Evaluation of Chiral Recognition Ability of a Novel Uranyl–Salophen-Based Receptor: An Easy and Rapid Testing Protocol

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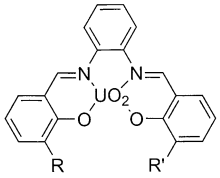
Abstract: A novel member of a new class of chiral uranyl–salophen complexes has been synthesised. The chiral recognition ability of this receptor toward the enantiomers of two primary amines, a sulfoxide, and a quaternary ammonium chloride has been evaluated for the first time. The enantioselectivities obtained are encouraging. The NMR method developed for this purpose allows a fast, quantitative determination of the enantioselectivity of the host directly from its racemic mixture and could find application as a preliminary screening tool in the search for new receptors using combinatorial methods. The experiments carried out in this context demonstrated also that the activation barrier for the racemisation of such chiral uranyl–salophen receptors is much higher than the lower limit of 21 kcal mol^{-1} previously reported.

Keywords: chirality · enantioselective recognition · high-throughput screening · host–guest systems · NMR spectroscopy

Introduction

The development of artificial receptors able to bind preferentially one of the two enantiomers of a given substrate is an essential target in bioorganic and supramolecular chemistry.[1] The fundamental role played by stereochemistry in chemical interactions is clearly envisioned, for example, in the context of drug/receptor chemistry. Moreover, enantiomeric recognition is a key feature of many enzyme-catalysed reactions and is the basis of asymmetric catalysis. In recent years much work has been devoted to the development of chiral supramolecular receptors devoid of the classical elements of chirality. This wide field encloses purely covalent structures such as inherently chiral calixarenes,[2] and noncovalent assemblies whose chirality arises from desymmetrising interactions between achiral molecular components.[3] In many of these cases synthetic procedures lead to racemic mixtures, whose resolution is not always a simple task. In a time-saving and low-cost perspective, the ability of the host to achieve chiral recognition should conveniently be assessed at the racemic mixture level. Also, efficient tools for rapid determination of enantioselectivity are a requirement for the application of combinatorial methods to the synthesis of artificial receptors.[4]

In the present work we describe a NMR-based protocol to evaluate the chiral recognition ability of synthetic hosts directly from their racemic mixture. The method described here has been applied to a novel derivative of nonsymmetrically substituted uranyl–salophen complexes (**1**, R ≠ R′).[5] In these compounds the uranyl dication employs four of its coordination positions for complexation with the salophen ligand.[6] The fifth site is free and has been widely used for complexation of anions[7] and neutral molecules endowed with a hard donor site.[5,8] For this reason uranyl–salophen complexes have found applications as receptors,[9] catalysts,[10] carriers[11] and sensors.[12]



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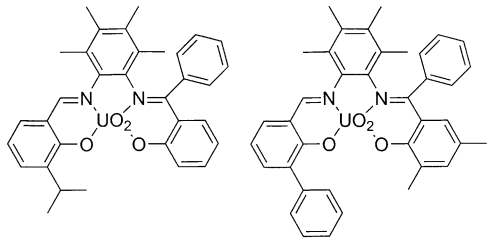
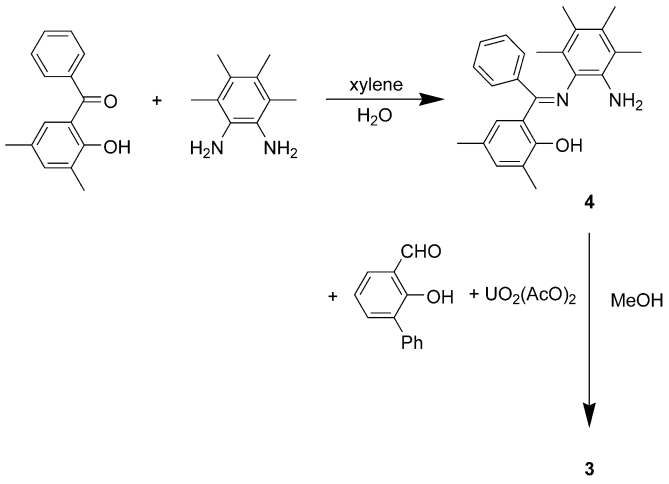
 DOI: 10.1002/chem.200400016

