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Enantioselective Discrimination in the Self-Assembly of [2]Pseudorotaxanes

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The combination of (i) an optically active, axially chiral π-electron-deficient tetracationic cyclophane derivative of cyclobis(paraquat-*p*-phenylene), in which both of the *p*-phenylene spacers have been replaced by axially-chiral 3,3′-disubstituted binaphthol spacers, and (ii) enantiomeric, π-electron-rich substrates, in which a hydroquinone ring is inserted into the polyether backbone terminated by carboxyl groups and substituted in a C_2-symmetric manner by two methyl groups, thus creating two equivalent chiral centers in the substrate, produces in solution 1:1 complexes in which the π-electron-rich substrates are inserted into the π-electron-deficient cavities of the cyclophanes in a pseudorotaxane-like manner. The differences in the free energies of complexation for (*RR*) and (*SS*) enantiomers of the π-electron-rich substrates span the range from 0.1 to 0.7 kcal mol^{-1}. Chiral recognition becomes more effective the closer the chiral centers are to the hydroquinone templating unit. CD spectroscopy reveals that the different modes of binding of the enantiomeric substrates by the axially chiral tetracationic cyclophane are not accompanied by drastically different core geometries for the [2]pseudorotaxanes. Thus, the chirality of the complex is governed primarily by the properties of the rigid receptor. The combination of the D_2 symmetry of the receptor with the C_2 symmetry of the substrates has been found to be particularly effective, considering that the chiral centers on the substrates are located on polyether chains which possess a high degree of conformational freedom.

Introduction

The design and the synthesis of artificial enantioselective receptors, able to differentiate between enantiomers of racemic compounds is an area of on-going activity.[1] Recently, we reported on the synthesis and the characterization of two novel optically-active receptors (*RR*)-**1**$^{4+}$ and (*R*)-**2**$^{4+}$ (Figure 1), in which optically active, axially chiral binaphthol spacers are located between two well-spaced π-electron-deficient bipyridinium units.[2] Both receptors showed good enantioselective discrimination in the formation of 1:1 inclusion complexes with amino acids bearing π-electron-rich aromatic side chains and could be self-assembled[3] around π-electron-rich macrocycles to form mechanically interlocked compounds.[2b][4]

In this paper, we report on the self-assembly in solution of chiral [2]pseudorotaxanes[5] consisting of receptor (*RR*)-**1**$^{4+}$ and a series of chiral hydroquinone-containing "threads" **3**−**5** (Figure 1). The "threads" **3**−**5** possess carboxylic acid terminal groups and contain a variable number of ethylene glycol subunits that are connected to a central hydroquinone ring. The chirality within the "threads" **3**−**5** originates from methyl side groups in the polyether chain. The position of chiral centers is varied from being close to the hydroquinone unit to being far away from this unit. Previously, the syntheses of the (*SS*) and the (*RR*) enantiomers of the chiral "threads" **3**−**5** had been reported[6] and so the enantiodifferentiation of these "threads" by the receptor (*RR*)-**1**$^{4+}$ could be examined. This supramolecular system is of particular interest, since the [2]pseudorotaxanes incorporate a D_2-symmetrical cyclic component and a C_2-symmetrical linear component. To our knowledge, such a combination of symmetries has never been examined before in artificial receptor systems. The complexation of the various "threads" with the receptor molecule (*RR*)-**1**$^{4+}$ to give [2]pseudorotaxanes has been studied by established techniques, such as ^{1}H-NMR and UV/Vis spectroscopies. Furthermore, the chiroptical properties of the receptor (*RR*)-**1**$^{4+}$ and of the [2]pseudorotaxanes it forms with "threads" **3**−**5** have been investigated by CD spectroscopy.

