Neutral Substrate Complexation by an "Expanded Porphyrin"

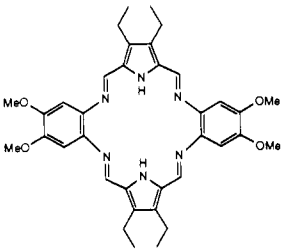
Jonathan L. Sessler,* Tarak D. Mody, and Vincent Lynch

Department of Chemistry and Biochemistry
University of Texas at Austin, Austin, Texas 78712

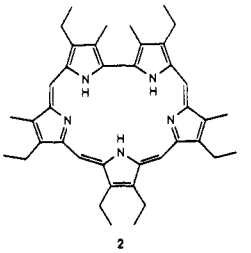
Received December 4, 1992

For the past several years, considerable effort has been devoted to the design of hosts for the complexation of neutral molecules.[1-3] In most instances, the host-guest interactions have depended upon the simultaneous and cooperative action of several noncovalent forces, such as hydrogen binding and π-π stacking.[1-3] However, short-chain alcohols have proved difficult to bind selectively with organic ligands, and few reports of the recognition of such substrates have appeared in the literature.[1,3] Recently, we have reported that certain "expanded porphyrins", e.g., **1**, complex large metal cations (i.e., trivalent lanthanides and UO_2^{2+}),[4] whereas others, such as sapphyrin (**2**)[5] and rubyrin (**3**),[6] bind inorganic and organic anions (i.e., F^-, Cl^-, $H_2PO_4^-$, $ROPO_3H^-$).[7] In this communication, we report the synthesis and structural characterization of a new expanded porphyrin, **4**.[8] Macrocycle **4** binds methanol in solution and in the solid state and provides the first example of neutral substrate complexation with an expanded porphyrin.[9]

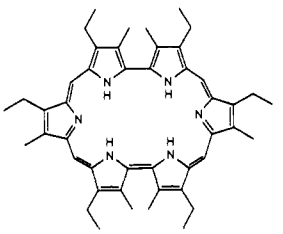
The diprotonated form of ligand **4** was synthesized by a nitric acid-catalyzed condensation[10] between 4,4'-diethyl-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole (**5**)[5c] and 1,2-diamino-4,5-dimethoxybenzene (**6**).[4b] With this acid "catalyst", the diprotonated nitrate



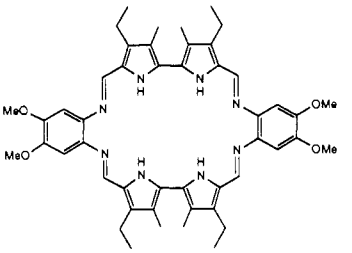
1



2



3



4

salt **4**·$(HNO_3)_2$ precipitates from the reaction mixture after several minutes in near quantitative yield. The neutral free-base form of ligand **4** is then obtained by dissolving this salt in CH_2Cl_2 and adding a few drops of triethylamine.[11] Following crystallization, induced by the addition of methanol, X-ray quality single crystals of **4** may be obtained by redissolving in CH_2Cl_2 and layering with methanol. Attempts to prepare ligand **4** using other acids were also made. In all cases, the yields of **4** were substantially lower than if HNO_3 were used.[12] This latter finding leads us to suggest, as an aside, that this particular [2 + 2] Schiff base condensation may be subject to a general "anion template" effect;[4a,13] such effects, although rare,[4a] are known in the literature.[14]

X-ray diffraction analysis[15] of the neutral entity **4**, obtained above, revealed a 2:1 complex of methanol (see Figure 1). Two unique 2:1 complexes are observed to lie around crystallographic inversion centers at 0, $^1/_2$, $^1/_2$ and at $^1/_2$, 0, $^1/_2$ referred to as 1 and 2, respectively. The methanol molecules lie above and below the macrocycle by 1.186(2) and 1.034(2) Å for the two unique molecules, respectively. The bipyrrole hydrogens are hydrogen bound to the methanol oxygens. The methanol hydrogen is also involved in a bifurcated hydrogen bond with the imine nitrogen atoms. The mode of complexation of the two methanols in **4** is thus reminiscent of that seen in the earlier-reported chloride complexes of diprotonated sapphyrin[7d] and diprotonated rubyrin,[6] and in the 2:1 complex of monobasic phenyl phosphate with diprotonated sapphyrin.[16] However, in the present instance, the expanded porphyrin is formally in its unprotonated (i.e., neutral), free-base form.

Evidence for hydrogen bonding in solution was obtained from IR spectroscopy. Whereas a ca. 4:1 solution of CH_3OH (0.62

(1) For an overview of neutral substrate recognition, see: Diederich, F. In *Cyclophanes*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1991; Chapters 2 and 5.

