Chiral Recognition of Dicarboxylate Anions by Sapphyrin-Based Receptors

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Abstract: The synthesis and characterization of the open-chain and cyclic sapphyrin dimers **2**−**4** and **7**, bearing various bisamide spacers is reported. This family of receptors was shown to display excellent recognition properties for various dicarboxylate anions, as judged from mass spectrometric analyses, U-tube aqueous I/CH_2Cl_2/aqueous II through-model-membrane transport experiments, and equilibrium binding studies. These latter were carried out in either methanol or dichloromethane using ^{1}H or ^{2}H NMR and visible spectroscopic titrations. The flexible, first-generation system **2**, featuring a 1,3-bisamidopropane spacer was found to display a high affinity for dicarboxylate anions even in polar solvents, such as methanol. Within a range of substrates, this receptor showed a strong preference toward linear over bent, and aromatic over aliphatic dicarboxylate anions, a fact that is readily rationalized in terms of extra, stabilizing $\pi-\pi$, C−H···π, or C−H···N interactions. This latter C−H···N hydrogen-binding motif was observed in the single crystal structure of the 1:1 complex formed between benzoate anion and the monoprotonated form of sapphyrin **1a**. The second-generation, open-chain chiral sapphyrin dimers **3** and **4** (containing (1*S*,2*S*)-1,2-bisamidocyclohexane and (*S*)-2,2′-bisamido-1,1′-binaphthalene chiral auxiliaries, respectively) were found to form strong complexes with *N*-carbobenzyloxy-protected aspartate and glutamate anions (K_a values are on the order of 10^4-10^5 M^{-1} in 19:1 (v/v) dichloromethane−methanol), and displayed a preference for glutamate over aspartate, with receptor **4** showing a modest level of enantiomeric selectivity. The cyclic dimer **7** binds these anions less effectively, but displays excellent chiral discrimination between the D- and L-antipodal forms of *N*-carbobenzyloxy-protected glutamate anion.

Introduction

Achieving the selective recognition and transport of biologically active *polyanions* constitutes an important yet difficult task facing supramolecular chemists.[1,2] These species are not only strongly solvated in protic media; they are also characterized by multiple charges and complex shapes. This complexity and architectural diversity accounts for their involvement in a wide range of biological processes. These run the gamut from nucleic acid-based information storage and processing, to enzymatic catalysis and inhibition, transmembrane transport, signal induction, protein folding, and metabolism, to name a few.[3,4] Unfortunately, the very features, *e.g.*, charge density and structural complexity, that make many polyanions of biological interest also make them challenging substrates to recognize in a supramolecular sense.

In this paper we address the problem of *dicarboxylate* recognition and transport. The simplest dicarboxylate anions, *i.e.*, oxalate and malonate, possess elongated shapes and some degree of conformational freedom. Other biologically relevant dicarboxylate anions feature more complex spatial arrangements. For instance, malate, fumarate, succinate, oxaloacetate, and ketoglutarate (important intermediates in the citric acid and glyoxylate cycles)[3a] and aspartate and glutamate (excitatory amino acid neurotransmitters)[4] have long, flexible alkyl chains that separate the individual carboxylate moieties. In addition, these more complex dicarboxylate anions often feature chiral centers as well as extra functional groups (*e.g.*, keto, amino, or hydroxy). It is a need to *complement* many if not all of these functional groups, as well as neutralize most of the anionic charge,[5] that has made the design of receptors for dicarboxylates so challenging. So far, approaches based on the use of positively

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(2) For the most recent review on receptors for carboxylates and other organic anions, see: Seel, C.; Galan, A.; de Mendoza, J. *Top. Curr. Chem.* **1995**, *175*, 102−132.

(3) (a) Voet, D.; Voet, J. G. *Biochemistry*, 2nd ed.; Wiley: New York, 1995. (b) Branden, C.; Tooze, J. *Introduction to Protein Structure*, Garland, New York, 1991. (c) Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; Freeman, New York, 1985.

(4) For an overview, see: Krogsgaard-Larsen, P., Hansen, J. J., Eds. *Excitatory Amino Acid Receptors*; Ellis Horwood: Chichester, 1992. For recent structural work, see: Yeh, J. I.; Biemann, H. P.; Prive, G. G.; Pandit, J.; Koshland, D. E., Jr.; Kim, S. H. *J. Mol. Biol.* **1996**, *262*, 186−201.

(5) Depending on the structural characteristics and microenvironment, the carboxylate groups, either individually or jointly, can be in their neutral (protonated) or anionic (deprotonated) forms. This complicates the problem of dicarboxylate/dicarboxylic acid recognition. In this paper we have elected to concentrate on dicarboxylate dianion binding only. For a few examples of receptors for neutral dicarboxylic acids, see: (a) Rebek, J., Jr.; Nemeth, D.; Ballester, P.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 3474−3475. (b) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807−2808. (c) Prevot-Halter, I.; Smith, T. J.; Weiss, J. *J. Org. Chem.* **1997**, *62*, 2186−2192. (d) Raposo, C.; Luengo, A.; Almaraz, M.; Martin, M.; Mussons, L.; Caballero, C.; Moran, J. R. *Tetrahedron* **1996**, *52*, 12323−12332 and references therein. (e) Goodman, M. S.; Hamilton, A. D.; Weiss, J. *J. Am. Chem. Soc.* **1995**, *117*, 8447−8455 and references therein. (f) Owens, L.; Thilgen, C.; Diederich, F.; Knobler, C. B. *Helv. Chim. Acta* **1993**, *76*, 2757−2774 and references therein. (g) Alcazar, V.; Moran, J. R.; Diederich, F. *Isr. J. Chem.* **1992**, *32*, 69−77. (h) Garcia-Tellado, F.; Goswami, S.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393−7394.

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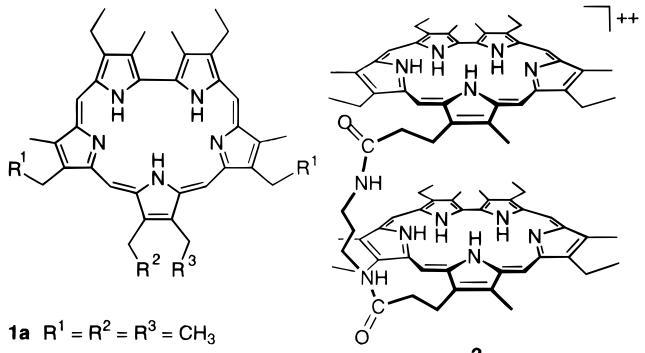
charged binding sites, such as protonated polyammonium macrocycles[6] and guanidinium units[1i,7] have been extensively explored by the groups of Lehn,[6a−d,7a] Kimura,[6e−g] Schmidtchen,[7b] and Anslyn.[1i] The use of Lewis acids has also been extensively investigated by Beer[8] and Reinhoudt.[9] In addition, Hamilton has developed neutral receptors featuring hydrogen-bonding donors derived from urea- and thiourea-binding subunits.[10] While the detailed approaches used vary, in all cases, chelation of the dicarboxylate substrates in question is achieved via the formation of several, often cooperative, noncovalent bonds. In many cases, it has proved necessary to add extra stabilizing interactions in order to increase binding efficacy and selectivity. Further, in the case of chiral dicarboxylates, enantiomeric recognition has been achieved only at the neutral, diprotonated (*i.e.*, free acid) level, not the dianionic one extant at physiological pH.[11] Therefore, there remains a need for receptors that effect the enantioselective binding of dicarboxylate anions.

