Published in final edited form as:

Org Lett. 2012 March 16; 14(6): 1370–1373. doi:10.1021/ol203249x.

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

MariJo Wienkers², Josmalen Ramos¹, Hikma Jemal¹, Chaz Cardenas¹, Paul Wiget², Alfreda Nelson², Shiloh Free¹, Jun Wu², Rebecca Roach², Marius Vulcan², Kristopher Waynant², Kyle Fort¹, Anna Vladimirova¹, Jeffery Sun¹, Samuel Eli Hunt¹, Dmitry M. Rudkevich^{3,§}, and Stephen D. Starnes¹

Stephen D. Starnes: stephen_starnes@tamu-commerce.edu

¹Department of Chemistry, Texas A&M University Commerce, Commerce, Texas 75429

²Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, New Mexico, 88003, USA

³Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019

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 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

Correspondence to: Stephen D. Starnes, stephen_starnes@tamu-commerce.edu.

[§]Beloved colleague and friend who passed away August 4, 2007.

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

Hay³ suggests 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.

There is active research in the design of optical and fluorescent sensors for anions⁴ 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 nucleobases⁹ and synthetic Heme analogs¹⁰ 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 eleven anion guests that vary in geometry: spherical (chloride, bromide, and iodide), 'bent' (acetate, nitrite), trigonal planar (nitrate, carbonate), and tetrahedral (perchlorate, perrhenate, hydrogen sulfate, and dihydrogen phosphate) was examined.

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 metallation with zinc (II) acetate gave receptors **2** - **6**.

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 CH₂Cl₂ (~1×10⁻⁶ M) with CH₂Cl₂ solutions of the tetrabutylammonium salts of the anions (the bis(tetraethylammonium salt of carbonate was used). Non-linear 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 isobestic 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 be offer other challenges in host-guest chemistry whereas

sulfonamide analogs can be better behaved.¹⁶ We then synthesized receptor **6** and indeed found that it gave sharp isobestic points with all guests. We are currently working towards the synthesis of sulfonamide derivatives of hosts **2**, **3** and **5**. Figures 2–3 show representative examples of the UV/vis titration curves of hosts **1** and **2** with anion guests. The inset shows the non-linear 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 intermolecular interaction. This is supported by ¹H-NMR and Uv/Vis spectroscopic studies. For model compound zinc-tetraphenylporphyrin (Zn-TPP), $\lambda_{\text{max}} = 419$ nm. For host **1**, $\lambda_{\text{max}} = 420$ nm. Upon anion complexation, a new band ~ 431 nm appears for the host **1**:anion complex. Zn-TPP complexes with anions typically show $\lambda_{\text{max}} = 429$ – 432 nm. For hosts **2** - **5**, $\lambda_{\text{max}} = 428$ nm. For hosts **2** - **5**, the complexes with anions typically show $\lambda_{\text{max}} \sim 432$ nm. For host **6** however, $\lambda_{\text{max}} = 424$ nm. Host **6**:anion complexes typically have $\lambda_{\text{max}} \sim 432$ nm. Thus, anion binding to zinc porphyrin hosts typically results in a red shift of the Soret band. Hosts **2** - **6** which have λ_{max} at a longer wavelength than host **1** suggests that these hosts exist in a conformation such that the zinc metallo center is coordinated to the urea and sulfonamide groups of each hosts (it is not clear at this point 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 receptors¹⁸ and enzymes.¹⁹

Furthermore, we believe this induced-fit mechanism leads to selectivity in guest binding (between guests and hosts that mimic the shape of the guest after the host conformational change) – thus we believe this illustrates an examples 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 compliments the tetrahedral shape of the anions dihydrogenphosphate, hydrogen sulfate, perhenate and perchlorate. Table 1 shows that host **1** does not bind guests with selectivity towards 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 tetrahedral 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 re-organization upon guest binding. If the energy cost is not compensated by strong host-guest interactions, guest binding is precluded.

¹H-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 ¹H-NMR signals significantly more upfield than their non-metallated derivatives indicating that metallation of the 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 pi-surface. We are currently carrying out ¹H-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the late Professor Dmitry Rudkevich, who initially encouraged Professor Starnes to utilize porphyrins for molecular recognition during his post-doctoral studies and he later suggested we examine the anion recognition properties of host **1**. Professor Starnes misses dearly his mentorship but mostly his friendship. We gratefully acknowledge support from the Robert A. Welch Foundation (T-0014), NSF-REU (Grant No. 0851966), the Chemistry Department and the Office of Graduate Studies & Research at Texas A&M-Commerce, NIH Grant Number RR-16480 from the BRIN program of the National Center for Research Resources and the Department of Chemistry and Biochemistry at New Mexico State University for funding this work.