(2) For examples of neutral substrate complexation, see: (a) Chang, S.-K.; Engen, D. V.; Fan, E.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 7640-7645 and references therein. (b) Nijenhuis, W.; van Doorn, A. R.; Reichwein, A. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 3607-3608 and references therein. (c) Park, T. H.; Schroeder, J.; Rebek, J., Jr. *Tetrahedron* **1991**, *47*, 2507-2518. (d) Jeong, K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201-209. (e) Zimmerman, S.; Wu, W.; Zeng, Z. *J. Am. Chem. Soc.* **1991**, *113*, 196-201.

(3) For examples of alcohol recognition, see: (a) Méndez, L.; Singleton, R.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J.; Williams, M. K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 478-480 and references therein. (b) Allwood, B. L.; Méndez, L.; Stoddart, J. F.; Williams, D. J.; Williams, M. K. *J. Chem. Soc., Chem. Commun.* **1992**, 331-333. (c) Cochran, J. E.; Parrott, T. J.; Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1992**, *114*, 2269-2270. (d) Kikuchi, Y.; Kato, Y.; Tanaka, Y.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1349-1354.

(4) (a) Sessler, J. L.; Mody, T. D.; Lynch, V. *Inorg. Chem.* **1992**, *31*, 529-531. (b) Sessler, J. L.; Mody, T. D.; Ramasamy, R.; Sherry, A. D. *New J. Chem.* **1992**, *16*, 541-544. (c) Burrell, A. K.; Hemmi, G.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 4690-4692. (d) Burrell, A. K.; Cyr, M. J.; Lynch, V.; Sessler, J. L. *J. Chem. Soc., Chem. Commun.* **1991**, 1710-1713. (e) Sessler, J. L.; Hemmi, G.; Murai, T. *Inorg. Chem.* **1989**, *28*, 3390-3393.

(5) (a) Bauer, V. J.; Clive, D. L.; Dolphin, D.; Paine, J. B., III; Harris, F. L.; King, M. M.; Loder, H.; Wang, S.-W. C.; Woodward, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 6429-6436. (b) Sessler, J. L.; Cyr, M. J.; Lynch, V.; McGhee, E.; Ibers, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 2810-2813. (c) Sessler, J. L.; Cyr, M. J.; Burrell, A. K. *Synlett* **1991**, 127-133 and references therein.

(6) Sessler, J. L.; Morishima, T.; Lynch, V. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 977-980.

(7) (a) Sessler, J. L.; Mody, T. D.; Ford, D. A.; Lynch, V. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 452-455. (b) Král, V.; Sessler, J. L.; Furuta, H. *J. Am. Chem. Soc.* **1992**, *114*, 8704-8705. (c) Sessler, J. L.; Weghorn, S. J.; Morishima, T.; Rosingana, M.; Lynch, V.; Lee, V. *J. Am. Chem. Soc.* **1992**, *114*, 8306-8307. (d) Shionoya, M.; Furuta, H.; Lynch, V.; Harriman, A.; Sessler, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 5714-5722.

(8) The systematic name for macrocycle **4** is 13,17,31,36-tetraethyl-6,7,-24,25-tetramethoxy-14,17,32,35-tetramethyl-3,10,21,28,37,38,39,40-octaaza-heptacyclo[32.2.1.1^{2,15}.1^{16,19}.1^{30,33}.0^{4,9}.0^{22,27}]tetraconta-2,4,6,8,10,12,14,16,-18,20,22,24,26,28,30,32,34,36-octadecaene.

(9) An X-ray structure of an "accordion" porphyrin ligand, containing a water molecule hydrogen bound in the cavity, was presented by Prof. K. Bowman-James at the 203rd ACS National Meeting, San Francisco, CA (Inorg. Abstr. No. 543).

(10) Sessler, J. L.; Johnson, M. J.; Lynch, V. *J. Org. Chem.* **1987**, *52*, 4394-4397.

(11) Satisfactory spectroscopic and mass spectrometric data were obtained for macrocycle **4** and its dinitrate salt, **4**·$(HNO_3)_2$; cf. supplementary material.

(12) After workup, the following yields, reproducible to ±3%, were obtained for macrocycle **4**: HNO_3, 95%; H_2SO_4, 84%; $HClO_4$, 81%; trifluoroacetic acid, 74%; HCl, 47%; HI, 37%; HCl + tetrabutylammonium nitrate ($TBANO_3$) (1:3), >80%; HCl + $TBANO_3$ (2:3), 67%; and HNO_3 + $TBANO_3$ (2:3), >92%.

(13) The scope and generality of this proposed anion template effect is under investigation.

(14) (a) Yang, X.; Knobler, C. B.; Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1507-1508. (b) Yang, X.; Zheng, Z.; Knobler, C. B.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1993**, *115*, 193-195 and references therein.