The large radius of the uranium atom forces the salophen ligands to deviate from planarity in the complexes.[9,13] As a consequence, nonsymmetrically substituted uranyl–salophen complexes are chiral owing to the lack of any element of symmetry. We have recently shown that a fast flipping motion inverts the curvature of the ligand and makes such chirality so labile that it cannot be detected by NMR spectroscopy even at 233 K.[14] We found that the flipping can be slowed down by the introduction of substituents both on the imine carbon atoms and on the central aromatic ring. The ^{1}H NMR spectrum of compound **2** in [D$_6$]DMSO does not show coalescence of the diastereotopic methyl groups of the isopropyl group up to 385 K. This indicates that the energy barrier for the interconversion between the enantiomers is higher than 21 kcal mol^{-1} and the half-life time is longer than 5 minutes at room temperature.



2 **3**

In the newly synthesised compound **3**, structurally analogous to **2**, the binding site has been shaped by introducing a phenyl and a methyl group on the two phenoxyde rings in the *ortho* positions with respect to the oxygen atoms. The phenyl group is known to act as an additional interaction site,[5] whilst the methyl group should introduce more strict shape requirements by establishing unfavourable interactions with the bound substrate. The compound was prepared via phenol **4** according to the procedure in Scheme 1 and fully characterised. Although we have not yet resolved the racemic mixture of **3**, we have been able to determine the differences in stabilities of its diastereomeric complexes with a number of chiral guests by means of a new NMR protocol. The method described here is quite general and can be applied whenever the diastereomeric adducts show even small but detectable chemical shift differences for complexes in either fast or slow regimes on the NMR timescale. It is simple, quick and accurate and has the advantage that it can be used on the racemic mixture of the receptor, allowing the evaluation of its discriminating properties before resolution.

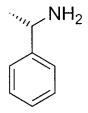


Scheme 1.

Results and Discussion

All resonances in the ^{1}H NMR spectrum of **3** in [D$_6$]acetone were assigned (Figure 1, spectrum a) by means of a series of three two-dimensional TOCSY, COSY and NOESY experiments. The upfield positions of M3, M4, and ○ indicate that the corresponding protons are located in the shielding region generated by the ring current of the phenyl substituent on the imine carbon atom, consistent with the computer calculated structure in Figure 2. Exchange peaks in the NOESY spectrum between protons Δ1 and Δ5, and Δ2 and Δ4 indicate slow rotation of the phenyl group.

To provide evidence for the formation of diastereomeric host–guest complexes, one equivalent of enantiomerically pure (*S*)-α-methylbenzylamine (**5**) was added to a solution of **3** in CDCl$_3$ (0.02 M). Preliminary studies indicated that in



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this solvent the association is almost quantitative. Although the spectrum is less resolved than that in [D$_6$]acetone (Figure 1, spectrum b), splitting of a number of host signals was observed, namely all methyl resonances other than M4 and the aromatic protons □1 and ○. Additional signals may have a similar behaviour, but could not be quantified due to spectral overlap in CDCl$_3$. It should be noted that the largest splittings are observed for the signals of protons closest to the free coordination position of the uranyl dication. This makes us confident that the bound guest is actually hosted inside the cleft formed by the phenyl and methyl groups. The signals at 1.5 and 1.7 ppm correspond to the guest methyl group in the two diastereomeric complexes. The guest, but not the host, exchanges between the two complexes on a slow–intermediate timescale. This is further confirmed by the presence of a positive cross peak between the two signals in the NOESY spectrum.

When one equivalent of racemic (±)-**5** is added to racemic **3** in CDCl$_3$, splitting of host signals is no longer observed and resonances fall at different frequencies with respect to those of the pure host (Figure 1, spectrum c).

