Bioorganometallic Chemistry. 8. The Molecular Recognition of Aromatic and Aliphatic Amino Acids and Substituted Aromatic and Aliphatic Carboxylic Acid Guests with Supramolecular (η^5-Pentamethylcyclopentadienyl)rhodium−Nucleobase, Nucleoside, and Nucleotide Cyclic Trimer Hosts via Non-Covalent $\pi-\pi$ and Hydrophobic Interactions in Water: Steric, Electronic, and Conformational Parameters

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Abstract: Molecular recognition, via non-covalent processes such as hydrogen bonding, $\pi-\pi$, and hydrophobic interactions, is an important biological phenomenon for guests, such as drugs, proteins, and other important biological molecules with, for example, host DNA/RNA. We have studied a novel molecular recognition process using guests that encompass aromatic and aliphatic amino acids [L-alanine, L-glutamine (L-**Gln**), L-histidine, L-isoleucine (L-**Ile**), L-leucine (L-**Leu**), L-phenylalanine (L-**Phe**), L−proline, L-tryptophan (L-**Trp**), L-valine (L-**Val**)], substituted aromatic carboxylic acids [*o*-, *m*-, *p*-aminobenzoic acids (**G1**-**3**), benzoic acid (**G4**), phenylacetic acid (**G5**), *p*-methoxyphenylacetic acid (**G6**), *o*-methyoxybenzoic acid (**G9**), *o*-nitrobenzoic acid (**G10**)], and aliphatic carboxylic acids [cyclohexylacetic acid (**G7**), 1-adamantanecarboxylic acid (**G8**)] with supramolecular, bioorganometallic hosts, (η^5-pentamethylcyclopentadienyl)rhodium (Cp*Rh)−nucleobase, nucleoside, and nucleotide cyclic trimer complexes, $[Cp^*Rh(9\text{-methyladenine})]_3(OTf)_3$ (**1**) (OTf = trifluoromethanesulfonate), $[Cp^*Rh(\text{adenosine})]_3(OTf)_3$ (**2**), $[Cp^*Rh(2'\text{-deoxyadenosine})]_3(OTf)_3$ (**3**), $[Cp^*Rh(2',3'\text{-dideoxyadenosine})]_3(OTf)_3$ (**4**), and $[Cp^*Rh(\text{Me-}5'\text{-AMP})]_3$ (**5**), in aqueous solution at pH 7, utilizing ^{1}H NMR, NOE, and molecular modeling techniques, and, as well, determining association constants (K_a) and free energies of complexation ($\Delta G°$). The host−guest complexation occurs predominantly via non-covalent $\pi-\pi$, hydrophobic, and possible subtle H-bonding interactions, with steric, electronic, and molecular conformational parameters as important criteria. Moreover, we note that both the $\pi-\pi$ and hydrophobic interactions seem to be equally important when competing aromatic and aliphatic carboxylic acid guests, **G5** and **G7**, for host **3**. The solvophobic effects in H_2O also control the extent of host−guest interaction and will be discussed.

Introduction

Supramolecular interactions that encompass recognition, reaction, transport, etc. are fundamental phenomena in biological systems that are involved in a number of processes between biologically important molecules, such as double and single strand DNA/RNA with, for example, proteins, drugs, and metal-ion containing probes, to name a few examples.[1] Organic chemists have exploited these interesting phenomena to a very significant extent and many supramolecular hosts have been synthesized to investigate the role of these interactions through the molecular recognition of guests, such as nucleosides, nucleotides, amino acids, peptides, and small organic molecules, by predominately non-covalent hydrogen bonding, $\pi-\pi$, and hydrophobic interactions.[2]

Surprisingly, few molecular recognition studies have been attempted with inorganic or organometallic hosts.[3] A pertinent organometallic example is the macrocyclic organopalladium hosts, synthesized by Loeb et al.,[3a] that can recognize nucleo-

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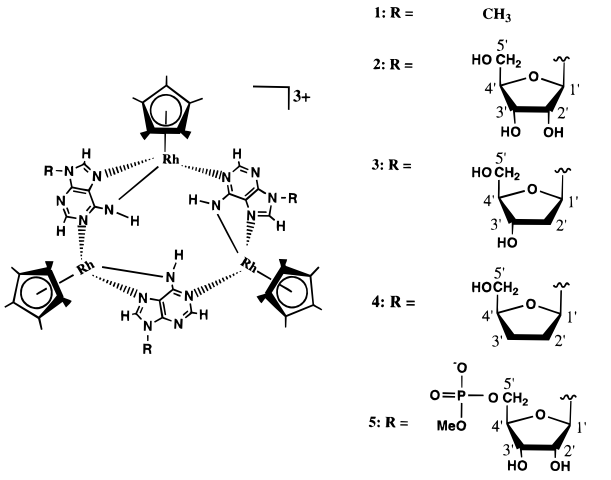
Chart 1. Hosts **1**−**5**

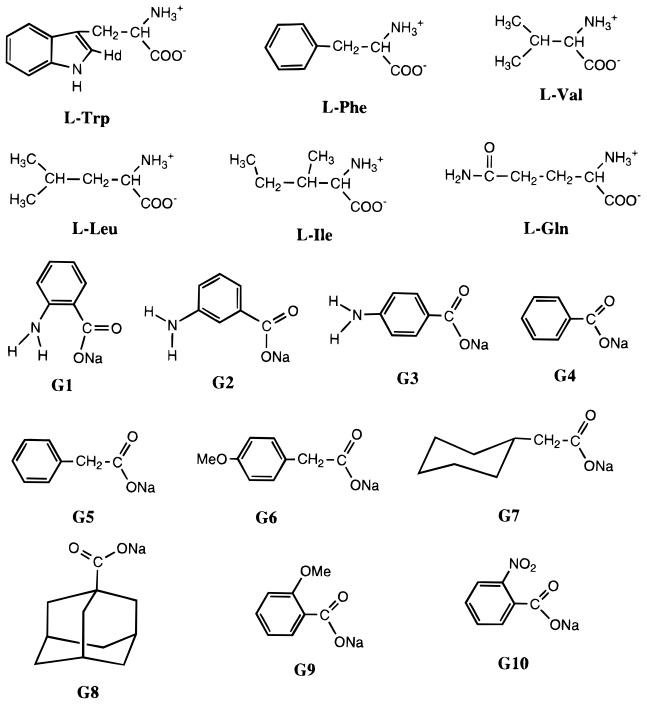


bases via simultaneous first- and second-sphere coordination, i.e., σ-donation to Pd and hydrogen bonding to the macrocycle heteroatoms. It is important to note that these latter host−guest chemistry studies were performed in *non-aqueous* media presumably because of the instability of their macrocyclic organometallic hosts in water or their lack of solubility in aqueous solution. As well, chiral metalloporphyrin receptors in organic solvents have also been studied to show preferential binding to amino acids,[3b] while Stang and co-worker synthesized a series of platinium and palladium macrocyclic squares for host−guest complexation using a dihydroxynaphthalene compound as an example, also in organic solvents.[3c]

Among the limited inorganic or organometallic supramolecular hosts studied, none of them, however, were constructed by incorporating nucleobase, nucleoside, or nucleotide molecules as crucial components of the host framework. Recently, in our preliminary communication,[4a] we reported on the molecular recognition of aromatic and aliphatic amino acid guests by supramolecular Cp*Rh−nucleobase, nucleoside, and nucleotide cyclic trimer hosts, **1**,[4b] **2**,[4b] **3**, and **5**[4c] in aqueous solution at pH 7 (Chart 1). This type of host−guest chemistry in aqueous solution is important, since it could be considered as the simplest model for the interactions between DNA/RNA molecules and their binding proteins, such as those that regulate genes. Moreover, the non-covalent hydrophobic effect is more fully dramatized in water by solvophobic forces that enhance host−guest interactions.[5]

In this full account, we will discuss the scope of our molecular recognition studies by extending the guest examples from aromatic and aliphatic amino acids to substituted aromatic and aliphatic carboxylic acids (Chart 2) and determine the importance of $\pi-\pi$, hydrophobic, and H-bonding effects as a function of steric, electronic, and conformational parameters, along with host−guest thermodynamic parameters, K_a (association constants) and $\Delta G°$ (free energies of complexation) values. As well, a new host, [Cp*Rh(2′,3′-dideoxyadenosine)]$_3$(OTf)$_3$ (**4**), was introduced (Chart 1) in an attempt to fine-tune the hydrophobic interaction with the designated guests.

