyde rings are perpendicular to the plane of the *o*-phenylenediamine ring. Calculated values of δ and δ' for the model compounds **2a**, **2b**, **3a**,

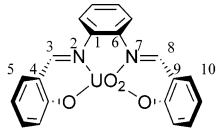


FIGURE 2. Definition of the torsion angles used in eqs 1 and 2. The uranyl-salophen complex is observed from its concave side, and torsion angle values are within the range of 0−360°.

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TABLE 1. Calculated Values of δ and δ' (deg)

entry	compound	δ	δ'
1	**2a**	49.0	46.0
2	**2b**	51.2	66.9
3	**3a**	64.6	60.2
4	**3b**	66.5	78.7
5	**5**, $n = 11$	52.2	52.4
6	**5**, $n = 12$	46.6	47.6
7	**5**, $n = 13$	48.5	44.2
8	**5**, $n = 14$	48.7	33.0

and **3b** are listed in Table 1 (entries 1−4). The relatively small differences between δ and δ' values found for the symmetric compounds **2a** and **3a** are presumably due to a computational artifact. The values calculated for the parent compound **2a** (entry 1) can be compared with the values of 45.8° and 45.6° resulting from a DFT optimized geometry of the same compound,[13] as well as with one of 45.6° obtained from its X-ray crystal structure.[12] Differences between our values and the most reliable values available in the literature amount to only a few degrees and are much smaller than variations caused by the introduction of bulky substituents (entries 2−4). It appears therefore that our computational approach is accurate enough for the purposes of the present work despite the modest level of theory employed.

Introduction of a phenyl group on the imine carbon atom increases the δ value on its side by about 18−20° (compare entries 2 and 4 with 1 and 3, respectively) but has a very small influence, if any, on the other side of the ligand. The methyl substituents on the *o*-phenylenediamine ring cause an increase by about 15−17° (compare entries 3 and 4 with 1 and 2, respectively). When both a phenyl and a methyl group are simultaneously present a very significant increase by about 32° in the side of the phenyl is seen (compare entry 4 with 1). Since the geometrical distortion of the ligand backbone in the parent compound **2a** is expected to correspond to an optimal situation, the straightforward conclusion was reached that the highest stability of complexes is attained when both δ and δ' fall in the range of 45−50°. With this idea in mind, we designed the bridged compounds of general structure **5** in which the para positions of the two phenoxyde rings are connected by polymethylene chains of varying length. As to the choice of the chain length, we assumed as a general criterion that the best n values are those that keep both δ and δ' values as close as possible to the *unperturbed* values found for the parent compound **2a**. The results listed in Table 1 show that when $n = 11$ (entry 5), both δ and δ' values are larger than the optimum range, whereas when $n = 14$ (entry 8) one of the two values is normal while the other becomes as small as 33°, which corresponds to a considerable flattening of the ligand presumably caused by conformational constraints in the 14-methylene chain. Entries 6 and 7 indicate that the 12- and 13-methylene chains have the appropriate length for spanning the uranyl-salophen unit without perturbing in a significant way its natural shape. As shown by the calculated geometries of the *c*S[5] enantiomers of **4b** and **4c** (Figure 3), the polymethylene chains fit the gap between the phenoxyde rings so well that the possibility of jump-rope inversions of the curvature should be considered out of question. On the basis of the above results, compounds **5**, $n = 12$, 13 were considered as the best candidates for the synthesis of strainless nonflipping uranyl-salophen compounds.

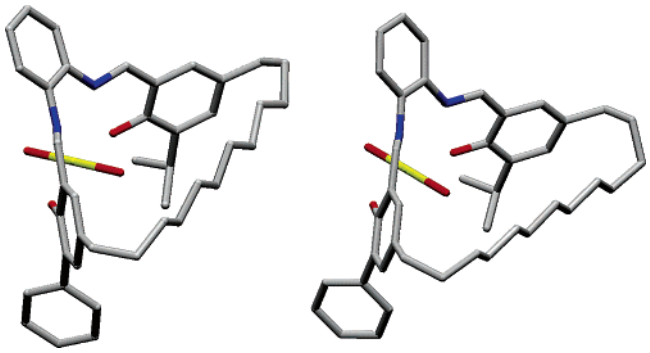

FIGURE 3. Calculated structures of uranyl-salophen complexes *c*S-**4b** (left) and *c*S-**4c** (right). Hydrogen atoms are omitted.