Coalescence of the host signals in the presence of a racemic guest indicates that the interconversion of the two dia-

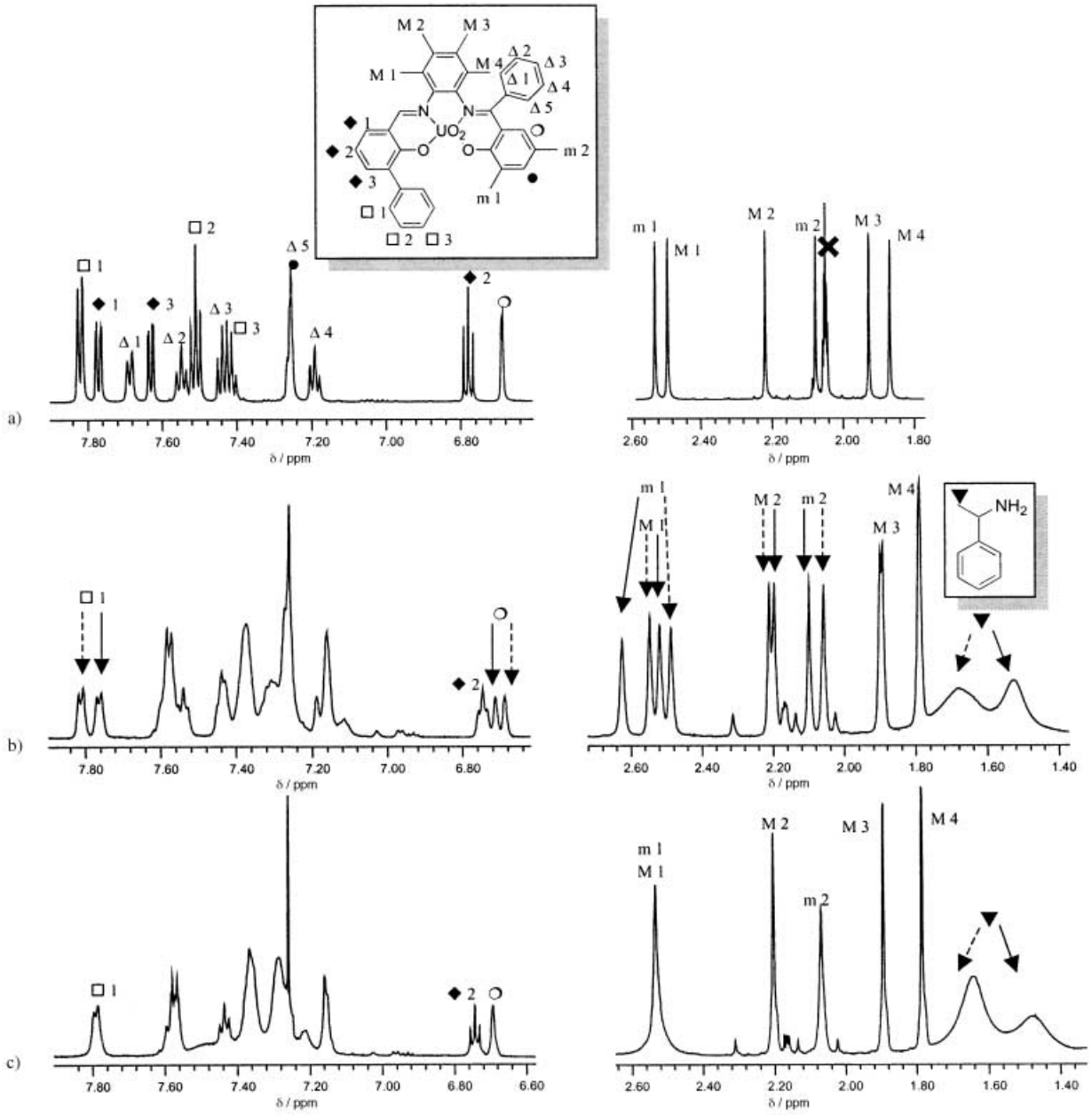


Figure 1. Portions of ^{1}H NMR spectra (600 MHz) of a) compound **3** in [D$_6$]acetone, b) an equimolar solution (2×10^{-2} M) of compounds **3** and (*S*)-**5** in $CDCl_3$ and c) an equimolar solution (2×10^{-2} M) of compounds **3** and (±)-**5** in $CDCl_3$. Protons belonging to the same spin system are labelled with the same symbol. Dotted (full) arrows indicate signals from the major (minor) diastereomer.

stereomeric complexes is faster than the chemical shift difference between the host signals in the two complexes. The process is illustrated in Scheme 2. The guest signals, in slow exchange, appear as two broad resonances. The different behaviour of the host and guest signals reflects the different chemical shifts of the exchanging sites and, in this particular example, illustrates the application of the method to NMR systems in fast or slow–intermediate exchange.