Results and Discussion

By mixing equimolar amounts in MeCN solutions of the tetracationic cyclophane (*RR*)-**1** · 4 PF_6 and any of the synthesized chiral polyether "threads" separately, the ^{1}H-NMR and UV/Vis spectra of the 1:1 mixtures undergo specific and telling changes, indicating that the π-electron-rich

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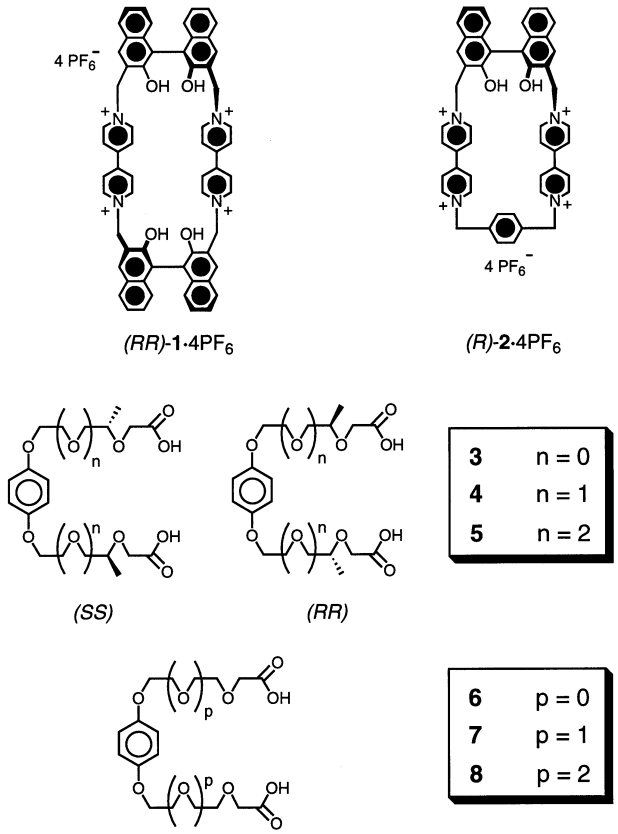
Figure 1. The axially chiral receptor (*RR*)-**1** · 4 PF_6, the π-electron-rich chiral "threads" (*SS*)-**3**−(*SS*)-**5** and (*RR*)-**3**−(*RR*)-**5** and their corresponding achiral "threads" **6**−**8**



"threads" are inserted into the π-electron-deficient cavity of the receptor. The ^{1}H-NMR spectra indicate substantial upfield shifts for the hydroquinone protons resonances of the "threads" upon complexation,[7] together with less pronounced downfield shifts of the α-CH and β-CH proton resonances of the tetracationic cyclophane.[8] The UV/Vis spectrum of the tetracationic receptor (*RR*)-**1** · 4 PF_6 shows a large absorption band around 380−390 nm, with the addition of a residual absorption band, not very well defined, from 420 to 500 nm (see Figure 2). Upon titration of (*RR*)-**1** · 4 PF_6 with any of the π-electron-rich "threads" **3**−**5** [as an example, the titration of (*RR*)-**1** · 4 PF_6 with "thread" (*RR*)-**3** is shown in Figure 2], the UV/Vis spectra indicate the development of a detectable but very weak charge-transfer band between 420 and 500 nm,[8] a marked reduction in the absorbance at 380 nm and an increase in absorbance at 340 nm. Notably, isosbestic points (at ca. 350 and 425 nm) are found in all the titration curves. This finding confirms that there is a transition from one state to another, i.e., there is a transition from uncomplexed receptor and "thread" molecules to [2]pseudorotaxane complexes consisting of (*RR*)-**1** · 4 PF_6 and a linear "thread".[9]

The association constants and the corresponding free energies of complex formation for the [2]pseudorotaxanes of receptor (*RR*)-**1** · 4 PF_6 and the different enantiomers of the chiral threads have been determined by UV/Vis spectroscopy,[10] by monitoring the absorbance changes at 380 nm upon titration of the "threads" **3**−**5**. The measured association constants are reported in Table 1.