Chart 2. Guests



Results

Hosts 1−5: Synthesis, Structure, and Aqueous Stability. The hosts **1**−**5** are shown in Chart 1 and the synthetic procedures are described in the Experimental Section.[4b,c,6] Trimer **1** is a racemic mixture, while other cyclic trimers, **2**−**5**, are mixtures of two diastereomers. The single-crystal X-ray structure of an enantiomer of **1** was reported previously and showed that it has a triangular dome-like supramolecular structure, 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 in the top of the dome.[4b] This molecule also possesses a C3 axis, which passes from the top of the dome to the bottom. The distance between the adjacent methyl groups at the bottom of the dome, i.e., at the opening of this molecular receptor, is about 7.5 Å, while the cavity depth is a consequence of the substituent on N9 of the nucleobase, nucleoside, or nucleotide and is in the range of ∼4 Å.

The structures of **2**−**5** are similar to that of **1**, except that the three Me groups are replaced by these ribose, 2′-deoxyribose, 2′,3′-dideoxyribose, or three Me-5′-ribose monophosphate ester units, respectively. The substitutions made **2**−**5**, and especially **5**, more sterically hindered at the opening of these molecular cavities than that of **1**. Figure 1 shows the stick model (side view) and the CPK model (bottom view) of host **3**. The reason cyclic trimers **3** and **4** were chosen is that they can be used to probe the hydrophobic influences of the host in the recognition process, since 2′-deoxyribose and 2′,3′-dideoxyribose units have only two OH groups at 3′ and 5′ positions, and one OH group at the 5′ position, respectively. Alternatively, trimer **5** was selected for monitoring the steric effects of the host, since the Me-5′-ribose monophosphate ester unit was bulkier than the other N9 substituents, methyl, ribose, 2′-deoxyribose, or 2′,3′-dideoxyribose.

These five Cp*Rh cyclic trimers are quite stable in aqueous solution; for example, complexes **1** and **3** were observed by ^{1}H NMR spectroscopy, for 2 weeks, at pH 6−9, with no apparent decomposition.[4b] Therefore, all the critical parameters for host−

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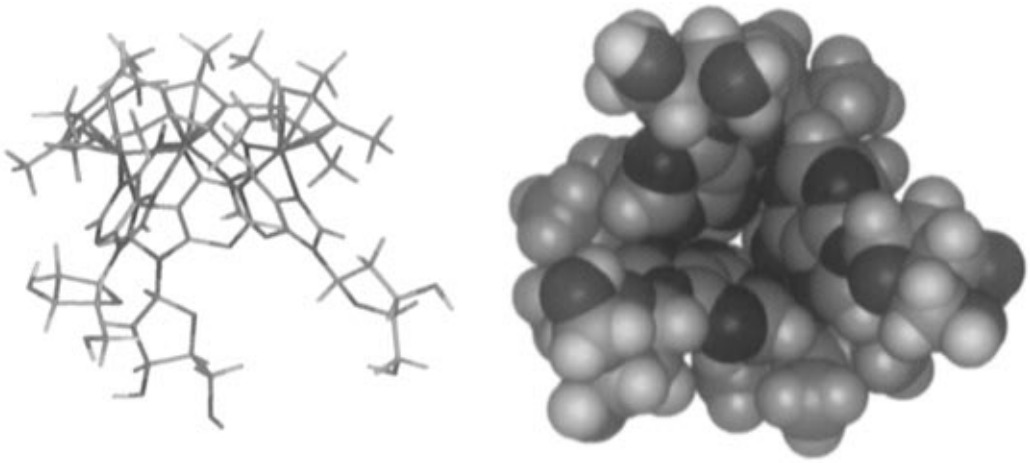


Figure 1. (left) Stick model (side view) and (right) CPK model (bottom view) of host **3**.

Table 1. Complexation-Induced ^{1}H NMR Chemical Shifts (CICS, ppm) of Various Amino Acid Guests by Hosts **1**−**5** at pH 7 and 25 °C

guest	aromatic regions	nonaromatic regions
		Host **1**
L-**Phe**	−0.30 (Hp); −0.13 (Ho, Hm)	−0.01 (*CH); −0.02 (CH_2)
L-**Trp**	−0.36 (Ha, Ha′); −0.16 (Hb, Hc); −0.02 (Hd)	−0.02 (*CH); −0.03 (CH_2)
L-**Ile**		−0.14 (γ-Me); −0.07 (CH_2); −0.04 (β-Me); m[a] (CH); −0.02 (*CH)
		Host **2**
L-**Phe**	−0.26 (Hp); −0.11 (Ho, Hm)	−0.02 (*CH); −0.02 (CH_2)
L-**Trp**	−0.40 (Ha, Ha′); −0.17 (Hb, Hc); −0.02 (Hd)	−0.03 (*CH); −0.03 (CH_2)
L-**Ile**		−0.11 (γ-Me); −0.05 (CH_2); −0.03 (β-Me); m[a] (CH); −0.01 (*CH)
		Host **3**
L-**Phe**	−0.18 (Hp); −0.07 (Ho, Hm)	−0.01 (*CH); −0.01 (CH_2)
L-**Trp**	−0.45 (Ha, Ha′); −0.19 (Hb, Hc); −0.02 (Hd)	−0.02 (*CH); −0.03 (CH_2)
L-**Ile**		−0.06 (γ-Me); −0.02 (CH_2); −0.01 (β-Me); −0.02 (CH); −0.01 (*CH)
L-**Leu**		−0.05 (Me); −0.01 (CH); −0.01 (CH_2); m[a] (*CH)
L-**Val**		−0.01 (Me); <−0.01 (CH); 0.00 (*CH)
		Host **4**
L-**Phe**	−0.14 (Hp); −0.07 (Ho, Hm)	0.00 (*CH); −0.01 (CH_2)
L-**Trp**	−0.32 (Ha, Ha′); −0.11 (Hb, Hc); −0.02 (Hd)	−0.02 (*CH); −0.02 (CH_2)
L-**Ile**		−0.06 (γ-Me); −0.03 (CH_2); −0.01 (β-Me); m[a] (CH); −0.01 (*CH)
		Host **5**
L-**Phe**	−0.14 (Hp); −0.06 (Ho, Hm)	m[a] (*CH); −0.01 (CH_2)
L-**Trp**	−0.21 (Ha, Ha′); −0.09 (Hb, Hc); −0.02 (Hd)	m[a] (*CH); −0.02 (CH_2)
L-**Ile**		−0.07 (γ-Me); −0.03 (CH_2); −0.02 (β-Me); m[a] (CH); −0.01 (*CH)

[a] m indicates masked by the host signals.

guest chemistry, such as the supramolecular bowl shape, the large cavity size, and the aqueous stability of these Cp*Rh−nucleobase/nucleoside/nucleotide cyclic trimers, **1**−**5**, provided the opportunity to utilize them as molecular receptors to recognize biologically relevant molecules in aqueous media at a physiological pH of 7.[4a]

Molecular Recognition of Aromatic and Aliphatic Amino Acids. About one-half of the 20 common amino acids were selected in this molecular recognition study, and several criteria were considered in the selection process: (1) solubility in H_2O; (2) representativeness; and (3) stability of the hosts in the presence of the amino acids. According to these criteria, tyrosine, cysteine, and methionine were excluded, since the first example is not soluble in H_2O, and the latter two apparently caused the slight decomposition of the hosts. The structures of six key amino acids [L-tryptophan (L-**Trp**), L-phenylalanine (L-**Phe**), L-valine (L-**Val**), L-leucine (L-**Leu**), L-isoleucine (L-**Ile**), and L-glutamine (L-**Gln**)] are shown in (Chart 2). The pK_a values of these amino acids are indicative of the zwitterion forms being the predominant species at pH 7.[7]