Chiral discrimination is described by the position of the equilibrium represented by Equation (1), in which K_{exc} is defined by Equation (2). In Equation (1) the two enantiomers of the uranyl–salophen are differentiated by the use of the (+) (−) notation.

$$(+)\mathbf{3}(R)\mathbf{5} + (-)\mathbf{3}(S)\mathbf{5} \overset{K_{exc}}{\rightleftharpoons} (+)\mathbf{3}(S)\mathbf{5} + (-)\mathbf{3}(R)\mathbf{5} \quad (1)$$

$$K_{exc} = \frac{[(+)\mathbf{3}(S)\mathbf{5}][(-)\mathbf{3}(R)\mathbf{5}]}{[(+)\mathbf{3}(R)\mathbf{5}][(-)\mathbf{3}(S)\mathbf{5}]} = \frac{[(+)\mathbf{3}(S)\mathbf{5}]^2}{[(+)\mathbf{3}(R)\mathbf{5}]^2} \quad (2)$$

From the thermodynamic cycle depicted in Scheme 2, Equation (3) is easily obtained, in which K_1 is the association constant for the two enantiomeric complexes (+)**3**(*R*)**5** and (−)**3**(*S*)**5** and K_2 is the association constant for (+)**3**(*S*)**5** and (−)**3**(*R*)**5**.

$$K_{exc} = \frac{K_2^2}{K_1^2} \quad (3)$$

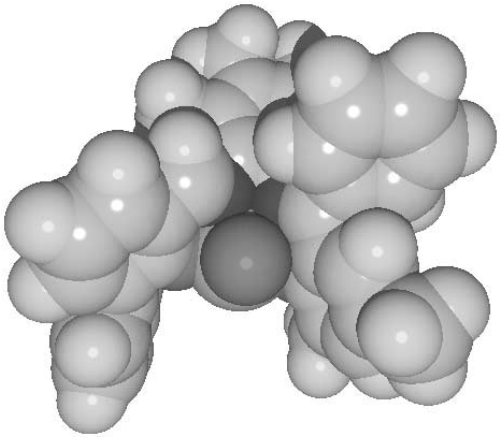
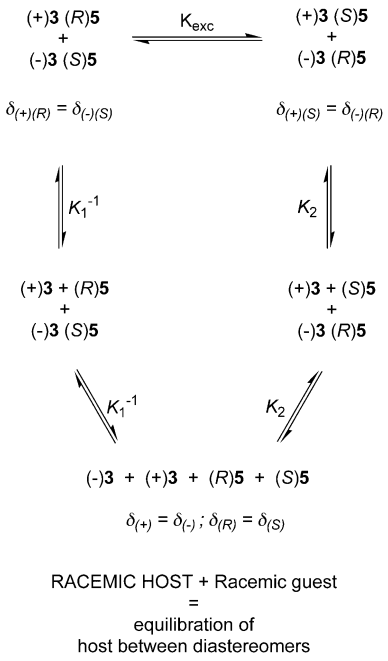


Figure 2. Calculated geometry of the uranyl salophen complex **3**. For computational details see reference [14].



Scheme 2.

Comparison between Equations (2) and (3) leads to Equation (4), which shows that the ratio of the stability constants of the two diastereomeric complexes is equal to the ratio of their concentrations. This value represents the selectivity of (+)**3** toward one of the two enantiomers of **5**, and of course that of (−)**3** toward the other one. A value equal to 1 would mean no difference in the receptor affinity toward the two enantiomers, whereas a value different from 1 gives the degree of the enantioselectivity. The relative concentrations are easily determined by comparison of the NMR spectra of the racemic host with a racemic guest and with one of its enantiomers.

