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New Synthetic Receptors Derived from Porphyrins

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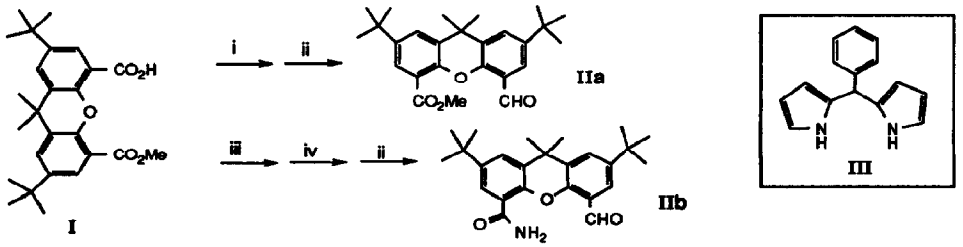
Abstract: *A new porphyrin-based molecular cleft has been synthesized: it shows high affinity for appropriate guests.*

Convergent, or inwardly-directed functional groups have been of considerable use in studies of molecular recognition.[1] Even so, it has been difficult to excercise conformational control over the longer distances needed for recognizing sizable guest species.[2] We describe here a new system that offers promise in this regard. The new structure takes advantage of a xanthene skeleton fixed rigidly on a tetraaryl porphyrin platform.[3]

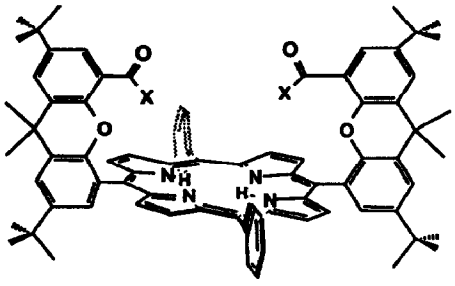
The xanthene aldehydes **IIa,b** were synthesized from the parent acid/methyl ester[4] **I** via Scheme 1. Borane reduction[5] in THF of **I** produced the alcohol/methyl ester, and a Swern[6] oxidation yielded the desired aldehyde/methyl ester **IIa**. Conversion of the acid functionality in **I** to an amide, followed by reduction of the methyl ester using $LiBH_4$,[7] and finally another Swern oxidation gave the target aldehyde **IIb**. Porphyrin assembly loosely followed Adler-Longo[8] conditions; dipyrrophenylmethane **III**[9] and a xanthene aldehyde were condensed in hot propionic acid. Two rotationally isomeric porphyrin products resulted, and by-products from aldehyde exchange or fragmentation[10] were not isolated. Although this process was low yielding (9-15%), other approaches were either not appropriate[11] for this system, or were unsuccessful (precipitation of a porphyrinogen, followed by oxidation[12]).

Scheme 1

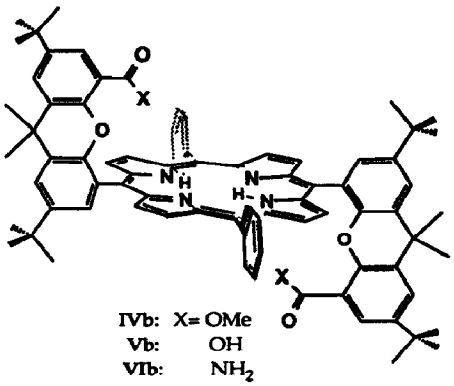


Conditions: i. BH_3·THF; ii. oxalyl chloride, DMSO, NEt_3; iii. a) $SOCl_2$, b) NH_4OH; iv. $LiBH_4/Et_2O$

Cleavage of the methyl ester functionality of **IVa,b** proved problematic, as has been reported in other clefts,[13] conventional routes either failed due to porphyrin solubility (hydroxides in alcohols, TMS-I/CH_3CN) or were too slow (LiI/pyridine, HBr/CH_2Cl_2), success was finally achieved using sodium thiomethoxide in warm (80°C) DMSO for three days.[14]



IVa: X= OMe
Va: OH
VIa: NH_2



IVb: X= OMe
Vb: OH
VIb: NH_2

Structural Characterization

The xanthene aldehydes and porphyrins were characterized by ^1H NMR and high resolution mass spectroscopy. Identification of the porphyrin atropisomers was guided by literature reports[15] that the syn isomer has a lower Rf on silica gel. This was confirmed by exploiting the slow rotation of the phenyl rings on the NMR timescale. Since the two porphyrin faces are inequivalent in the syn isomer, slow rotation causes the ortho phenyl protons to be at different chemical shifts. Variable temperature ^1H NMR studies of the more polar isomer **IVa** in toluene show two nearly coalescent signals at 100°C, with actual coalescence close to 110°C. The less polar isomer **IVb** contained only a sharp multiplet for the ortho phenyl protons, invariant of temperature. The diamide cleft **VIa** and its less polar isomer showed similar temperature dependence and invariance, respectively. No interconversion between atropisomers was observed by NMR up to 100°C. However, a TLC analysis revealed that after 30 minutes of refluxing one isomer in toluene the other isomer was detectable.