Results and Discussion

The synthethic procedure to obtain bridged complexes **4a**−**c** was first developed for the symmetrically substituted compound **4a** and subsequently extended to nonsymmetrical compounds **4b** and **4c** (Scheme 1). Although compound **4a** is not chiral, the isopropyl group can be used as a NMR diastereotopic probe of the flipping motion.[7]

The synthesis of α,ω-bis(*p*-hydroxyphenyl)alkanes reported by Doroshenko[14] gave us hints for the routes to the macrocycle precursors **8a**−**c**. Double Friedel−Craft acylation of 2-alkylanisoles with the appropriate acid dichloride yielded the corresponding dicarbonyl derivatives **6a**−**c**.[15] When a 1:1 mixture of two different anisoles was used, as required by the target compounds **4b** and **4c**, separation of the nonsymmetrical intermediates **6b** and **6c** from the symmetrical byproducts was carried out by column chromatography at this stage. Because Wolf−Kishner reduction of diketones **6** gave poor and scarcely reproducible results, we found more convenient the use of $ZnI_2/NaCNBH_3$ in 1,2-dichloroethane.[16] The phenolic compounds **8a**−**c**, obtained upon treatment of compounds **7a**−**c** with BBr_3,[17] proved to be unreactive under the Reimer−Tienmann and Hofslokken−Skattebol[18] formylation conditions previously used by us in the synthesis of salycilaldehyde derivatives.[7,8,19] Good results were obtained under the more vigorous conditions of the Gross formylation reaction.[20] Although this reaction is usually carried out on anisoles, the phenolic compounds **8a**−**c**

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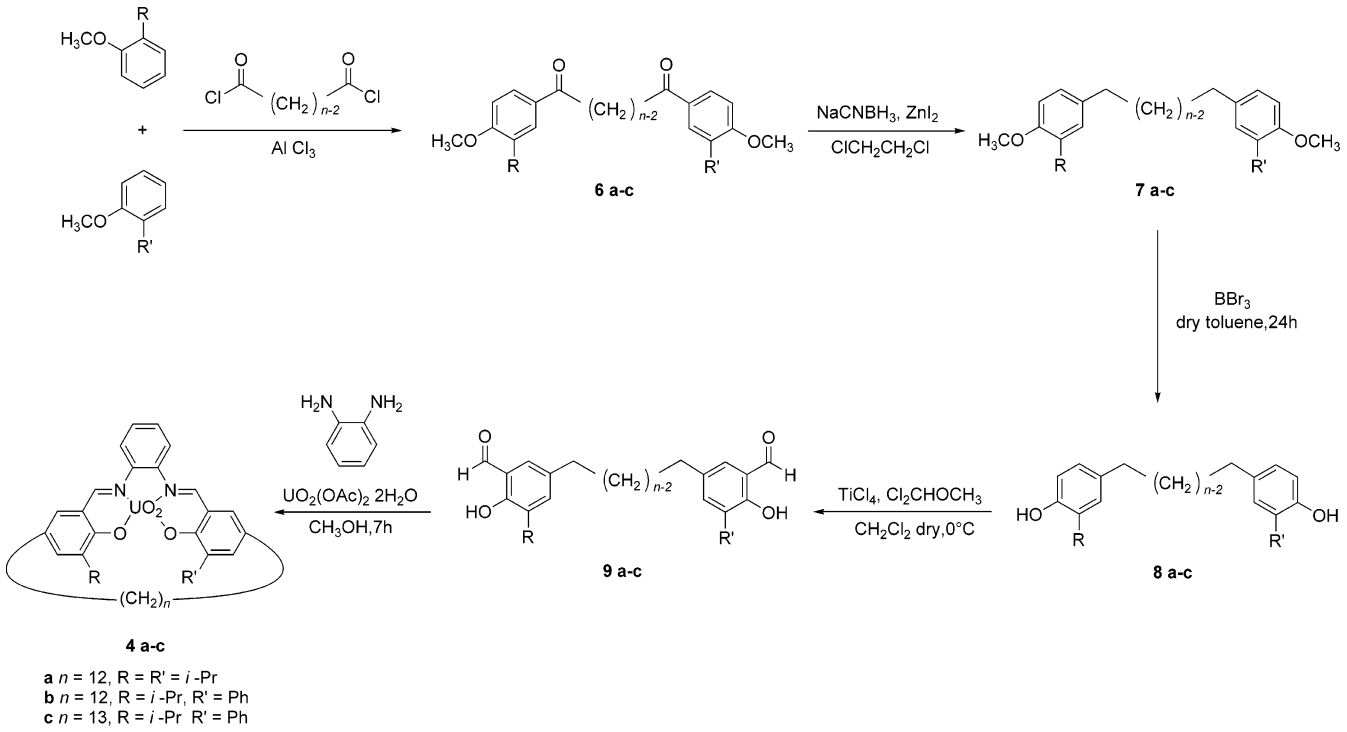
SCHEME 1. Synthesis of Bridged Uranyl-Salophen Complexes 4a−c