In this paper, we report the synthesis of receptors that allow for the stereogenic recognition of several prototypic dicarboxylate anions. The approach used is based on the use of sapphyrin macrocycles as the binding subunits.[12] *Sapphyrins* (*e.g.*, **1**) are pentapyrrolic "expanded" porphyrins[13] that are known to act as efficient fluoride and phosphate (but not dicarboxylate) anion receptors under a wide range of conditions.[14] This versatility reflects the fact that among other things, the large and relatively basic pentaaza core of sapphyrin is (*i*) monoprotonated at neutral pH and that (*ii*) the pyrrolic NH protons of this same center act as effective hydrogen-bond donors. This gives rise to a propitious combination of Coulombic attractions and hydrogen-bonding interactions that makes sapphyrin an excellent receptor for these anions, even in polar protic solvents such as methanol or water.[15] Given this, we became intrigued with the question of whether it might be possible to construct sapphyrin-based *polytopic* (*multidentate*) receptors, such as **3**, **4**, and **7**, that could be used to effect the recognition of dicarboxylate anions. Here, part of our interest stemmed from the fact that such systems, if made chiral, could act as enantiodifferentiating anion recognition elements. Consistent with this thinking we have found, as detailed below, that receptor **7** permits a high level of enantioselective discrimination between the two antipodes of *N*-carbobenzyloxy-protected glutamate anion.



1a $R^1 = R^2 = R^3 = CH_3$

1b $R^1 = CH_3$; $R^2 = CH_2CO_2H$; $R^3 = H$

1c $R^1 = CH_2CO_2H$; $R^2 = R^3 = CH_3$

2

Experimental Section

General Methods and Materials. Proton and ^{13}C NMR spectra were recorded using either General Electric QE-300 (300 MHz), General Electric GN-500 (500 MHz), or Bruker AM-500 (500 MHz) instruments. ^2H NMR spectra were recorded on the Bruker AM-500. Visible spectral studies were made on a Beckman DU 640 instrument using cuvettes of 1 cm path length. The sapphyrin mono- and dicarboxylic acids, **1b** and **1c**, were prepared according to procedures previously described.[14e] The sapphyrin dimer **2** was also prepared using methods described earlier.[12] (*S*)-2,2′-Diamino-1,1′-binaphthalene and (1*S*,2*S*)-1,2-diaminocyclohexane were purchased from Fluka. Mono-*t*-Boc-protected (1*S*,2*S*)-1,2-diaminocyclohexane was synthesized using a modification of a general procedure with DMF as the solvent.[16] 1,3-Diisopropylcarbodiimide (DIC), 1,1′-carbonyldiimidazole (CDI), 1-hy-

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droxybenzotriazole hydrate (HOBt), trimethylamine gas, terephthalic acid-d_4, trifluoroacetic acid (TFA), oxalyl chloride, pyridine (Py), and dimethylformamide (DMF) were purchased from Aldrich. *N*-Cbz-L-aspartic acid, *N*-Cbz-D-aspartic acid, and *N*-Cbz-L-glutamic acid were purchased from Sigma. *N*-Cbz-D-glutamic acid was purchased from Advanced Chemtech. Isophthalic acid-d_3 was prepared according to a modification of a literature procedure.[17]

Transport Experiments. Transport experiments were performed at 293 K using a standard glass U-tube model membrane system.[18] Conditions were as follows: source phase, 1 mL of a 1:1:1 molar ratio of 4-nitrophthalic acid, 5-nitroisophthalic acid, and nitroterephthalic acid (10 mM of each) at pH 7.2 (adjusted by the careful addition of NaOH); (membrane (6 mL); carrier (**1a** or **2**), 0.1 mM in dichloromethane; receiving phase, 1 mL of H_2O, pH 7.0. The release of the dicarboxylate anions into the receiving phase was monitored as a function of time via HPLC product analysis (Waters) using adenosine or uridine as internal standards. Error is within ±10%.

Binding Studies. Binding studies were effected by means of ^{1}H NMR (General Electric QE-300), ^{2}H NMR (Bruker AM-500), and visible (Beckman DU 640) titrations and were carried out at 293 K. Methanol-d_4 was used for the ^{1}H NMR titrations and nondeuterated methanol was used for the ^{2}H NMR analyses. For both sets of NMR titrations, the dicarboxylate substrate concentration was held constant and the receptor concentration varied. Change in the chemical shifts of the aromatic hydrogen/deuterium atoms of the substrates were then followed and used to calculate the stoichiometry of complexation and the binding constants.[12,19] For the visible titrations, the sapphyrin dimer concentration was held constant and the substrate concentration varied. In this case, the increase in absorption of the red-shifted Soret-like bands of the sapphyrin dimers at ~450 nm was followed. All receptors were used in the form of their bis-HCl salts. Dicarboxylate substrates were used as their trimethylammonium salts.

X-ray Structural Analysis. A single crystal of $[\mathbf{1a}\cdot H]^+\cdot(C_6H_5CO_2)^-\cdot(C_4H_8O)$ was obtained by vapor diffusion of hexanes into a solution of $[\mathbf{1a}\cdot H]^+\cdot(C_6H_5CO_2)^-$ in THF. The data crystal was a dark green needle of approximate dimensions 0.14 × 0.21 × 0.54 mm; triclinic, $P\bar{1}$, $Z = 2$ in a cell of dimensions of $a = 13.210(1)$, $b = 13.936(1)$, $c = 14.960(2)$ Å; $\alpha = 99.258(8)$, $\beta = 111.011(8)$, $\gamma = 110.480(8)°$; $V = 2275.7(4)$Å^3, $\rho_{calc} = 1.16$ g cm^{-3}, F(000) = 856. A total of 8567 reflections were measured, 7725 unique ($R_{int}(F^2) = 0.069$) at −85 °C on a Siemens P4 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was refined on F^2 to an $R_w = 0.195$, with a conventional $R = 0.0821$, with a goodness of fit = 1.047 for 549 refined parameters. Further details of crystal data, data collection, and structure refinement are given in the Supporting Information.

Sapphyrin Dimer 3. Compound **3** was obtained from sapphyrin monocarboxylic acid **1b** and (1*S*,2*S*)-1,2-diaminocyclohexane using DIC as the coupling reagent. This was done using a modification of a standard, one-pot procedure commonly employed in peptide synthesis.[20] Acid **1b** (189 mg, 0.3 mmol), (1*S*,2*S*)-1,2-diaminocyclohexane (11.4 mg, 0.1 mmol), and 0.1 mL of dry Py were dissolved in 10 mL of anhydrous DMF under argon. A solution of DIC (76 mg, 0.6 mmol) in 1 mL of anhydrous DMF was then added, followed by HOBt (13.5 mg, 0.1 mmol). The resulting reaction mixture was stirred at room temperature under argon for 3 days. The second portion of DIC (76 mg, 0.6 mmol) was then added as a solution in 1 mL of anhydrous DMF, and the reaction mixture was stirred for additional 3 days. TFA (0.1 mL) was then added, the solvents evaporated, and the solids dried *in vacuo*. The resulting product was then purified via column chromatography using silica gel as the solid support and a gradient of 1−15% methanol in dichloromethane as the eluent. The yield of compound **3** is 106 mg (TFA salt, 68%). ^{1}H NMR (500 MHz, $CDCl_3$, with 5% CD_3OD): δ 0.93 (2H, d, cyclohexane protons), 1.02−1.22 (4H, m, cyclohexane Hs), 1.85−2.25 (28H, m, cyclohexane Hs, CH_2CH_3), 3.15 (4H, m, CH_2CO), 3.90−4.30 and 4.33−4.90 (50H, br m, CH_3, CH_2CH_3, CH_2CH_2CO), 10.8−11.8 (8H, m, methine). ^{13}C NMR (126 MHz, $CDCl_3$, with 5% CD_3OD): δ 12.44, 12.51, 12.63, 12.78, 16.193, 17.61, 17.67, 17.78, 20.36, 20.45, 20.50, 20.60, 20.73, 21.95, 22.07, 22.67, 22.88, 22.91, 23.16, 24.05, 31.29, 38.91, 38.96, 41.40, 41.51, 53.38, 53.48, 90.77 (m), 95.75 (m), 104.24, 111.68, 114.02, 115.56, 116.35, 118.69, 120.81, 121.10, 123.77, 127.39, 128.90 (m), 131.85, 132.50, 133.81, 134.67 (m), 135.34 (m), 137.18, 137.64, 138.20, 138.86, 140.51, 141.10, 142.21, 142.69, 143.21, 143.96 (m), 157.68, 172.78, 172.86. UV−vis (in MeOH): λ_{max} (ϵ) 420 (387 500), 442 (191 700), 620 (13 400), 672 (14 200). UV−vis (in CH_2Cl_2 with 5% CH_3OH): λ_{max} (ϵ) 427 (204 500), 448 (261 300), 620 (15 400), 677 (11 200). HRMS FAB calcd for $C_{86}H_{105}N_{12}O_2$ ($[M + H]^+$) 1337.8483, obsd 1337.8473.