References

1. Schmidtchen FP. *Coord Chem Rev.* 2006; 250:2918.
2. Tobey SL, Anslyn EV. *Org Lett.* 2003; 5:2029. [PubMed: 12790520]
3. Hay BP, Gutowski M, Dixon DA, Garza J, Vargas R, Moyer BA. *J Am Chem Soc.* 2004; 126:7925. [PubMed: 15212541]
4. For recent reviews of anion optical sensors see: (a) Suksai C, Tuntulani T. *Chem Soc Rev.* 2003; 32:192. [PubMed: 12875025] (b) Snowden TS, Anslyn EV. *Curr Opin Chem Biol.* 1999; 3:740. [PubMed: 10651521]
5. (a) Czarnik AW. *Chem Biol.* 1995; 2:423. [PubMed: 9383444] (b) Czarnik, AW. *ACS Symp Ser.* Vol. 538. ACS; Washington D.C: 1993. *Fluorescent Chemosensors for Ion and Molecule Recognition*; p. 1
6. (a) Ogoshi H, Mizutani T. *Acc Chem Res.* 1998; 31:81.(b) Ogoshi H, Kuroda Y, Mizutani T, Hayashi T. *Pure Appl Chem.* 1996; 68:1411.
7. Imai H, Misawa K, Munakata H, Uemori Y. *Chem Lett.* 2001:688.
8. Mizutani T, Murakami T, Matsumi N, Kurahashi T, Ogoshi H. *J Chem Soc Chem Commun.* 1995:1257.
9. Ogoshi H, Hatakeyama H, Kotani J, Kawashima A, Kuroda Y. *J Am Chem Soc.* 1991; 113:8181.
10. Ito F, Nishide H, Tsuchida E. *Chem Lett.* 1999:1149.
11. Jagessar RC, Shang M, Scheidt WR, Burns DH. *J Am Chem Soc.* 1998; 120:11684.
12. Beer PD, Drew MGB, Jagessar RC. *J Chem Soc, Dalton Trans.* 1997:881.
13. Lee C, Lee DH, Hong JI. *Tetrahedron Lett.* 2001; 42:8665.
14. Landrum JT, Grimmett D, Haller KJ, Scheidt R, Reed CA. *J Am Chem Soc.* 1981; 103:2640.
15. Collman JP, Wang Z, Straumanis A. *J Org Chem.* 1998; 63:2424. [PubMed: 11672096]
16. Sasaki Y, Shukla R, Smith BD. *Org Biomol Chem.* 2004; 2:214. [PubMed: 14737645] We are thankful to Professor Bradley Smith who suggested we make receptor **6**.
17. (a) Swinburne AN, Paterson MJ, Beeby A, Steed JW. *Chem Eur J.* 2010:2714. [PubMed: 20131345] (b) Beeren SR, Sanders JKM. *J Am Chem Soc.* 2011; 133:3804. [PubMed: 21361379] (c) Beeren SR, Sanders JKM. *Chemical Science.* 2011; 2:1560.
18. Weiss JJ. *Incl Phenom Macrocycl Chem.* 2001; 40:1.
19. Schneider S, Sharp KH, Barker PD, Paoli M. *J Biol Chem.* 2006; 281:32606. [PubMed: 16943192]

Figure 1.
Porphyrin hosts.

Figure 2. The 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. The 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.

Figure 4.
Induced-fit binding of anion guests.

Scheme 1.
Synthesis of Porphyrin Hosts

Table 1

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

anion	Association Constants					
	Zn-TPP	1	2	3	6	
I ⁻	0	68,000	3,500	2,000	500	
Br ⁻	15	100,000	23,000	10,000	1,500	
Cl ⁻	300	480,000	50,000	35,000	55,000	
NO ₂ ⁻	6,000	150,000	30,000	24,000	15,000	
CH ₃ CO ₂ ⁻	9,000	400,000	45,000	50,000	700,000	
NO ₃ ⁻	0	33,000	3,500	4,200	300	
CO ₃ ²⁻	8,000	450,000	150,000	<i>a</i>	840,000	
ClO ₄ ⁻	0	0	0	0	<i>a</i>	
ReO ₄ ⁻	0	6,000	0	0	2,000	
HSO ₄ ⁻	0	110,000	<i>a</i>	<i>a</i>	65,000	
H ₂ PO ₄ ⁻	16,000	500,000	<i>a</i>	<i>a</i>	3,000,000	

^a complex UV.

^b anions as their tetrabutylammonium salts for solubility in dichloromethane. Error $\pm$ 10%.

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

anion	selectivity $\text{H}_2\text{PO}_4^-/\text{anion}$		selectivity $\text{H}_2\text{PO}_4^-/\text{anion}$	
	1	6	1	6
I^-	7.4	6000.0	NO_3^-	15.2
Br^-	5.0	2000.0	CO_3^{2-}	11.1
Cl^-	1.0	54.5	ReO_4^-	83.3
NO_2^-	3.3	200.0	HSO_4^-	4.5
CH_3CO_2^-	1.3	4.3	H_2PO_4^-	1.0