Figure 2. UV spectra of the titration of receptor (*RR*)-**1** · 4 PF_6 with "thread" (*RR*)-**3**; the arrows indicate the shifts of the curves upon titration; concentration of (*RR*)-**1** · 4 PF_6 (in all lines): 0.051 mg/ml; concentrations of "thread" (*RR*)-**3** are 0, 0.075, 0.189, and 2.10 mg/ml for the solid, dashed, dotted and dash-dot lines, respectively

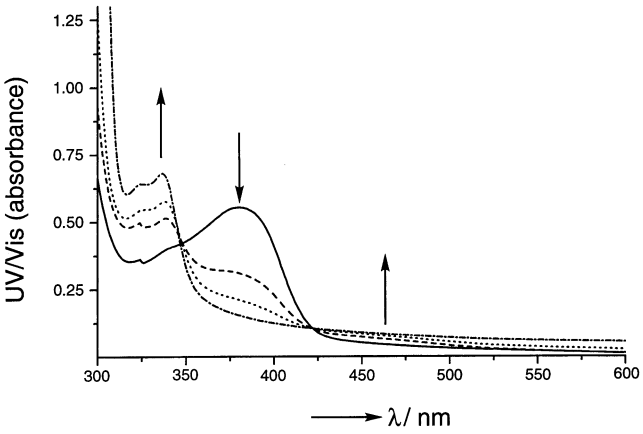


Table 1. Association constants K_a for the [2]pseudorotaxanes formed by the receptor (*RR*)-**1** · 4 PF_6 and the chiral "threads" **3**−**5** determined by UV/Vis titration at 25°C in MeCN

Entry	Substrate	(*RR*)-**1** · 4 PF_6[a] $K_{a(RR)}/K_{a(SS)}$		$\Delta\Delta G$[b]
1	(*RR*)-**3**	5000 (−5.1)		
2	(*SS*)-**3**	1530 (−4.4)	3.3	0.7
3	(*RR*)-**4**	7230 (−5.2)		
4	(*SS*)-**4**	2450 (−4.6)	3.0	0.6
5	(*RR*)-**5**	10100 (−5.5)		
6	(*SS*)-**5**	8930 (−5.4)	1.1	0.1

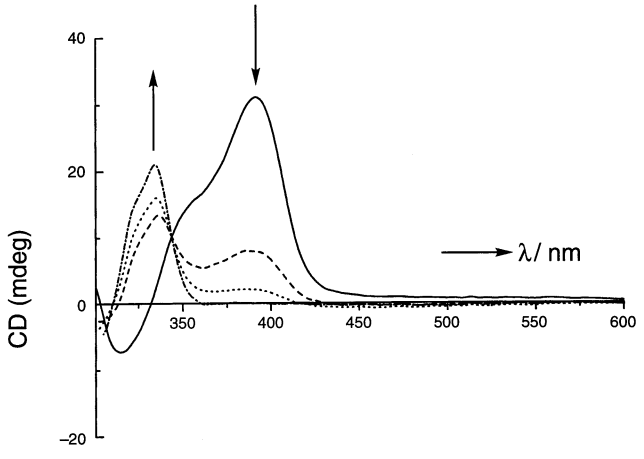
[a] The values refer to the association constants in l/mol; the values in parentheses refer to the free energy of association in kcal/mol; all K_a values have experimental errors of ca. 10%, which is common for this type of spectrophotometric titrations. − [b] $\Delta\Delta G = \Delta G_{(SS)} - \Delta G_{(RR)}$.

Inspection of the K_a values obtained using this method shows that the strengths of the investigated [2]pseudorotaxanes scales with the number of the polyether oxygen atoms present in the chiral "thread". Since this result has also been found for other [2]pseudorotaxane systems,[7] it confirms that the polyether chains play an important role in the stabilization of the [2]pseudorotaxanes. Comparison of the K_a values for the formation of the 1:1 complexes between **1** · 4 PF_6 and the "threads" **3**−**5** indicate that the enantioselection [$K_a(RR)/K_a(SS)$] varies from significant values of 3.3 and 3.0 for "threads" **3** and **4** to an insignificant value of 1.1 for "thread" **5**. Thus, the enantioselectivities increase as the chiral centers in the polyether backbone get closer to the chiral cavity of the cyclophane. In a previous study on asymmetric [2]pseudorotaxanes,[6] it has been proposed that the polyether chains of the "threads" − although these are highly flexible units − are locked in preferred conformations onto the receptor molecule. Such a locking principle could also be proposed here, since it can