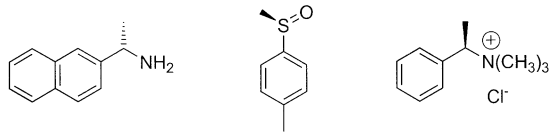
$$S = \frac{K_2}{K_1} = \frac{[(+)\mathbf{3}(S)\mathbf{5}]}{[(+)\mathbf{3}(R)\mathbf{5}]} \qquad (4)$$

In spectrum c of Figure 1, we observe a difference in the integrals of the methyl protons of the amine belonging to the two adducts, indicating that the equilibrium of Equation (1) is shifted towards one of the diastereomers. Therefore, the two enantiomers of host **3** show different binding affinities toward the two enantiomers of **5**. The selectivity ratio could in principle be obtained by the measurement of the two integrals, although in this case the broadening of these signals and their partial overlap would introduce a considerable uncertainty. The relative concentration of the two species can also be evaluated from the average chemical shift of host protons, which are in fast exchange in the presence of racemic guest.

The observed chemical shift is the concentration-weighted average from the chemical shift of the individual diastereomers, which are directly observed in the spectrum obtained in the presence of an enantiomerically pure guest.

The most reliable signal for this evaluation is that corresponding to the m2 methyl group, which shows a considerable separation between the split signals and whose coalescence position is well separated from other resonances (Figure 1, spectra b and c). The ratio obtained from the m2 signal is 2.15 and it is in good agreement with the values obtained by considering the M1, M2, and M3 signals, all in the range of 2.1–2.2. Further validation of these figures comes from the observation that integrals of the amine methyl signals in the two diastereomeric complexes are in a 2:1 ratio. When the same pair of experiments was carried out at 5 °C, the observed selectivity increased up to 3.1.

Results on the enantioselectivity of **3** toward **5**, 1-(2-naphthyl)ethylamine (**6**) methyl-*p*-tolylsulfoxide (**7**) and *N*,*N*-dimethyl-α-methylbenzylammonium chloride (**8**) are reported in Table 1. In the case of **8**, the chloride ion occupies the



6 **7** **8**

Table 1. Selectivity values (*S*), corresponding diastereomeric excesses (*de*) and free-energy differences ($\delta\Delta G_a$ [kcal mol^{-1}]) at 25 °C obtained for the enantioselective recognition of guests **5**, **6**, **7**, and **8** by chiral host **3**.

	5	**6**	**7**	**8**
S	2.15	1.60	1.70	1.30
% *de*	36	23	26	13
$\delta\Delta G_a$	0.45	0.28	0.31	0.16

fifth coordination site of the uranyl, thus forming a large anionic complex with the salophen–uranyl receptor.[13e,15] Since recognition of the chiral cation occurs through the formation of two diastereomeric ion pairs, less stringent requirements should be needed, consistent with the low selectivity observed. It is likely that the cation is located above the ligand surface, presumably in the concave side, as in this case the highest splitting is observed for the resonance of the iminic proton.

