

Anion binding: a new direction in porphyrin-related research

Jonathan L. Sessler,* Michael Cyr, Hiroyuki Furuta, Vladimir Král, Tarak Mody, Takashi Morishima, Mitsuhiro Shionoya, and Steven Weghorn

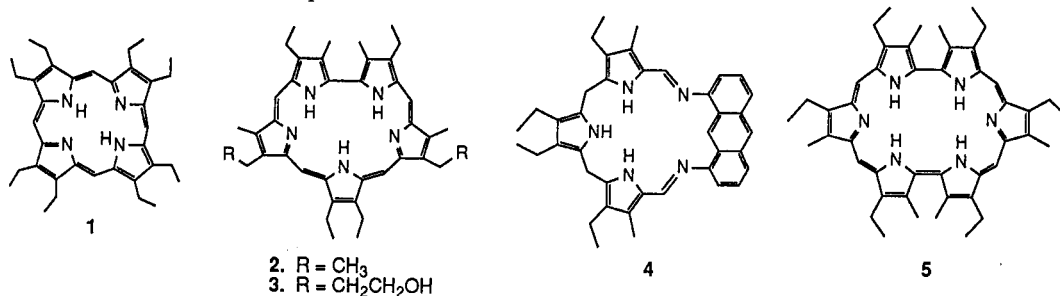
Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712 USA

Abstract

A new approach to the chelation of anionic substrates, based on the use of large, pyrrole-containing macrocycles, the so-called "expanded porphyrins", is described. This anion binding, which is without precedent in simpler porphyrin-type systems, is manifest both in the solid state and in solution. In the present paper, it is illustrated in terms of solid state structural results obtained from single-crystal X-ray diffraction structural analyses of various anion complexes of three prototypic systems, namely the sapphyrins, anthrapphyrins, and rubyrins.

The porphyrins (e.g. octaethylporphyrin, **1**) and related tetrapyrrolic compounds are among the most versatile of all macrocyclic systems (ref. 1). They play, for instance, a critical role in a large number of biological processes and are widely recognized as being metal-binding ligands *par excellence*. Nonetheless, the porphyrins and related systems fail with regards certain applications. They are not, for instance, capable of forming hydrolytically stable, non-labile 1:1 complexes with many cations of the lanthanide or actinide series (ref. 2). Nor, do they work as anion complexing agents (ref. 3). Recently, however, we have found that certain larger pyrrole-containing macrocyclic analogues of the porphyrins, members of the so-called expanded porphyrin series (ref. 4), can serve not only to bind cations of the lanthanide (ref. 5) and actinide series (ref. 6), but also in certain instances to chelate anions (refs. 7-17). It is this latter finding, namely the discovery of anion binding (ref. 18) in simple porphyrin-like systems, that engenders the present report. In particular, the results of solid state structural studies, carried out using three prototypic series of expanded porphyrins, the sapphyrins (e.g. **2** and **3**), anthrapphyrins (e.g. **4**), and rubyrins (e.g. **5**), will be detailed and relevant solution phase results presented.

Our first realization that expanded porphyrins are capable of chelating anionic substrates arose out of an attempt to obtain X-ray diffraction quality of sapphyrin **2**, a decaalkyl derivative of a class of compounds first reported by Woodward nearly 25 years ago (ref. 19). Here, an X-ray crystal analysis of what was thought to be the bis- H^+PF_6^- salt of **2**, revealed the presence of only one PF_6^- counteranion per macrocycle as well as the presence of unexpected electron density in the center of the fully protonated pentaaza core (ref. 7). On the basis of ^{19}F NMR and independent synthesis, this unexpected electron density was ascribed to a hydrogen-bonded fluoride anion, indicating, as shown in Figure 1, that the diprotonated form of **2** acts as a fluoride anion receptor--at least in the solid state.



