Communication

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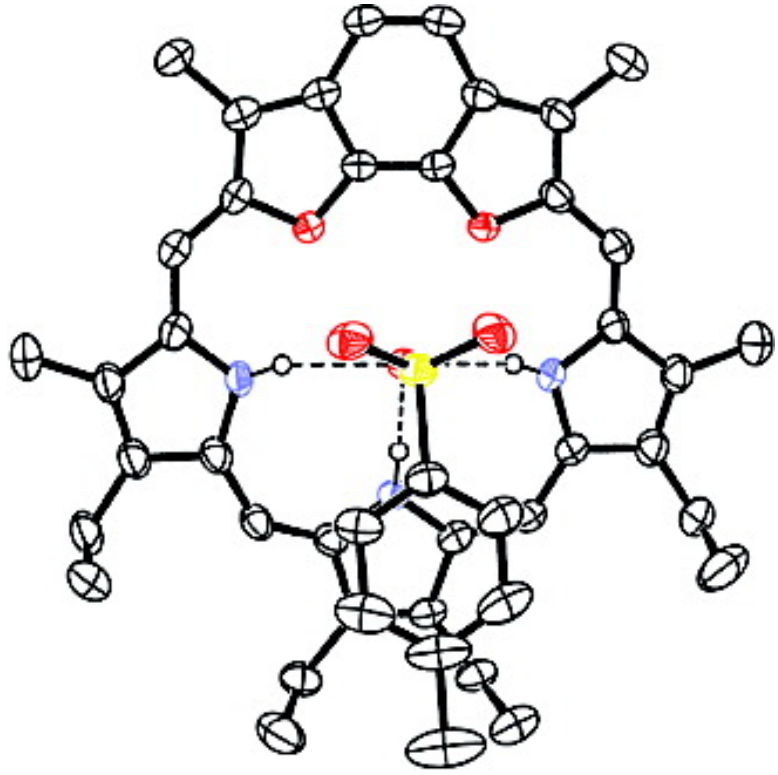
J. Am. Chem. Soc., **2008**, 130 (32), 10502-10503 • DOI: 10.1021/ja804090w • Publication Date (Web): 19 July 2008



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Published on Web 07/19/2008

Dioxabenzosapphyrin: A New Benzodifuran-Derived Sapphyrin Analogue

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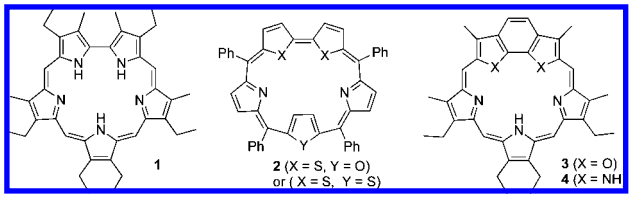
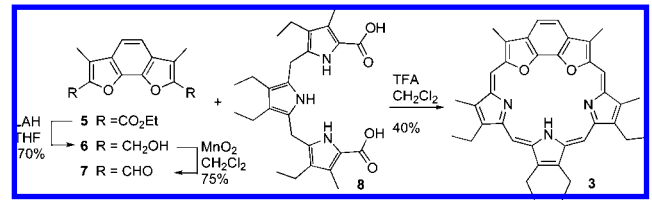
Since sapphyrin was first reported by Woodward in 1966 and subsequently prepared by Johnson[1] and Woodward and coworkers,[2] in the 1970s and 1980s, respectively, considerable effort has been devoted to improving its synthesis[3] and exploring its anion binding properties.[4] Sapphyrin has also been studied for its therapeutic potential[5] and for its optical and materials properties.[6] This combination of historical importance and current interest is rather unique among conjugated macrocycles and has made sapphyrin among the best studied of all expanded porphyrins. One of the foci of our group involves understanding the anion binding properties of sapphyrins, and in the context of this work, we have become interested in understanding how modifications to the system can affect the anion binding properties. In this report, we show that replacement of two pyrrolic nitrogen atoms (potential NH donors) by two oxygen atoms in a rigidified sapphyrin framework serves to preclude anion binding for the fully protonated system but gives rise to a system that can be considered as a rudimentary neutral substrate receptor.