Sapphyrin Dimer 4. The DIC-induced coupling used for the synthesis of dimer **3** was successfully employed for preparation of dimer **4**, except that (*S*)-2,2′-diamino-1,1′-binaphthalene was used as the diamino component instead of (1*S*,2*S*)-1,2-diaminocyclohexane (yield 62%). Alternatively, this same dimer **4** could be obtained via the acid chloride coupling method. In this case, the sapphyrin acid **1b** (189 mg, 0.3 mmol) was first converted to its corresponding acid chloride. This was done by dissolving it in 25 mL of dry dichloromethane under argon and adding oxalyl chloride (1 mL, as a 2 M solution in dichloromethane), followed by 0.03 mL of dry DMF. The reaction mixture was stirred under argon at room temperature for 3 h and then evaporated to dryness *in vacuo*. The sapphyrin acid chloride so obtained was then redissolved in dry dichloromethane (20 mL) and added over the course of 30 min to a solution of (*S*)-2,2′-diamino-1,1′-binaphthalene (28.4 mg, 0.1 mmol) in dry dichloromethane (10 mL) that contained 10 mg of 4-(dimethylamino)pyridine and 0.1 mL of dry Py. The resulting reaction mixture was stirred for 48 h at room temperature under argon. TFA (0.1 mL) was then added, and the mixture was washed with water. The organic phase was then separated off and evaporated to dryness. Product **4** (TFA salt, 76% yield) was then isolated via column chromatography as described for dimer **3**. ^{1}H NMR (500 MHz, $CDCl_3$, with 5% CD_3OD): δ 1.8−2.4 (24H, m, CH_2CH_3), 2.9 (4H, m, CH_2CO), 3.7−4.9 (50H, br m, CH_3, CH_2CH_3, CH_2CH_2CO), 6.8 (4H, br s, binaphthalene protons), 7.4 (2H, br s, binaphthalene protons), 7.8 (2H, br s, binaphthalene protons), 8.1 (2H, br s, binaphthalene protons), 8.6 (2H, br s, binaphthalene protons), 10.8−11.9 (8H, m, methine). ^{13}C NMR (126 MHz, $CDCl_3$, with 5% CD_3OD): δ 12.60, 12.63, 12.84, 16.46 (m), 17.77 (m), 20.50, 20.69, 20.87, 22.51, 28.90, 34.54, 38.60 (m), 53.20, 91.17 (m), 96.00 (m), 112.25, 114.57, 116.90, 119.23, 123.86 (m), 125.31, 126.40, 127.57, 128.66 (m), 128.99 (m), 131.46, 132.45, 134.37, 137.67, 141.00 (m), 143.12 (m), 171.93. UV−vis (in MeOH): λ_{max} (ϵ) 420 (419 700), 442 (261 600), 620 (17 000), 675 (14 500). UV−vis (in CH_2Cl_2 with 5% CH_3OH): λ_{max} (ϵ) 427 (127 400), 448 (317 800), 622 (14 800), 679 (19 600). HRMS FAB calcd for $C_{100}H_{106}N_{12}O_2$ ($[M]^+$) 1506.8562, obsd 1506.8555.

Diamine 6. Sapphyrin bisacid **1c** (207 mg, 0.3 mmol) was dissolved under argon in 10 mL of anhydrous DMF containing 0.1 mL of dry Py. A solution of CDI (146 mg, 0.9 mmol) in 2 mL of anhydrous DMF was then added, followed by HOBt (13.5 mg, 0.1 mmol). The resulting mixture was stirred at room temperature under argon for 2 h. Solution of mono-*t*-Boc-protected(1*S*,2*S*)-1,2-diaminocyclohexane (193 mg, 0.9 mmol) in 3 mL of anhydrous DMF was then added, and the resulting reaction mixture was stirred at room temperature under argon for 24 h. The solvent was then evaporated off using a rotorary evaporator, and the resulting protected diamine **5** was purified via column chromatography using silica gel as the solid support and a gradient of 2−10% methanol in dichloromethane as the eluent. The yield of compound **5** thus obtained was 273 mg (84%). Compound **5** was then immediately subjected to deprotection. This was done by treating it with a 1:1 dichloromethane/TFA mixture (5 mL). The deprotection process requires ~1 h and was carefully monitored via TLC analysis. After the deprotection was complete, the solvents were evaporated off, and the residue redissolved in dichloromethane containing 20% methanol (100 mL). The resulting solution was washed consecutively twice with 1 M NaOH (2 × 30 mL), and three times

(17) Lockley, W. J. S. *J. Labelled Compd. Radiopharm.* **1984**, *21*, 45−57.

(18) Tsukube, H. in *Liquid Membranes: Chemical Applications*; Araki, T., Tsukube, H., Eds., CRC Press: Boca Raton, FL, 1990.

(19) Connors, K. A. *Binding Constants. The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.

(20) See, for instance: Bailey, P. D. *An Introduction to Peptide Chemistry*; Wiley: Chichester, 1990.

Table 1. Selected Sapphyrin Dimer **2**−Dicarboxylate Complexes Detected by HR FAB MS

dicarboxylate[a]	composition	HR FAB MS calculated	HR FAB MS observed
oxalate	$[(C_{83}H_{100}N_{12}O_2)H_3]\cdot C_2O_4$	1387.8124	1387.8115
4-nitrophthalate	$[(C_{83}H_{100}N_{12}O_2)H_4]\cdot C_8H_3NO_6$	1509.8366	1509.8382
5-nitroisophthalate	$[(C_{83}H_{100}N_{12}O_2)H_4]\cdot C_8H_3NO_6$	1509.8366	1509.8386
nitroterephthalate	$[(C_{83}H_{100}N_{12}O_2)H_4]\cdot C_8H_3NO_6$	1509.8366	1509.8382

[a] Regardless of whether the substrates in question were added as the corresponding acids to the free-base form of **2**, or as the dicarboxylate anions to the protonated form of **2**, intense peaks, ascribed to the ensuing complex, were observed.

