Bioorganometallic Chemistry. 5. Molecular Recognition of Aromatic Amino Acid Guests by Cp*Rh−Nucleobase/Nucleoside/Nucleotide Cyclic Trimer Hosts in Aqueous Solution

Hong Chen, Marcos F. Maestre, and Richard H. Fish*

Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720

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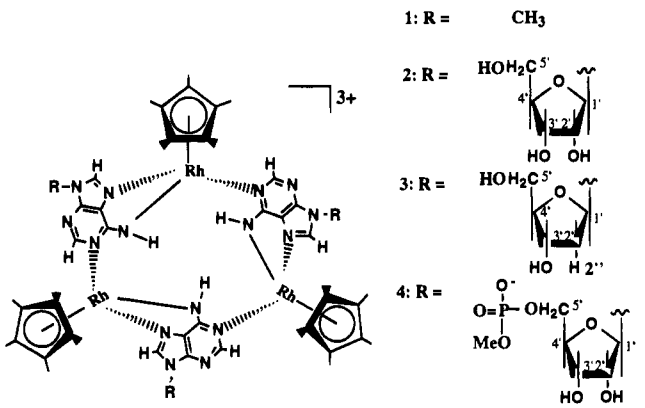
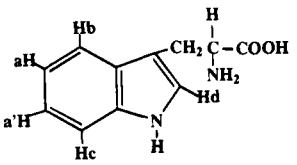
Noncovalent interactions, such as hydrogen bonding, $\pi-\pi$, and hydrophobic, are crucial elements for catalysis and molecular recognition in biosystems. Many supramolecular hosts have been synthesized to investigate the role of these interactions through recognition of biologically important guests, such as DNA/RNA nucleobases. The majority of these hosts that have been studied are organic compounds,[1] while relatively few studies have been attempted with inorganic or organometallic hosts.[2] For example, the macrocyclic organometallic hosts, synthesized by Loeb et al.,[2a] can recognize nucleobases via simultaneous first- and second-sphere coordination, i.e., σ-donation and hydrogen bonding. It is important to note that these latter host−guest chemistry studies were performed in *non-aqueous* media.

Recently, we reported on the synthesis of several Cp*Rh−DNA/RNA cyclic trimer complexes, $[Cp^*Rh(9\text{-methyladenine})]_3(OTf)_3$ (**1**),[3a] $[Cp^*Rh(adenosine)]_3(OTf)_3$ (**2**),[3a,c] $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ (**3**),[3c] and $[Cp^*Rh(Me\text{-}5'\text{-AMP})]_3$ (**4**).[3b,c] These four Cp*Rh cyclic trimers are quite stable in aqueous solution; for example, complex **1** was observed by NMR spectroscopy for 2 weeks at pH 6−9, with no apparent decomposition.[3a]

Complex **1** is a racemic mixture, while cyclic trimers **2**−**4** are mixtures of two diastereomers. The X-ray crystal structure of an enantiomer of **1** showed that it has a triangular domelike cavity, with three Cp* groups stretching out from the top of the dome, three Me groups pointing to the bottom, three adenine planes forming the surrounding shell, and three Rh atoms embedded on the top of the dome.[3a] This molecule also possesses a C3 axis, which passes from the top of the dome to the bottom. The distance between the adjacent Me groups at the bottom of the dome, i.e., at the opening of this molecular cavity, is about 7.5 Å.



The structures of **2**−**4** are similar to that of **1**, except that the three Me groups are replaced by three ribose, deoxyribose, or three Me-5′-ribose monophosphate ester units, respectively. The substitutions made **2**−**4**, and especially **4**, more sterically hindered at the opening of these molecular cavities than **1**. Therefore, the shape, the cavity size, and the aqueous stability of these Cp*Rh−nucleobase/nucleoside/nucleotide cyclic trimers, **1**−**4**, prompted us to utilize them as potential hosts to possibly recognize biologically relevant molecules in aqueous media at a physiological pH of 7. We report what we believe is the first example of bioorganometallic hosts, **1**−**4**, being able to recognize aromatic amino acid guests L-tryptophan (L-Trp) and L-phenylalanine (L-Phe) *in aqueous media at pH 7.*



L-Trp

The scope of the molecular recognition of different amino acid guests with hosts **1**−**4** was studied by using ^1H NMR spectroscopy at ambient temperature. The complexation-induced ^1H NMR chemical shifts (CICS) of both guests and hosts are tabulated and presented in the supplementary material. These data show that cyclic trimers **1**−**4** can only recognize aromatic amino acids such as L-Phe and L-Trp, while nonaromatic amino acids, such as L-histidine, L-alanine, and L-proline, apparently do not interact with these hosts, the exception being some hydrophobic amino acids, such as L-isoleucine (L-Ile) and L-leucine (L-Leu), which only interact slightly.

