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Enhanced Shape-Selective Recognition of Anion Guests through Complexation-Induced Organization of Porphyrin Hosts

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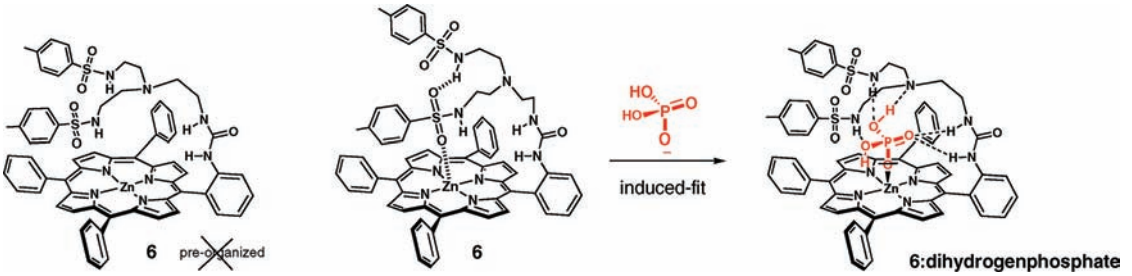
ABSTRACT



We present a fortuitous discovery of enhanced shape-selective recognition of anion guests that stems from a complexation-induced conformational change in porphyrin hosts upon anion binding. Porphyrin hosts reported here exist in a conformation that is not favorable to guest binding. Anions that bind strongly are those that can induce a conformational change in the host to allow guest binding. Furthermore, guests that mimic the shape of the newly formed pocket bind the strongest.

The field of anion recognition has received considerable interest over the last 15 years, but researchers in this area are still learning the rules needed to achieve selectivity in anion binding. There has been some debate surrounding the notion that one can develop selective receptors for anions through rational host design,[1] in particular, through the design of receptors that complement the shape and binding motif of the target anion—as nature does in sulfate and phosphate binding proteins. We initiated this project with the idea that one can consider an anion's geometry, basicity, electron density distribution, and charge and then design a receptor to mimic these properties, which should lead to improved selectivity in anion recognition. Anslyn's group has reported a receptor capable of analyzing for inorganic phosphate in serum and saliva.[2] This is one of the rare examples of a host that truly complements the shape of the target anion. The host possesses a tetrahedral cavity that matches the shape of the tetrahedral phosphate guest. Recent calculations (and an examination of the crystal structures of 945 hydrogen-bonded nitrate anions) performed by Hay[3] suggest that the optimal binding of nitrate will require a host that provides three bifurcated interactions arranged in a trigonal planar manner; Hay's work suggests that selective receptors for anions might be achieved by host designs that complement the shape of the guest.

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There is active research in the design of optical and fluorescent sensors for anions[4] for sensitivity and ease of signal detection reasons.[5] Due to the multitude of spectroscopic tools available to study porphyrin derivatives, they are ideally suited for the design of synthetic receptors.[6] Furthermore, the porphyrin platform presents a convergent surface that can be functionalized with recognition elements to create a binding pocket for target guests. Porphyrin-based receptors for amino acids,[7] carbohydrates,[8] nucleobases,[9] and synthetic heme analogues[10] are known. There are only a handful of porphyrin-based anion receptors, primarily work by the research groups of Burns,[11] Beer,[12] Hong,[13] and Imai.[7] There is nothing intuitive as to which anion these receptors should be selective for however.

We report here the synthesis and anion recognition properties of several meso-substituted porphyrin hosts that we envisioned would complement the shape and Lewis basic sites of anion guests. The porphyrin hosts (Figure 1) are functionalized at one meso position with one, two, or three anion binding sites that we anticipated would be prepositioned to mimic the geometry of the anion target and work in tune with the porphyrin metal center for selective anion binding. As it turns out, our vision was only partly realized. The porphyrin host's recognition properties with 11 anion guests that vary in geometry were examined: spherical (chloride, bromide, and iodide), "bent" (acetate, nitrite), trigonal planar (nitrate, carbonate), and tetrahedral (perchlorate, perrhenate, hydrogen sulfate, and dihydrogen phosphate).