gave much better yields than their methylated precursors **7a**−**c**. As a first attempt to the synthesis of bridged compounds **4**, macrocyclization was carried out batchwise by mixing equimolar amounts of dialdehyde **9**, diamine, and uranyl salt at room temperature in methanol at a relatively high concentration of ca. 0.1 M in each reactant (procedure A). Macrocycle **4a** spontaneously separated from the reaction mixture as a solid material in 23% yield uncontaminated by its higher cyclic oligomers that remained in solution. The more soluble macrocycle **4b** was isolated instead from the reaction mixture in 22% yield by preparative TLC on silica gel, which allowed good separation from its higher cyclic oligomers, showing at the same time the tolerance of such compounds to chromatographic treatment. To increase the yield of the desired macrocycles at the expense of their higher cyclic oligomers, an influxion procedure was used for the slow simultaneous addition of the reactants into the reaction medium (Ziegler's high dilution technique, procedure B). No trace of the presence of higher oligomers was found in the crude reaction products, from which compounds **4b** and **4c** were isolated in 70% and 73% yield, respectively, by preparative TLC.

The ^{1}H NMR spectra of **4a**−**c** in acetone-d_6 at room temperature show that the geminal methyl groups of the isopropyl display in all cases a pair of doublet signals, heavily overlapped to the resonances of the methylene groups in the central part of the chains. The spectrum of **4a** (Figure 4) is the clearest one, because of the double intensity of the isopropyl signals compared with those of **4b** and **4c**. Cleaner results were obtained from the ^{13}C NMR spectra (Figure 4, on the right), where the signals of the methyl groups are well separated from other signals. A variable temperature ^{1}H NMR experiment

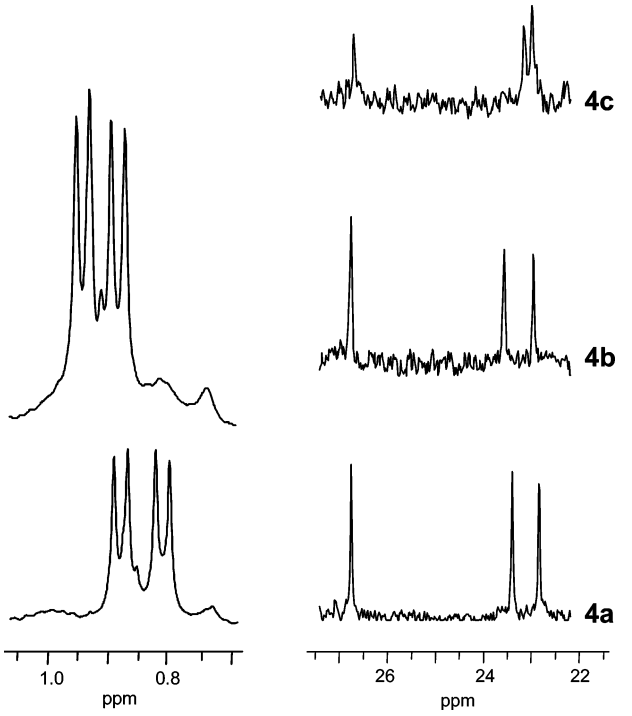


FIGURE 4. Portions of the ^{1}H spectra of **4a** (300 MHz, DMSO-d_6) displaying the resonances of the methyl groups at 298 K (left, bottom) and 386 K (left, top). Portions of the ^{13}C spectral regions of **4a**, **4b**, and **4c** (50 MHz, acetone-d_6) displaying the resonances of the isopropyl group at 298 K (right).