The strongest complexation observed was between **3** and L-Trp. The two protons (a and a′, see L-Trp structure for proton designation) on the benzene ring of L-Trp were influenced to the greatest extent by what appears to be classical $\pi-\pi$ interactions,[4] with a 0.45 ppm upfield shift, while the other two proton resonances (b and c) were shifted upfield by only 0.19 ppm; proton (d) on the five-membered ring and the asymmetric CH_2 and *CH protons were also slightly affected by this $\pi-\pi$ interaction, with 0.01−0.02 ppm upfield shifts. The chemical shifts of host **3** do not show significant changes; only slight upfield shifts of 0.01 to 0.08 ppm were observed. It is important to note that no enantio- or diastereoselectivity was observed by NMR for hosts **1**−**4** in the molecular recognition reactions, and thus, it appears that all stereoisomers were affected in a similar manner.

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(2) (a) Kickham, J. E.; Loeb, S. J.; Murphy, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7031 and reference therein. (b) Stang, P. J.; Cao, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4981 and reference therein. (c) Fujita, M.; Yazaki, J.; Ogura, K. *J. Am. Chem. Soc.* **1990**, *112*, 5645. (d) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240 and reference therein.

(3) (a) Smith, D. P.; Baralt, E.; Morales, B.; Olmstead, M. M.; Maestre, M. F.; Fish, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 10647. (b) Smith, D. P.; Kohen, E.; Maestre, M. F.; Fish, R. H. *Inorg. Chem.* **1993**, *32*, 4119. (c) Complex **2**: FAB/MS (relative intensity), $[M - OTf]^+$ (2.2), $[M - Ado + 4H]^+$ (2.1), $[M - Ado - OTf]^+$ (1.6), and $[(Cp^*RhAdo)_2(OTf)-2Cp^* + H]^+$ (100). Elemental analysis for $C_{63}H_{81}F_9N_{15}O_{21}Rh_3S_3{\cdot}7H_2O$, calcd: C, 36.6; H, 4.6; N, 10.1. Found: C, 36.7; H, 4.4; N, 9.6. Complex **3**: FAB/MS (relative intensity), $[M - OTf]^+$ (5.4), $[M - OTf - dAdo]^+$ (3.1), $[M - OTf - 2(dAdo)]^+$ (1.7), and $\{[Cp^*Rh(dAdo - H)]_2(OTf)_2 - OTf\}^+$ (100). Elemental analysis for $C_{63}H_{81}F_9N_{15}O_{18}Rh_3S_3{\cdot}8H_2O$, calcd: C, 36.8; H, 4.7; N, 10.2. Found: C, 36.9; H, 4.5; N, 9.8. Complex **4**: FAB/MS (relative intensity), $[M + 2Na]^+$ (1.1), $[M + Na]^+$ (2.2), and $[M + Na - (Me\text{-}5'\text{-AMP})]^+$ (4.0). Elemental analysis for $C_{63}H_{87}N_{15}O_{21}P_3Rh_3{\cdot}3\text{-}NaOTf{\cdot}10H_2O$, calcd: C, 31.8; H, 4.3; N, 8.4. Found: C, 32.3; H, 4.7; N, 8.3. Complete synthetic procedures for **2**−**4** are presented in the supplementary material.

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Table 1. Estimated Association Constants ($\mathbf{K_a}$)[a,b] for Molecular Recognition

	host			
guest	**1**	**2**	**3**	**4**
L-Trp	43	472	607	<10
L-Phe	16	12	<10	<10

[a] Spectra were taken on a 400 MHz NMR instrument. The $\mathbf{K_a}$ units are M^{-1}. The R values of least-square plots were 0.98 or higher, and the limit of error ranged from 5% to 10%. [b] Values encompass both of the enantiomers or the diastereomers.

Although L-Trp is slightly larger in size than L-Phe, it shows stronger interactions with **1**−**4** compared to L-Phe. The steric effect is minimized since the cavities of the hosts, especially **1**−**3**, are large enough to fit L-Trp without significant hindrance. We feel that both electronic and possible hydrophobic effects provide the interaction differences between L-Trp and L-Phe and hosts **1**−**3**. For example, the lone electron pair on the nitrogen atom of the five-membered heterocyclic ring of L-Trp could donate electron density to the adjacent phenyl ring to make this ring more electron-rich in comparison to L-Phe. Presumably, this electron enrichment is one reason that L-Trp has stronger $\pi-\pi$ interactions with the electron-deficient π systems of **1**−**4**.[1b,5] Greater hydrophobicity of L-Trp might be another reason that it has stronger interactions with **1**−**4**. This latter reasoning was supported by the apparent weak interactions of **1**−**4** with some hydrophobic aliphatic amino acids, such as L-Ile and L-Leu.

To verify that the molecular recognition of aromatic amino acid guests occurs inside of the cavities of hosts **1**−**4**, the steric effect of host **4** on the CICS of the guests was studied. As mentioned previously, the steric effect on the cavity opening of **4** is much greater than that on **1**−**3**. Therefore, we rationalized that it should be more difficult for the L-Trp and L-Phe guests to enter the cavity of **4** than to enter **1**−**3**. Indeed, we observe that the CICS of both L-Trp and L-Phe by host **4** were dramatically reduced in comparison to those induced by hosts **1**−**3**.