The molecular recognition process of these different amino acid guests with hosts **1**−**5** was studied using ^{1}H NMR spectroscopy at ambient temperature. The complexation-induced ^{1}H NMR chemical shifts (CICS) of both guests and amino acid hosts are presented in Tables 1 and 2, respectively. The presence of upfield chemical shifts for any guest studied with a host was an indication of a possible host−guest interaction. We found by varying the concentration of the hosts **1**−**5** from 0 to 1 equiv in the presence of the appropriate amino acid guest, at a constant concentration of 1.0 equiv, that the CICS values for the guests were maximized at ∼0.8−1.0 equiv. Therefore, in all subsequent host−amino acid guest experiments, we utilized 1.0 equiv of each host and 1.2 equiv of each guest. Furthermore, the data show that cyclic trimers, **1**−**5**, can only recognize aromatic amino acids (L-**Phe**, L-**Trp**) and several aliphatic amino acids with relatively long hydrophobic side chains (L-**Leu**, L-**Ile**), pointing to the possibility of classical $\pi-\pi$ and/or hydrophobic interactions. Other amino acids, such as L-**Val**, L-**Gln**, L-histidine, L-alanine, and L-proline (the latter three amino acids were not listed in Table 1 or shown in Chart 2), however, do not apparently interact with these hosts. It is important to note that no enantio- or diastereoselectivity was observed by ^{1}H NMR for hosts **1**−**5** in the molecular recognition reactions, and thus, it appears that all stereoisomers were affected in a similar manner.

(7) *Lange's Handbook of Chemistry*, 14th ed.; Dean, J. A., Ed.; McGraw-Hill: New York, NY, 1992.

Table 2. Complexation-Induced ^{1}H NMR Chemical Shifts (CICS, ppm) of Hosts **1**−**3** by Amino Acid Guests

	CICS of **1**			
guest	H2	H8	Me	Cp*
L-**Phe**	<−0.01	<−0.01	−0.02	−0.01
L-**Trp**	−0.01	−0.01	−0.04	−0.03
L-**Ile**	<−0.01	0.00	0.00	<−0.01

	CICS of **2**							
guest	H2	H8	H1′	H2′	H3′	H4′	H5′ & H5″	Cp*
L-**Phe**	<0.01	<0.01	−0.01	−0.02	−0.03	<−0.01	<−0.01	0.00
L-**Trp**	<−0.01	<0.01	−0.03	−0.04	−0.06	−0.01	−0.03	−0.01

	CICS of **3**								
guest	H2	H8	H1′	H2′	H2″	H3′	H4′	H5′ & H5″	Cp*
L-**Phe**	<0.01	<0.01	−0.01	−0.01	−0.01	−0.01	<−0.01	<−0.01	0.00
L-**Trp**	<0.01	<−0.01	−0.05	−0.09	−0.05	−0.04	−0.01	−0.02	−0.01

One question that we needed to address concerns whether the molecular recognition process we observe between the amino acid guests and hosts **1**−**5** is occurring *inside* or *outside* of the molecular receptor, since one may argue that the observed CICS values of the amino acid guests might come from the interaction of the guests with the three Cp* groups of the hosts. In order to definitively answer this question, we studied the steric effect of host **5** on the CICS values of the guests. As mentioned previously, the steric effect on the cavity opening of host **5** is much greater than those of **1**−**4**. Therefore, we rationalized that it should be more difficult for the guest molecules, such as L-**Trp** and L-**Phe**, to enter the cavity of host **5** in comparison to those of **1**−**4**.

Indeed, we observe that the CICS values of both L-**Trp** and L-**Phe** by host **5** were dramatically reduced in comparison to those induced by hosts **1**−**4** (see Table 1). These results support the conclusion that the molecular recognition of amino acid guests occurs *inside* of the cavities of hosts **1**−**5**. The steric effect of host **5** in comparison to hosts **1** and **2**, for the molecular recognition of guest L-**Phe**, can be illustrated in the stacked ^{1}H NMR plot presented in Figure 2. Thus, Figure 2 clearly shows that the CICS value for the L-**Phe** Hp proton with **5** (spectrum c) is much less than similar values with hosts **1** and **2** (spectra a and b). Further support for a host−guest interaction occurring *inside* the host cavity comes from the fact that guest molecules, such as L-**Phe**, interact with hosts **1**−**5** differently. If the CICS values of the amino acid guests came from the interactions with the three Cp* groups on the *top* of the supramolecular hosts, then the values would be similar, regardless of the steric hindrance at the *bottom* of the receptor's opening.

Interestingly, when comparing the extent of the molecular recognition process of the guests, L-**Phe** and L-**Trp**, by hosts **1**−**5**, we found that the latter guest showed the greater interaction even though it is slightly larger in size than the former guest. This observation may be rationalized by the following three factors: (1) Sterically, the cavity sizes of the hosts, especially **1**−**4**, were large enough to fit L-**Trp** without any significant hindrance, and furthermore, L-**Trp** entered the cavities by using the most favored steric orientation. It is necessary to note that the major portion of L-**Trp**, which entered the receptor, was the benzene ring, which was very similar to the L-**Phe** case and, therefore, the steric influences of L-**Trp** and L-**Phe** during the recognition process were about the same. (2) Electronically, the lone electron pair on the nitrogen atom of the five-member heterocyclic ring of L-**Trp** could donate electron density to the adjacent benzene 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**.[2b,5b]

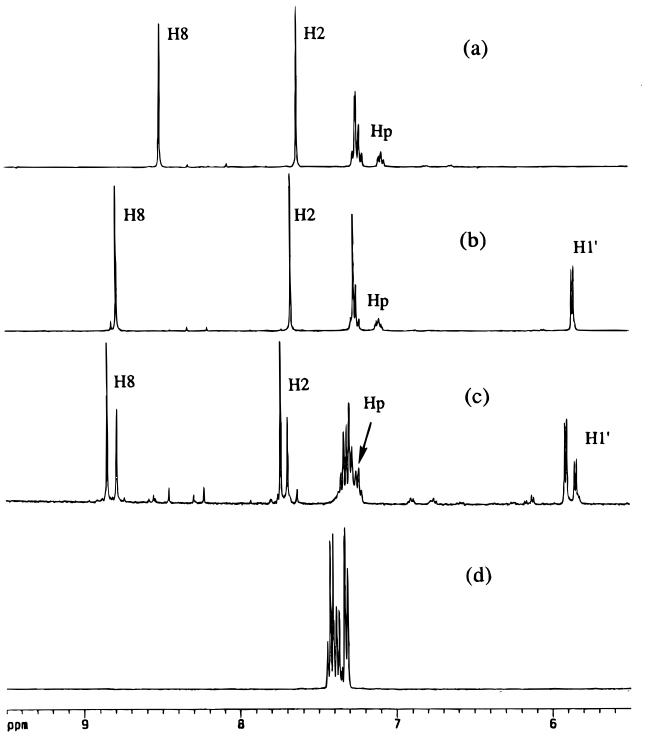


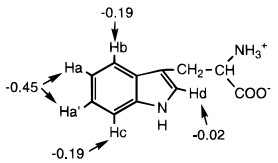
Figure 2. The steric effects of host **5** in comparison to hosts **1** and **2** with 1.2 equiv of the L-**Phe** guest: (a) **1** + 1.2 L-**Phe**; (b) **2** + 1.2 L-**Phe**; (c) **5** + 1.2 L-**Phe**; and (d) L-**Phe**.