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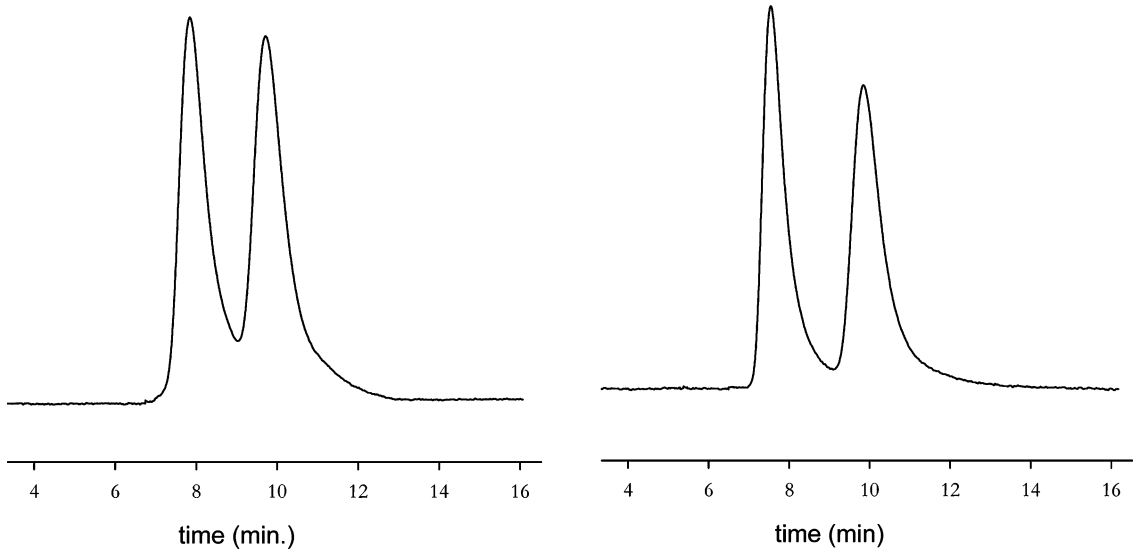

FIGURE 5. HPLC resolution of the enantiomers of **4b** (left) and **4c** (right) at room temperature on Chiralcel-OD-H column (eluent, *n*-hexane/ethanol 80:20; flow rate, 0.8 mL/min) with UV detection at 400 nm.

carried on compound **4a** in DMSO-d_6 (Figure 4, on the left) showed that the splitting persists up to at least 386 K.

The tolerance of the synthesized macrocycles to chromatographic treatments allowed the racemic mixtures of compounds **4b** and **4c** to be resolved by chiral HPLC. The chromatograms obtained using a Chiralcel OD-H column (Figure 5) with eluent hexanes−ethanol 80:20 at a flow rate 0.800 mL min^{-1} show in both cases a nearly complete separation of two peaks of equal intensity.

Conclusion

Three complexes belonging to a new class of macrocyclic uranyl salophen derivatives have been prepared. The goal of obtaining configurationally stable complexes that do not dissociate under chromatographic treatments was achieved on the basis of a computational study that relates the stability of uranyl-salophen compounds to the extent of the deviation from planarity of the ligand upon complexation. Stable noninterconverting complexes were obtained by linking the para positions with respect to the oxygen atoms of the phenoxide rings in cyclic structures, by means of a polymethylene chain. The optimized synthetic procedure is fast and reliable and leads to the dialdehydic precursor with good overall yields. The variety of ortho-substituted phenols easily available as starting materials makes the procedure very flexible.

The complexes **4 a**−**c** have proven to be stable under chromatographic conditions in that they have been easily purified by preparative silica gel TLC and furthermore the enantiomers of nonsymmetrical complexes **4b** and **4c** have been resolved by chiral HPLC.

In view of the well recognized ability of uranyl-salophen compounds to behave as receptors for anions and neutral molecules, and as catalysts in a number of important reactions, the present work opens the way toward a new family of chiral receptors with prospects of applications to enantioselective recognition and catalysis.

Experimental Section

General Procedure for Compounds 6. $AlCl_3$ (0.55 g, 4.15 mmol) and dichloromethane (0.50 mL) were placed under argon atmosphere in a dry flask cooled with an ice bath. A solution of the proper acid dichloride (4.05 mmol) in dichloromethane (0.70 mL) was added. 2-Isopropylanisole (2.00 mmol) or a mixture of 2-isopropylanisole (1.00 mmol) and 2-phenylanisole (1.00 mmol) in dichloromethane (0.50 mL) was slowly added, and finally the mixture was diluted with dichloromethane (0.50 mL) and stirred for 45 min at room temperature. The resulting mixture was poured into ice cold 6 M hydrochloric acid (20 mL). The organic layer was then washed with $NaHCO_3$ (saturated) and dried over anhydrous sodium sulfate.

1,12-Bis(3-isopropyl-4-methoxyphenyl)-dodecane-1,12-dione (6a) was prepared starting from 2-isopropylanisole and dodecandioic acid dichloride. The desired product was recovered without any purification in 90% yield, mp = 74−77 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.84 (dd, 2H, J = (Hz, 2.3 Hz); 7.77 (d, J = 2.3 Hz); 6.84 (d, 2H, J = 8.5 Hz); 3.87 (s, 6H); 6.84 (d, 2H, J = 6.9 Hz); 3.87 (s, 6H); 3.3 (m, 2H, J = 6.9 Hz); 2.9 (t, 4H, J = 7.6 Hz); 1.22 (d, 12H, J = 6.9 Hz); 1.15−1.80 (m, 26H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.4, 161.4, 137.7, 130.6, 128.6, 127.0, 110.2, 56.2, 38.9, 30.2, 27.5, 25.4, 23.1 ppm. MS-ESI-TOF for $C_{32}H_{46}O_4$ = 494.3, found *m/z* (+) 517.3 ($[M + Na]^+$).

