Enantioselective Recognition of Amino Acids by Axially-Chiral π-Electron-Deficient Receptors

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The development of chiral hosts capable of exhibiting enantiomeric differentiation toward racemic guests has become an important and rapidly growing field of chemistry.[1] Recent work has led to the design and syntheses of chiral hosts for alkaloids,[2] amino acids,[3] peptides,[4] and other neutral guests.[5] Meanwhile, cyclobis(paraquat-*p*-phenylene) (**1**$^{4+}$), which has been self-assembled[6] around numerous cyclic and acyclic templates to produce catenanes and rotaxanes,[7] has been shown[8,9] —as its tetrakis(hexafluorophosphate) salt **1**·4PF_6—to complex (Figure 1) with π-electron-rich substrates like 1,4-bis(2-(2-hydroxyethoxy)ethoxy)benzene (BHEEB) strongly in organic solvents.

Furthermore, as its tetrachloride salt **1**·4Cl in H_2O, **1**$^{4+}$ forms strong 1:1 complexes with biologically-important compounds like π-electron-rich aromatic amino acids,[10] a series of catechol-containing neurotransmitters,[11] and phenyl glycopyranosides.[12] One of its main features as a host[13] is its rigid rectangular cavity wherein the distance between the π-electron-deficient bipyridinium units (7 Å) is ideal for the inclusion of a π-electron-rich aromatic ring. In order to provide ourselves with optically-active derivatives of **1**$^{4+}$ that retain its receptor characteristics, we decided to investigate introducing axially-chiral 3,3′-linked-2,2′-dihydroxy-1,1′-binaphthyl spacers sequentially, in place of the *p*-phenylene rings, into the tetracationic cyclophane. Not only should it hold the two bipyridinium units *ca.* 8 Å apart, but it is also among the most versatile and popular chiral building block with C_2 symmetry used[14] in the resolution of enantiomers and in asymmetric syntheses and catalyses. In this paper, we (1) describe the template-directed synthesis (Scheme 1) of the new axially-chiral tetracationic cyclophanes *(R)*-**4**·4PF_6 and *(RR)*-**6**·4PF_6 and (2) report on their abilities to differentiate between the D- and L-enantiomers of the aromatic amino acids phenylalanine, tyrosine, and tryptophan, in H_2O and their N-acetylated derivatives in organic solvents.

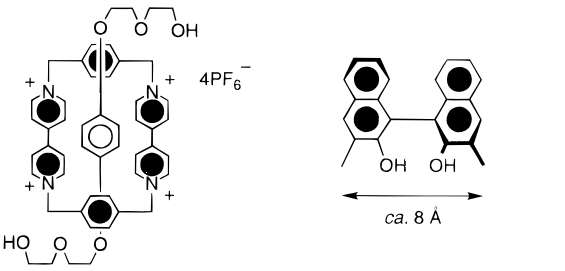

Figure 1. 1:1 complex between **1**·4PF_6 and BHEEB (on the left) and the rigid, axially-chiral binaphthol spacer (see text for details).

The synthesis of the optically-active dibromide *(R)*-**2** was carried out as described previously.[15] The tetracationic cyclophane *(R)*-**4**·4PF_6 was self-assembled by stirring equimolar amounts of *(R)*-**2** and **3**·2PF_6[9] in the presence of an excess of BHEEB for 14 days at room temperature. The highly colored reaction mixture was purified[9] by liquid−liquid extraction ($CHCl_3/H_2O$), followed by column chromatography (SiO_2: MeOH−2 M NH_4Cl−$MeNO_2$, 7:2:1) and counterion exchange (NH_4PF_6, H_2O). The crystalline product was recrystallized from MeCN/*i*-Pr_2O to give the optically-active—$[\alpha]^{25}_D = +86°$ ($c = 0.009$, Me_2CO)—C_2 symmetrical[16] receptor *(R)*-**4**·4PF_6 in 27% yield. Employing similar isolation and purification techniques, the optically-active—$[\alpha]^{25}_{578} = +103°$ ($c = 0.006$, MeCN)—D_2 symmetrical[16] receptor *(RR)*-**6**·4PF_6 was self-assembled by mixing equimolar amounts of *(R)*-**2** and *(R)*-**5**·2PF_6[17] in the presence of an excess of the

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(16) The symmetry elements present in *(R)*-**4**·4PF_6 and *(RR)*-**6**·4PF_6 mean that in both cases the faces of the receptors are homotopic. Thus, irrespective of which face binds the substrate, only one 1:1 complex can be formed by *(R)*-**4**·4PF_6 and *(RR)*-**6**·4PF_6.