(3) The greater hydrophobicity of L-**Trp** (solubility = 0.01 g/g of H_2O, Hansch partition coefficient, log $P_{octanol}$ = −1.04) appears to be another important reason, with the solvophobic effect of water as the driving force for this rather facile molecular recognition process. The stronger interaction of L-**Trp** with **1**−**4** must be multicomponent, encompassing $\pi-\pi$, hydrophobic, and solubility effects, since some amino acids, such as L-**Ile** and L-**Leu**, have relatively long hydrophobic side chains and were shown to be weakly associated with hosts **1**−**4**; the later mentioned aliphatic amino acids are also more soluble in water in comparison to L-**Trp**. As well, L-**Gln**, which also has a relatively long hydrophilic side chain, apparently did not interact with **1**−**4**, and again dramatizes the solvophobic effect.

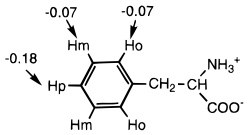
For nucleoside hosts, **2**−**4**, the role of the hydroxyl groups on the ribose may be understood by comparing their interactions with guests, L-**Phe** and L-**Trp**. Hosts **2**, **3**, and **4** have three, two, and one OH group per each ribose unit, and therefore, at the opening of these host cavities, the hydrophobicity increases from **2** to **4**. More importantly, the steric hindrance increases from **2** to **4** as well. For example, the three ribose units on **4**,

which has the fewest OH groups, still have a propensity for the surrounding H_2O molecules, and to minimize this unfavorable interaction (desolvate), these three ribose units come close to each other, and presumably, this effect tends to increase the steric hindrance at the opening of the host cavity. Alternatively, the three OH groups on each ribose unit in **2** should have relatively favorable interactions with the surrounding H_2O molecules, and hence less steric demand at the opening of the host cavity. This rationale was supported by comparing the CICS values of L-**Phe** with **2**−**4**, which showed the largest value for the least hindered host **2**, and the smallest value for the most hindered host **4**. In the case of L-**Trp**, the situation is more complicated, since the CICS values of L-**Trp** with **2**−**4** were in the order **3** > **2** > **4**. This sequence may be explained by considering the contribution of the hydrophobicity of the host, or hydrophobic effect of the host−guest complexation. As mentioned, L-**Trp** has greater hydrophobicity than L-**Phe**, and therefore, the hydrophobic interactions between L-**Trp** and **2**−**4** appear to play an important role during the recognition process, besides the $\pi-\pi$ interactions and the steric effect at the opening of the host cavities. With the decreasing number of OH groups on the ribose units from **2** to **4**, the hydrophobicity increases, but at the same time, the steric hindrance increases as well. These two factors, which have the opposite influences on the recognition process of L-**Trp**, appear to be responsible for the interaction between **3** and L-**Trp** being optimal.

The ^{1}H NMR signals of Ha and Ha′ on L-**Trp** were influenced to the greatest extent by host **3**,[1a,2,5b] with a 0.45 ppm upfield shift, while those of the other two protons, Hb and Hc, had significantly smaller upfield shifts (0.19 ppm). The ^{1}H NMR resonances of Hd on the five-member ring and the asymmetric CH_2 protons and the *C−H proton at the chiral center were only slightly affected with 0.01−0.02 ppm upfield shifts. From Table 2, it is apparent that the chemical shifts of host **3** do not show significant changes; only slight upfield shifts of 0.01 to 0.08 ppm were observed. The following structures illustrate the CICS values of guests L-**Trp** and L-**Phe** with host **3**:



L-Trp



L-Phe

Several points may be garnered from these results: (1) the Ha and Ha′ side of L-**Trp**, which can be viewed as the "head" of this guest molecule, deeply penetrated the cavity of **3** and experienced the largest $\pi-\pi$ influence; (2) the hydrophilic zwitterion end of L-**Trp**, which can be viewed as the "tail" of this molecule, was left outside the cavity in contact with H_2O; and (3) the cavity of **3** appears to be very shallow. These three points can be easily rationalized, since the "head" of L-**Trp** has the highest π-electron density available, and is very hydrophobic. In aqueous solution, this hydrophobic end wants to interact with other hydrophobic groups, such as the cavity of **3**, to minimize the thermodynamically unfavorable interactions with H_2O molecules. On the other hand, the hydrophilic zwitterion "tail" of L-**Trp** would likely be hydrogen bonded to the surrounding H_2O molecules, which are mostly outside of the cavity of **3**.

This type of interaction in H_2O is reminiscent of protein molecules in which the majority of the hydrophilic, polar amino acid residues are located on the surface of these biopolymers in contact with H_2O, while the hydrophobic residues are mainly buried in the interior of these polymers to interact with each other. Finally, the depth of the cavity of **3** can easily be

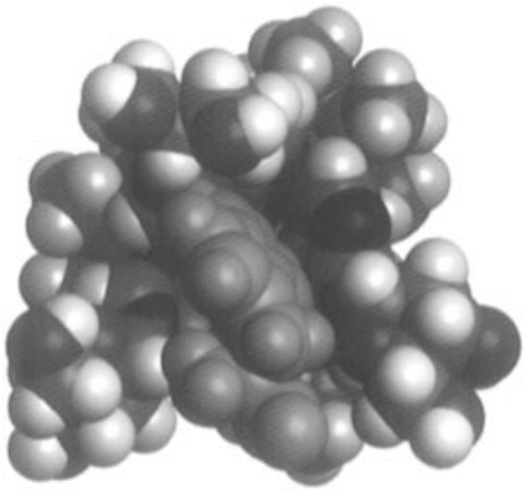


Figure 3. CPK model (bottom view) of host **3** and the docking of the guest, L-**Trp**.

Table 3. Estimated Association Constants (K_a)[a−c] and Free Energies of Complexation ($\Delta G°$)[d] for the Molecular Recognition Process

	host			
guest	**1**	**2**	**3**	**4**
L-**Trp**	43 (−2.2)	472 (−3.7)	607 (−3.8)	<10 (>−1.4)
L-**Phe**	16 (−1.6)	12 (−1.5)	<10 (>−1.4)	<10 (>−1.4)
G1			810 (−4.0)	
G2			15 (−1.6)	
G3				
G4			710 (−3.9)	
G5			710 (−3.9)	
G6			40 (−2.2)	
G7			760 (−3.9)	
G8			15 (−1.6)	
G9			15 (−1.6)	
G10			15 (−1.6)	

[a] Spectra were taken on a 400-MHz NMR instrument at 298 K. The unit of K_a is M^{-1}. The R values of least-squares plots were 0.98 or higher and the error limits ranged from 5% to 10%. L-**Trp** and L-**Phe** and hosts **1**−**4**. [b] Values encompass both of the enantiomers or the diastereomers. [c] Values for **G1**−**G10** are estimated from their chemical shifts with host **3**. [d] Values in parentheses, kcal/mol (error limits, 5−10%).

observed from the CPK model of **3** (Figure 1), and this resulted in a significantly smaller upfield shift of Hb and Hc, which were not shielded as much as Ha and Ha′ by the π-electron density of **3**. The above description of the molecular recognition process of L-**Trp** with **3** was shown in the energy-minimized, space-filling model of **3** and the docking of L-**Trp** (Figure 3). These overall results suggest that the molecular recognition of L-**Trp** with **3** can be described in a way that places the L-**Trp** aromatic rings inside of 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 association constants (K_a) for the host−guest complexation were estimated by using a standard NMR method[8] to confirm the trends which were observed. The estimated K_a values, a value that encompasses both enantiomers and diastereomers of **1**−**4**, are summarized in Table 3, along with the free energies of host−guest complexation, $\Delta G°$ values, and these data agreed with the chemical shift changes of the guests upon interactions with the sterically demanding hosts. It is noteworthy to mention that L-**Trp**, with its optimized steric orientation, electron-donating N atom, and hydrophobic effects, has the larger K_a and more favorable $\Delta G°$ values with hosts **2** and **3** compared to similar interactions with L-**Phe**. We also see that the $\Delta(\Delta G°)$ between L-**Trp** and L-**Phe** with host **3** is ∼2.4 kcal/