1-(3-Isopropyl-4-methoxy-phenyl)-12-(6-methoxy-biphenyl-3-yl)-dodecane-1,12-dione (6b) was prepared starting from 2-isopropylanisole, 2-phenylanisole, and dodecandioic acid dichloride. Chromatographic purification of the statistical mixture (silica gel, 10% ethyl acetate in light petroleum) afforded the desired product in 38% yield, mp = 77−79 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.99−7.93 (m, 2H); 7.85−7.78 (m, 2H); 7.52−7.50 (d, 2H, J = 7.0 Hz); 7.44−7.32 (m, 3H); 7.02−6.99 (d, 1H, J = 8.6 Hz); 6.86−6.83 (d, 1H, J = 8.4 Hz); 3.88 (s, 3H); 3.87 (s, 3H); 3.35−3.25 (m, 1H, J = 6.96 Hz); 2.95−2.87 (m, 4H); 1.74−1.60 (m, 4H); 1.32−1.29 (m, 12H); 1.23−1.21 (d, 6H, J = 6.96 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 200.0, 161.4, 160.9, 138.3, 137.8, 131.9, 131.3, 130.9, 130.6, 130.22, 130.25, 128.8, 128.6, 128.1, 127.0, 111.3, 110.2, 56.5, 56.2, 39.1, 39.0, 30.2, 30.1, 27.5, 25.5, 25.3, 23.2 ppm. MS-ESI-TOF for $C_{35}H_{44}O_4$ = 528.3, found *m/z* (+) 551.4 ($[M + Na]^+$).

1-(3-Isopropyl-4-methoxy-phenyl)-13-(6-methoxy-biphenyl-3-yl)-tridecane-1,13-dione (6c) was prepared from 2-isopropylanisole, 2-phenylanisole, and tridecandioic acid

dichloride. Chromatographic purification of the statistical mixture (silica gel, 10% ethyl acetate in light petroleum) afforded the desired product in 37% yield, mp = 81−83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99−7.95 (dd, 1H, J_o = 8.34 Hz, J_m = 2.19 Hz); 7.94−7.93 (d, 1H, J = 2.19 Hz); 7.86−7.85 (d, 1H, J = 1.97 Hz); 7.82−7.79 (dd, 1H, J_o = 10.76 Hz, J_m = 2.2 Hz); 7.52−7.50 (d, 2H, J = 7.03 Hz); 7.44−7.35 (m, 3H); 7.02−6.99 (d, 1H, J = 8.57 Hz); 6.86−6.83 (d, 1H, J = 8.57 Hz); 3.37−3.23 (m, 1H, J = 6.81 Hz); 2.95−2.87 (m, 4H); 1.77−1.66 (m, 4H); 1.33 (m, 8H); 1.27 (m, 8H); 1.23−1.21 (d, 6H, J = 6.81 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.4, 200.0, 161.3, 160.8, 138.3, 137.7, 131.9, 131.3, 130.6, 130.2, 128.8, 128.6, 128.0, 127.0, 111.2, 110.2, 56.4, 56.2, 39.0, 38.9, 30.24, 30.16, 30.09, 27.5, 25.5, 25.3, 23.1 ppm. MS-ESI-TOF for $C_{36}H_{46}O_4$ = 542.3, found *m/z* (+) 565.5 ([M + Na]$^+$).

General Procedure for Compounds 7. ZnI_2 (0.97 g, 3.04 mmol) and 1,2-dichloroethane (10 mL) were placed in a flask together with the appropriate precursor **6** (1.07 mmol). $NaCNBH_3$ (0.936 g, 14.90 mmol) was added, and the reaction mixture was stirred for 24 h at room temperature and then filtered on a Celite plug that was washed throughly with dichloromethane. By evaporation of the solvent, the desired products were isolated as colorless oils in quantitative yields.