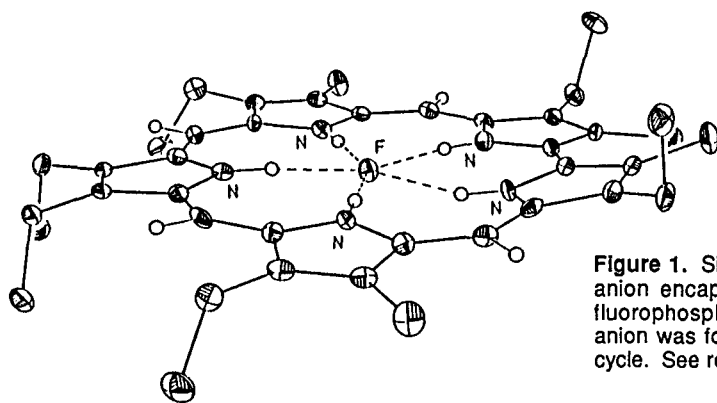


Figure 1. Single crystal X-ray structure of the fluoride anion encapsulated mixed hydrofluoride-hydrohexafluorophosphate salt of sapphyrin 2. The fluoride anion was found to lie within the plane of the macrocycle. See ref. 7 for further details.

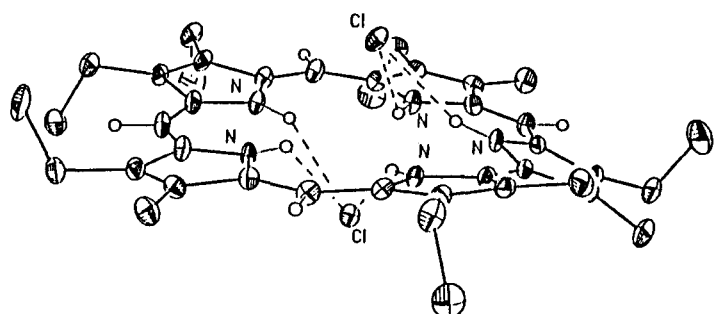


Figure 2. Single crystal X-ray structure of the dihydrochloride salt of sapphyrin 2. The two chloride anions were found to lie roughly 1.88 and 1.77 Å above and below the plane of the macrocycle, respectively. See ref. 8 for further details.

Subsequent to the above findings, defraction-grade single crystals of the bis-hydrochloride salt of sapphyrin 2 were also obtained (ref. 8). Here, the solid state structure revealed the presence of two chloride counteranions ligated both above and below the sapphyrin plane (Figure 2). This result was considered to be of considerable significance: Not only did it serve to indicate that two very different kinds of binding patterns are operative in the solid state for fluoride and chloride, it also served to suggest that the diprotonated form of sapphyrin might be a selective chelend capable of distinguishing between these two ostensibly similar halide anions. As discussed in detail, in a recent full paper (ref. 8), this has in fact proved to be the case. In methanol, for instance, fluoride anion is bound by the diprotonated form of 2 with a K_s of ca. $1 \times 10^5 \text{ M}^{-1}$, whereas chloride and bromide are both bound with K_s of $\leq 10^2 \text{ M}^{-1}$.

In addition to halide binding, the diprotonated form of sapphyrin also shows affinity for phosphate-type anions (refs. 9-12). For instance, as shown in Figure 3, a 2:1 complex is formed between the

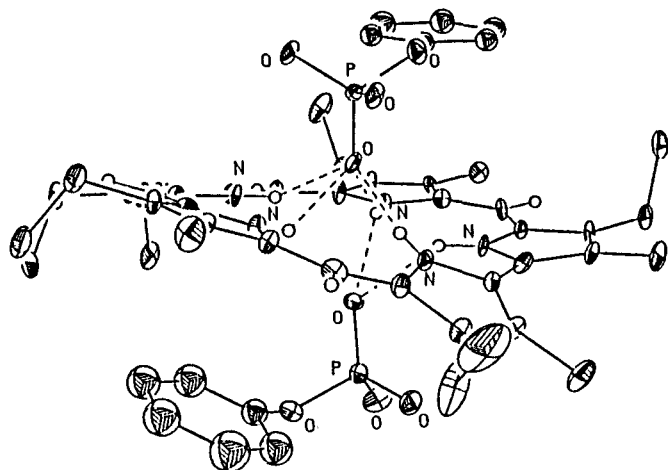


Figure 3. Single crystal X-ray structure of the bisphenylphosphate salt of sapphyrin 2. The two monobasic phosphate anions are held 1.22 and 1.60 Å above and below the sapphyrin plane and are chelated by 3 and 2 hydrogen bonds, respectively.