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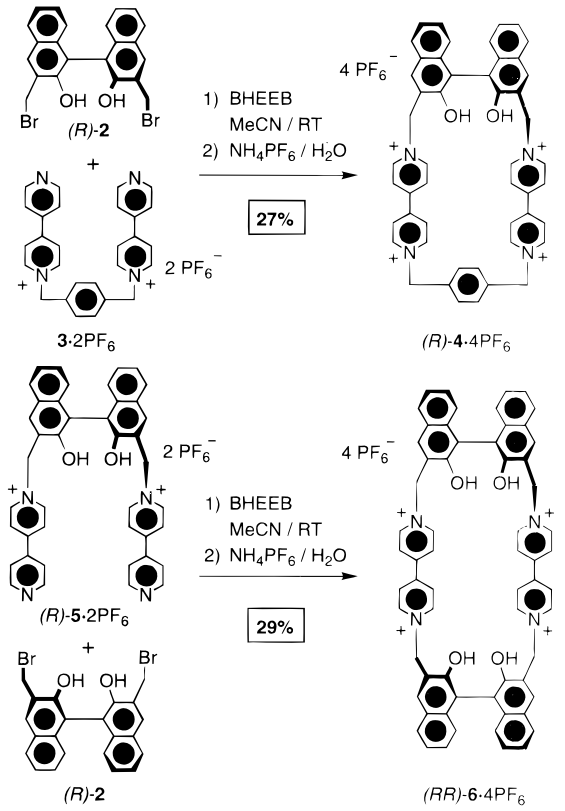
Table 1. Binding Constants (K_a) and Free Energies of Complexation ($-\Delta G°$) for the 1:1 Complexes between Cyclophanes (*R*)-4·X (X = PF_6 or Cl) and (*RR*)-6·4PF_6 and π-Electron-Rich Amino Acids[a]

			K_2 (M^{-1})		K_a(L)/K_a(D)		$-\Delta G°$ (kcal/mol)		$\Delta\Delta G°$ (kcal/mol)[b]	
entry	substrate	solvent	(*R*)-**4**	(*RR*)-**6**	(*R*)-4	(*RR*)-**6**	(*R*)-**4**	(*RR*)-**6**	(*R*)-**4**	(*RR*)-**6**
1	L-Try	H_2O[c]	2470	ND[d]			4.63			
2	D-Try	H_2O[c]	5860	ND[d]	0.42		5.14		−0.51	
3	L-Try OMe·HCl	H_2O[c]	753	ND[d]			3.92			
4	D-Try OMe·HCl	H_2O[c]	803	ND[d]	0.94		3.96		−0.04	
5	*N*-Ac-L-Try	A[e]	20700	4280			5.89	4.95		
6	*N*-Ac-D-Try	A[e]	2670	1080	7.75	3.96	4.67	4.14	1.22	0.81
7	*N*-Ac-L-Tyr	B[e]	10060	2340			5.45	4.60		
8	*N*-Ac-D-Tyr	B[e]	2125	1047	4.73	2.23	4.53	4.12	0.92	0.48
9	*N*-Ac-L-Phe	A[e]	1220	219			4.21	3.19		
10	*N*-Ac-D-Phe	A[e]	2260	137	0.54	1.60	4.57	2.91	−0.36	0.28

[a] All binding constants were determined by UV/vis titration at 25 °C. [b] $\Delta\Delta G° = \Delta G°$(L) − $\Delta G°$(D). [c] In H_2O as a solvent, (*R*)-**4**·4Cl was used. [d] Not determined. [e] Solvent mixture A:MeCN 90% DMF 10%; solvent mixture B: MeCN 90% DMSO 10%.