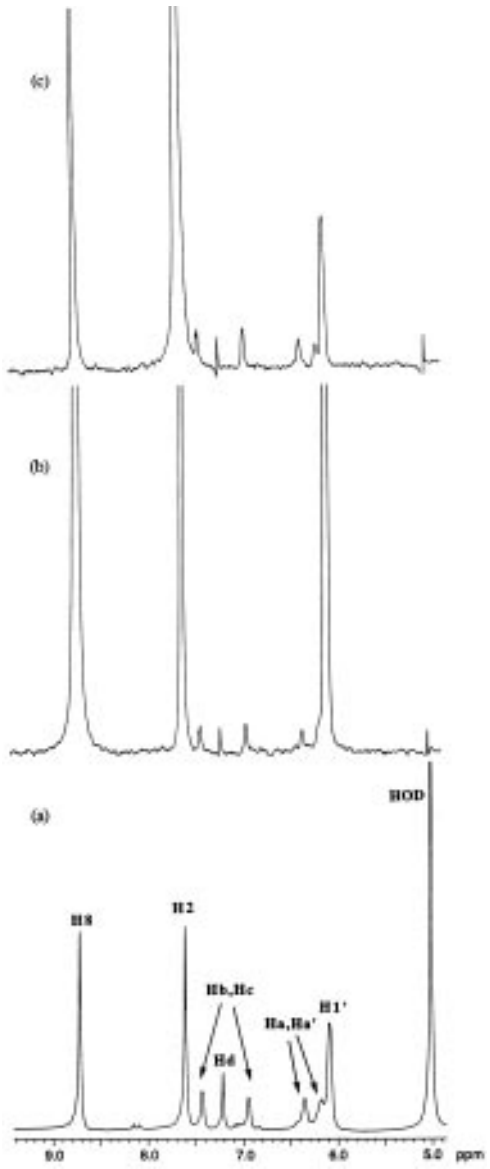
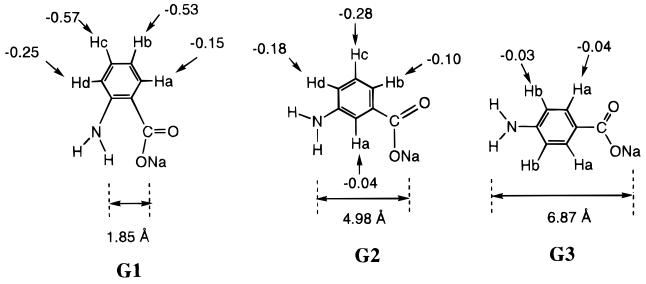


Figure 4. Intermolecular NOE study between **3** and L-**Trp**: (a) reference spectrum of **3** + L-**Trp**; (b) differential spectrum for the irradiation on **3**'s H8 proton; (c) differential spectrum for the irradiation on **3**'s H2 proton.

mol, and thus, this represents the greater stability of the L-**Trp-3** host−guest complex over that of the similar complex with L-**Phe**.

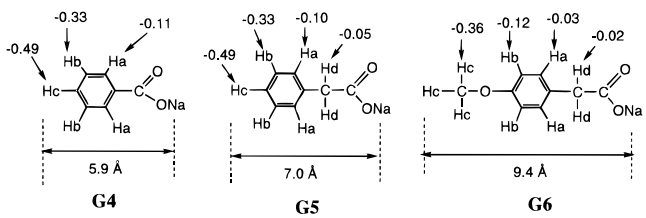
The host−guest molecular recognition process was also further substantiated by an intermolecular NOE study between **3** and L-**Trp** (Figure 4). In that study, the line-broadening parameter was set to 4 Hz to minimize the subtraction error. When H8 of **3** was irradiated, weak negative intermolecular NOE signals of L-**Trp's** Ha, Ha′, Hb, and Hc aromatic protons were observed. It is important to note that no intermolecular NOE signal was found between **3** and the solvent, D_2O, which excludes the possibility that the NOE data were an artifact. The moderate association constant ($K_a = 607\ M^{-1}$) for **3** and L-**Trp**, in comparison to the range of literature reported values[2a,2i,3b] of 10 to $10^6\ M^{-1}$, was thought to be partially responsible for the somewhat weak intermolecular NOE signals that were observed. Negative intramolecular NOE signals of **3**'s H1′, H2, H2′, H2″, H3′, and H4′ protons were also observed when H8 was irradiated, and the intensities of these intramolecular NOE signals varied according to the distances between H8 and these protons. Similar results were seen when H2 of **3** was irradiated (Figure 4c).

Molecular Recognition of Substituted Aromatic Carboxylic Acids. Three substituted aromatic carboxylic acids, *o*-, *m*-, and *p*-aminobenzoic acids (**G1**, **G2**, and **G3**), were selected as guests to extend the scope of our molecular recognition studies by interaction with host **3**. All three guests, **G1**, **G2**, and **G3**, have the same functional groups, i.e., an electron-donating NH_2 group and an electron-withdrawing COO^- group; however, the two groups are separated from each other at different distances (positional isomers). At pH 7, the anionic forms of **G1**, **G2**, and **G3** are the predominant species in concert with their pK_a values.[7] The CICS values of these three guests by host **3** are presented in the following manner, with the upfield shifts denoted on the structures and the distances between the NH_2 and the COO^- groups designated in angstroms:



Interestingly, the minor substitution changes of these three positional isomers showed dramatically different CICS values and their interrelated K_a and $\Delta G°$ values, by both $\pi-\pi$ and hydrophobic interactions with **3**. The largest CICS values for **G1** (Hc) and **G2** (Hc) are 14 and 7 times larger, respectively, than that of **G3** (Ha). This observation can be explained by the steric effects of the guests, since the two hydrophilic functional groups which form H-bonds with the bulk H_2O need to avoid unfavorable interactions with the hydrophobic cavity of **3**. Moreover, these H-bonds with the bulk H_2O determine the orientations of **G1**−**G3** as they approach host **3**; the hydrophobic end of guests **G1**−**G3** must enter **3** more favorably. Therefore, guests with the most exposed hydrophobic portions, such as **G1**, should have the largest CICS values, as was observed. Molecular modeling studies confirm that the distances between the amino H atom and carboxylate O atoms for **G1**, **G2**, and **G3** are 1.85, 4.98, and 6.87 Å, respectively. With the increasing distances between these two hydrophilic functional groups, from **G1** to **G3**, the steric hindrance also dramatically increases and, at the same time, the exposed hydrophobic portions decrease.

Molecular Recognition of Aromatic and Aliphatic Carboxylic Acids. Three aromatic carboxylic acids, benzoic acid (**G4**), phenylacetic acid (**G5**), and 4-methoxyphenylacetic acid (**G6**), were selected as guests to probe the depth of penetration in host **3**, and as well, two aliphatic carboxylic acid guests, cyclohexylacetic acid (**G7**) and 1-adamantanecarboxylic acid (**G8**), were also used to further study the importance of hydrophobic effects in the molecular recognition process with host **3**. According to their pK_a values, all of these carboxylic acids existed in the anionic form at pH 7.[7] The CICS values of the three guests, **G4**, **G5**, and **G6**, by host **3** are presented in a similar fashion as described above for the substituted aromatic carboxylic acids:



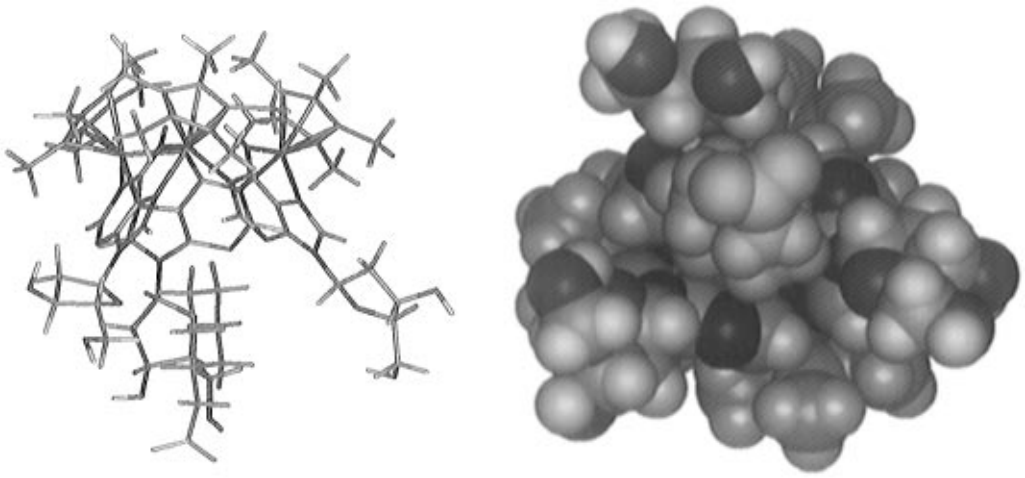
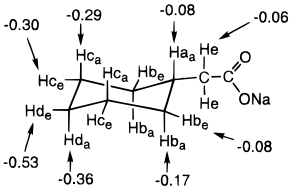


Figure 5. (left) Stick model (side view) and (right) CPK model (bottom view) of host **3** and the docking of guest **G7**.