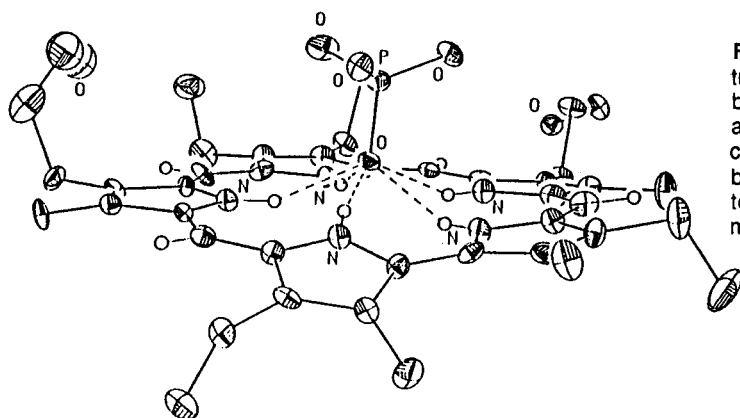


Figure 4. Single crystal X-ray structure of the 1:1 chelated complex formed between monobasic phosphoric acid and sapphyrin 3. The phosphate is held ca. 0.83 Å above the sapphyrin plane by 5 hydrogen bonds. For each diprotonated 3, there is also a non-ligated monobasic phosphate (not shown).

monobasic form of phenylphosphate and diprotonated form of 2 (ref. 12). Similarly, as shown in Figure 4, a 1:1 complex is formed between diprotonated 3 and monobasic phosphoric acid (ref. 12). In both cases, multiple hydrogen bonds serve to chelate the anion to the macrocycle. In fact, these two structures reveal that anywhere from 2 to 5 such NH-to-O interactions can serve to effect phosphate-to-protonated sapphyrin ligation in the solid state. Thus, it appears that a flexibility in binding is a hallmark of this type of phosphate chelation.

Evidence for sapphyrin-based phosphate anion binding in solution has come from a variety of transport experiments using simple Aq I-CH₂Cl₂-Aq II U-tube type model membrane systems. This work, which was initiated as part of a program to develop new adjuvants for the into-cell delivery of phosphorylated nucleotide analog antiviral agents, has so far served to show that sapphyrin 2 is capable of transporting GMP and other nucleotides under conditions where it remains doubly protonated, i.e. at pH ≤ 3.5 (ref. 9). In addition, this same system has also been found to be effective as a mediator for enhancing the through-membrane transport of both cyclic-AMP (ref. 12) and fluoride anion (ref. 13) at neutral pH. Finally, in very recent and as yet unpublished work, it was found that an appropriately designed sapphyrin-cytosine synthetic conjugate could be used to effect the efficient and selective through-membrane transport of GMP at neutral pH (refs. 10 and 11). Taken together, therefore, these results provide an important augury that the proposed approach (ref. 10) to antiviral adjuvant development might in fact be viable.

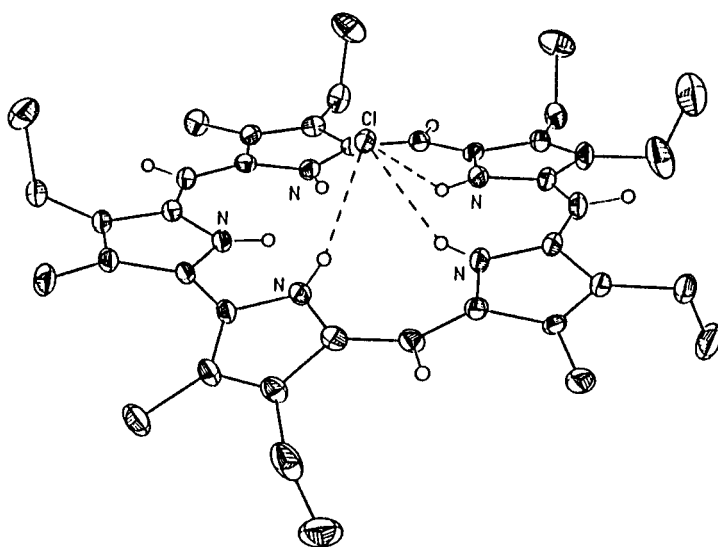


Figure 5. Single crystal X-ray structure of the chloride anion complex of monoprotonated sapphyrin 2. The chloride anion was found to lie ca. 1.72 Å above the macrocyclic plane.