To date, a variety of modified sapphyrins have been prepared. Among these, are ones where one pyrrole or two pyrrolic subunits have been replaced by some other building block. This has led to the creation inter alia of N-confused,[7] carbasapphyrin,[8] benzosapphyrin,[9] inverted sapphyrin,[10] various oxasapphyrins,[1,11] and dithiabenzisapphyrin.[12] Many of these modified sapphyrins show dramatic changes in such canonical properties as aromacity, UV−vis absorption features, and metal cation complexation behavior. For the most part, however, the anion binding properties of these analogues have not been explored, even in the case of rather simple heterosapphyrin systems. One exception is the *meso*-aryl functionalized heterosapphyrins of Chandrashekar (cf. structures **2**).[13] Unfortunately, the results of this study could not be compared with those for decaalkyl sapphyrin reported by our group (e.g., **1**), in part because the unsubstituted thiophene subunits in their system were found to lie outside of the macrocycle in the solid state and to undergo facile "inversion" in solution, in contrast to what is true for the nitrogen atoms of **1**. Dioxabenzosapphyrin **3**, an analogue of benzosapphyrin reported by Lee[9] was designed to allow us to examine the effect of oxygen-for-nitrogen atom replacement in a more restricted sapphyrin-type environment. The resulting comparisons, it was thought, would both help elucidate the determinants of anion binding in expanded porphyrins and advance our understanding of heterosapphyrin derivatives.[1,11]

Scheme 1. Synthetic Scheme



The synthesis of dioxabenzosapphyrin is shown in Scheme 1. It is based on intermediate **5**. Although compound **5** was first reported by Nuth in 1887,[14] to the best of our knowledge, this species has neither been fully characterized nor used as an intermediate in the construction of macrocyclic systems. Accordingly, intermediate **5** was resynthesized using the original procedure and fully characterized. LAH reduction then afforded diol **6** in 70% yield. Oxidation with manganese dioxide gave the bisformyl derivative, **7**, in 75% yield. Condensation of this latter intermediate with the tripyrrane diacid **8**[15] in the presence of TFA afforded the diprotonated dioxabenzosapphyrin **3** as its bis-TFA salt, **3**•$(TFA)_2$, in 40% yield.

The structure of dioxabenzosapphyrin **3** was established by a single-crystal X-ray diffraction analysis of the diprotonated bis-toslyate salt. This analysis revealed that, in the solid state, one oxygen atom of one tosylate counteranion is bound to the three NH protons present in the core of the macrocycle. Two additional tosylates are present per unit of **3** and are bound to a hydronium ion external to the macrocycle. The tosylate anion bound to the macrocycle core is located closer to the NH "bottom" of the framework than to the two oxygen atoms at the "top" of the core. Although crystal packing effects could be responsible, electrostatic repulsion between the benzodifuran oxygen atoms and those of the tosylate anion is likely responsible for this finding. The average NH···OTs and O···OTs bond distances are 2.107 and 2.839 Å, respectively (cf. Supporting Information).

The UV−vis spectrum of dioxabenzosapphyrin in its neutral (free-base) and diprotonated (bis-TFA salt) forms displays Q-type and Soret bands that are analogous to those seen for both decaalkylsapphyrins (e.g., **1**) and Lee's benzosapphyrin (studied as **4**, a new analogue with the same substitution pattern as **3**; cf. Supporting Information). However, there are subtle differences. For instance, the position and intensities of the Soret band are different for all three systems (e.g., λ_{max} (ϵ) = 456 nm ($\epsilon = 5.37 \times 10^5$ M^{-1} cm^{-1}; CH_2Cl_2), 455 nm ($\epsilon = 8.80 \times 10^4$ M^{-1} cm^{-1}; CH_2Cl_2), and 470 nm ($\epsilon = 2.04 \times 10^5$ M^{-1} cm^{-1}; $CHCl_3$) for the diprotonated forms of **1**•$(HCl)_2$, **3**•$(TFA)_2$, and **4**•$(HCl)_2$, respectively.

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10.1021/ja804090w CCC: $40.75

Table 1. Affinity Constants (K_a, M^{-1}), Corresponding to the Interaction of Halide Anions and Neutral Ar-OH Species with the Diprotonated Forms of **3** and **4** at 23 °C

	F^-	Cl^-	phenol	4-nitrophenol
3	550 ± 70^a	N/A[b]	18 ± 2^c	25 ± 2^c
4	$5600 \pm 200^{a,d}$	1100 ± 100^a	N/A[b]	N/A[b]

[a] K_a values were determined by UV−vis titration in MeOH using the corresponding diprotonated and tetrabutylammonium salt. [b] No effective K_a value for anion binding could be calculated. [c] K_a values were determined from UV−vis titrations using the bisperchlorate salts of the protonated sapphyrin derivatives in 1,2-dichloroethane. [d] Approximate value. Clean isosbestic behavior was only seen for the addition of 1−10 equiv; see Supporting Information.