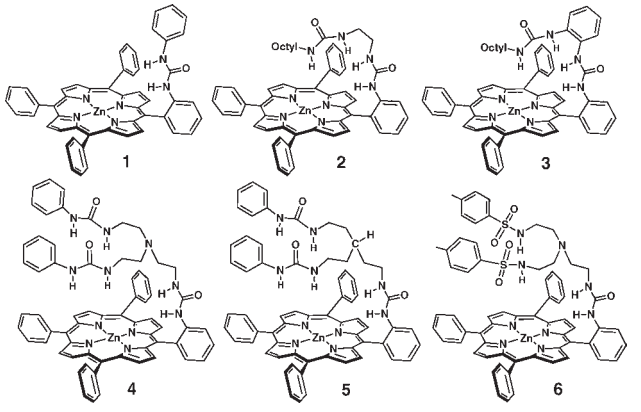
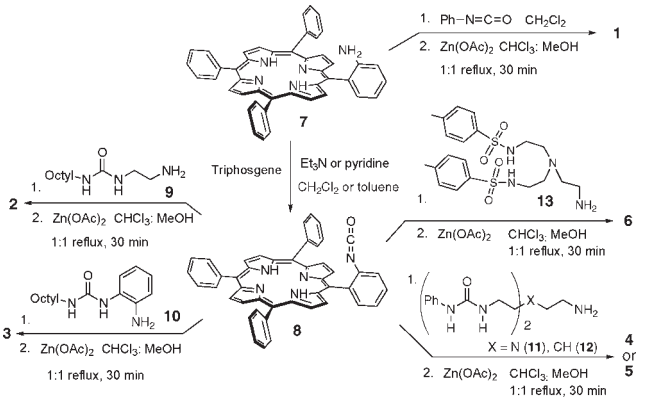


Figure 1. Porphyrin hosts.

The synthesis of receptors **1**–**6** (Scheme 1) began with the condensation of benzaldehyde, 2-nitrobenzaldehyde, and pyrrole using the standard procedure to give the known mononitroporphyrin.[14] Reduction of the mononitro compound with tin(II) chloride readily gave amine **7**, which was coupled with phenylisocyanate to give host **1**. Amine **7** is readily converted to isocyanate **8** by reaction with triphosgene.[15] Condensation of **8** with a variety of amines, followed by standard metalation with zinc(II) acetate, gave receptors **2**–**6**.

Scheme 1. Synthesis of Porhyrin Hosts



Our design considerations envisioned host **1** complementing the bent anions acetate and nitrite; host **1** has two binding sites—the metal center and one urea hydrogen bond donating site. Hosts **2** and **3** were designed to complement the shape and binding motifs of the trigonal planar anions carbonate and nitrate; hosts **2** and **3** have three binding sites—the metal center and two urea groups. Hosts **4** and **5** were designed to complement the shape of the tetrahedral anions perchlorate, perrhenate, hydrogen sulfate, and dihydrogen phosphate; hosts **4** and **5** have four binding sites—the metal center and three urea groups.

We initially prepared hosts **1**–**5**, the urea derivatives. Host **5** served as a model compound to investigate the role played by the central amine of **5** in anion recognition (if any). We then evaluated their anion recognition properties. Anion binding studies were performed by titrating a solution of the porphyrin receptor in CH_2Cl_2 ($\sim 1 \times 10^{-6}$ M) with CH_2Cl_2 solutions of the tetrabutylammonium salts of the anions (the bis(tetraethylammonium salt of carbonate

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Table 1. Association Constants (K, M^{-1}) and Selectivity of Anions with Receptors[a,b]

anion	Zn-TPP	**1**	**2**	**3**	**6**
I^-	0	68000	3500	2000	500
Br^-	15	100000	23000	10000	1500
Cl^-	300	480000	50000	35000	55000
NO_2^-	6000	150000	30000	24000	15000
$CH_3CO_2^-$	9000	400000	45000	50000	700000
NO_3^-	0	33000	3500	4200	300
CO_3^{2-}	8000	450000	150000	[a]	840000
ClO_4^-	0	0	0	0	[a]
ReO_4^-	0	6000	0	0	2000
HSO_4^-	0	110000	[a]	[a]	65000
$H_2PO_4^-$	16000	500000	[a]	[a]	3000000

[a] Complex UV. [b] Anions as their tetrabutylammonium salts for solubility in dichloromethane. Error ±10%.

