A Covalently Linked Sapphyrin Dimer. A New Receptor for Dicarboxylate Anions

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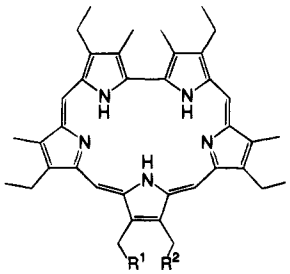
Received November 30, 1994

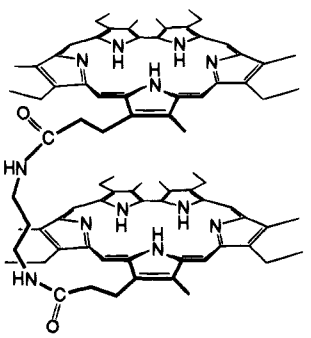
While the chemistry of dimeric porphyrins is now well developed,[1] the corresponding chemistry of expanded porphyrin dimers is all but unknown. Indeed, to the best of our knowledge, no such systems exist.[2] These latter, however, might be of potential interest in a range of applications, including anion recognition, that are not accessible using simple porphyrin derivatives. Recently, we reported that nucleic acid base ("nucleobase") substituted derivatives of sapphyrin (cf. parent structure **1**), a prototypical expanded porphyrin,[3] act as carriers for the through-model-membrane transport of nucleotide monophosphates at neutral pH[4] and that sapphyrins, either free in solution[5] or bound to solid supports,[6] show high affinities for various oligonucleotides, including DNA. In this communication we report the synthesis of a first generation sapphyrin–sapphyrin dimer (**2**) that, unlike the control monomer **1a**, acts as an effective receptor for dicarboxylate anions.



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

1b. $R^1=H$; $R^2=CH_2CO_2H$

1c. $R^1=H$; $R^2=CH_2COCl$



2

Di- and tricarboxylates are critical components of numerous metabolic processes[7] including, for instance, the citric acid and glyoxylate cycles.[7a] They also play an important role in the generation of high-energy phosphate bonds[7b] and in the biosynthesis of important intermediates.[7c] Recently, several elegant receptor systems for the selective binding of dicarboxylate anions have been reported.[8–13] These have been based on the use of two guanidinium (or guanidinium-like) units,[8] redox-responsive ditopic bis(cobaltocenium) calix[4]arene receptors,[9] ditopic polyammonium macrocycles,[10] resorcinol–aldehyde cyclotetramer multidentate hosts,[11] and bis-urea and bis-thiourea receptors,[12] as well as the clever use of amidopyridine hydrogen-bonding subunits within well-defined structural arrays.[13] In the present instance (i.e., **2**), two protonated sapphyrins serve as the key carboxylate-binding "building blocks" while a flexible diaminopropane "spacer" serves as the all-important macrocycle-to-macrocycle linking chain. This choice provides a system that rivals the best of the extant systems in terms of absolute binding efficacy in highly polar solvents (e.g., methanol) while displaying a very different kind of inherent substrate binding selectivity..

The synthesis of receptor **2** is straightforward. It involves mixing 1,3-diaminopropane with 2 equivs of an activated form of the sapphyrin mono acid **1b**. In general, the best yields (≥70%) were obtained when the sapphyrin acid chloride **1c** was used; however, the corresponding acylimidazole, mixed anhydrides, and activated esters could also be used.[14]

Analysis of the visible spectra revealed that compound **2** has two distinct conformations in both methanol and dichloromethane. In particular, two Soret-like maxima were observed at λ_{max} = 422 and 441 nm and 426 and 450 nm in methanol and dichloromethane, respectively. On the basis of prior work,[15] these could be assigned to closed-up, *endo*-like (i.e., self-stacked but still monomeric) and extended, *exo*-like forms, respectively.[16] Efficient opening up of the *endo*-like form also was observed in the presence of dicarboxylic acids, at least as judged by the spectroscopic changes. Such an opening up, it was realized, could be the result of either general protonation phenomena or specific anion binding effects. Only the latter, however, would be of interest in the context of the present study. Thus, efforts were made to distinguish these two limiting possibilities.