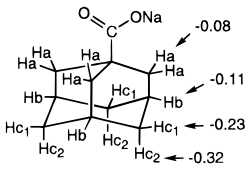
It is apparent that the CICS values for **G4** and **G5** are almost identical, indicating that one more CH_2 group between the benzene ring and the carboxylate has very little or no influence on the $\pi-\pi$/hydrophobic recognition process; the CH_2 group is close to the hydrophilic group of the guest and, therefore, is not intimately involved in the molecular recognition process. The CICS values for **G6**, which has a CH_3O group on the 4-position, are quite different from those for **G4** and **G5**. The CICS values for **G6** with **3** are −0.36, −0.12, −0.03, and −0.02 ppm for the Hc (methyl), Hb (aromatic), Ha (aromatic), and Hd (CH_2) protons, respectively. The small CICS values for aromatic protons of **G6** suggest that the hydrophobic interaction is the major recognition effect, while $\pi-\pi$ stacking is the minor contributor in this molecular recognition example. This result also suggests that the cavity of host **3** is shallow, which agrees well with the estimated cavity depth of ∼4 Å.

Although the structure of guest **G5** is very similar to that of L-**Phe**, their CICS values with **3** are quite different (see Table 1). This difference may be explained by inspecting the hydrophilic end of both guests. Guest L-**Phe** has two hydrophilic functional groups, NH_3^+ and COO^-, while **G5** has only one, and therefore, the hydrophilic end of L-**Phe** forms stronger H-bonds with the bulk H_2O solution. The strong H-bonds between L-**Phe** and the surrounding H_2O should prevent L-**Phe** from entering the cavity of **3** too deeply; the desolvation energies appear to be higher in this case.

For aliphatic carboxylic acid guests, **G7** and **G8**, the CICS values of the two guests with host **3** are shown as before:



G7



G8

Surprisingly, the CICS values for these two aliphatic guests, especially **G7**, are comparable, and in some cases even greater than, certain aromatic carboxylic acid guests. These results are in sharp contrast to the CICS values of several aliphatic amino acids, such as L-**Leu** and L-**Ile**, which have relatively long hydrophobic side chains, indicating that the conformation and the number of C atoms (hydrophobicity, solubility in H_2O) of the guest molecules are of significant importance in the molecular recognition process. The "chair" form of **G7** should be predominant during the host−guest interaction, since it should be locked in this conformation by the relatively large CH_2COO^- group, and this should be a less sterically demanding conformation than the alternative "boat" conformation. The molecular recognition process of **G7** with **3** (K_a = ∼760 M^{-1}, $\Delta G°$ = −3.9 kcal/mol) is shown in the energy-minimized space-filling model of **3** and the docking of **G7** (Figure 5).

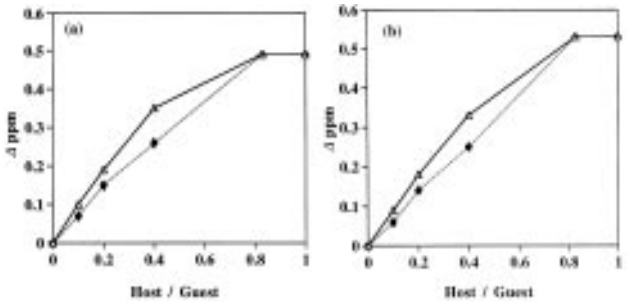


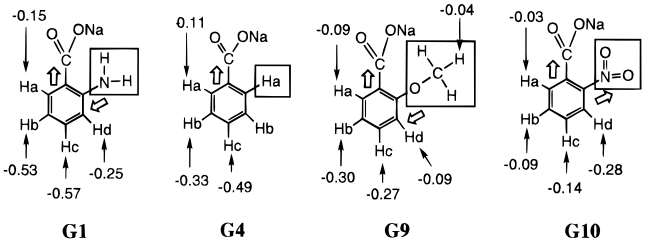
Figure 6. Competition study of aromatic guest **G5** and its closely related aliphatic guest **G7** for host **3**. The concentrations of **G5** and **G7** were kept constant, while that of **3** increased from 0 to 1 equiv. (a) Chemical shift of Hc of **G5**: (△) **3** + **G5**, control experiment; (◆) **3** + **G5** + **G7**, competitive experiment. (b) Chemical shift of Hd_e of **G7**: (△) **3** + **G7**, control experiment; (◆) **3** + **G7** + **G5**, competitive experiment.

The bulky and rigid aliphatic carboxylate guest, **G8**, also showed relatively large CICS values, which further strengthens the argument that conformational parameters and the hydrophobic effect of the guest molecules are important in the overall molecular recognition process. The interactions between **G8** and **3** (K_a = ∼15 M^{-1}, $\Delta G°$ = −1.6 kcal/mol; the $\Delta(\Delta G°)$ between **G7** and **G8** with host **3** is ∼2.3 kcal/mol) also may be due to the flexibility of the three 2′-deoxyribose groups, which can possibly rotate away to make room for the bulky **G8**; overall the apparent steric effect of **G8** limits this process.

In order to further determine the relative importance of $\pi-\pi$ and hydrophobic effects in the molecular recognition process, a competition study between aromatic guest **G5** and its closely related aliphatic guest, **G7**, was undertaken. During this study, the concentrations of **G5** and **G7** were kept constant, while that of **3** increased from 0 to 1 equiv. Two control experiments, which held constant the concentration of *one* guest (**G5** or **G7**), while varying the concentration of **3**, were also performed. The results (Figure 6a,b) show similar plots for the control and the competitive experiments for **G5** and/or **G7**. In the competitive experiment, the CICS values of *both* **G5** or **G7** were only slightly reduced, *which suggest that the* $\pi-\pi$ *and hydrophobic effects may be of similar importance in aqueous solution*. If in fact there was a dominant $\pi-\pi$ or hydrophobic effect, we would have expected a much more pronounced decrease in the CICS

values of either **G5** or **G7** in the competitive experiment, and this was not observed.

Two other guest molecules, *o*-methoxybenzoic acid (**G9**) and *o*-nitrobenzoic acid (**G10**), were selected to study the steric and electronic influences of the different functional groups at the 2 position of benzoic acid with host **3**. Their CICS values, together with those of **G1** and **G4**, are shown in the following manner as before:



G1 **G4** **G9** **G10**

It is apparent that the electron-donating abilities of the four functional groups in the boxes (see above) follow the order of $NH_2 > OCH_3 > H > NO_2$, while the steric hindrance order is $OCH_3 \sim NO_2 > NH_2 > H$. Favorable electronic and steric properties for **G1** ($K_a = \sim 810\ M^{-1}$, $\Delta G° = -4.0$ kcal/mol) provide the largest CICS values, and hence K_a and $\Delta G°$ values, while the steric advantage of **G4** ($K_a = \sim 710\ M^{-1}$, $\Delta G° = -3.9$ kcal/mol; $\Delta(\Delta G°)$ between **G1** and **G4** is ~0.1 kcal/mol) makes its CICS values larger than those of **G9** ($K_a = \sim 15\ M^{-1}$ $\Delta G° = -1.6$ kcal/mol), even though OCH_3 is more electron donating than an H atom. When **G9** was compared to **G10**, contrary to our expectation, their CICS values were about the same, indicating that the recognition process is much more complicated than we have anticipated. Nevertheless, sterically less demanding and more electron rich aromatic guests should have the largest CICS values, and therefore, K_a and $\Delta G°$ values, in the molecular recognition process.