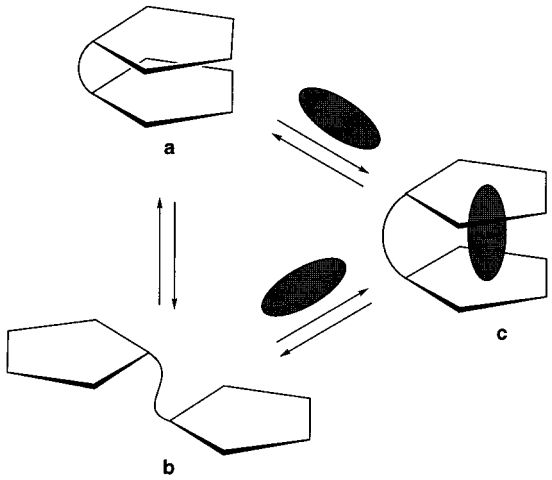
with water. The organic phase was then separated off and taken to dryness on the rotorary evaporator and subsequently dried *in vacuo*. The yield of compound **6** obtained in this way is 208 mg (free-base; 93% from **5**). It was used as produced for the synthesis of the cyclic sapphyrin dimer **7** (see below). For ^{13}C NMR spectral analysis, however, this free-base diamine was converted into its TFA salt. This conversion was achieved by dissolving the free-base form of **6** in dichloromethane containing 20% methanol, and washing it three times with an aqueous pH 6 solution of TFA, followed by evaporative removal of solvent and drying *in vacuo*. Data for the TFA salt of **6**: ^{1}H NMR (300 MHz, $CDCl_3$, with 5% CD_3OD): δ 0.59−1.70 (14H, m, cyclohexane protons), 2.08−2.28 (8H, m, cyclohexane protons), 2.55 (12H, br s, CH_2CH_3), 3.49 (6H, m, CH_2CO, $CHNH$), 4.24 (6H, s, CH_3), 4.28 (6H, s, CH_3), 4.63 (4H, q, CH_2CH_3), 4.81 (4H, q, CH_2CH_3), 5.08 (4H, m, CH_2CH_2CO), 11.59 (2H, s, methine), 11.73 (2H, s methine). ^{13}C NMR (75 MHz, $CDCl_3$, with 5% CD_3OD): δ 12.66, 16.61, 17.74, 18.51, 20.55, 20.62, 23.29, 24.35, 27.11, 31.58, 38.91, 53.75, 54.81, 91.39, 95.17, 128.52, 128.98, 129.63, 131.73, 133.94, 134.52, 138.91, 139.85, 144.28, 145.05, 172.72, 172.79. HRMS FAB calcd for $C_{54}H_{74}N_9O_2$ ($[M + H]^+$) 880.5965, obsd 880.5941.

Cyclic Sapphyrin Dimer 7. Compound **7** was obtained from the sapphyrin bisacid **1c** and sapphyrin diamine **6** using a DIC-based coupling procedure carried out under high dilution conditions. Specifically, the reactants **1c** (102 mg, 0.148 mmol) and **6** (free base, 130 mg, 0.148 mmol), along with 0.1 mL of dry Py, were dissolved in 100 mL of anhydrous DMF under argon. A solution of DIC (93 mg, 0.738 mmol) in 1 mL of anhydrous DMF was then added, followed by HOBt (13.5 mg, 0.1 mmol). The resulting reaction mixture was stirred at room temperature under argon for 3 days. A second aliquot of DIC (93 mg, 0.738 mmol) was then added (in the form of a solution in 1 mL of anhydrous DMF), and the reaction mixture was stirred for 3 additional days. TFA (0.1 mL) was then added, the solvents were evaporated off, and the solids were dried *in vacuo*. The crude product **7** (TFA salt, 46%) was then purified via column chromatography using the conditions described for dimer **3**. ^{1}H NMR (500 MHz, $CDCl_3$, with 5% CD_3OD): δ 0.80−0.91 (4H, m, cyclohexane protons), 1.02−1.30 (8H, m, cyclohexane protons), 1.4−2.51 (32H, m, cyclohexane protons, CH_2CH_3), 2.9−5.5 (56H, br m, CH_2CO, CH_3, CH_2CH_3, CH_2CH_2CO), 9.50−12.00 (8H, m, methine). ^{13}C NMR (126 MHz, $CDCl_3$, with 5% CD_3OD): δ 10.74, 12.50 (m), 15.49 (m), 17.53 (m), 18.30 (m), 20.47, 22.05, 22.33, 24.92, 28.75, 30.19, 30.89, 32.42 (m), 38.56, 38.89, 43.83, 44.69, 44.76, 46.95, 54.18 (m), 95.13 (m), 103.98, 115.22, 120.47, 120.62, 120.77, 123.11, 125.29 (m), 126.12, 127.68, 128.89, 130.27 (m), 130.84, 133.20 (m), 136.64 (m), 138.39, 173.17 (m). UV−vis (in MeOH): λ_{max} (ϵ) 420 (398 900), 442 (142 700), 620 (14 100), 675 (11 500). UV−vis (in CH_2Cl_2 with 5% CH_3OH): λ_{max} (ϵ) 433 (229 500), 447 (152 800). HRMS FAB calcd for $C_{96}H_{120}N_{14}O_4$ ($[M + 2H]^+$) 1532.9617, obsd 1532.9654.

Results and Discussion

Synthesis and Dicarboxylate Recognition Properties of Sapphyrin Dimer 2. The first-generation sapphyrin-sapphyrn dimer **2** was designed to function as a flexible ditopic receptor for dicarboxylate substrates.[12] Here, two protonated sapphyrins serve as the key carboxylate-binding "building blocks" while a diaminopropane spacer allows for the kind of generalized conformational mobility needed to accommodate a range of substrates. The synthesis of receptor **2** is accomplished by the EDC- or DCC-induced coupling of the sapphyrin mono acid **1b** with 1,3-diaminopropane in DMF followed by chromatographic purification. Alternatively, direct reaction of 1,3-diaminopropane with the sapphyrin acid chloride obtained from **1b** affords **2** in high (≥70%) yield.[12]

Scheme 1[a]



[a] Key: Pentagon, sapphyrin; oval, dicarboxylate substrate.

The initial work involved "screening" dimer **2** as a potential receptor for various dicarboxylate anions via the use of fast-atom bombardment mass spectrometric (FAB MS) analysis (nitrobenzyl alcohol matrix).[21] Without exception, if a peak corresponding to the receptor−anion complex could be detected in the mass spectrum, binding in solution was later confirmed. Relevant results, summarized in Table 1, provide anecdotal evidence that supramolecular complexes are formed between the protonated forms of **2** and representative dicarboxylate species under the matrix-desorption/gas-phase conditions of the MS experiments.

More detailed analyses of dicarboxylate anion chelation in solution were made using a full range of methods frequently used in the supramolecular field. Thus, both spectroscopic techniques (*e.g.*, NMR, UV−vis spectroscopy)[19] and transport studies (carried out in a model Pressman-type U-tube membrane system)[18] were employed.

Analysis of the visible spectra of **2** revealed the presence of two Soret-like maxima at λ_{max} 422 and 441 nm and 426 and 450 nm in methanol and dichloromethane, respectively.[22] This result was interpreted in terms of the dimer **2** being able to assume two distinct conformations in these solvents. On the basis of prior work,[12,14b] the high-energy transition is assigned to a closed-up, self-stacked (but still monomeric) form (species **a**, Scheme 1), whereas the red-shifted low energy transition is ascribed to an extended, nonaggregated form of **2** (species **b**, Scheme 1).[23] Addition of dicarboxylate anions to solutions of

(21) Whiteford, J. A.; Rachlin, E. M.; Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2524−2529 and references therein.

