

Self-Assembly of a Hydrophobic Binding Site

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Hydrophobic binding of aromatic groups is a critical aspect of biomolecular recognition, leading to catalysis, signal transduction, and structural organization. Effective synthetic models^{1,2} have allowed detailed study of such binding in well-defined systems. These studies have clarified, among other aspects,^{2a-d} the nature of the hydrophobic effect,^{2e} the attractive interactions between aromatics and other species,^{2f-i} and the geometric orientations conducive to binding.^{2j,k}

Since we are unable to predict the effect on binding affinity and geometry of subtle structural variation of host, methods of simply preparing a family of closely related potential binding sites are of particular interest. We present herein a novel approach to this end and note also that the self-assembly³ of the receptor⁴ is itself a biomimetic feature.⁵

Figure 1 shows the complex we designed as a new class of potential binding site. We have retained the diphenylmethane connectivity introduced by Koga⁶ and elaborated upon by others to good effect,^{1a,2f,7} but have introduced a polar solubilizing functionality by connecting the aromatic rings with a phosphorus atom. Such diarylphosphinic acid derivatives possess the desired concave hydrophobic surface, while presenting exterior hydrophilicity. A novel aspect of the design is the use of metals as an integral part of the structure. Amino acids are known to form metal complexes with a large variety of metals, and the shapes and sizes of the resulting complexes vary considerably. Several groups have taken advantage of the versatility of metal-ligand binding to encourage peptide secondary structure,⁸ analogously to the natural motifs.⁹ A few examples of hydrophobic^{4a,10} and

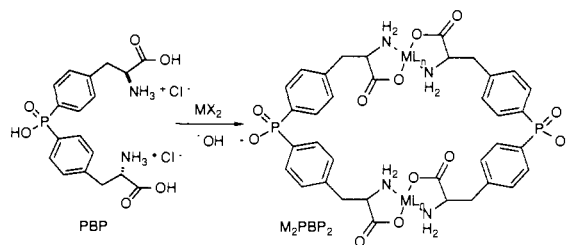


Figure 1.

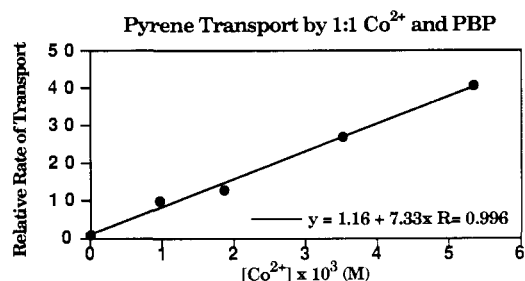
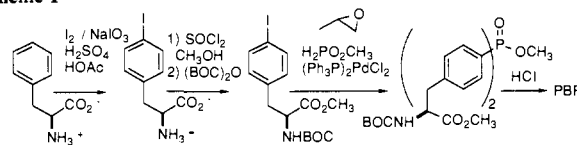


Figure 2. Rate of U-tube pyrene transport from isoctane (3 mL, 9.6×10^{-4} M) through 5 mL of aqueous Co^{2+} /PBP complex (0.79 cm^2 interface) to a second 3-mL isoctane layer. The rate is given relative to a background rate (without Co^{2+}) of $(1.09 \pm 0.12) \times 10^{-7} \text{ M h}^{-1}$ (95% conf, $N = 17$).

Scheme I

Table I. Transport of Pyrene Mediated by Metal/PBP Complexes^a

	Mn ²⁺	Fe ²⁺	Co ²⁺	Ni ²⁺	Cu ²⁺	Zn ²⁺	Cd ²⁺
relative rate ^b	1.15	1.12	9.96	9.92	1.07 ^c	1.43	1.33 ^c
% of ML ₂ complex ^d	5.0	48.0	51.0	79.0	99.0 ^c	70.0	37.0 ^c

^a Transport of pyrene from a $10.1 \times 10^{-3} \text{ M}$ isoctane solution through a 24°C , $\text{pH} \geq 9.5$, aqueous layer $9.6 \times 10^{-4} \text{ M}$ in 1:1 PBP and metal salt, except as noted. ^b Rates are relative to background rate measured without metal ($\pm 20\%$). ^c $[\text{M}^{2+}] = [\text{PBP}] = 1.86 \times 10^{-3} \text{ M}$. ^d Calculated fraction of metal at this concentration and $\text{pH} 9.5$ that would exist as $\text{M}(\text{Phe})_2$ complex.¹³

other¹¹ binding sites organized by a metal exist.