was used). Nonlinear regression analysis of the binding curves gave binding constants (Table 1) for the porphyrin:anion complexes. Titration of porphyrin host **1** with anion guests gave sharp isosbestic points for all anions studied. The rest of the results were disappointing (at the time, when they were not understood). Bis-urea receptors **2** and **3** and tris-urea receptors **4** and **5** gave complex UV/vis titration curves upon anion addition for several of the guests. Several anions showed no binding at all to hosts **2**–**5**. Ureas are known to aggregate and, in general, can offer other challenges in host–guest chemistry, whereas sulfonamide analogues can be better behaved.[16] We then synthesized receptor **6** and indeed found that it gave sharp isosbestic points with all guests. We are currently working toward the synthesis of sulfonamide derivatives of hosts **2**, **3**, and **5**. Figures 2 and 3 show representative examples of the UV/vis titration curves of hosts **1** and **2** with anion guests. The inset shows the nonlinear regression curve fits of absorbance change versus guest concentration.

We believe the binding pockets of hosts **2**–**5** are blocked by urea coordination to the zinc center through either an intramolecular or an intermolecular interaction. This is supported by ^{1}H NMR and UV/vis spectroscopic studies. For model compound zinc-tetraphenylporphyrin (Zn-TPP), λ_{max} = 419 nm. For host **1**, λ_{max} = 420 nm. Upon anion complexation, a new band ~431 nm appears for the host **1**:anion complex. Zn-TPP complexes with anions typically show λ_{max} = 429–432 nm. For hosts **2**–**5**, λ_{max} = 428 nm. For hosts **2**–**5**, the complexes with anions typically show λ_{max} ~ 432 nm. For host **6**, however, λ_{max} = 424 nm. Host **6**:anion complexes typically have λ_{max} ~ 432 nm. Thus, anion binding to zinc porphyrin hosts typically results in a red shift of the Soret band. It is suggested that hosts **2**–**6**, which have λ_{max} at a longer wavelength than host **1**, exist in a conformation such that the zinc metallo center is coordinated to the urea and sulfonamide groups of each host (it is not clear at this point

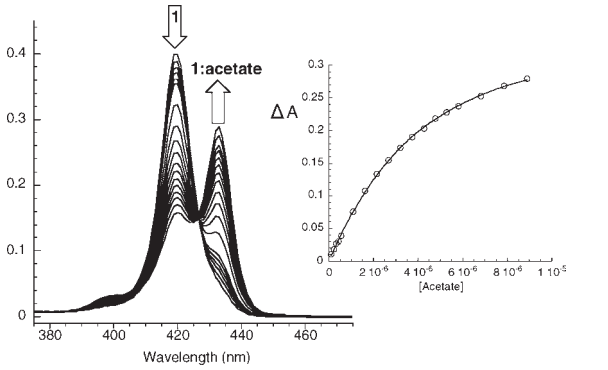

Figure 2. UV/vis spectra of **1** with tetrabutylammonium acetate (CH_2Cl_2). The inset represents the change in absorbance of **1** with varying molar equivalents of acetate.

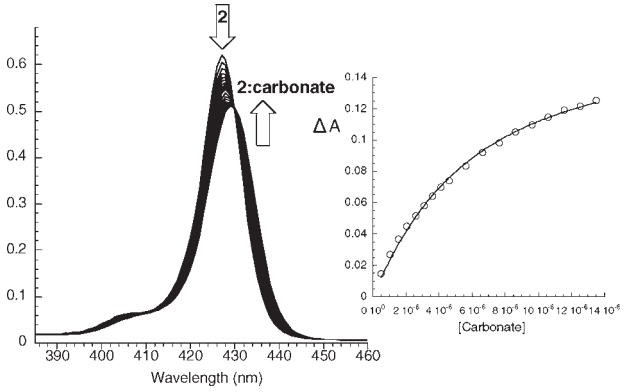

Figure 3. UV/vis spectra of **2** with bistetraethylammonium carbonate (CH_2Cl_2). The inset represents the change in absorbance of **2** with varying molar equivalents of carbonate.

if the interaction is intramolecular or intermolecular; more detailed NMR and concentration-dependent UV studies are warranted). Figure 4 illustrates the conformations that we believe these porphyrin hosts exist in as well as their proposed host:anion complexes. We believe that anion binding to these hosts represents an example of a complexation-induced organization of the host upon anion binding. This has been observed in other anion hosts.[17] This is also an important feature in the dynamics of porphyrin-based receptors[18] and enzymes.[19]