(22) On the other hand, dichloromethane and methanol solutions of control monomer **1a** display one Soret maximum at ∼450 nm at concentrations ≤ 10^{-4} M.

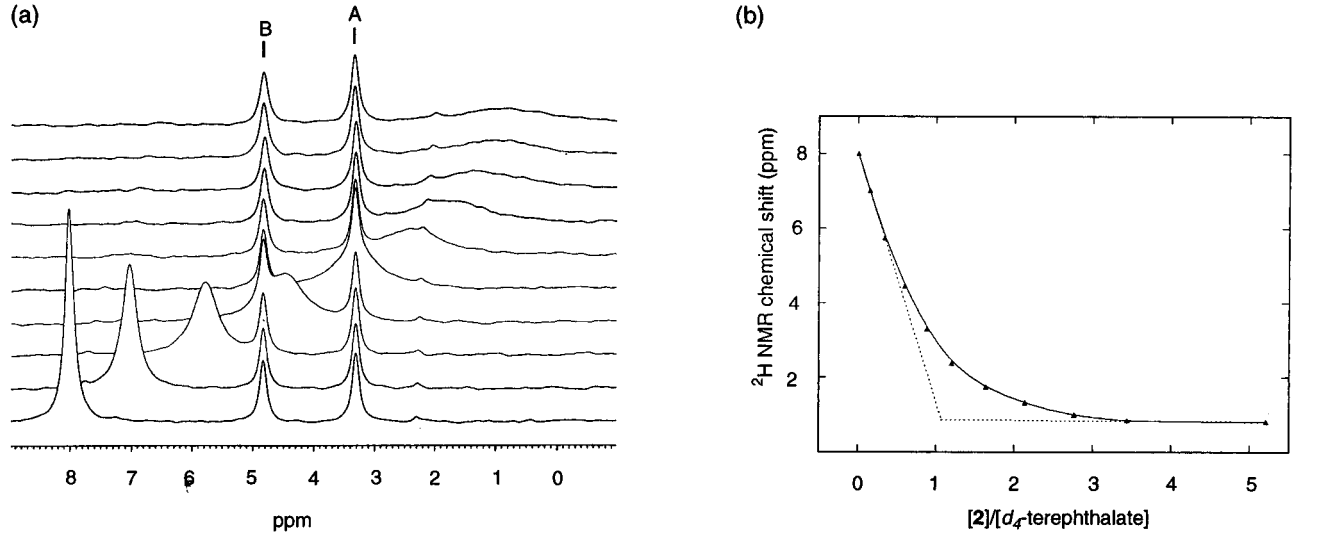


Figure 1. (a) Stacked plot obtained from an ^{2}H NMR titration involving the bis-trimethylammonium salt of terephthalate-d_4 with the bis-HCl salt of dimer **2**. The signal corresponding to the aromatic deuterium atoms of the terephthalate dianion was seen to undergo an ~7.18 ppm upfield shift (from 8.00 to 0.82 ppm) upon addition of ~5.2 equiv of **2**. The signals of the solvent, nondeuterated methanol, are labeled A and B. (b) Molar ratio plot derived from this titration.

protonated dimer **2** in methanol or dichloromethane causes the Soret-like band with the higher wavelength maximum to increase in intensity at the expense of the lower wavelength one. This kind of behavior is consistent with a binding model wherein the dicarboxylate substrate binds *inside* the sapphyrin "sandwich" (giving rise to species **c**, Scheme 1).[24]

Since the visible spectra of the various species involved are different, the above observations provided a basis for quantitative assessments of binding constants. Specifically, by following the increase in relative absorbance at ~450 nm as a function of substrate-to-receptor ratio, it was possible to determine association constants for the formation of 1:1 complexes between receptor **2** and oxalate, malonate, isophthalate, 5-nitroisophthalate, and nitroterephthalate anions. Here, the relevant values, summarized in Table 2, were determined using the Benesi−Hildebrand method.[19,25]

NMR spectroscopic "titrations", carried out in CD_3OD, provided another means of monitoring the interactions between receptor **2** and putative dicarboxylate substrates. Here, the concentrations of the chosen dicarboxylate anions were kept constant while the concentration of the receptor **2** was gradually increased. The resulting changes in the chemical shifts of the dicarboxylate protons were recorded as a function of receptor-to-substrate ratio. These results were then used to deduce both the binding stoichiometry and the association constants via nonlinear regression analyses and molar ratio plots (Table 2).[12,19]

In all cases, dicarboxylate proton signals were seen to shift upfield as the result of chelation by the sapphyrin dimer. Often, however, the magnitude of the shifts involved was so large that chemical shift values near the point of "saturation" (*i.e.*, complete complex formation) could not be recorded accurately due to overlap with signals arising from various aliphatic substituents on the sapphyrin periphery. In these instances, either visible spectroscopic titrations were employed (see above), or *deuterated* substrates were used. This latter approach allowed the binding processes to be followed by ^{2}H NMR. Here, nondeuterated methanol was used as the solvent, and the chemical shifts of the deuterium-enriched dicarboxylate substrates were monitored as a function of increased receptor concentration. As a general rule, substantial shifts were recorded (*c.f.*, *e.g.*, Figure 1). By contrast, much smaller shifts were seen (generally less than 0.4 ppm) when monocarboxylate substrates were allowed to react with monomeric sapphyrins. This contrasting behavior was considered as yet further evidence that in the case of **2** the dicarboxylate substrates are interacting with the sapphyrin dimer *via* the formation of a complex in which these bound dicarboxylate dianions are "sandwiched" between the two protonated sapphyrin macrocycles (as shown in Scheme 1).

Once dicarboxylate binding was unambiguously proved as taking place in solution, we became curious as to whether these same sapphyrin dimer−dicarboxylate chelation effects could provide the basis for effecting through liquid membranes transport of dicarboxylate anions. Using a standard Pressman-

Table 2. Binding Constants Measured for Receptor **2** and Various Dicarboxylate Anions in Methanol

substrate[a]	K_a (M^{-1})[b]	selectivity[c]
phthalate	$K_1 = 310$;[d] $K_2 = 280$[d]	1.2
isophthalate	2400,[e] 2500[f]	9.4
5-nitroisophthalate	5300[f]	20.4
terephthalate	4600[e]	17.7
nitroterephthalate	9100[f]	35.0
benzoate	K_1, $K_2 = 1380$[d] K_1, $K_2 = 1530$[e]	5.6
oxalate	260[f]	−
malonate	450[f]	1.7

[a] To prevent unwanted proton transfer processes and to attain desirable solubility, receptor **2** was used as its bis-HCl salt, and the dicarboxylic substrates were used as their bis-trimethylammonium salts (see Experimental Section). [b] Values of binding constants in selected cases were measured by two or more methods. In these cases good internal agreement was observed (estimated errors are ±15%). Complexes of 1:1 stoichiometry were formed unless noted otherwise. [c] Compared to the worst bound substrate, oxalate. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by ^{2}H NMR spectroscopy. [f] Determined by visible spectroscopy.

(23) (a) Valdes-Aguilera, O.; Neckers, D. C. *Acc. Chem. Res.* **1989**, *22*, 171−177. (b) Ojadi, E.; Selzer, R.; Linschitz, H. *J. Am. Chem. Soc.* **1985**, *107*, 7784−7785.

(24) These changes result strictly from anion chelation by the dimer **2** and not from the protonation of its constituent sapphyrin macrocycles. This is because the substrates are studied in the form of their dicarboxylate salts, rather than as the free acids. They therefore lack "free" protons that could be transferred to the sapphyrin.