The above results also provide an indication that the monoprotonated form of sapphyrin is capable of recognizing and binding monoanionic substrates. This important conclusion is presently supported by two X-ray structural studies. As shown in Figures 5 and 6, respectively, the monoprotonated form of sapphyrin 2 interacts with and binds both chloride and azide in the solid state (refs. 12 and 14). As expected, both of these anions are bound by oriented electrostatic interactions involving hydrogen bonds.

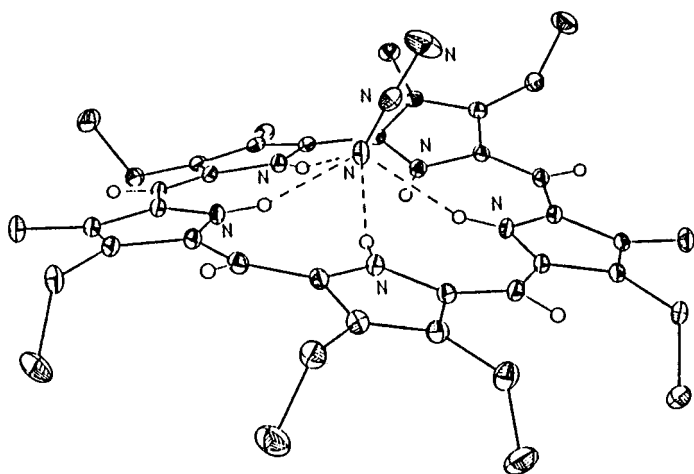


Figure 6. Single crystal X-ray structure of the azide anion complex of monoprotonated sapphyrin 2. The azide anion was found to lie ca. 1.16 Å above the macrocyclic plane. See ref. 14 for further details.

Interestingly, however, these interactions appear to be reminiscent of "half" of those seen in the corresponding structures obtained using the analogous diprotonated sapphyrin derivative (c.f. Figures 2 and 5). Nonetheless, it is clear from this work that a single positive charge on the sapphyrin is enough, in and of itself, to effect anion recognition in the case of appropriately chosen monoanionic substrates.

Although most anion binding studies carried out to date have focused on the use of protonated sapphyrins as the chelend, it is important to appreciate that other expanded porphyrins also bind anions. In fact, we presently believe that this approach to anion recognition could be quite general (ref. 4). Consistent with this conclusion is the finding that both anthrephyrin (4) and rubyrin (5) bind chloride anion in the solid state (c.f. Figures 7 and 8).

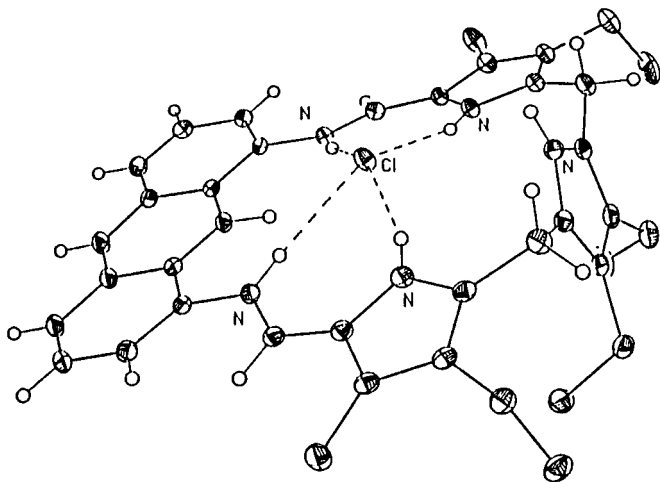


Figure 7. Single crystal X-ray structure of the chloride anion complex of diprotonated anthrephyrin 4. The chloride anion was found to lie ca. 0.80 Å above the macrocyclic plane. See ref. 15 for further details.