explain the observed enantioselectivities. Steric hindrance of the methyl groups of the (*SS*) "threads" **3** and **4** prevents these "threads" from adopting the energetically favored conformations. In the enantiomeric (*RR*) "threads" **3** and **4**, such a hindrance is less pronounced, resulting in higher stabilities of the corresponding [2]pseudorotaxanes. When the methyl group is located further away from the central hydroquinone ring, as in the case of the "threads" **5**, the importance of the incorporated chirality − i.e. the incorporated steric hindrance − vanishes.

The complexation behavior of the D_2-symmetrical receptor with the C_2-symmetrical "threads" **3−5** can be studied further by circular dichroism (CD) spectroscopy.[11] Such CD measurements are of relevance since they can give information about the geometry of [2]pseudorotaxanes in solution, as shown in previous work.[6] In Figure 3, the CD spectrum of (*RR*)-**1** · 4 PF_6 in MeCN shows that all transitions display CD activity. Upon addition of the π-electron-rich "threads" **3−5**, or even their corresponding non-methyl-substituted achiral "threads" **6−8** (see Figure 1), the nature of the CD spectrum changes. For all the "threads", chiral or achiral, a similar change is observed: as the CD activity in the band at 380 nm vanishes, the activity in the band at 340 nm increases, resulting in an isosbestic point at ca. 350 nm. The weak charge-transfer band at 420−500 nm does not exhibit a detectable CD activity. This chiroptical behavior is illustrated in Figure 3 for the complexation of receptor (*RR*)-**1** · 4 PF_6 with the "thread" (*RR*)-**3**.

Figure 3. CD spectra of the titration of receptor (*RR*)-**1** · 4 PF_6 with "thread" (*RR*)-**3**; the arrows indicate the shifts of the curves upon titration; concentration of (*RR*)-**1** · 4 PF_6 (in all lines): 0.051 mg/ml; concentrations of "thread" (*RR*)-**3** are 0, 0.075, 0.189, and 2.10 mg/ml for the solid, dashed, dotted and dash-dot lines, respectively; these CD spectra correspond to the UV spectra shown in Figure 2



The wavelength region (290−450 nm) investigated in the chiroptical studies is associated with transitions in the bipyridinium units of the receptors (*RR*)-**1** · 4 PF_6. Therefore, CD changes in this wavelength region give information about the geometry of the [2]pseudorotaxanes in the core of the complex. The CD measurements show that this geometry is governed by the rigid receptor (*RR*)-**1** · 4 PF_6 and that it is not significantly different for the enantiomeric couples **3−5** or even their achiral derivatives. Apparently, the different modes of binding for the enantiomeric "threads" **3−5** in the receptor (*RR*)-**1** · 4 PF_6 − leading to the measured enantioselectivities − are not accompanied by drastically different core geometries for the individual [2]pseudorotaxanes.

Conclusions

The receptor (*RR*)-**1** · 4 PF_6, possessing a rigid and preorganized π-electron-deficient chiral cavity, has demonstrated its ability to differentiate between enantiomers of π-electron-rich "threads" **3−5** in the formation of 1:1 [2]pseudorotaxane complexes. The combination of the D_2 geometry of the receptor (*RR*)-**1** · 4 PF_6 with the C_2 geometries of the "threads" has been found to be particularly effective, especially considering that the chiral centers of the "threads" are located on polyether chains, which usually possess a considerable degree of rotational freedom. In future, we will address the possibility of constructing interlocked molecular compounds, in the shape of catenanes and rotaxanes, with a high degree of selectivity at a stereochemical level.