As an initial "screening study", mixtures of sapphyrin dimer **2** and several representative dicarboxylate anions, such as oxalate, 4-nitrophthalate, 5-nitroisophthalate, and nitroterephthalate, were made up in methanol and subjected to high-resolution FAB mass spectrometric (HR FAB MS) analysis. The results obtained (supplementary Table 1), provide a clear indication that *bona fide* supramolecular complexes are being produced and sustained under the matrix desorption/gas phase conditions of these MS experiments.

More definitive proof of binding came from transport experiments. Here, in analogy to earlier work involving phosphate anion transport,[4] a standard U-tube model membrane system was used. It was found that at neutral pH dimer **2** acts as an efficient carrier for a range of dicarboxylates, including various isomeric ones derived from nitrobenzene (Table 1).[17] Further, in direct competition experiments (made using **2**), nitroterephthalate dianion was found to be transported 3 times faster than 4-nitrophthalate dianion, suggesting a level of anion-based

(1) For reviews, see: (a) Wasielewski, M. *Chem. Rev.* **1992**, *92*, 435. (b) Collman, J. P.; Wagenknecht, P. S.; Hutchison, J. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1537.

(2) The synthesis of a cofacial porphyrin–sapphyrin pseudodimer was recently reported: Sessler, J. L.; Brucker, E. A.; Král, V.; Harriman, A. *Supramol. Chem.* **1994**, *4*, 35.

(3) Sessler, J. L.; Burrell, A. K. *Top. Curr. Chem.* **1991**, *161*, 177.

(4) (a) Král, V.; Sessler, J. L.; Furuta, H. *J. Am. Chem. Soc.* **1992**, *114*, 8704. (b) Sessler, J. L.; Furuta, H.; Král, V. *Supramol. Chem.* **1993**, *1*, 209.

(5) Iverson, B. L.; Shreder, K.; Král, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 11022.

(6) Iverson, B. L.; Thomas, R. E.; Král, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 2663.

(7) (a) Stryer, L. *Biochemistry*, 3rd ed.; Freeman and Co.: New York, 1988; pp 373–394; (b) p 376; (c) pp 575–625.

(8) (a) Dietrich, B.; Fyles, D. L.; Fyles, T. M.; Lehn, J.-M. *Helv. Chim. Acta* **1979**, *62*, 2763. (b) Schiessl, P.; Schmidtchen, F. P. *Tetrahedron Lett.* **1993**, *34*, 2449.

(9) Beer, P. D.; Drew, M. G. B.; Hazlewood, C.; Hesek, D.; Hodacova, J.; Strokes, S. E.; *J. Chem. Soc., Chem. Commun.* **1993**, 229.

(10) (a) Hosseini, M. W.; Lehn, J.-M. *J. Am. Chem. Soc.* **1982**, *104*, 3525. (b) Kimura, E.; Sakonaka, A.; Yatsunami, T.; Kodama, M. *J. Am. Chem. Soc.* **1981**, *103*, 3041. (c) Kimura, E.; Kuramoto, Y.; Koike, T.; Fujioka, H.; Kodama, M. *J. Org. Chem.* **1990**, *55*, 42. (d) Kataoka, M.; Naganawa, R.; Odashima K.; Umezawa, Y.; Kimura, E.; Koike, T. *Anal. Lett.* **1989**, *22*, 1089.

(11) Tanaka, Y.; Kato, Y.; Aoyama, Y. *J. Am. Chem. Soc.* **1990**, *112*, 2807.

(12) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369.

(13) (a) Owens, L.; Thilgen, C.; Diederich, F.; Knobler, C. B. *Helv. Chim. Acta* **1993**, *76*, 2757 and references therein. (b) Geib, S. J.; Vicent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119 and references therein. (c) Flack, S. S.; Chaumette, J.-L.; Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc., Chem. Commun.* **1993**, 399.

(14) Satisfactory spectroscopic and analytical data were obtained for **2**: 1,3-bis[[[2-(3,8,17,22-tetraethyl-2,7,13,18,23-pentamethylsapphyrin-12-yl)-ethyl]carbonyl]amino]propane; see supplementary material.

(15) (a) Maiya, B. G.; Cyr, M.; Harriman, A.; Sessler, J. L. *J. Phys. Chem.* **1990**, *94*, 3597. (b) Judy, M. M.; Matthews, J. L.; Newman, J. T.; Skiles, H. L.; Boriack, R. L.; Sessler, J. L.; Cyr, M.; Mayia, B. G.; Nichol, S. T. *Photochem. Photobiol.* **1991**, *53*, 101.