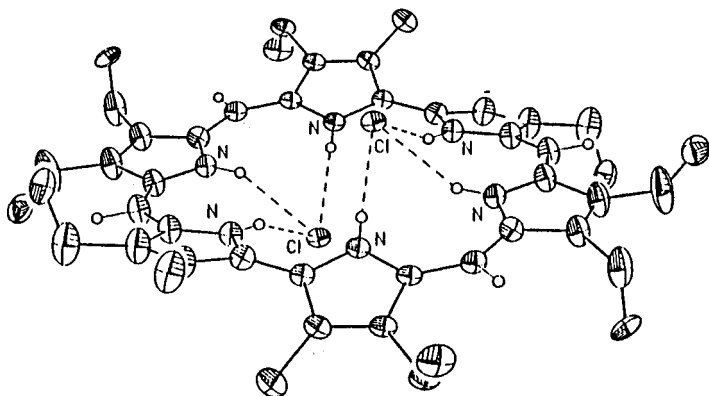


Figure 8. Single crystal X-ray structure of the bishydrochloride salt of rubyrin 5. The two chloride anions were found to lie ca. 1.6 Å above and below the macrocyclic plane. See ref. 16 for further details.

In the case of anthraphyrin, the chloride anion is held nearly within the protonated center of the larger-than-sapphyrin core (ref. 15). As might be expected on the basis of this near in-plane encapsulation, the affinity for chloride anion is much higher than for fluoride in this system ($K_s = 2 \times 10^5 \text{ M}^{-1}$ and $1.4 \times 10^4 \text{ M}^{-1}$, in CH_2Cl_2 , for Cl^- and F^- , respectively). This relative affinity is clearly quite different than that observed for diprotonated sapphyrin ($K_s \approx 1.8 \times 10^7 \text{ M}^{-1}$ and $\geq 1 \times 10^8 \text{ M}^{-1}$ in CH_2Cl_2 , for Cl^- and F^- , respectively). On the other hand, anthraphyrin serves as a much more effective mediator for the through-membrane transport of fluoride anion than does sapphyrin ($\Phi_P = 5.0 \mu\text{mol h}^{-1}$ vs. $0.86 \mu\text{mol h}^{-1}$). This anthraphyrin-mediated anion transport, however, is significantly inhibited by the presence of chloride anion (ref. 15). This has led us to suggest that it is actually the rate of anion release, rather than overall binding affinity, that determines the efficacy of expanded porphyrin mediated anion transport (ref. 10). Consistent with this supposition is the recent finding (using the new synthetic sapphyrin-cytosine conjugate described in ref. 11) that GMP transport is greatly enhanced when the receiving phase (Aq II) is kept highly basic (ref. 11). Under these conditions, deprotonation of the macrocycle at the Aq II- CH_2Cl_2 interface presumably serves to accelerate substrate release. In any case, as for the sapphyrins discussed above, the very fact that through-membrane transport is observed using anthraphyrin provides proof *inter alia* that this particular expanded porphyrin binds anions in solution.

Less is currently known about the anion binding behavior of ruyrin, **5** (refs. 16 and 17). As is true for sapphyrin, **2**, in the solid state structure of the bis-hydrochloride salt, the chloride counter anions are held above and below the plane of the macrocycle (ref. 16). However, these two chloride anions lie closer to the plane in the case of ruyrin than in the case of sapphyrin. This, could reflect the fact that intracore N^+H -to- H^+N electrostatic repulsive interactions are reduced in the larger ruyrin system. To the extent this is true, one would expect the two pyridine-like nitrogens of ruyrin to be more basic than those of sapphyrin. This, in turn, one would predict should be reflected in a higher apparent pK_a value for the deprotonation of either mono- or diprotonated ruyrin (as compared to sapphyrin) and a greater ability to transport dibasic substrates, such as GMP, at, or near, neutral pH. As detailed elsewhere (ref. 17), such a prediction has recently been borne out by experiment: In the presence of an added solubilized Watson-Crick molecular recognition co-carrier, ruyrin (but not octaethylporphyrin, **1**, or sapphyrin, **2**) acts as an efficient carrier for the through-membrane transport of GMP and other mononucleotide species. Thus, different expanded porphyrins appear to have different anion recognition and transport capabilities.