1,12-Bis(3-isopropyl-4-methoxyphenyl)-dodecane (7a). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.9−7.0 (m, 6H); 6.77 (d, 2H, J = 5.2 Hz); 3.8 (s, 6H); 3.3 (m, 2H, J = Hz); 2.5 (t, 4H, 7.8 Hz); 1.57 (m, 4H); 1.19−1.29 (m, 28H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.5, 137.3, 135.6, 126.8, 126.7, 110.9, 56.2, 36.1, 32.6, 30.4, 30.3, 30.2, 30.1, 27.4, 23.4 ppm. MS-ESI-TOF for $C_{32}H_{50}O_2$ = 466.4, found *m/z* (+) 489.5 ([M + Na]$^+$).

1-(3-Isopropyl-4-methoxy-phenyl)-12-(6-methoxy-biphenyl-3-yl)-dodecane (7b). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53−7.51 (d, 2H, J = 7.05 Hz); 7.42−7.37 (t, 2H, J = 7.62 Hz); 7.33−7.31 (d, 1H, J = 7.04 Hz); 7.13(s, 1H); 7.13−7.10 (d, 1H, J = 7.63 Hz); 6.99−6.88 (m, 3H); 6.77−6.74 (d, 1H, J = 8.22 Hz); 3.80 (s, 3H); 3.78 (s, 3H); 3.33−3.24 (m, 1H, J = 7.04 Hz); 2.61−2.50 (m, 4H); 1.58 (m, 4H); 1.30 (m, 6H); 1.26 (m, 6H); 1.1.21−1.19 (d, 6H, J = 7.04 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.5, 155.2, 139.4, 137.3, 135.9, 135.6, 131.6, 131.1, 130.2, 128.9, 128.6, 127.5,126.8, 126.7, 111.9, 110.9, 56.4, 56.2, 36.1, 35.8, 32.5, 32.4, 30.34, 30.30, 30.2, 30.1 ppm. MS-ESI-TOF for $C_{35}H_{48}O_4$ = 500.4, found *m/z* (+) 523.5 ([M + Na]$^+$).

1-(3-Isopropyl-4-methoxy-phenyl)-13-(6-methoxy-biphenyl-3-yl)-tridecane (7c). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54−7.52 (d, 2H, J = 7.43 Hz); 7.42−7.31 (m, 3H); 7.13−7.10 (m, 2H); 7.00−6.88 (m, 3H,); 6.77−6.74 (d, 1H, J = 8.23 Hz); 3.80 (s, 3H), 3.78 (s, 3H), 3.34−3.25 (m, 1H, J = 7.03 Hz); 2.61−2.50 (m, 4H); 1.59 (m, 4H); 1.30 (m, 9H); 1.26 (m, 9H); 1.22−1.19(d, 6H, J = 7.03 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.5, 155.2, 139.4, 137.3, 135.9, 135.6, 131.7, 131.1, 130.2, 128.9, 128.6, 127.5, 126.8, 126.7, 111.9, 110.9, 56.4, 56.2, 36.1, 35.8, 32.6, 32.4, 30.4, 30.3, 30.2, 30.1, 30.0, 27.4, 23.4 ppm. MS-ESI-TOF for $C_{36}H_{50}O_2$ = 514.4, found *m/z* (+) 537.5 ([M + Na]$^+$).

General Procedure for Compounds 8. The proper compound **7** (0.29 mmol) and dry toluene (2.0 mL) were placed under an argon atmosphere in a dry flask. A solution of boron tribromide (0.069 mL, 0.73 mmol) in dry toluene (2.0 mL) was added dropwise to the stirred solution cooled at 0 °C. The reaction mixture was stirred for 24 h at room temperature and then cooled again in an ice bath, and water (20 mL) was added. The solution was extracted with three portions of diethyl ether (10 mL each), and the combined organic layers were washed twice with water and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the products as dark brown oils, pure enough to be used as such in the following steps.

General Procedure for Compounds 9. The proper compound **8** (1.8 mmol) was dissolved in dry dichloromethane (9 mL) and placed under an argon atmosphere in a dry two-neck flask together with α,α′-dichloromethyl methyl ether (1.06 mL, 11.7 mmol). Titanium tetrachloride (0.594 mL, 5.4 mmol) was added dropwise over 1 h to the stirred solution cooled at 0 °C. After 2 h, the reaction mixture was diluted with water (30 mL). The aqueous layers were extracted with two portions of dichloromethane (30 mL each). The combined organic layers were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated to afford oils that were purified by flash chromatography (silica gel, 3% ethyl acetate in light petroleum) to give the desired products as yellow oils.