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Table 1. Initial Rates of Nitrobenzene Dicarboxylate Dianion Transport

carrier[a,b]	k_T[c] (10^{-10} mol/cm^2·h)		
	4-nitrophthalic acid	5-nitroisophthalic acid	nitroterephthalic acid
1a	0.96	0.71	0.83
2	2.19	2.93	6.80

[a] 0.1 mM in dichloromethane. [b] Aqueous(I): 10 mM in each of 4-nitrophthalic acid, 5-nitroisophthalic acid, and nitroterephthalic acid at pH 7.2 (adjusted by NaOH), aqueous(II): pH 7.0. [c] Transport experiments were performed as described in ref 4; see supplementary material.

Table 2. Binding Constants for Complex Formation Between Receptor **2** and Various Dicarboxylate Substrates (S) in Methanol at 293 K[a]

S	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]	5.6
	$K_1, K_2 = 1530$[e]	
oxalate	260[f]	1
malonate	450[f]	1.7

[a] Sapphyrin dimer **2** was used as its bis HCl salt, **2**·2HCl. Substrates (S) were used as their $(CH_3)_3N^+H$ salts in order to prevent proton transfer to **2**. Values of K_a in selected cases were measured by two or more methods, with complete internal agreement being found. [b] Complexes of 1:1 stoichiometry ($K_a = K_1$) were formed unless otherwise noted. [c] Relative to the worst bound substrate, oxalate. [d] Determined by ^{1}H NMR by titrating with receptor **2** while the concentration of the studied carboxylate ion was held constant at a value of 1−5 mM, depending on the measurement. [e] Determined by ^{2}H NMR by titrating with receptor **2** while the concentration of the carboxylate anion was held constant at a value of 1−5 mM, depending on the measurement. [f] Determined by visible spectroscopy by titrating in increasing amounts of the studied carboxylate anions (from 1×10^{-6} to 1×10^{-3} M) into solutions of receptor 2 (initial concentration between 1×10^{-6} and 5×10^{-6} M).

selectivity. On the other hand, none of the isomeric nitrophthalates were found to be transported effectively by the monomeric control system, **1a**.

Quantitative assessments of dicarboxylate binding efficacy in methanol were made using standard spectroscopic techniques. In general, ^{1}H NMR methods were employed with the observed changes in the ^{1}H NMR chemical shifts of the aromatic protons of the carboxyl-containing substrate (kept constant in the millimoles/liter concentration range) being monitored as a function of increased receptor concentration. In some instances, well-resolved shifts could not be observed in the appropriate ^{1}H NMR spectra. Here, either visible spectroscopic titration procedures were used or deuterated substrates were employed such that the binding process could be followed by ^{2}H NMR.[18] Selected results are given in Table 2.

The results contained in Table 2 confirm what was concluded from the transport studies, namely, that system **2** is both an *excellent* and *inherently selective* receptor for dicarboxylate anions. System **2**, for instance, shows little affinity for monocarboxylate-derived substrates ($K_a \leq 20$ M^{-1} for trifluoroacetate)[19] while showing affinities for certain dicarboxylates (e.g., $K_a = 9100$ M^{-1} for nitroterephthalate dianion) that rival those of the best receptor systems known.[20] Interestingly, system **2** also displays a preference for linear over bent substrates and aromatic over aliphatic substrates that is remarkable given the inherently floppy nature of this receptor.

Taken together, these data lead us to suggest that this receptor and its dicarboxylate substrates interact *via* the formation of a well-defined supramolecular complex such as that shown in Figure 1. These same data lead us to suggest that analogs of the simple dimer **2**, containing different tethering groups and/or a higher degree of preorganization in their design, might act as yet-more-selective receptors for various chosen dicarboxylate-type substrates.