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Experimental Section

General: All chemicals were purchased from commercial suppliers and used as received. The tetracationic cyclophane (*RR*)-**1** · 4 PF_6,[2] the chiral substrates **3−5**[6] and the achiral substrates **7** and **8**[12] were prepared as described previously. − Thin-layer chromatography (TLC) was performed on aluminum sheets (10 × 5 cm) coated with silica gel. Developed plates were air-dried, scrutinized under a UV lamp, and, if necessary, then either sprayed with cerium(IV) sulfate/sulfuric acid reagent and heated to ca. 100°C, or sprayed with an aqueous KI/I_2 solution or developed in an iodine tank. − Column chromatography was performed using silica gel (SiO_2, 0.040−0.063 mm mesh). − ^{1}H-NMR spectra were recorded at either 300 or 400 MHz. − ^{13}C-NMR spectra were recorded at either 75.5 or 100 MHz. − Infrared spectra were taken with wave numbers between 4400 and 450 cm^{-1}. − CD spectra were recorded at room temperature with a JASCO J-600 Spectropolarimeter.

1,4-[(tert-Butoxycarbonylmethoxy)ethoxy]benzene: 1,4-Bis(2-hydroxyethoxy)benzene (1.0 g, 5.05 mmol) and *t*BuOK (1.41 g, 12.6 mmol) were suspended in *t*BuOH (15 ml) and DMF (5 ml). The mixture was stirred for 1 h at 30−40°C, after which time *tert*-butyl bromoacetate (3.94 g, 20.2 mmol) was added dropwise in two portions. The second portion was added 1 h after the first. Addition of the *tert*-butyl bromoacetate resulted in an instantaneous formation of a white precipitate (KBr). The suspension was stirred for a further 3 h before the solvent was removed in vacuo. The resulting mixture was suspended in H_2O and extracted with CH_2Cl_2. The collected organic layers were dried ($MgSO_4$), filtered, and concentrated. Column chromatography (SiO_2; hexane/EtOAc, 4:1) gave a slightly impure product, which was purified by crystallization from hexane/EtOAc to yield the pure diester (0.95 g, 45%). M.p. 78−79°C. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.85 (4 H, s), 4.11 (4 H, m), 4.08 (4 H, s), 3.90 (4 H, m), 1.45 (18 H, s). − ^{13}C NMR

($CDCl_3$, 100 MHz): δ = 169.5, 153.0, 115.5, 81.6, 69.9, 69.1, 68.0, 28.0. – FTIR (KBr, cm^{-1}): $\tilde{\nu}$ = 2990, 2933, 2885, 1748, 1510, 1456, 1386, 1366, 1286, 1226, 1140, 1072. – $C_{22}H_{34}O_8$ (426.51): calcd. C 61.95, H 8.05; found C 61.58, H 7.85.

1,4-[(Carboxymethoxy)ethoxy]benzene (**6**): The diester (450 mg, 1.06 mmol) was dissolved in dry CH_2Cl_2 (10 ml) and TFA (1 ml) and stirred for 2 h. Evaporation of the solvents gave a colorless compound which was precipitated in PhMe/MeCN (10:1). Filtration of the suspension yielded **6** as a white compound (280 mg, 84%). M.p. 99°C. – ^{1}H NMR (CD_3CN, 400 MHz): δ = 6.85 (4 H, s), 4.15 (4 H, s), 4.10 (4 H, m), 3.85 (4 H, m). – ^{13}C NMR (CD_3CN, 100 MHz): δ = 171.7, 154.0, 116.5, 70.8, 68.8, 68.7. – FTIR (KBr, cm^{-1}): $\tilde{\nu}$ = 3063, 2940, 2879, 1718, 1511, 1482, 1449, 1287, 1226, 1148. – $C_{14}H_{18}O_8$ (314.29): calcd. C 53.50, H 5.78; found C 53.79, H 5.78.