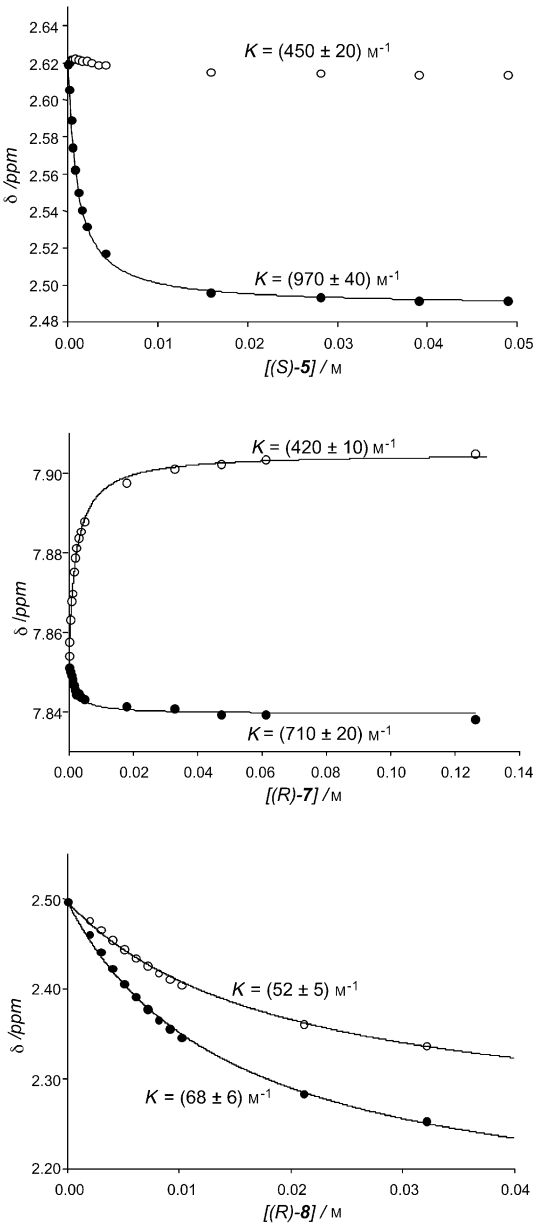


Figure 3. ^{1}H NMR titrations (300 MHz, $CDCl_3/CD_3OD$ 99:1 v/v) of **3** (2×10^{-2} M). Top: with (*S*)-**5**, M1 methyl group. Middle: with (*S*)-**7**, iminic proton. Bottom: with (*S*)-**8**, M1 methyl group.

Equilibration between the two enantiomers of **3** by flipping of the salophen ligand would provide a mechanism for interconversion between the two diastereomers of its complex with **5**, resulting in different populations. The observation of equal populations of both diastereomers (Figure 1, spectrum b) indicates that equilibration was not significant during the time span from sample preparation to acquisition of the NMR spectra (few hours). This gives a lower limit for the activation barrier for the interconversion of the enantiomers of **3** much higher than the 21 kcal mol^{-1} lower limit previously estimated for the closely related compound **2**.

In order to obtain the stability constants of the diastereomeric complexes, ^{1}H NMR titrations were carried out in $CDCl_3$ containing 1% and in one case 3% of CD_3OD. The small amount of methanol ensures a good quality of the spectra and lowers the association constants so as to make them measurable. We assume that in the above mixtures the selectivity values remain substantially unchanged, as methanol establishes the strongest interactions with the uncomplexed species that are the same for the two diastereomers.

The addition of increasing amounts of (*S*)-**5** to a solution of (±)-**3** induces the splitting of host signals and their regular shifts. Experimental points in Figure 3 (top) refer to the resonances relative to the methyl group m1 and are consistent with a 1:1 complex formation. In the simple case of achiral host–guest complexes, the association constant values can be obtained by fitting the titration data to the binding isotherm of Equation (5), in which $\Delta\delta_\infty$ represents the limiting upfield shift and K_a is the equilibrium constant. This can be done only if the concentration of the unbound free guest [G] is precisely known along the titration. Since [G] depends on the association constant, an iterative procedure is usually employed.

$$\delta = \delta_o + \frac{K_a \Delta\delta_\infty [G]}{1 + K_a [G]} \quad (5)$$

When this method is applied to the more complex case of the simultaneous formation of two diastereomeric complexes, free-guest concentrations are calculated after each iteration step by solving a third-grade equation. In this case a new problem is met, because K_1 and K_2 values obtained in each iteration are of course dependent on the free-guest concentrations, which are in turn dependent on both association constant values found in the previous step. This means that a reciprocal dependence between approximate values of the two constants is artificially created. As a consequence, when experimental points are affected by scattering, as it is always the case, we have found that the iterative procedure converges to a result that is dependent on the trial values of K_1 and K_2 used in the first iteration. In other words, when different starting values are introduced, a different pair of final values is obtained. Such a problem can be solved by imposing an additional constraint, that is, the ratio between the two association constants obtained in the previous NMR experiments. The introduction of this parameter improves the reliability of the fitting procedure and provides accurate binding constant values that are independent of the starting values. By this method only data points from one diastereomer are needed and, hence, both association constants can be determined even when one of the diastereomers gives negligible chemical shift variations (see Figure 3, top).

The association constants for the formation of diastereomeric complexes between **3** and guests **5**, **7**, and **8** obtained using the above procedure (Figure 3) are reported in Table 2.[15]

Conclusion

In this work we report the synthesis of a new chiral uranyl–salophen complex. The ability of this receptor to perform chiral recognition toward a number of neutral and charged guests has been shown. The enantioselectivities obtained are

Table 2. Association constant pairs [M^{-1}] for diastereomeric complexes between host **3** and guests **5**, **7**, and **8** at 25°C.