To the extent that the promise inherent in the above conclusion proves true, it would appear that the appropriate design and synthesis of new expanded porphyrins of differing sizes, shapes, and $\text{NH} / \text{N}^+\text{H}$ chelating denticity would be worthwhile: It, would provide a means of "modulating" the basic anion binding and transport characteristics associated with this generalized class of compounds. Work along these lines is, therefore, currently in progress. In fact, in very recent work, we have succeeded in preparing and characterizing the bipyrrrole-derived cyclotrimer **6**. This interesting non-aromatic, 24π -electron system, to which the trivial name rosarin has been assigned (ref. 20), binds two chloride anions within the highly distorted central hexaaza core (Figure 9). It and related systems are presently the subject of ongoing inves-

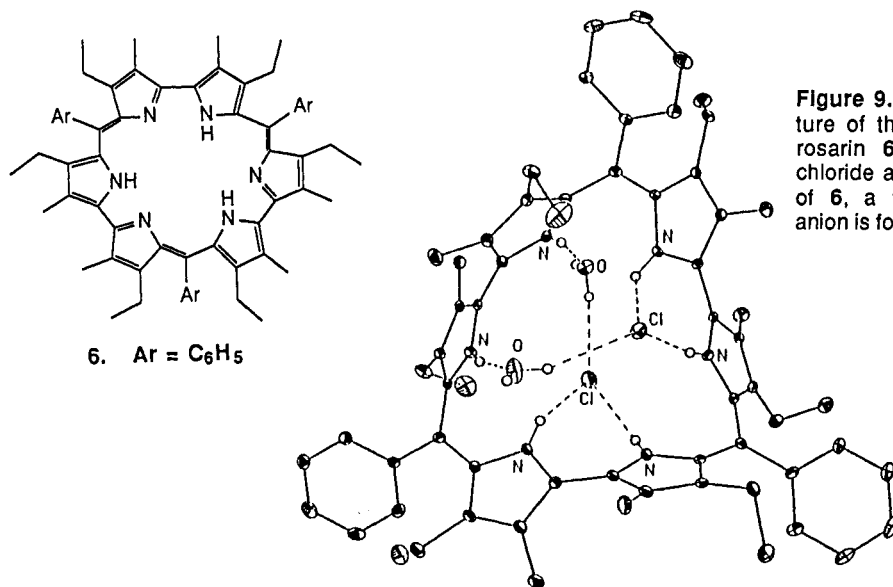


Figure 9. Single crystal X-ray structure of the tris-hydrochloride salt of rosarin **6**. In addition to the two chloride anions shown, for each unit of **6**, a third non-chelated chloride anion is found within the crystal lattice.

tigation. Nonetheless, the conclusion seems clear: Expanded porphyrins represent a new and potentially exciting approach to the chelation of anions that is without precedent in either the porphyrin or molecular recognition literature. Thus, the prediction emerging from this paper, and the oral presentation on which it is based, is that this research direction is apparently a rich one indeed.

Acknowledgment This work was supported by NIH grant AI 28845 to J.L.S and by more recent funding from Pharmacyclics Inc. and the NSF. J.L.S. also thanks the Camille and Henry Dreyfus Foundation for a Teacher-Scholar Award (1988-1992).