(15) Crystallographic summary for **4**·$(CH_3OH)_2(CH_2Cl_2)_2$: triclinic, $P\bar{1}$ (No. 2), $Z = 2$ in a cell of dimensions $a = 8.4933(14)$ Å, $b = 18.484(4)$ Å, $c = 18.917(4)$ Å, $\alpha = 113.265(14)°$, $\beta = 91.419(14)°$, $\gamma = 90.784(15)°$, $V = 2726.6(8)$ Å^3, $\rho_{calc} = 1.27$ g cm^{-3} (193 K), $F(000) = 1104$. Data collected at 193 K on a Nicolet R3 diffractometer with graphite-monochromatized Mo Kα radiation ($\lambda = 0.7107$ Å) using the ω-scan technique out to 55° in 2θ at 3-6 deg min^{-1}; 12 263 unique reflections, 6243 with $F_o > 6\sigma(F_o)$. The final $R = 0.0616$, $R_w = 0.0682$, goodness of fit = 1.878 for 649 parameters refined in blocks.

(16) Sessler, J. L.; Cyr, M.; Furuta, H.; Král, V.; Mody, T.; Morishima, T.; Shionoya, M.; Weghorn, S. *Pure Appl. Chem.* **1993**, *65*, 393-398.

0002-7863/93/1515-3346$04.00/0

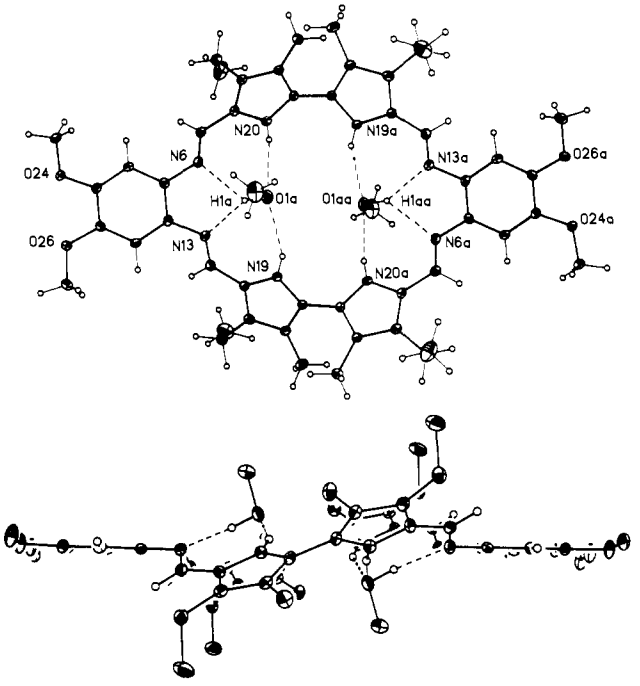


Figure 1. Views of one of the $4\cdot(CH_3OH)_2$ complexes. The macrocycle lies around an inversion center at 0, $^1/_2$, $^1/_2$. Thermal ellipsoids are scaled to the 30% probability level. H bonds are indicated by dashed lines. Top: View direction is perpendicular to the plane through the eight N atoms of the macrocycle. Two molecules of CH_3OH are H-bonded to the cavity of the macrocycle. The relevant H-bond contacts are as follows: O1a···N6 3.026(4) Å, O–H···N 134(4)°; O1a···N13 2.896(4) Å, O–H···N 149(4)°, N6···H1a···N13 76(1)°; N19···O1a 3.157(4) Å, N–H···O 154(4)°; N20···O1a 3.026(4) Å, N–H···O 165(3)°. Bottom: Side view showing the nonplanarity of the macrocycle. The bipyrroles are twisted to accommodate the H-bonding interaction. The dihedral angle between the pyrrole groups is 52.5(1)°.

M) and ligand **1** (0.15 M) in CD_2Cl_2 displayed peaks characteristic of both free and self-associated (i.e., hydrogen bound) OH stretching modes (at 3625 and 3341 cm^{-1}, respectively), the intensity of this same self-associated OH stretch was found to be reduced substantially, if not completely, when ligand **1** was replaced by macrocycle **4** (cf. supplementary material). The peak at 3418 cm^{-1}, ascribed to the pyrrole NH stretch,[17] was also found to be broadened substantially upon the addition of methanol. Taken together, these data are considered consistent with the notion that macrocycle **4**, in contrast to its smaller analogue **1**, may act as an effective receptor for methanol in solution.