(25) The linear character of these plots is consistent with the proposed 1:1 stoichiometry. This contention is further supported by the fact that both the low and high energy Soret bands of dimer **2** obey Beer's law over the course of the concentration regime used for the binding studies. The equilibria followed this way are thus strictly bimolecular in nature.

Table 3. Rates of Nitrobenzene Dicarboxylate Transport

	k_T (10^{-10} mol cm^{-2} h^{-1})		
carrier	4-nitrophthalate	5-nitroisophthalate	nitroterephthalate
1a	0.96	0.71	0.83
2	2.19	2.93	6.80

type, model U-tube membrane system,[18] we found that under neutral conditions dimer **2**, but not the corresponding monomeric control **1a**, acts as an efficient carrier for a range of isomeric dicarboxylates derived from benzene and nitrobenzene (Table 3). In direct competition experiments, the order of anion transport rates was found to be as follows: nitroterephthalate (fastest) > 5-nitroisophthalate > 4-nitrophthalate. Thus, in addition to proving a level of anion-based selectivity, these results were also found to correlate with the order of the relative binding strength observed in methanol solution (*vide supra*).

Taken together, the U-tube transport and solution-phase binding studies provide support for the contention that the sapphyrin dimer **2**, when protonated, acts as both an excellent and inherently selective receptor for dicarboxylate anions while showing little affinity for aliphatic monocarboxylate substrates (*e.g.*, $K_a \leq 20$ M^{-1} for trifluoroacetate). These same studies also serve to show that system **2** displays a preference for linear over bent substrates and for aromatic anions over aliphatic ones. Such findings can be rationalized in terms of the extra, stabilizing effects that would derive from either $\pi-\pi$ attractions, or edge-bound C—H···N or C—H···π hydrogen-bonding interactions involving the aromatic surfaces of the sapphyrin receptor and benzene-containing substrates.[26,27] The presence of these interactions in solution was confirmed via NMR analyses. Specifically, the meso-like methine signals of sapphyrin were seen to shift upfield when aromatic (but not aliphatic) substrates were titrated in.

In addition to the solution-phase work, solid-state evidence was obtained that served to confirm that additional, noncovalent interactions could be playing a role in stabilizing complexes formed from protonated sapphyrins and aromatic carboxylate substrates. In particular, a single-crystal structure of a 1:1 inner-sphere, neutral complex formed between benzoate anion and monoprotonated sapphyrin **1a** was obtained. In this structure a single, close, presumably hydrogen-bonding C—H···N contact is observed (H···N distance: 2.38 Å; *c.f.*, Figure 2).[27c,d]

Synthesis and Binding Studies of Chiral Sapphyrin Dimers 3, 4, and 7. Encouraged by the successful results obtained with system **2**, we sought to prepare other sapphyrin-based dimeric receptors that were based on the use of more rigid, chiral spacers. Such systems, it was hoped, would allow for both more selective dianion recognition and enantioselective chiral dicarboxylate anion binding.

In pursuit of the above goal, we again decided to make use of diamino-functionalized spacer units. This is because (*i*) various chiral diamines are commercially available and are easily converted into their corresponding bisamides using generalized amide coupling procedures, and (*ii*) multiple amide functionalities, once incorporated into receptor structures, provide an additional source of both hydrogen-bonding donor (*i.e.*, NH) and acceptor (*i.e.*, C═O) functionality that could complement the "main" sapphyrin-to-carboxylate binding motif.[28]

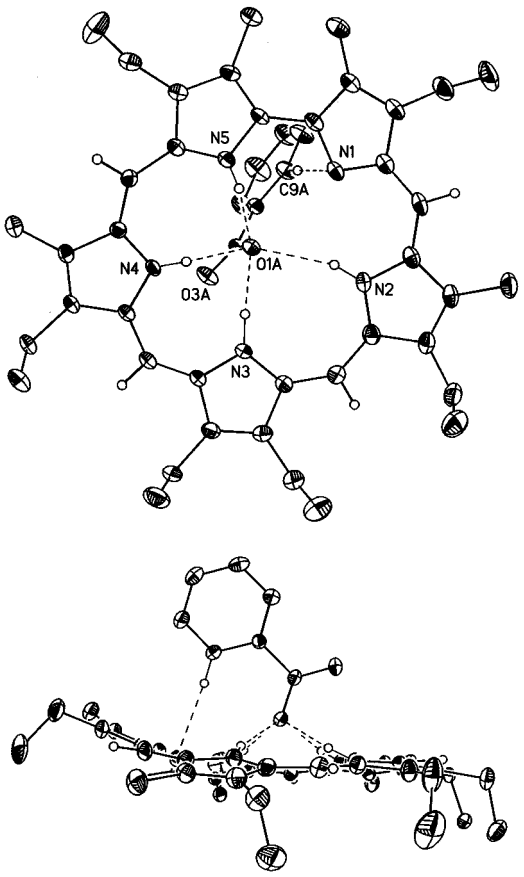


Figure 2. Two views of the molecular structure of the [**1a**·H]$^+$·$C_6H_5CO_2^-$ complex showing the atom-labeling scheme. Some important distances (Å) and angles (°) are as follows: N2—H2N···O1A; N···O 3.123(6) Å, H···O 2.27(6) Å, N—H···O 161(5)°; N3—H3N···O1A; N···O 2.777(6) Å, H···O 1.82(6) Å, N—H···O 173(5)°; N4—H4N···O1A; N···O 2.867(5) Å, H···O 1.97(4) Å, N—H···O 172(4)°; N5—H5N···O1A; N···O 2.929(5) Å, H···O 2.02(5) Å, N—H···O 167-(5)°. The unprotonated pyrrole is pointed away from the benzoate with a N1···O1A distance of 3.256(5) Å. O1A is 1.195 Å from the plane through the five pyrrolic nitrogens and displaced 0.373 Å from the center of these nitrogen atoms. Solvent molecule (THF, cocrystallized in the lattice) is omitted for clarity. Thermal ellipsoids are scaled to the 30% probability level.

With the above considerations in mind, we selected two different chiral diamines, namely, (*S*)-2,2′-diamino-1,1′-binaphthalene and (1*S*,2*S*)-1,2-diaminocyclohexane, to serve as stereogenic linkers in our systems.[29] Using these precursors, two open-chain chiral sapphyrin dimers, **3** and **4**, were synthesized in good yield from the sapphyrin monoacid **1b** using a 1,3-diisopropylcarbodiimide-mediated coupling procedure (Scheme 2). In a similar way, the cyclic sapphyrin dimer **7** was prepared in 46% yield from the sapphyrin bisacid **1c** and mono-*t*-Boc-

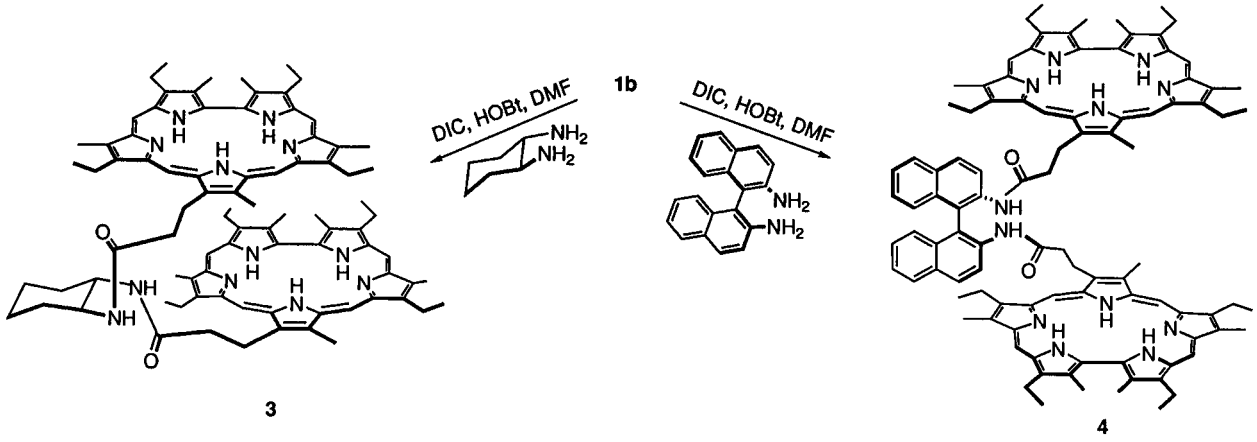
(26) This extra stabilization presumably also leads to the higher binding affinities observed for the aromatic monocarboxylate controls (Table 2).