REFERENCES

1. See, for instance: (a) D. Dolphin (Ed.), The Porphyrins, Vols I-VII, Academic Press, New York (1978). (b) K. M. Smith (Ed.), Porphyrins and Metalloporphyrins, Elsevier, Amsterdam (1975).
2. (a) J. W. Buchler, in ref. 1a, Vol. 1, Chapter 10. (b) T. S. Srivastava, Bioinorg. Chem. **8**, 61-76 (1978). (c) W. DeW. Horrocks, Jr. J. Am. Chem. Soc. **100**, 4386-4392 (1978); (d) S. Haye and P. Hambright, J. Chem. Soc., Chem. Commun. 666-668 (1988). (f) R. C. Lyon, P. J. Faustino, J. S. Cohen, A. Katz, F. Mornex, D. Colcher, C. Baglin, S. H. Koenig and P. Hambright, Magn. Reson. Med. **4**, 24-33 (1987).
3. For structurally characterized examples of protonated porphyrin-anion salts, see: (a) J. L. Hoard, in ref. 1b; pp. 317-376. (b) C. P. Hsung, M. Tsutsui, D. L. Cullen and E. F. Meyer, J. Am. Chem. Soc. **98**, 7878-7880 (1976). (c) E. B. Fleischer, Acc. Chem. Res. **3**, 105-112 (1970). (d) A. Stone and E. B. Fleischer, J. Am. Chem. Soc. **90**, 2735-2748 (1968). (e) W. R. Scheidt, in ref. 1a, Vol. III, p. 463-511. (f) E. F. Meyer, D. L. Cullen, in ref. 1a, Vol. III, pp. 513-529. (g) N. Hirayama, A. Takenaka, Y. Sasada, E.-I. Watanabe, H. Ogoshi and Z.-I. Yoshida, J. Chem. Soc., Chem. Commun. 330-331 (1974). (h) E. Cetinkaya, A. W. Johnson, M. F. Lappert, G. M. MacLaughlin and K. W. Muir, J. Chem. Soc. Dalton Trans. 1236-1243 (1974).
4. J. L. Sessler and A. K. Burrell, Top. Curr. Chem. **161**, 177-273 (1991).
5. J. L. Sessler, T. Murai and G. Hemmi, Inorg. Chem. **28**, 3390-3393 (1989).
6. (a) A. K. Burrell, G. Hemmi, V. Lynch and J. L. Sessler, J. Am. Chem. Soc. **113**, 4690-4692 (1991). (b) J. L. Sessler, T. D. Mody and V. Lynch, Inorg. Chem. **31**, 529-531 (1992).
7. J. L. Sessler, M. Cyr, V. Lynch, E. McGhee and J. A. Ibers, J. Am. Chem. Soc. **112**, 2810-2813 (1990).
8. M. Shionoya, H. Furuta, V. Lynch, A. Harriman and J. L. Sessler, J. Am. Chem. Soc. **114**, 5714-5722 (1992).
9. H. Furuta, M. Cyr and J. L. Sessler, J. Am. Chem. Soc. **113**, 6677-6678 (1991).
10. J. L. Sessler, H. Furuta and V. Král, Supramolec. Chem., in press.
11. V. Král, J. L. Sessler and H. Furuta, submitted to J. Am. Chem. Soc.
12. H. Furuta, V. Král and J. L. Sessler, unpublished results.
13. J. L. Sessler, D. Ford, M. Cyr and H. Furuta, J. Chem. Soc., Chem. Commun. 1733-1735 (1991).
14. J. L. Sessler, M. Cyr and A. K. Burrell, SynLett 127-133 (1991).
15. J. L. Sessler, T. D. Mody, D. Ford and V. Lynch, Angew. Chem. **104**, 461-464 (1991); Angew. Chem., Int. Ed. Engl. **31**, 452-455 (1991).
16. J. L. Sessler, T. Morishima and V. Lynch, Angew. Chem. **103**, 1018-1020 (1991); Angew. Chem., Int. Ed. Engl. **30**, 977-980 (1991).
17. H. Furuta, T. Morishima, V. Král and J. L. Sessler, Supramolec. Chem., in press.
18. For overviews of other anion binding receptors, see: (a) R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, Chem. Rev. **91**, 1721-2085 (1991). (b) F. P. Schmidtchen, Top. Current Chem. **132**, 101-133 (1986). (c) E. Kimura, Top. Curr. Chem. **128**, 113-141 (1985).
19. See: V. J. Bauer, D. L. J. Clive, D. Dolphin, J. B. Paine III, F. L. Harris, M. M. King, J. Loder, S. W. C. Wang and R. B. Woodward, J. Am. Chem. Soc. **105**, 6429-6436 (1983), and references therein.
20. J. L. Sessler, S. J. Weghorn, T. Morishima, M. Rosingana, V. Lynch and V. Lee, submitted to J. Am. Chem. Soc.