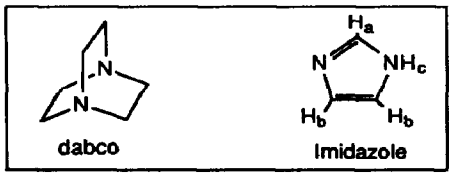
Binding Studies

Titrations were performed in $CDCl_3$ by addition of aliquots of guest solution to an NMR tube containing the host at room temperature. Changes in host or guest protons were used to generate titration curves which were then analyzed using nonlinear regression to obtain association constants.

The synthetic investment in these molecules was justified by the high affinity that they show

to guests of appropriate size, shape and chemical surface. For example, dabco was bound within the **Va** system with a Ka>10^5 M^{-1} as shown by the titration experiment. The NMR spectrum of the complex showed the anticipated upfield shift of the dabco protons to δ= -0.5ppm (free dabco has a single resonance at 2.8ppm) when bound above the macrocyclic ring of the porphyrin. The position of the dabco peak did not vary with concentration until after one equivalent had been added, then signals for both free and bound dabco were detected. This slow exchange between free and bound states is a consequence of two strongly polarized hydrogen bonds between the concave diacid and the convex diamine. **Vb**, its S-shaped counterpart, also showed strong binding, but the dabco was in more rapid exchange. The derived binding constants were still high (Ka_1= 12,000 M^{-1} and Ka_2= 3,900 M^{-1}) causing dabco to be shifted by ≈-2.6ppm to δ= 0.17ppm. The much weaker base pyrazine did not bind to either host to any measurable extent.

Imidazole was also bound by **Va** with a Ka of 1500M^{-1}, with strong upfield shifts (Δδ's) of 4.4ppm (H_a) and 2.6ppm (H_b). Again, host **Vb** showed weaker (2:1) binding, with Ka_1≈Ka_2= 40M^{-1} and smaller Δδ values of 0.88ppm and 0.55ppm for H_a and H_b, respectively. Due to substantial broadening in the nmr signal of H_c its maximum upfield position could not be determined for either diacid receptor.



In summary, a synthetic molecular cleft has been constructed based on a xanthene skeleton with a porphyrin spacer unit. We will report on their future applications in due course.

Acknowledgments

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References

(1). (a) Rebek, J., Jr. *J. Heterocyclic Chem.* **1990**, *27*, 111-117. (b) Pascal, R. A.; Ho, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 8507-8508. (c) Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055-8057. (d) Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549-6551. (e) Galán, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.*. **1992**, *114*, 1511-1512. (f) Tecilla, P.; Chang, S.-K.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9586-9590. (g) Zimmerman, S. C.; Wu, W. *J. Am. Chem. Soc.* **1989**, *111*, 8054-8055. (h) Iimori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439-3430. (i) Schmidtchen, F. P. *Tetrahedron Lett.* **1989**, *30*, 4493-4496. (j)

Medina, J. C.; Gay, I.; Chen, Z.; Echegoyen, L.; Gokel, G. W.; *J. Am. Chem. Soc.* **1991**, *113*, 365-366. (k) Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673-3674.

(2) Shimizu, K. D.; Dewey, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 5145-5149.

(3) (a) Aoyama, Y.; Asakawa, M.; Matsui, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1991**, *113*, 6233-6240. (b) Hayashi, T.; Miyahara, T.; Hashizume, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 2049-2051.

(4) Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902-8906. The corresponding diacid precursor is an article of commerce from Aldrich Chemical Company.

(5) Brown, H. C.; Heim, P.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 1637-1646.

(6) Mancuso, J.; Swern, D. *Synthesis* **1981**, 165-185.

(7) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000-4005.

(8) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.

(9) Dipyrrophenylmethane was synthesized by refluxing, in toluene, 6 equivalents of pyrrole with benzaldehyde under Ar for 90 minutes with a catalytic amount of para-toluenesulfonic acid, concentrating, then purifying using flash column chromatography. From Carell, T. Ph. D. Thesis, Ruprecht-Karls-Universität Heidelberg, 1993.

(10) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245-7257.

(11) The well optimized approach detailed by Lindsey *et al* would yield a multitude of porphyrin compounds: see Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827-836.

(12) Young, R.; Chang, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 898-909. One possible explanation is that the xanthene's ortho oxygen renders the resultant tetraarylporphyrin susceptible to destructive oxidation, see Zhang, H.-Y.; Blasko, A.; Yu, J.-Q.; Bruice, T. C. *J. Am. Chem. Soc.* **1992**, *114*, 6621-6630.

(13) Güther, R.; Nieger, M.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 601-603.

(14) For a review of related approaches see McMurry, J. *Org. React.* **1976**, *24*, 187-224.

(15) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240-4250 and references therein.

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