We prepared 4,4'-(hydroxyphosphinylidene)bis-L-phenylalanine (PBP) as shown in Scheme I. The key step is the conversion of protected iodophenylalanine in 59% yield into protected PBP using our newly developed palladium-catalyzed process.¹²

Metal complexes were prepared in solution by addition of equimolar metal salt to PBP in the presence of NaOH. Because the paramagnetic and redox-active nature of these complexes made NMR and fluorescence titrations impractical, U-tube transport experiments^{7a} were used to investigate their binding.

Aqueous solutions 1 mM each in metal salt and PBP were screened for their ability to transport pyrene. As shown in Table I, Co^{2+} and Ni^{2+} are highly effective, while Fe^{2+} , Mn^{2+} , Cu^{2+} , Zn^{2+} , and Cd^{2+} are much less so. Examination of CPK models led us to predict that certain isomers of octahedral metal complexes would be appropriate for pyrene binding and that square planar

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(e.g., Cu) complexes would not be, but we cannot yet explain the peculiarity of Co^{2+} and Ni^{2+} . Solutions of Co^{2+} or Ni^{2+} without PBP, or their complexes with tyrosine, or mixtures of metal and PBP without base are ineffective for pyrene transport. The binding ability of the self-assembled Co^{2+} complex is destroyed by addition of EDTA, which sequesters the metal; pyrene transport returns to the background rate. A Job's plot¹⁴ (data not shown) at $[\text{PBP}] + [\text{Co}^{2+}] = 1.74 \text{ mM}$ confirms that the species responsible for transport has a 1:1 ratio of PBP: Co^{2+} , as expected for a 2:2 PBP: Co^{2+} complex.

The pyrene transport rate (Figure 2) is directly proportional to the concentration of 1:1 Co^{2+} and PBP added.¹⁵ We have measured (see below) an 8-fold increase in the concentration of pyrene in water at equilibrium with 10 mM pyrene in isoctane due to the presence of $9.6 \times 10^{-4} \text{ M}$ each of Co^{2+} and PBP. This nicely matches the 8-fold increase in transport rate of the regression line.

The transport rate depends on the amount of pyrene dissolved in the aqueous phase, which in turn depends on the concentration of host and on the binding constant of the host for pyrene. The concentration of host complex is related to the concentration of $\text{M}(\text{amino acid})_2$, which we have estimated from known stability constants¹³ for metal complexes of phenylalanine; these are displayed in Table I. They are minimal estimates of ML_2 formation for the macrocyclic case. The transport rate does not correlate with stability, which suggests that transport rate is dependent not only on the amount of host complex formed but also, as we expected, on the geometry of the complex.

If the binding species is of composition Co_2PBP_2 , its concentration must be $\leq 4.8 \times 10^{-4} \text{ M}$ at $9.6 \times 10^{-4} \text{ M}$ added Co^{2+} . An upper limit for the dissociation constant for pyrene may be calculated on the basis of concentrations of pyrene measured (by extraction^{7a}) in water with and without Co_2PBP_2 (2.07×10^{-6} and 2.60×10^{-7} , respectively). A value of $K_D \leq 6.9 \times 10^{-5} \text{ M}$ is obtained, which favorably compares with the value of $5.5 \times 10^{-7} \text{ M}$ observed by Diederich^{7a} for pyrene binding by a related host bearing eight ortho methyl groups. Our self-assembled structure appears to bind within an order of magnitude as well as would a covalent host without methyl groups.¹⁶