Discussion

The driving force for the novel molecular recognition process that we presented in this paper for hosts **1**−**5** (Chart 1) and the designated guests (Chart 2) is directly related to the use of water as the solvent. As clearly pointed out by Breslow,[5a] water maximizes the hydrophobic effect and the desolvation energies dictate the extent of the host−guest complexation. Therefore, water will solvate the hydrophilic end of the guests, while the desolvated hydrophobic substituent enters the host cavity and interacts via non-covalent processes.

The unique structure of the cyclic trimer hosts, which can be modified by substituents on the N9 position of the adenine nucleus, represents a supramolecular bowl shaped molecule with a cavity opening of ~7.5 Å that is sufficiently large enough to accommodate many guests. The adenine ligands form the inner shell of the bowl, with the rhodium atoms basically acting as an anchor for both the dome (Cp*) and the inner shell (adenine). It is also apparent that the coordinatively saturated Rh atoms are spectators during the molecular recognition process and do not directly take part in any of the non-covalent host−guest interactions.

The electron-deficient adenine inner shell, which forms intramolecular η^2 bonds to Cp*Rh via NH6 and N7 and an intermolecular η^1 bond to Rh via N1 of another adenine (a self-assembly mechanism that provides a cationic Cp*Rh cyclic trimer complex), was able to interact more favorably with the aromatic guests that contained electron-donating groups, such as L-**Trp**, **G1**, and **G9**. This result seemed to dictate that $\pi-\pi$ interactions predominated in the molecular recognition process. However, by judiciously modifying the N9 substituent with the 2′-deoxyribose group, host **3**, one could maximize the host−guest process and show that aliphatic carboxylic acids, such as **G7**, interacted as favorably with host **3** as did aromatic guests, L-**Trp**, **G1**, and **G9**. Moreover, competition experiments with **G5** and **G7**, for host **3**, verified the equal importance of both non-covalent $\pi-\pi$ and hydrophobic effects in the overall molecular recognition process.

We also studied two other parameters, along with the above-mentioned electronic effect, that appeared to affect the host−guest, molecular recognition process, namely, steric and conformational aspects. The importance of the steric effect can be seen with guests, **G1**−**3**, upon interaction with host **3**. As the positional isomers of aminobenzoic acids are changed from the ortho, to the meta, and then to the para positons, the extent of the host−guest interaction is dramatically decreased. The conformational effect is seen with a comparison of the aliphatic amino acid guests, such as L-**Leu** and L-**Ile**, that appeared to interact weakly with the hosts **1**−**4**, and guests **G7** and **G8**, that were able to readily interact with the hosts **1**−**4**. Moreover, the solvophobic effects cannot be minimized, since the aliphatic amino acids are more soluble in water and, as well, their Hansch partition coefficients, log $P_{octanol}$, show them to have greater solubility in water than octanol.[5b]

It appears that conformationally rigid guests, as epitomized by **G7** and **G8**, were better able to interact with host **3**, presumably by a hydrophobic effect, although the apparent steric effect of **G8** somewhat limits this molecular recognition process. In contrast, the aliphatic amino acids, L-**Leu**, L-**Ile**, L-**Gln**, valine, alanine, and proline, suffer from conformational flexibility and, more importantly, their increased solubility in water, compared to L-**Trp** and L-**Phe**, significantly limits host−guest complexation. To reiterate, the electronic effect with electron-donating substituents, e.g., $-NH_2$ and N-heterocyclic rings, enhanced the host−guest interaction, as shown by guests, **G1** and L-**Trp**, while a guest with an electron-withdrawing substituent, guest **G10** with a *o*-NO_2 group on a benzoic acid nucleus, appears to have a more complicated host−guest interaction. Interestingly, the proton ortho to the NO_2 group in **G10** is upfield shifted to as great an extent as that ortho proton in guest **G1** containing an electron-donating *o*-NH_2 group. Apparently, the *o*-NO_2 group positions itself in proximity to the host cavity opening via a possible non-covalent H-bonding effect with the 2′-deoxyribose group, but this reasoning is speculative as of now. In contrast, guest **G9** with an *o*-CH_3O- group, that has the largest steric demand of the ortho-substituted benzoic acid appears to position itself quite differently, since the ortho proton is slightly affected by the host−guest interaction. This latter discussion clearly shows that the extent of these host−guest interactions is a consequence of subtle changes of a multiple of parameters that are far more complicated than our current understanding.

Conclusions

We have found that novel, bioorganometallic, supramolecular hosts, **1**−**4**, can readily recognize biologically important guests by a variety of non-covalent processes. The complexity of the interplay between these non-covalent processes, namely, $\pi-\pi$, hydrophobic, and subtle H-bonding effects, with further parameters of steric, electronic, conformational effects, and the ever present solvophobic effect in H_2O, clearly provides a driving force for future studies with these unique hosts. For example, we envision being able to use host **3** to recognize certain protein sequences with terminal amino acids that favorably interact via the non-covalent processes we have attempted to elucidate in this paper. Thus, conformational information that relates protein structure via the interaction of

a supramolecular, bioorganometallic host is an exciting area of research we will pursue further.

Experimental Section

Materials, Instrumentation, and Graphical Software. All chemicals (the highest purity available) were purchased from either Aldich or Sigma and used as received. The ^{1}H NMR spectra were recorded on a Bruker AM 400 spectrometer. Proton chemical shifts were reproducible within 0.002 ppm. Intermolecular NOE experiments were carried out on a Bruker AM500 spectrometer by using a NOEDIF program with irradiation time = 6 s, acquisition time = 0.74 s, 90° pulse = 26.2 μs, line broadening = 4 Hz, and temperature = 2.3 °C. After ~500 scans for each irradiation frequency, differential spectra were obtained by subtraction of the reference spectrum. 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 forcefield. In that manipulation, the R group on the cyclic trimer could be replaced with a ribose or deoxyribose. The guest molecules were then docked and energy minimized to produce Figures 3 and 5.

Synthesis of Hosts 1−5. (a) [Cp*Rh(9-methyladenine)]$_3$(OTf)$_3$ (1). To a solution of $[Cp^*RhCl_2]_2$ (0.11 g, 0.178 mmol) in H_2O (15 mL, degassed once) was added AgOTf (0.18 g, 0.71 mmol). The reaction mixture was stirred at ambient temperature for 3 h, and then it was filtered. To the resulting filtrate was added 9-methyladenine (9-MA, 0.054 g, 0.362 mmol). After all the 9-MA was dissolved, the pH was adjusted to 7.1 by the addition of 0.1 N NaOH. The final reaction mixture was degassed and stirred overnight. The reaction was then stripped in vacuo and the yellow residue was slurried in MeOH (10 mL). The slurry was filtered and the volume of the filtrate was reduced to ~5 mL. After this concentrated solution was kept at −20 °C for 24 h, the desired product **1** was crystallized as orange crystals (0.083 g, 40% yield). ^{1}H NMR (500 MHz, DMSO-d_6, reference to TMS) δ 8.83 (s, 1H, H8), 7.67 (s, 1H, H2), 4.51 (s, 1H, NH6), and 1.85 (s, 15H, Cp*). FAB/MS (%), $[M - OTf]^+$ (4), $[M - 2OTf]^+$ (3), $[M - 3OTf]^+$ (1), $[\{Cp^*Rh(9\text{-}MA)\}_2(OTf)_2 - OTf]^+$ (10), $[\{Cp^*Rh(9\text{-}MA)\}_2(OTf)_2 - 2OTf]^+$ (16), $[Cp^*Rh(9\text{-}MA)]^+$ (100). Anal. Calcd for $C_{51}H_{63}F_9N_{15}O_9Rh_3S_3\cdot 6H_2O$: calc: C, 35.7; H, 4.4; N, 12.3. Found: C, 35.4; H, 4.0; N, 11.9.