Scheme 1



template (BHEEB) in 29% yield. Both receptors gave good elemental analyses and were characterized by LSIMS and ^{1}H-NMR and ^{13}C-NMR spectroscopies.

Although inspection of molecular models show that *(R)*-**4**$^{4+}$ and *(RR)*-**6**$^{4+}$ have slightly enlarged and distorted cavities compared with **1**$^{4+}$, both chiral tetracationic cyclophanes form strong 1:1 complexes with BHEEB: for *(R)*-**4**·4PF_6 and *(RR)*-**6**·4PF_6 in MeCN at 25 °C, the K_a values are 810 and 2640 M^{-1}, respectively, as determined by UV/vis titration. Binding constants and derived free energies of complexation for the 1:1 complexes formed between either *(R)*-**4**·4X (X = PF_6 or Cl)[18] or *(RR)*-**6**·4PF_6 and the L- and D-enantiomers of phenylalanine (Phe), tyrosine (Tyr), and tryptophane (Try)—as free, methyl esterified, or *N*-acetylated—in H_2O and organic solvents are listed in Table 1. Comparison of the K_a values between *(R)*-**4**·4Cl and L-Try and D-Try in H_2O (Table 1, entries 1 and 2) indicate a modest amount of enantioselectivity in favor of D-Try that was reduced drastically when the corresponding L- and D-methyl ester hydrochloride salts were investigated (Table 1, entries 3 and 4), suggesting that the carboxylic acid function in these amino acids might be playing a role in binding and enantioselection. When the amino groups on L-Try and D-Try are *N*-acetylated, the enantioselectivity in MeCN/DMF (90:10) is even larger but favors the L- over the D-enantiomer (Table 1, entries 5 and 6). In both cyclophanes, the enantioselectivities decrease on going from *N*-acetyltryptophan to *N*-acetyltyrosine[19] (Table 1, entries 7 and 8) and to the less π-electron-rich *N*-acetyl phenylalanine (Table 1, entries 9 and 10). All these data suggest to us a model, where the more π-electron rich is the guest (primary mode of binding), the more the secondary stereoelectronic interactions of the functional groups of the guest with the bulky optically-active binaphthol spacer(s) of the cyclophane(s) are effective[20] in recognition terms. Indeed, on comparing the 1:1 complexes between *N*-acetyl L- and D-tryptophan and *(R)*-**4**$^{4+}$, molecular mechanics Monte Carlo conformational searching[21] using Macromodel 5.0 (1000 structures, OPLS force field, and the GB/SA solvation model for water) predicts that the L-enantiomer complex will be more stable by approximately 1.5 kcal/mol compared with the D-enantiomer complex. A fully systematic molecular modeling study aimed at further interpreting the observations recorded in Table 1 is underway currently.

We believe that the axially-chiral π-electron-deficient receptors *(R)*-**4**$^{4+}$ and *(RR)*-**6**$^{4+}$ can be adapted (1) to effect the resolutions of racemic substrates containing π-electron-rich aromatic rings and also (2) to act as asymmetric catalysts of appropriate reactions performed on suitably bound and oriented substrates.

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Supporting Information Available: Experimental section and spectroscopic data for compounds *(R)*-**4**·4PF_6, *(R)*-**5**·2PF_6, and *(RR)*-**6**·4PF_6 and curves obtained from selected UV/vis titrations (5 pages).

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(17) Compound *(R)*-**5**·2PF_6 was prepared in a manner similar to that for **3**·2PF_6. See ref 9.

(18) Compound *(R)*-**4**·4Cl was obtained by adding a saturated solution of *n*-Bu_4NCl in Me_2CO to a solution of *(R)*-**4**·4PF_6 in Me_2CO until no further precipitation occurred.

(19) *N*-Acetyl-D-tyrosine was prepared according to: Du Vigneaud, V.; Meyer, C. E. *J. Biol. Chem.* **1933**, *97*, 295−308.

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