The Co^{2+} /PBP complex transports pyrene selectively. Co^{2+} /PBP solutions ($9.6 \times 10^{-4} \text{ M}$) transport aromatic compounds at the following rates ($\pm 20\%$), relative to background: pyrene, 10; acenaphthene, 2.3; naphthalene, 1.2; 9-bromoanthracene, 1.3, *p*-iodotoluene, 1.0; biphenyl, 0.94. Bromoanthracene has a shape incompatible with the expected cavity, but naphthalene does not show enhanced transport even though it is expected to fit into the cavity. The background transport rate for naphthalene exceeds the facilitated pyrene rate, so that even if binding occurs, it may not manifest itself as measurably enhanced transport. Consistent with this interpretation, addition of $7.1 \times 10^{-4} \text{ M}$ *N*-methylquinolinium iodide to $8.1 \times 10^{-4} \text{ M}$ Co^{2+} and PBP causes a 46% decrease in pyrene transport rate, presumably by competing for well-defined binding sites.

These complexes have many interesting features, not least the open coordination sites on the octahedral metal ions available for catalysis of reactions of bound substrates and the capability for oxidation to substitutionally inert and diamagnetic Co^{3+} , which should make isolation and characterization of the isomer(s) responsible for the binding possible.

In conclusion, we have shown that binding of aromatic hydrocarbons from water by a binding site self-assembled by metal-ligand interactions is feasible and that significant variation of binding propensity may be achieved by choice of metal. The structures of these complexes remain to be elucidated.

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Synthesis and X-ray Crystallographic Analysis of Pentacoordinate 1,2-Oxasiletanides, Intermediates of the Peterson Reaction

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The Peterson reaction has been widely utilized for olefin synthesis as a silicon analog of the Wittig or Horner-Emmons reaction.¹ One of the features of this reaction is that (*E*) and (*Z*) olefins can be obtained stereospecifically from a single diastereomer of (β -hydroxyalkyl)silanes by changing reaction conditions (acidic vs basic).^{1b,d,2} From analogy with the Wittig reaction and from studies on the stereochemistry of the reaction (syn-elimination),² a pentacoordinate 1,2-oxasiletanide has been considered as a reaction intermediate or transition state, but neither isolation nor spectroscopic observation of such a species has been reported. Very recently, we succeeded in the synthesis of isolable pentacoordinate 1,2-oxaphosphetanes bearing the Martin ligand, i.e., intermediates of the Wittig reaction.³ We now report the first synthesis and X-ray crystallographic analysis of 1,2-oxasiletanides, intermediates of the Peterson reaction.

Sequential treatment of vinylsilane **1**⁴ bearing the Martin ligand with 1.5 equiv of *t*-BuLi (THF, -78°C), 5 equiv of hexamethylphosphoric triamide (HMPA), and then excess carbonyl compounds (**2a,b**) (THF, -78°C , 1 h) gave a diastereomeric mixture of the corresponding β -hydroxy silanes **3a** (34%) and **3b** (56%), together with olefins **4** and byproducts **5** and **6** (Scheme I).⁵ During purification by chromatography on silica gel, the more reactive diastereomer(s) decomposed to give olefins and only the less reactive one remained (recovery: **3a** (67%) and **3b** (38%)).⁶

Deprotonation of a single diastereomer of **3a** thus obtained with *n*-BuLi in THF was monitored by ¹⁹F and ²⁹Si NMR spectroscopy to show that 1,2-oxasiletanide **7a** was formed quantitatively and that two sets of double quartets with centers of $\delta_{\text{F}} -77.77$, -74.63 ($^4J_{\text{FF}} = 9.5 \text{ Hz}$) and -76.13 , -73.89 ($^4J_{\text{FF}} = 9.8 \text{ Hz}$) and a singlet ($\delta_{\text{Si}} -72.45$ at -50°C) in the ¹⁹F and ²⁹Si NMR spectra, respectively, for **7a** were unchanged from -50°C to room temperature. The large upfield shift in δ_{Si} from **3a** (δ_{Si} 10.66)⁷ to **7a** strongly supports the structure of a pentacoordinate silicate.⁸

It was found by ¹⁹F NMR spectroscopy that **7a** provided olefin **4a** and lithium silanoxide **9** in 86% yield together with unreacted **7a** (14%) upon heating (40°C , THF, 24 h), indicating that **7a** is a real intermediate of the Peterson reaction. Treatment of **7a** with acetic acid at room temperature resulted in the quantitative recovery of **3a**.⁹

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