1,12-Bis(3-formyl-4-hydroxy-5-isopropylphenyl)-dodecane (9a) was prepared from **8a** in 41% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 11.12 (s, 2H); 9.77 (s, 2H); 7.09 (s, 2H); 3.2 (m, 2H, J = 6.7 Hz); 2.5 (t, 4H, J = 7,3 Hz); 2.08 (s, 2H); 1.50 (m, 4H); 1.00−1.35 (m, 24H); ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 196.8, 157.3, 136.9, 134.2, 133.9, 130.2, 119.9, 35.0, 31.5, 29.62, 29.57, 29.5, 29.2, 26.3, 22.3 ppm. MS-ESI-TOF for $C_{32}H_{46}O_4$ = 494.3, found *m/z* (+) 517.5 ([M + Na]$^+$).

1-(3-Formyl-4-hydroxy-5-isopropyl-phenyl)-12-(5-formyl-6-hydroxy-biphenyl-3-yl)-dodecane (9b) was prepared from **8b** in 35% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 11.18 (s, 1H); 11.02 (s, 1H); 9.73 (s, 1H); 9.65 (s, 1H); 7.42−7.39 (d, 2H, J = 6.7 Hz); 7.29−7.20 (m, 4H); 7.16 (s, 1H); 7.08 (s, 1H); 6.98 (s, 1H); 3.23−3.10 (m, 1H, J = 6.85 Hz); 2.48−2.34 (m, 4H); 1.41 (m, 4H); 1.12 (m,12H); 1.07−1.04 (d, 6H, J = Hz, 6.85 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 197.7, 197.6, 158.1, 157.7, 139.0, 137. 7, 137.5, 137.2, 135.1, 135.0, 134.6, 131.0, 133.1, 130.9, 130.0, 129.0, 128.3, 127.2, 123.6, 122.7, 121.4, 120.6, 118.5, 109.6, 36.3, 35.7, 35.6, 32.5, 32.3, 32.2, 30.4, 30.3, 30.2, 30.0, 27.0, 23.1 ppm. MS-ESI-TOF for $C_{35}H_{44}O_4$ = 528.3, found *m/z* (+) 551.4 ([M + Na]$^+$).

1-(3-Formyl-4-hydroxy-5-isopropyl-phenyl)-13-(5-formyl-6-hydroxy-biphenyl-3-yl)-tridecane (9c) was prepared from **8c** in 36% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 11.28 (s, 1H); 11.12 (s, 1H); 9.82 (s, 1H); 9.75 (s, 1H); 7.56−7.49 (m, 2H); 7.39−7.25 (m, 4H); 7.19−7.16 (m, 2H); 7.08 (bs, 16H); 3.33−3.19 (m, 1H, J = 6.92 Hz); 2.58−2.45 (m, 4H); 1.54−1.51 (m, 4H); 1.22 (m, 9H); 1.18 (m, 9H); 1.17−1.14 (d, 6H, J = 6.92 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ = 197.6, 197.5, 158.0, 157.6, 138.9, 137.4, 137.2, 135.0, 134.9, 134.5, 133.0, 130.9, 130.8, 129.9, 128.9, 128.2, 121.3, 120.6, 35.6, 35.5, 32.2, 32.1, 30.31, 30.26, 30.1, 30.0, 29.9, 29.8, 26.9, 23.0 ppm. MS-ESI-TOF for $C_{36}H_{46}O_4$ = 542.3, found *m/z* (+) 565.4 ([M + Na]$^+$).

Complex 4a. Procedure A. A solution of 1,12-bis(3-formyl-4-hydroxy-5-isopropylphenyl)-dodecane (**9a**) (0.227 g, 0.46 mmol) and 1,2-diaminobenzene (0.050 g, 0.46 mmol) in MeOH (5 mL) was stirred at room temperature. After 30 min $UO_2(OAc)_2{\cdot}2H_2O$ (0.191 g, 0.46 mmol) was added, and the solution was stirred for 30 min. The reaction mixture was filtered, and the desired product was obtained as a pale orange solid in 23% yield. Elemental analysis calcd (%) for $C_{38}H_{48}N_2O_4U{\cdot}3H_2O$: C, 51.35; H, 6.12; N, 3.15. Found: C, 51.48; H, 6.28; N, 3.35. ^{1}H NMR (200 MHz, acetone-d_6) δ = 9.30 (s, 2H); 7.69 (m, 2H); 7.50 (m, 2H); 7.24 (m, 4H) 3.84 (m, 2H); 2.56 (t, 4H); 1.0−1.6 (m, 18H); 0.30−1.0 (m, 14H) ppm. ^{13}C NMR (50 MHz, acetone-d_6) δ = 205.8, 167.7, 166.7, 147.6, 138.6, 132.8, 131.4, 130.4, 129.2, 123.1, 119.3, 34.8, 31.9, 30.6, 29.8, 29.3, 28.2, 26.7, 23.4, 22.8 ppm. HRMS-ESI-TOF for $C_{38}H_{48}N_2O_4UNa^+$ calcd 857.4020; found 857.4031.