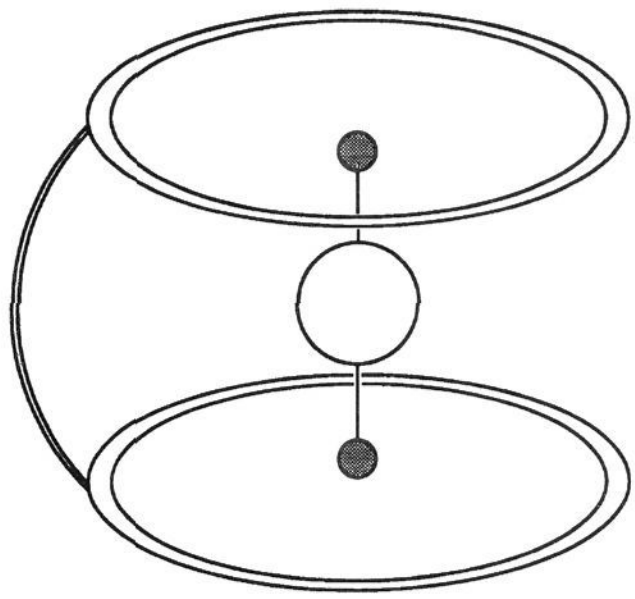

Figure 1. Schematic representation of the proposed supramolecular complex formed between receptor **2** and dicarboxylate substrates.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. AI 33577) and by Pharmacyclics, Inc. We thank Steve Sorey for his assistance in carrying out the NMR analyses.

Supplementary Material Available: Synthetic experimental, binding, and transport details and mass spectrometric data (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(16) Nonaqueous solutions of control monomers **1a** and **1b** display one Soret maximum at $\lambda_{max} \approx 450$ nm at concentrations $\leq 10^{-3}$ M.

(17) Nonnitrated phthalate anions are also transported. However, the corresponding nitrated analogs proved easier to detect (by HPLC) and were hence used for quantitative work.

(18) Nonlinear regression analyses were used to deduce the association constants and the stoichiometry of binding (cf. supplementary material); Benesi−Hildebrand plots (for 1:1 complexes) and the Whitlock algorithm (for 1:1 and 1:2 complexation processes) were employed. Receptor-to-substrate stoichiometries were determined from molar ratio plots (as opposed to simple curve-fitting procedures; cf. supplementary material). For the majority of the ^{1}H and ^{2}H NMR titrations, the concentrations of the studied dicarboxylate anions were kept constant in the 1−5 mM range while the concentration of receptor **2** was increased from 0.1 to 25 mM. However, in some select cases, "reverse titrations" were also carried out wherein the receptor concentration was kept constant and the concentration of the carboxylate substrate increased. Such reverse titrations were also employed in the case of the visible spectral titrations. Here, the initial concentrations of **2** were generally chosen to be in the 1−5 μM range and then kept constant while increasing quantities of the carboxylate substrates were added over the 0.1−500 μM range. (a) Connors, K. A. *Binding Constants*; John Wiley & Sons: New York, 1987. (b) Lenkinski, G. A.; Elgavish, G. A.; Reuben, J. *J. Magn. Reson.* **1978**, *32*, 367. (c) Friedrichsen, B. P.; Powell, D. R.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990,** *112,* 8931.

(19) Benzoate anion, when used as an aromatic monocarboxylate control, produced a larger value of K_a (1460 M^{-1}) than did typical aliphatic monocarboxylates ($K_a \leq 50$ M^{-1}); this higher binding affinity is rationalized in terms of π-π stacking effects. Evidence for $\pi-\pi$ stacking was obtained from ^{1}H NMR studies. When sapphyrin **2** (as its TFA salt) was titrated with the triethylammonium salt of benzoic acid-d_5, upfield shifts in the signals corresponding to the sapphyrin-derived methine, methyl and ethyl protons were observed. For instance, addition of 10 molar equivalents of perdeuterated benzoate anion caused the two *meso*-like methine signals to shift to 11.12 and 11.27 ppm, respectively (from initial values of 11.35 and 11.42) while inducing upfield shifts in the exocyclic CH_3, CH_2CH_3, and CH_2CH_3 signals of roughly 0.08, 0.10, and 0.17 ppm, respectively. On the other hand, as expected, such upfield shifts could not be induced by adding similar or greater molar quantities of various aliphatic substrates to receptor **2**.

(20) See, for example, the guanidinium-based receptor recently reported by the Schmidtchen group;[8b] it shows binding constants that are of the same order of magnitude (in methanol) as those of **2**. However, the selectivity is entirely different: Malonate and 5-nitroisophthalate are the best-bound substrates.