Furthermore, we believe this induced-fit mechanism leads to selectivity in guest binding (between guests and hosts that mimics the shape of the guest after the host conformational change); thus we believe this illustrates

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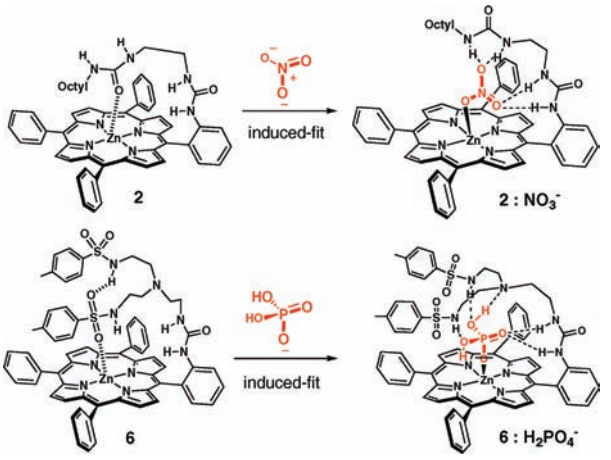

Figure 4. Induced-fit binding of anion guests.

an example of enhanced shape-selective recognition of anionic guests. Table 2 shows the selectivity of hosts **1** and **6** with anionic guests compared to $H_2PO_4^-$. Host **6** has two sulfonamides and one urea group that can participate in hydrogen bonding with guests as well as a metallo center. Thus, the host complements the tetrahedral shape of the anions dihydrogenphosphate, hydrogen sulfate, perrhenate, and perchlorate. Table 1 shows that host **1** does not bind guests with selectivity toward acetate or nitrite (thus the design consideration fails here). The binding constant of host **1** with anions somewhat follows the basicity of the anion. Host **6**, however, shows an enhanced selectivity (compared to host **1**) for tetrahedral anions (thus the design considerations seem to work here), and furthermore, within the series of tetrahderal anions, the selectivity parallels guest basicity. Thus host **6** shows enhanced selectivity for tetrahedral anions. All anions except for the most basic of the anions (acetate, carbonate, and dihydrogenphosphate) show weaker binding to host **6** than **1**, which would be expected from an induced-fit mechanism; there is an energy price to pay for host reorganization upon guest binding. If the energy cost is not compensated by strong host–guest interactions, guest binding is precluded.

^{1}H NMR studies indicate that the binding pockets of the hosts are blocked by urea and sulfonamide coordination to the metallo center; host **5** shows signals upfield of 0 ppm, whereas the metal-free version of **5** does not show signals upfield of 0 ppm (Supporting Information). Hosts **2**–**4** show ^{1}H NMR signals significantly more upfield than their nonmetalated derivatives, indicating that metalation of the

Table 2. Selectivity of Anions with Receptors **1** and **6** (Ratio of Binding Constants)

	selectivity $H_2PO_4^-$/anion			selectivity $H_2PO_4^-$/anion	
anion	**1**	**6**	anion	**1**	**6**
I^-	7.4	6000.0	NO_3^-	15.2	10000.0
Br^-	5.0	2000.0	CO_3^{2-}	11.1	3.6
Cl^-	1.0	54.5	ReO_4^-	83.3	1500.0
NO_2^-	3.3	200.0	HSO_4^-	4.5	46.2
$CH_3CO_2^-$	1.3	4.3	$H_2PO_4^-$	1.0	1.0

porphyrin results in the groups appended at the meso position being in closer proximity to the porphyrin surface (presumably due to a coordinative interaction) where they experience anisotropic shielding due to the porphyrin π-surface. We are currently carrying out ^{1}H NMR titration studies with guests to better understand the conformational properties of the host–guest complexes. Future studies will also include a detailed anion recognition study of sulfonamide derivatives of **2**, **3**, and **5**, which might show improved recognition properties compared to hosts **2**, **3**, and **5**, similar to **6** versus **4**.

In summary, porphyrin urea-based hosts generally lead to complex binding interactions. Porphyrin-sulfonamide-based hosts are better behaved and may be useful in the development of shape-selective anion receptors, taking advantage of the complexation-induced binding in host design.

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Supporting Information Available. HD mass spectral data for hosts **1**–**6**. ^{1}H NMR spectra for hosts **1**–**6** at room temperature and 45 °C. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.