Solvent mixture	**5**	**7**	**8**
$CDCl_3/CD_3OD$ 97:3 (v/v)	$K_{maj}=46\pm3$ $K_{min}=21\pm1$		
$CDCl_3/CD_3OD$ 99:1 (v/v)	$K_{maj}=970\pm40$ $K_{min}=450\pm20$	$K_{maj}=710\pm20$ $K_{min}=420\pm10$	$K_{maj}=68\pm6$ $K_{min}=52\pm5$

encouraging and we are currently carrying out further modifications of the receptor binding site to achieve more specific interactions.

The NMR protocol used to establish the enantioselectivity is fast, reliable and provides a useful way of monitoring the recognition capability of newly synthesised chiral receptors. It can be used in all cases in which the diastereomeric adducts show detectable chemical shifts differences in resonances by carrying out a limited number of NMR measurements. Moreover it applies even to association phenomena fast in the NMR timescale, for which the selectivity ratio cannot be calculated by comparing the integrals of the separate resonances of diastereomeric complexes. The main advantage is that it can be applied to a racemic mixture of the receptor prior to resolution. These considerations make it suitable for chemists working in the field of combinatorial receptor/substrate design and supramolecular chemistry.

Finally the experiments carried out showed that the racemisation of **3** has an energy barrier much higher than the lower limit of 21 kcal mol^{-1} previously calculated for the closely related compound **2**.

Current studies are investigating the possibility of separating the two enantiomers of **3**.

Experimental Section

Instruments and methods: NMR spectra were recorded on a Bruker AC 300 and a Bruker Avance 600. Nonlinear least-square calculations were carried out using the program SigmaPlot for Windows 8.0 (Jandel Scientific).

Materials: 2-Phenylphenol (Aldrich), pentamethylbenzene (Eastman Kodak), 2,4-dimethylphenol (Fluka), benzoyl chloride (Aldrich), uranyl acetate dihydrate (Fluka), racemic and enantiomerically pure α-methylbenzylamine (Aldrich), racemic and enantiomerically pure 1-(2-naphthyl)-ethylamine (Aldrich), and racemic and enantiomerically pure methyl-*p*-tolylsulfoxide (Aldrich) were used as received. 3,4,5,6-Tetramethyl-1,2-diaminobenzene,[16] 3-phenylsalicyladehyde,[17] and 2-hydroxy-3,5-dimethylbenzophenone[18] were prepared according to literature procedures. Racemic and enantiomerically pure *N*,*N*-dimethyl-α-methylbenzylammonium chloride was prepared through ion exchange from the corresponding iodides kindly provided by Prof. J. Lacour.

2-[(2-Amino-3,4,5,6-tetramethylphenylimino)phenylmethyl]-4,6-dimethylphenol (4): A solution of 3,4,5,6-dimethyl-1,2-diaminobenzene (0.732 g, 4.5 mmol), 2-hydroxy-3,5-dimethylbenzophenone (1.032 g, 1 equiv), and a catalytic amount of *p*-toluenesulfonic acid in *m*-xylene (15 mL) was refluxed in a Dean–Stark apparatus for two days. On cooling, the pure product precipitated from the reaction mixture as a yellow solid in 45% yield. M.p. 185–187°C; elemental analysis calcd (%) for $C_{25}H_{28}N_2O$: C 80.61, H 7.58, N 7.52; found: C 80.61, H 7.67, N 7.44; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=7.25$ (br s, 5H), 7.10 (s, 1H), 6.69 (s, 1H), 2.34 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.84 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=177.97$, 159.79, 135.96, 135.84, 133.73, 132.82, 131.48, 130.49, 129.60, 128.25, 128.16, 127.23, 126.78, 125.48, 123.07, 119.31, 118.92, 21.20, 17.03, 16.59, 16.52, 16.38, 14.27 ppm; MS (ES-MS): *m*/*z* calcd for $C_{25}H_{28}N_2O$: 372.50; found: 373.1 $[M+H]^+$.