(b) [Cp*Rh(adenosine)]$_3$(OTf)$_3$ (2). To a solution of $[Cp^*RhCl_2]_2$ (0.20 g, 0.324 mmol) in H_2O (20 mL, degassed once) was added AgOTf (0.30 g, 1.2 mmol). The reaction mixture was stirred at ambient temperature for 3 h, and then it was filtered. Adenosine (Ado, 0.16 g, 0.60 mmol) was added to the filtrate and after all the Ado was dissolved, the pH was adjusted to 7.3 by the addition of 0.1 N NaOH. The final reaction mixture was degassed and stirred overnight. The reaction was then stripped in vacuo and the yellow residue was slurried in MeOH (8 mL). The slurry was filtered and the filtrate was treated with diethyl ether (12 mL) to precipitate the product. The supernatant was discarded and the product was stripped in vacuo to give 0.20 g of a yellow solid (44 % yield). ^{1}H NMR (400 MHz, D_2O, reference to Me_4NOH, 3.180 ppm) δ 8.79 (s, 1H, H8), 7.66 (s, 1H, H2), 5.88 (m, 1H, H1′), 4.59 (m, 1H, H3′), 4.35 (m, 1H, H2′), 4.18 (m, 1H, H4′), 3.77 (m, 2H, H5′ and H5″), and 1.86 (s, 15H, Cp*). FAB/MS (%), $[M - OTf]^+$ (2.2), $[M - Ado + 4H]^+$ (2.1), $[M - Ado - OTf]^+$ (1.6), and $[(Cp^*RhAdo)_2(OTf) - 2Cp^* + H]^+$ (100). Anal. Calcd for $C_{63}H_{81}F_9N_{15}O_{21}Rh_3S_3\cdot 7H_2O$: C, 36.6; H, 4.6; N, 10.1. Found: C, 36.7; H, 4.4; N, 9.6.

(c) [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$ (3). The procedures for making **2** were followed. Yield, 59%. ^{1}H NMR (400 MHz, D_2O, reference to Me_4NOH, 3.180 ppm) δ 8.77, 8.76 (s, 1H, H8), 7.65, 7.64 (s, 1H, H2), 6.25, 6.23 (m, 1H, H1′), 4.58, 4.54 (m, 1H, H3′), 4.10, 4.10 (m, 1H, H4′), 3.74, 3.69 (m, 2H, H5′ and H5″), 2.66, 2.65 (m, 1H, H2′), 2.52, 2.45 (m, 1H, H2″), and 1.85, 1.85 (s, 15H, Cp*). FAB/MS (%), $[M - OTf]^+$ (5.4), $[M - OTf - dAdo]^+$ (dAdo = 2′-deoxyadenosine, 3.1), $[M - OTf - 2dAdo]^+$ (1.7), and $\{[Cp^*Rh(dAdo - H)]_2(OTf)_2 - OTf\}^+$ (100). Anal. Calcd for $C_{63}H_{81}F_9N_{15}O_{18}Rh_3S_3\cdot 8H_2O$: C, 36.8; H, 4.7; N, 10.2. Found: C, 36.9; H, 4.5; N, 9.8.

(d) [Cp*Rh(2′,3′-dideoxyadenosine)]$_3$(OTf)$_3$ (4). The procedures for making **2** were followed. Yield, 49%. ^{1}H NMR (400 MHz, D_2O, reference to Me_4NOH, 3.180 ppm) δ 8.82, 8.78 (s, 1H, H8), 7.62, 7.62 (s, 1H, H2), 6.09, 6.07 (m, 1H, H1′), 4.30, 4.30 (m, 1H, H4′), 3.82, 3.59 (m, 2H, H5′ and H5″), 2.45, 2.40 (m, 2H, H2′ and H2″), 2.10, 1.91 (m, 2H, H3′ and H3″), and 1.85, 1.85 (s, 15H, Cp*). FAB/MS (%), $[M - OTf]^+$ (7), $[M - 2OTf]^+$ (2.5) $[M - 3OTf - 2ddAdo + H]^+$ (ddAdo = 2′,3′-dideoxyadenosine, 12.8), $[M - 3OTf - 3ddAdo + H]^+$ (8), and $[(Cp^*Rh)_2 - 4H]^+$ (100). Anal. Calcd for $C_{63}H_{81}F_9N_{15}O_{15}Rh_3S_3\cdot 9H_2O$: C, 37.3; H, 4.89; N, 10.4. Found, C, 37.7; H, 4.62; N, 9.9.

(e) [Cp*Rh(Me-5′-AMP)]$_3$ (5). The procedures for making **2** were followed. Yield, 45%. ^{1}H NMR (400 MHz, D_2O, reference to Me_4NOH, 3.180 ppm) δ 8.85, 8.79 (s, 1H, H8), 7.74, 7.69 (s, 1H, H2), 5.91, 5.88 (d, 1H, H1′), 4.77, 4.77 (m, 1H, H3′), 4.42, 4.41 (m, 1H, H2′), 4.30, 4.30 (m, 1H, H4′), 4.04, 4.00 (m, 2H, H5′ and H5″), 3.08, 2.66 (d, 3H, Me), and 1.88, 1.88 (s, 15H, Cp*). FAB/MS, $[M + 2Na]^+$ (1.1), $[M + Na]^+$ (2.2), and $[M + Na - (Me\text{-}5'\text{-}AMP)]^+$ (4.0). Anal. Calcd for $C_{63}H_{87}N_{15}O_{21}P_3Rh_3\cdot 3NaOTf\cdot 10H_2O$: C, 31.8; H, 4.3; N, 8.4. Found: C, 32.3; H, 4.7; N, 8.3.

NMR Sample Preparation for Host−Guest Experiments. A typical NMR sample preparation is described as follows: Appropriate amounts of hosts **1**−**5** and 1.2 equiv of guest molecules in a 5-mm NMR tube were dissolved in 1.0 mL of D_2O. To this was added 20 μL of a 3 M phosphate buffer (pH 7) solution in D_2O and 5 μL of a 6 × 10^{-2} M Me_4NOH solution in D_2O as the internal reference with the methyl proton resonance set at 3.180 ppm. The final concentrations of host/guest molecules were (1−2) × 10^{-2} M. The samples of pure hosts **1**−**5** or guest molecules were prepared in the same manner. In a control NMR experiment with guest L-**Phe**, we found that the buffer, 20 μL of a 3 M phosphate, had no effect on the chemical shifts in comparison to an NMR sample of L-**Phe** that had no buffer (D_2O at pH 7.0).

NMR Competition Experiments with Host 3 and Guests, G5 and G7. A typical NMR sample preparation is described as follows: In a 5-mm NMR tube, we added 2.0 mg of both **G5** and **G7** dissolved in 1.0 mL of D_2O (0.014 M), while the amount of **3** was increased from 0 to 1 equiv along with 20 μL of a 3 M phosphate buffer (pH 7) solution in D_2O and 5 μL of a 6 × 10^{-2} M Me_4NOH solution in D_2O, as the internal reference with the methyl proton resonance set at 3.180 ppm. Moreover, two control experiments, which held constant the concentration of *one* guest (**G5** of **G7**) while varying the concentration of **3**, were also performed. The results (Figure 6a,b) show similar plots for the control and the competitive experiments for **G5** and/or **G7**.

Association Constants and Free Energies of the Host−Guest Complexation. The association constants (K_a) of host−guest complexation were measured by using a standard NMR method.[8] The changes in the 400-MHz ^{1}H 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. The free energies of the host−guest complexation, ΔG° ($\Delta G^\circ = -RT \ln K_a$), were calculated using the K_a values determined by the above-mentioned NMR technique.

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