Complex 4b. Procedure A. A solution of 1-(3-formyl-4-hydroxy-5-isopropyl-phenyl)-12-(3-formyl-4-hydroxy-5-phenyl-phenyl)-dodecane (**9b**) (0.243 g, 0.46 mmol) and 1,2-diaminobenzene (0.050 g, 0.46 mmol) in MeOH (5 mL) was stirred at room temperature. After 30 min $UO_2(OAc)_2{\cdot}2H_2O$ (0.191 g, 0.46 mmol) was added, and the solution was stirred for 30 min. The reaction mixture was concentrated and purified by preparative TLC (0.25 mm, silica gel, 30% acetone in cyclohexane) to separate **4b** from its higher oligomers. The desired product was obtained as a pale orange solid in 22% yield. **Procedure B.** A solution of **9b** (0.056 g, 0.106 mmol) in dichloromethane (2.5 mL) and a solution of 1,2-diaminobenzene (0.0115 g, 0.109 mmol) in the same solvent (2.5 mL) were added separately and simultaneously by syringe pump over 7 h to a solution of uranyl acetate (0.045 g, 0.106 mmol) in

methanol (100 mL). The mixture was left to stand overnight at room temperature and then concentrated to a volume of 5 mL and dissolved again in dichloromethane (100 mL). The organic phase was extracted with two portions of $NaHCO_3$ (saturated) (50 mL each), washed to neutrality with two portions of water (30 mL each), dried over anhydrous sodium sulfate, and concentrated to afford a dark red oil. Preparative TLC (0.25 mm, silica gel, 30% acetone in cyclohexane) gave the desired product as an orange solid in 70% yield. Elemental analysis calcd (%) for $C_{41}H_{46}N_2O_4U\cdot 3H_2O$: C, 53.36; H, 5.68; N, 3.04. Found: C, 53.62; H, 5.80; N, 3.30. ^{1}H NMR (200 MHz, acetone-d_6) δ = 9.41 (s, 1H); 9.36 (s, 1H); 7.90−7.28 (m, 13H); 3.85−3.71 (m, 1H); 2.69−2.53 (m; 4H); 1.74−1.00 (m, 20H); 0.84−0.68 (m, 6H) ppm. ^{13}C NMR (75 MHz, acetone-d_6) δ = 167.8, 166.7, 147.7, 140.6, 138.6, 137.5, 134.0, 133.1, 131.7, 131.5, 130.9, 130.7, 130.6, 130.0, 129.5, 129.4, 128.4, 128.1, 127.3, 127.0, 124.8, 123.4, 123.2, 122.4, 119.85, 119.78, 118.4, 35.7, 35.4, 34.9, 34.7, 32.4, 32.1, 31.9, 28.4, 26.8, 23.6, 23.0 ppm. HRMS-ESI-TOF for $C_{41}H_{46}N_2O_4UNa^+$ calcd 891.3863; found 891.3875.

Complex 4c. Preparation was accomplished following procedure B as described for **4b**. The desired product was recovered by preparative TLC (0.25 mm, silica gel, 30% acetone in cyclohexane) as an orange solid in 73% yield. Elemental analysis calcd (%) for $C_{42}H_{48}N_2O_4U\cdot 3H_2O$: C, 53.84; H, 5.81; N, 2.99. Found: C, 54.12; H, 6.10; N, 3.24. ^{1}H NMR (200 MHz, acetone-d_6) δ = 9.47 (s, 1H); 9.42 (s, 1H); 7.89−7.31 (m, 13H); 3.84−3.71 (m, 1H); 2.63−2.42 (m, 4H); 1.78−0.27 (m, 28H) ppm. ^{13}C NMR (50 MHz, acetone-d_6) δ = 174.0, 167.4, 147.6, 140.5, 139.0, 137.0, 134.6, 132.5, 132.4, 132.1, 132.0, 130.8, 130.6, 130.4, 129.3, 129.2, 128.3, 126.9, 124.4, 122.8, 119.9, 119.8, 35.1, 34.9, 31.5, 30.9, 30.5, 30.4, 28.0, 26.7, 23.2, 23.0 ppm. HRMS-ESI-TOF for $C_{42}H_{48}N_2O_4UNa^+$ calcd 905.4020; found 905.4032.

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Supporting Information Available: General experimental methods and computational details for calculated structures of compounds **2a**, **2b**, **3a**, **3b**, **5** (n =11, 12, 13, 14). This material is available free of charge via the Internet at http://pubs.acs.org.

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