More quantitative solution phase binding information was obtained from ^{1}H NMR titration experiments carried out in CD_2Cl_2. For instance, the stepwise addition of aliquots of CH_3OH to 2.5 mM solutions of **4** in CD_2Cl_2 led to the monotonic downfield shifting of a variety of ligand-centered proton signals, including those associated with the imine (CH=N) hydrogens, for which the greatest relative changes were observed.[18] From these titrations and standard curve-fitting procedures[19-21] were derived first and second affinity constants of $K_1 = (120 \pm 10)$ M^{-1} and $K_2 = (30 \pm 3)$ M^{-1}, respectively, for the binding of methanol to **4**.[22,23] The values of these two affinity constants were found to be independent of concentration in the 2.5–10 mM regime, as would be expected for a bona fide 2:1 complexation process.[24]

Similar NMR titrations were also carried out using a variety of other putative neutral substrates, including ethanol, trifluoroethanol, and phenol. As might be expected, the expanded porphyrin **4** showed affinity for all three of these substrates in CD_2Cl_2 solution [$K_{eq} = (80 \pm 10)$ M^{-1}, (100 ± 15) M^{-1}, and (720 ± 45) M^{-1}, respectively].[19,23] Further, preliminary experiments have served to show that catechol is bound by receptor **4** with an affinity constant that exceeds 10^4 M^{-1}.[26] Interestingly, however, in all cases a preference for 1:1 binding was revealed, with K_2 being less than 10% of K_1.[27] Although this stoichiometric proclivity is not yet understood, it is currently rationalized in terms of a steric argument: Unfavorable interactions between the "large" substrate (e.g., phenol) and ligand **4** could induce distortions of the macrocycle that disfavor complexation of a second substrate.

Whether the above explanation is true or not, however, awaits the results of further structural and calculational analyses. In any case, it is clear that compound **4** acts as a very effective receptor for the complexation of neutral, alcohol-type substrates in dichloromethane solution. This is in marked contrast to the smaller "control" system **1**. For instance, when typical ^{1}H NMR titrations were carried out with **1**, little or no change was observed for the imine or any other macrocycle proton signals. In addition, and this is considered critical, we found that in the presence of 1 equiv of ligand **1**, the effective binding constant for the complexation of phenol to receptor **4** was reduced by ca. 10%. Thus, the solution-phase affinity for methanol or ethanol is likely to be negligible in the case of **1**.

The results presented here support the hypothesis that certain expanded porphyrins, such as **4**, may be used to chelate neutral substrates both in solution and in the solid state. The high affinity observed for the complexation of certain substrates (e.g., phenol, catechol) leads us to suggest further that a generalized expanded porphyrin approach could provide the basis for an important new approach to the recognition and binding of neutral substrates, including those substrates such as catecholamines and carbohydrates, that are of obvious biological importance. We are currently exploring this possibility.

Acknowledgment. This work was supported by grants from the NIH (AI 28845), the NSF (CHE 9122161), the Camille and Henry Dreyfus Foundation (Teacher-Scholar Award to J.L.S., 1988–1992) and Pharmacyclics Inc. T.D.M. wishes to thank the UT Austin Department of Chemistry and Biochemistry for a Texaco Foundation Fellowship. The authors thank Prof. Eric Anslyn and Maria Dulay of this department for their assistance with the ^{1}H NMR and IR binding studies, respectively.

Supplementary Material Available: Synthetic and X-ray experimental details for compound **4**, IR spectra for systems **1** and **4** in the presence and absence of methanol, observed and calculated binding profiles for representative NMR titrations and Job plots, and tables of atomic thermal factors, atomic positional parameters, and bond distances and angles for **4** (54 pages); listing of observed and calculated structure factor amplitudes for **4** (45 pages). Ordering information is given on any current masthead page.

(17) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. In *Spectrometric Identification of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1991; p 131.

(18) The pyrrole NH signals were not observed either before or after the addition of methanol and, therefore, could not be used for quantitative analyses. In addition, no shifts in substrate-based signals were observed as a function of receptor-to-substrate ratio. This is not unexpected since macrocycle **4**, like ligand **1**, is not aromatic.

(19) ^{1}H NMR binding-derived affinity constants were determined in accord with methods reported earlier.[20,21]

(20) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.

(21) (a) Harriman, A.; Kubo, Y.; Sessler, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 388–340. (b) Furuta, H.; Magda, D.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 978–985.

(22) The affinity constants reported were derived by monitoring the change in the imine proton signal as a function of substrate concentration.

(23) Cf. supplementary material for binding profiles, Job plots, IR spectra, etc.

(24) The Job plot for this association[23] showed resemblance to that of a 1:1 binding process where the equilibrium process is $K_2 \ll K_1$.[25]

(25) Likaussar, W.; Boltz, D. F. *Anal. Chem.* **1971**, *43*, 1265–1272 and references therein.

(26) The apparent NMR-derived affinity constant of ca. 2.7×10^4 M^{-1} for catechol binding to **4** was confirmed by independent UV/vis spectroscopic titrations.

(27) The ^{1}H NMR binding data for these substrates was also fit to a 2:1 binding profile, but the derived K_2 value was found to be less than 10% of that of K_1.