(27) $\pi-\pi$ interactions featuring face-to-face orientations between aromatic surfaces as well as edge-to-face C—H···π attractions have been shown to stabilize various supramolecular complexes. See: (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534. (b) Hunter, C. A. *Chem. Soc. Rev.* **1994**, 101−109. The C—H···N binding motif, although not as common, has also been observed in certain noncovalent supramolecular aggregates. See: (c) Berkovitch-Yellin, Z.; Leiserowitz, L. *Acta Crystallogr.* **1984**, *B40*, 159−165. (d) Allen, F. H.; Goud, B. S.; Hoy, V. J.; Howard, J. A. K.; Desiraju, G. R. *J Chem. Soc., Chem. Commun.* **1994**, 2729−2730.

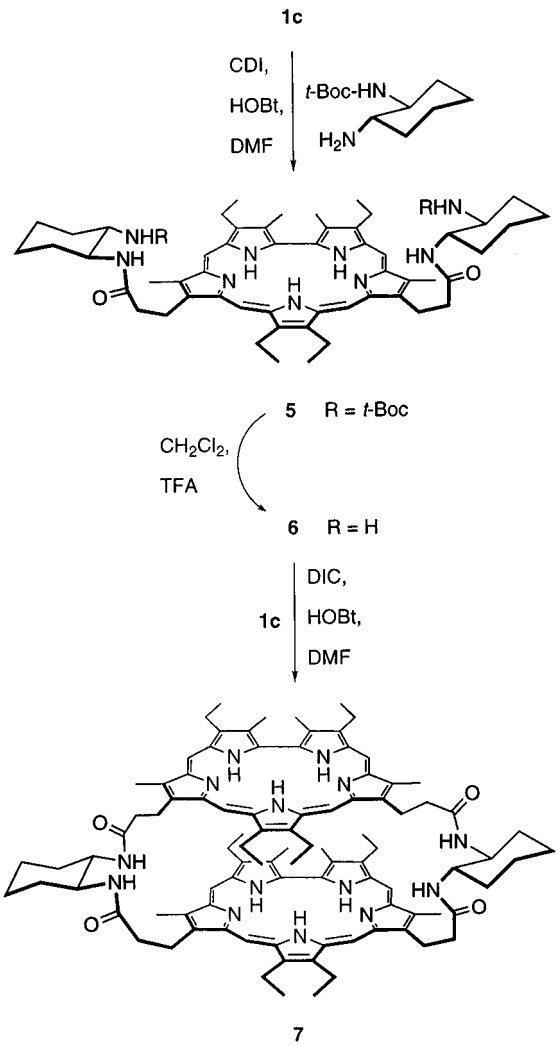
(28) The use of peptidic moieties for the construction of enantioselective receptors is borrowed from nature. A desire to understand the molecular recognition features of proteins has inspired development of abiotic receptors containing amide moieties. Groups that champion this approach have been able to achieve remarkable enantioselectivities in the binding of amino acids and short peptidic substrates. (a) For a short review, see: Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 848−850. See also: (b) Yoon, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 823−824. (c) Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111−5112. See also ref 11d.

(29) Binaphthalene and diaminocyclohexane spacers were previously used in chiral receptors for dicarboxylic acids (ref 11c) and short peptides (ref 28b).

Scheme 2. Synthesis of the Chiral Sapphyrin Dimers **3** and **4**



Scheme 3. Synthesis of the Cyclic Chiral Sapphyrin Dimer **7**



protected(1*S*,2*S*)-1,2-diaminocyclohexane (Scheme 3).[30] To the best of our knowledge, systems **3**, **4**, and **7** represent the first example of chiral dimers of "expanded" porphyrins.[31]

Following their synthesis, the new molecules **3**, **4**, and **7** were tested as receptors for chiral dicarboxylate dianions. Here, we chose protected (*N*-carbobenzyloxy, *N*-Cbz) aspartate and glutamate as prospective substrates. However, at present, much of the underlying recognition and transport biology for aspartate and glutamate is still in the process of being elucidated.[4,32] Therefore, there remains a clear need to create abiotic, model receptors for these species.[33]

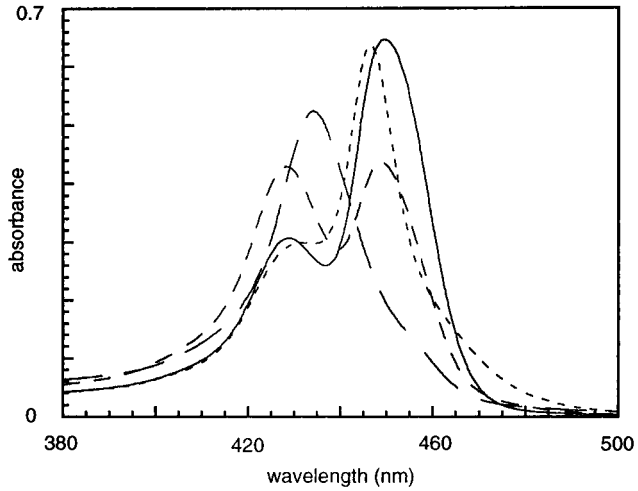


Figure 3. Overlay plot of visible spectra of the sapphyrin dimers **2**−**4** and **7** recorded at 2×10^{-6} M concentrated in CH_2Cl_2 containing 5% CH_3OH. **2** (- - -), **3** (− − −), **4** (—), **7** (— —).

In terms of characterization, systems **3** and **4** display visible spectroscopic characteristics similar to those of dimer **2**. For instance, these newer dimers display two Soret maxima in both dichloromethane and methanol (Figure 3). This corresponds to the two limiting conformations these materials can assume in solution, namely intramolecular "pseudo stacked" and completely open (see Scheme 1). As may be expected intuitively, the polar solvent methanol stabilizes the self-stacked

(30) No traces of larger macrocycles were found in the reaction mixture.

(31) For recent reports on the syntheses and applications of covalently-linked chiral porphyrin dimers, see: (a) Ema, T.; Nemugaki, S.; Tsuboi, S.; Utaka, M. *Tetrahedron Lett.* **1995**, *36*, 5905−5908 and references therein. (b) Crossley, M. J.; Mackay, L. G.; Try, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1925−1927. For reviews about dimeric porphyrins, see: (a) Collman, J. P.; Wagenknecht, P. S.; Hutchison, J. E. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1537−1554. (b) Wasielewski, M. *Chem. Rev.* **1992**, *92*, 435−461.