The association constants (K_a) of host−guest interactions were measured by using a standard NMR method to confirm the trends which were observed.[6] The estimated K_a values, a value that encompasses both enantiomers and diastereomers of **1**−**4**, are summarized in Table 1, and these data agreed with the chemical shift changes of the guests upon interactions with the sterically demanding hosts. It is noteworthy that L-Trp, with its N-donating atom and possible hydrophobic effects, has the largest K_a values with hosts **2** and **3**.

The host−guest interaction was also supported by an intermolecular NOE (supplementary material) between **3** and L-Trp, with negative NOE signals being observed between H8 and H2 on **3** and the L-Trp a, a′, b, and c aromatic protons; no intermolecular NOE signal was found between **3** and the solvent D_2O, which excludes the possibility that the NOE data was an artifact. The relatively small association constant ($K_a = 607$) for **3** and L-Trp, in comparison to the literature reported values[1a,i,2d] of 10^1-10^6 M^{-1}, was probably responsible for the weak intermolecular NOE signals that were observed.

The overall results suggest that the molecular recognition of L-Trp with **3** can be described in a way that places the L-Trp

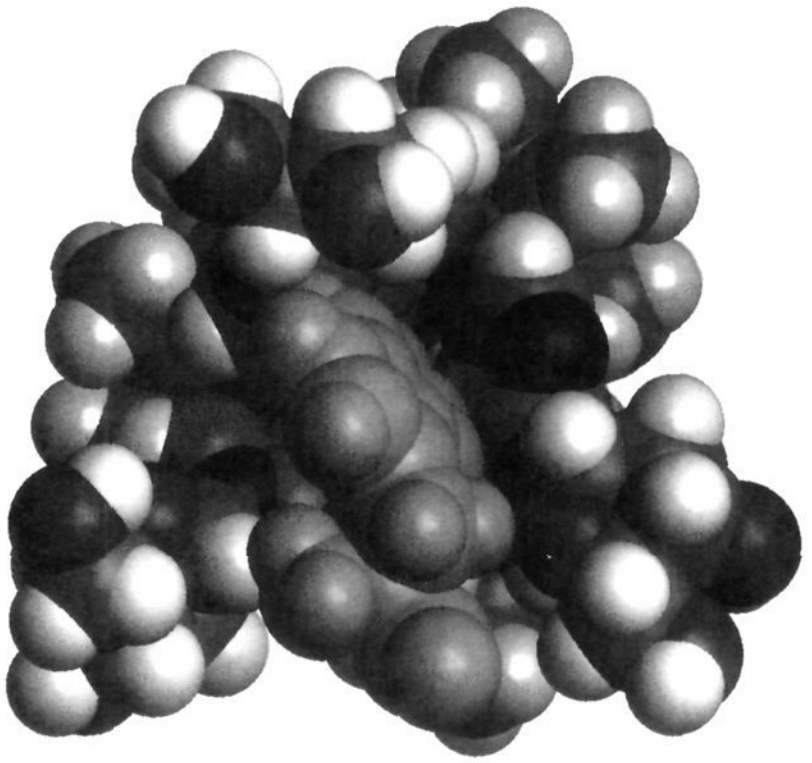

Figure 1. Molecular graphics space-filling model of host **3** and guest L-Trp.

aromatic rings inside the host cavity, with the aromatic plane, or more specifically, the line which bisects the C−H(a) and C−H(a′) bonds, parallel to the C3 axis of host **3**; the asymmetric CH_2 and *CH groups are around the opening of the host cavity, while the carboxylate tail is left outside the cavity. Figure 1 depicts the energy minimized space-filling model of **3** and the docking of L-Trp to visually demonstrate[7] the plausible host−guest interactions that were established by NMR spectroscopy.

In summary, the molecular recognition of aromatic amino acids with bioorganometallic hosts **1**−**4** in aqueous solution, as studied by ^1H NMR and NOE techniques, occurs predominately via a $\pi-\pi$ interaction, and, in the case of L-Trp, additional electronic/hydrophobic interactions with hosts are possible. Further molecular modeling studies and NMR experiments with other potential biological guests are being explored to understand the scope of these host−guest interactions, all in aqueous solution.

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Supplementary Material Available: Tables of CICS of hosts and guests **1**−**4** and various amino acids; synthetic and spectroscopic procedures; 1D-NOE spectra; ^1H NMR spectra of **3** and **3** + L-Trp (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(6) Foster, R.; Fyfe, C. A. *Prog. Nucl. Magn. Reson. Spectrosc.* **1969**, *4*, 1. The changes in the 400 MHz ^1H NMR of the guest, in the presence of constant concentration of the host, were monitored by incremental additions of guest at [host]:[guest] ratios of 1:20 to 1:60.

(7) The Biosym Technologies Insight II molecular graphics software was used to convert the X-ray crystallography data of complex **1** to an energy minimized (ribose only) space-filling model. The calculations were accomplished with the Discover program using CVFF force field. In that manipulation, the R group on the cyclic trimer could be replaced with a ribose or deoxyribose. The L-Trp was then docked and energy minimized to produce Figure 1.