UV-Spectrophotometric Titrations:[10] The changes in the optical densities of solutions of complexes were recorded as the relative concentrations of substrate components of the complexes were increased with respect to the tetracationic cyclophanes (*RR*)-**1** · 4 PF_6. All stability constants were determined in dry MeCN solution at 298 K from the same stock solutions of the cyclophane. In a typical experiment, a solution of the cyclophane was made up in a volumetric flask and its optical density recorded in a 1-cm path length cuvette. A known quantity of the guest was added to the solution. The optical density of this solution of the complex was recorded and the procedure repeated until no significant change in the optical density was observed when further guest was added. Molar ratios of substrates to the tetracationic cyclophane employed were in the range 0.1:1 to 20:1. The data were treated with a non-linear curve-fitting program (*UltraFit*, Biosoft, Cambridge, **1992**) running on an Apple Macintosh microcomputer.

The ε_{max} value of receptor (*RR*)-**1** · 4PF_6 is situated at 380 nm; $\varepsilon_{380} = 1.65 \cdot 10^5$ (dm^2/mol). The ε_{max} values of the various complexes are as follows: ε_{335} [(*RR*)-**3**/(*RR*)-**1**] = $2.0 \cdot 10^5$; ε_{339} [(*SS*)-**3**/(*RR*)-**1**] = $2.1 \cdot 10^5$; ε_{337} [(*RR*)-**4**/(*RR*)-**1**] = $1.7 \cdot 10^5$; ε_{337} [(*SS*)-**4**/(*RR*)-**1**] = $1.7 \cdot 10^5$; ε_{336} [(*RR*)-**5**/(*RR*)-**1**] = $1.7 \cdot 10^5$; ε_{336} [(*SS*)-**5**/(*RR*)-**1**] = $1.7 \cdot 10^5$. All ε_{max} values in dm^2/mol.

CD/UV Measurements: In all cases, the tetracationic cyclophane (*RR*)-**1** · 4 PF_6 was dissolved in MeCN with a few molar equivalents (between 1 and 10) of the chiral or achiral substrates **3**–**8**. Steps were taken to ensure that the optical densities of the solutions were between 0.1 and 1.5. – The $\Delta\varepsilon_{max}$ value of receptor (*RR*)-**1** · 4 PF_6 is situated at 391 nm: $\Delta\varepsilon_{391} = 2.8 \cdot 10^2$ (dm^2/mol). The corresponding *g* value is $g_{391} = 1.8 \cdot 10^{-3}$. The $\Delta\varepsilon_{max}$ values of the various complexes are as follows: $\Delta\varepsilon_{335}$ [(*RR*)-**3**/(*RR*)-**1**] = $1.9 \cdot 10^2$; $\Delta\varepsilon_{339}$ [(*SS*)-**3**/(*RR*)]-**1** = $1.7 \cdot 10^2$; $\Delta\varepsilon_{337}$ [(*RR*)-**4**/(*RR*)-**1**] = $2.3 \cdot 10^2$; $\Delta\varepsilon_{337}$ [(*SS*)-**4**/(*RR*)-**1**] = $2.3 \cdot 10^2$; $\Delta\varepsilon_{336}$ [(*RR*)-**5**/(*RR*)-**1**] = $2.4 \cdot 10^2$; $\Delta\varepsilon_{336}$ [(*SS*)-**5**/(*RR*)-**1**] = $2.3 \cdot 10^2$. These $\Delta\varepsilon_{max}$ values (in dm^2/mol) correspond to *g* values of g_{335} [(*RR*)-**3**/(*RR*)-**1**] = $9.4 \cdot 10^4$; g_{339} [(*SS*)-**3**/(*RR*)-**1**] = $7.8 \cdot 10^{-4}$; g_{337} [(*RR*)-**4**/(*RR*)-**1**] = $1.4 \cdot 10^{-3}$; g_{337} [(*SS*)-**4**/(*RR*)-**1**] = $1.4 \cdot 10^{-3}$; g_{336} [(*RR*)-**5**/(*RR*)-**1**] = $1.4 \cdot 10^{-3}$; g_{336} [(*SS*)-**5**/(*RR*)-**1**] = $1.4 \cdot 10^{-3}$.

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