(32) For reviews, see: (a) Kilberg, M. S., Häussinger, D., Eds. *Mammalian Amino Acid Transport. Mechanisms and Control*; Plenum Press: New York, 1992. (b) Kilberg, M. S.; Stevens, B. R.; Novak, D. A. *Annu. Rev. Nutr.* **1993**, *13*, 137−165. (c) Ring, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 345−356. See also ref 4.

(33) Reports of binding and/or transport of aspartic and glutamic acids and their derivatives in either neutral or anionic forms are relatively scarce: (a) Inokuma, S.; Sakai, S.; Yamamoto, T.; Nishimura, J. *J. Membr. Sci.* **1994**, *97*, 175−183. (b) Flack, S. S.; Chaumette, J.-L.; Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc., Chem. Commun.* **1993**, 399−401. See also refs 5e, 6a, and 7c. Enantioselective binding of neutral aspartic and glutamic acids and their derivatives was reported by Diederich: ref 11b,d.

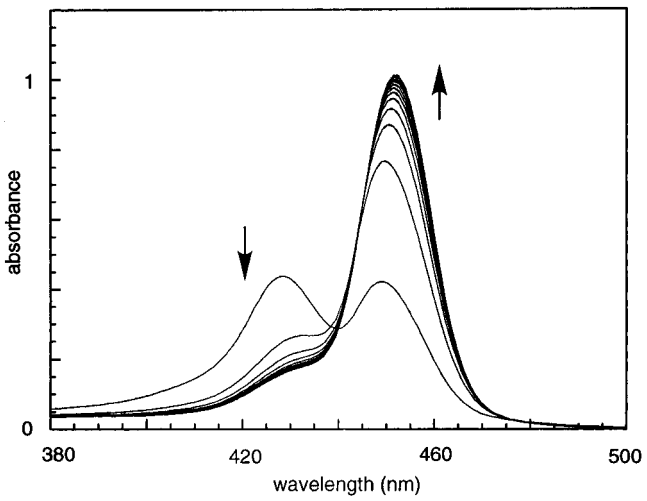


Figure 4.

form of the dimers **3** and **4**, whereas open conformations predominate in the less polar medium dichloromethane. Interestingly, the cyclic dimer **7** exists entirely in its self-stacked form regardless of the solvent (Figure 3).

In addition to undergoing processes of within-dimer "pseudo stacking", at higher concentrations, compounds **3**, **4**, and **7** are also subject to *bona fide* aggregation. Unfortunately, the relevant concentration regimes just happen to correspond to those needed to carry out ^{1}H NMR spectroscopic binding titrations. This aggregation effect, and the observed overlap between the proton signals of the dimeric sapphyrin receptors and dicarboxylate substrates, led us to use visible spectroscopic methods when seeking to determine the affinity constants associated with dicarboxylate binding (see Experimental Section).

In methanol, the strength of *N*-Cbz-aspartate and -glutamate complexation appeared to be quite low (generally, $K_a \leq 200$ M^{-1}). This result is consistent with the previous observations using dimer **2** and aliphatic dicarboxylates (see Table 2). As may be expected intuitively, switching to a less polar mixed-solvent system (dichloromethane containing 5% methanol)[34] resulted in a significant increase in the binding affinity. The findings, tabulated in Table 4, indicate that the second generation sapphyrin−sapphyrin chiral dimers **3**, **4**, and **7** (*i*) form strong complexes with *N*-Cbz-aspartate and -glutamate in these solvent mixtures and (*ii*) display excellent selectivity towards substrates that differ in length by only one carbon atom.

Elaborating on point ii above, it was found that the open-chain receptors **3** and **4** (as well as congener **2**) bind glutamate and aspartate anions with high affinity (3.9×10^4 $M^{-1} \leq K_a \leq 3.2 \times 10^5$ M^{-1}) and show a selectivity for the former substrate. The enantioselectivity of the binaphthalene-containing receptor **4** is higher than that of the diaminocyclohexane-derived dimer **3**.[35] The cyclic dimer **7**, on the other hand, displays a lower affinity for these anionic substrates. This system, however, shows excellent chiral discrimination (*i.e.*, $-\Delta(\Delta G°) = 0.84$ kcal M^{-1} for a pair of glutamate enantiomers). This result presumably reflects the fact that for a cyclic, more preorganized system, the importance of a good size and shape match (between the receptor and the stereogenic substrate) is emphasized. In any event, this system (dimer **7**) stands, to the best of our knowledge, as being the first receptor capable of achieving the selective recognition of chiral dianionic dicarboxylates. A range of uses for this and the other dimeric sapphyrin systems are thus currently being explored.

(34) It proved necessary to use this solvent mixture so as to enforce the concurrent solubility of the receptors, substrates, and complexes under consideration.

Table 4. Dicarboxylate-Binding Properties of Sapphyrin Dimers

receptor[a]	substrate[b]	K_a (M^{-1})[c]	selectivity[d]	$-\Delta G°$ (kcal M^{-1})[e]	$-\Delta(\Delta G°)$ (kcal M^{-1})[f]
2	N-Cbz-L-Asp	159 100	41.8	6.97	na[g]
2	N-Cbz-L-Glu	224 000	58.9	7.17	na[g]
3	N-Cbz-L-Asp	45 000	11.8	6.24	0.09
3	N-Cbz-D-Asp	38 900	10.2	6.15	
3	N-Cbz-L-Glu	112 700	29.7	6.77	
3	N-Cbz-D-Glu	119 900	31.5	6.81	0.04
4	N-Cbz-L-Asp	20 600	5.4	5.78	
4	N-Cbz-D-Asp	43 500	11.4	6.22	0.44
4	N-Cbz-L-Glu	324 500	85.4	7.39	0.24
4	N-Cbz-D-Glu	217 100	57.1	7.15	
7	N-Cbz-L-Asp	16 700	4.4	5.66	0.32
7	N-Cbz-D-Asp	9 700	2.6	5.34	
7	N-Cbz-L-Glu	3 800	−	4.80	
7	N-Cbz-D-Glu	16 200	4.3	5.64	0.84

[a] All receptors were used as their bis-HCl salts (see Experimental Section). In the course of the titrations (carried out in dichloromethane solutions containing 5% methanol) their concentrations were kept constant at 2×10^{-6} M. [b] Protected amino acid substrates were used as their bis-trimethylammonium salts (see Experimental Section). Increasing amounts of these substrates (as solutions of 10^{-2} M concentrated in CH_2Cl_2 with 5% CH_3OH) were titrated into solutions of the receptor in question while the change in the absorbance at 450 nm was measured. [c] The binding constants were determined by Benesi−Hildebrand data treatment (estimated errors are ±15%). In all cases, complexes of 1:1 stoichiometry were formed, as judged by the linearity of the double-reciprocal plots and by the fact that isosbestic points were observed over the whole range of binding isotherms. [d] Compared to the lowest binding constant (receptor **7**/N-Cbz-L-glutamate). [e] Binding free energies, determined at 293 K. [f] Enantioselectivity is defined as the difference in binding free energies between the two enantiomeric forms of a given dicarboxylate anion being tested with the same receptor. [g] Not applicable; receptor **2** is achiral.

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Supporting Information Available: Full X-ray diffraction data for the $[\mathbf{1a}\cdot H]^+\cdot C_6H_5CO_2^-$ complex (21 pages). See any current masthead page for ordering and Internet access instructions.

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(35) In all cases (using chiral receptors **3**, **4**, and **7**), the weaker bound dicarboxylates were also the ones that were found to allow for a higher level of enantioselective discrimination between their respective enantiomer pairs.