Tests of whether the diprotonated from of **3**•$(HF)_2$ would bind anions were made by carrying out standard UV−vis titrations in MeOH. Upon addition of additional equivalents of fluoride anion (as tetrabutylammonium fluoride; TBAF) to solutions of **3**•$(HF)_2$, an increase in the intensity of the band at 449 nm in the UV−vis spectra was seen, along with a concomitant decrease in the intensity of the band of 469 nm. The changes in the spectral features could be fit to a 1:1 binding stoichiometry, a fit that is consistent with the X-ray crystal structure of the tosylate complex and is in line with what was seen previously in the case of $[H_2\mathbf{1}\bullet F]^+$.[3] Standard curve fitting revealed that the diprotonated form of dioxabenzosapphyrin, $H_2\mathbf{3}^{2+}$ binds F^- roughly 170 times less effectively than the parent decasapphyrin $H_2\mathbf{1}^{2+}$ ($K_a = 96\,000 \pm 20\,000$).[4] This difference is ascribed to the reduced number of NHs in **3** versus **1**, as well as to repulsion between the furan oxygen lone pair electrons and the fluoride anion. However, it is also possible that anion binding serves to break up an internal network of hydrogen bonding involving the furan oxygen atoms and the pyrrole NH protons. To the extent this occurs, it too would be expected to lead to a reduction in the anion affinity compared to $H_2\bullet\mathbf{1}^{2+}$. In any case, it is clear that the number of the hydrogen bonds is important and that their contribution to the overall fluoride anion binding process relative to charge-based electrostatic effects may be more significant than hitherto realized.

Efforts to carry out analogous titrations with using TBACl instead of TBAF gave rise to abnormal-looking titration curves in the case of diprotonated **3** (studied as both **3**•$(HClO_4)_2$ and **3**•$(HCl)_2$).[16] In contrast, with the rigid control system, **4**•$(HCl)_2$, clean titration curves were obtained that could be fit to a 1:1 binding profile; this gave an association constant of 1100 M^{-1} for the binding of chloride anion to $H_2\bullet\mathbf{4}^{2+}$ (cf. Table 1).

Given the lack of clean binding behavior seen in the case of TBACl and $H_2\bullet\mathbf{3}^{2+}$, we postulated that the solvent, CH_3OH, was competing as a guest. Accordingly, we investigated the effect of MeOH in a less polar solvent, 1,2-dichloroethane. Although the titration-like addition of MeOH to a solution of $H_2\bullet\mathbf{3}^{2+}$ in 1,2-dichloroethane gives rise to a change in the UV−vis spectrum, the resulting changes could not be fit to a reasonable binding equation (cf. Supporting Information). However, when MeOH was replaced by more acidic hydroxyl-containing species, namely phenol and 4-nitrophenol, clean 1:1 binding isotherms were obtained. On the other hand, such a clean binding behavior was not seen for catechol or naphthol derivatives (cf. Supporting Information).

Such findings not only provide important, albeit indirect, support for the notion that MeOH could compete with chloride anion by acting as both a solvent and a guest but also lead to the proposal that $H_2\bullet\mathbf{3}^{2+}$ can act as a receptor for hydroxyl-containing neutral substrates. While the affinities for phenol and 4-nitrophenol are low, 18 and 25 M^{-1} in 1,2-dichloroethane, respectively, no evidence of corresponding binding behavior was seen in the case of $H_2\bullet\mathbf{4}^{2+}$ (cf. Supporting Information). On the basis of this observation, we propose that the two oxygen atoms present in dioxabenzosapphyrin are playing a role in the binding of these strongly hydrogen bond donating, hydroxyl-containing neutral substrates. This in turn leads us to suggest that $H_2\bullet\mathbf{3}^{2+}$ and its analogues could act as receptors for various neutral substrates, especially those capable of acting as strong hydrogen bond donors.

In summary, dioxabenzosapphyrin **3**, a new sapphyrin analogue wherein two pyrrolic NH hydrogen bond donor groups are replaced by oxygen atoms, was found to bind fluoride and chloride anions only weakly in MeOH in its diprotonated form. On the other hand, interactions with neutral Ar-OH species were observed. This behavior stands in marked contrast to what is seen for $H_2\mathbf{1}^{2+}$ and $H_2\mathbf{4}^{2+}$, systems with the same overall charge but a reduced number of H-bond donors. These findings, considered in concert, provide support for the notion that, in rigid systems, such as **1**, **3**, and **4**, the nature and number of hydrogen bonds plays a key role in defining the overall molecular recognition behavior.

Acknowledgment. This work was supported by the National Institutes of Health (GM 58907 to J.L.S.), the Robert A. Welch Foundation (Grant F-1018 to J.L.S.), and the Korea Research Foundation (KRF-2007-313-C00410 to C.H.L.).

Supporting Information Available: Synthetic experimental and characterization data for compounds **3**−**7**. Titration curves for binding studies involving the diprotonated forms of **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA804090W