{{3,4,5,6-Tetramethyl-1-phenylene[(*E*)-nitrilomethylidynephenyl(2-hydroxy-3,5-dimethylphenyl)]-2-phenylene[nitrilomethylidyne(2-hydroxy-3-phenylphenyl)]}(2−)-*N*,*N*',*O*,*O*']dioxouranium (3): A solution of **4** (0.367 g, 0.98 mmol) and 3-phenylsalicilaldehyde (0.195 g, 1 equiv) in MeOH (12 mL) was stirred at room temperature. After 30 min $UO_2(OAc)_2\cdot2H_2O$ (0.421 g, 1 equiv) was added and the solution was stirred for additional 30 min. The pure product precipitated from the reaction mixture as a pale orange solid in a 48% yield. Elemental analysis calcd (%) for $C_{38}H_{34}N_2O_4U\cdot3H_2O$: C 52.20, H 4.61, N 3.20; found: C 52.58, H 4.27, N 3.22; ^{1}H NMR (600 MHz, [D$_6$]acetone) $\delta=9.63$ (s, 1H), 7.83–7.81 (ddd, $J=1.22$, 8.24 Hz, 2H), 7.78–7.77 (ddd, $J=1.83$, 7.63 Hz, 1H), 7.69–7.68 (br d, $J=7.94$ Hz, 1H), 7.64–7.62 (ddd, $J=1.83$, 7.02 Hz, 1H), 7.56–7.54 (t, $J=7.32$ Hz, 1H), 7.52–7.50 (m, $J=7.94$ Hz, 2H), 7.45–7.40 (m, 2H), 7.25(br s, 1H), 7.20–7.18 (m, $J=7.63$ Hz, 1H), 6.79–6.77 (t, $J=7.32$ Hz, 1H), 6.69 (br s, 1H), 2.53 (s, 3H), 2.50 (s, 3H), 2.22 (s, 3H), 2.08 (s, 3H), 1.93(s, 3H), 1.87 ppm (s, 3H); ^{13}C NMR (50 MHz, [D$_6$]acetone) $\delta=174.91$, 169.70, 168.84, 145.22, 144.96, 140.90, 139.94, 136.82, 136.56, 135.62, 135.12, 133.35, 131.40, 131.27, 130.90, 130.36, 128.65, 128.31, 128.15, 127.21, 125.31, 125.22, 124.43, 123.40, 117.53, 20.28, 18.19, 17.44, 17.16, 16.69, 16.59 ppm; MS (ES-MS): *m*/*z* calcd for $C_{38}H_{34}N_2O_4U$: 820.72; found: 839 $[M-F]^-$, 820 $[M]^-$,

Selectivity measurements: A weighted amount of compound **3** was introduced into an NMR tube together with 0.500 mL of $CDCl_3$ and a spectrum at 600 MHz, $T=25.0$°C, was recorded. Then a given volume of a standard solution of either enantiopure or racemic guest was added and a second spectrum was recorded.

^{1}H NMR titrations: Titrations were carried out at 25.0°C in $CDCl_3$/CD_3OD 99:1 or 97:3 (v/v) by adding increasing amounts of the guest to a 0.02 M solution of **3** in the solvent mixture and following variations of the chemical shift of split host signals. Titration data were fitted to a standard binding isotherm for 1:1 complexation by imposing the independently determined selectivity as an additional constraint.

Acknowledgement

We gratefully acknowledge MIUR (Progetto Dispositivi Supramolecolari) for financial contributions. L.S. thanks the "Short Term Mobility" project of CNR-Dipartimento per le Attività Internazionali for financing a short-term scientific mission to Barcelona. J.I.M.M thanks the Basque Country Government (Spain) for a post-doctoral fellowship. We thank Prof. Jérome Lacour for a generous gift of a sample of *N*,*N*-dimethyl-α-methylbenzylammonium iodide. We thank Prof. Luigi Mandolini for helpful discussions. We acknowledge the use of the NMR facilities of the Scientific and Technical Services of the University of Barcelona and the Laboratory of Biomolecular NMR of the Barcelona Science Park.

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Received: January 8, 2004

Published online: May 6, 2004

