Bioorganometallic chemistry
Part 15. A novel molecular recognition process of host, *trans*-[Cp*Rh(η^1(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$, with L-aromatic amino acid guests: selective hydrogen bonding to the μ-OH groups and the 1-methylcytosine ligands

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Abstract

The ^{1}H-NMR and computer docking experiments have elucidated a novel molecular recognition process of host, *trans*-[Cp*Rh(η^1(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$ (**1**), with L-aromatic amino acids, which is predicated on a selective hydrogen bonding regime of the NH$_3^+$ of the amino acid to one of the Rh–μ-OH groups, as well as to a C=O group of one of the other 1-methycytosine ligands, while the COO$^-$ H-bonds to an NH$_2$ of the other 1-methycytosine ligand.
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1. Introduction

Organometallic complexes with bioligands represent new directions for structural diversity [1], possible new drug discoveries [2], and the ability of these complexes to be hosts for biologically important guests [3]. In the last category, several Cp*Rh-2′-deoxyadenosine cyclic trimer, supramolecular complexes have recently been discovered to be hosts for a variety of aromatic amino and carboxylic acid guests in water at pH 7.0 [3]. The molecular recognition process was found to consist of non-covalent π–π and hydrophobic interactions, with hydrogen bonding as a plausible aspect of the recogni-

tion process, being rather difficult to ascertain using ^{1}H-NMR spectroscopic techniques.

Therefore, we wish to define, in this communication, a new molecular recognition process based on selective hydrogen bonding interactions between the host, *trans*-[Cp*Rh(η^1(N3)-1-methylcytosine)(μ-OH)]$_2$(OTf)$_2$ (**1**), and several examples of aromatic amino acid guests, L-tryptophan and L-phenylalanine, **2** and **3**, in water at pH 7.0. The X-ray structure of host **1** (Fig. 1), which was previously reported [4], clearly shows the unique intramolecular H-bonding aspects of the ligand, 1-methylcytosine, with the Rh$_2$(μ-OH)$_2$ center. Thus, the μ-OH groups act as both H-donor and acceptor with the 2-carbonyl (OH–O=C, 1.96(1) Å) and NH$_2$ groups (HO–HNH, 1.93(1) Å), respectively.

Moreover, we surmised that an intermolecular recognition process also based on H-bonding to the μ-OH groups and the cytosine NH$_2$ and C=O functionalities might be feasible with the aromatic amino acid NH$_3^+$

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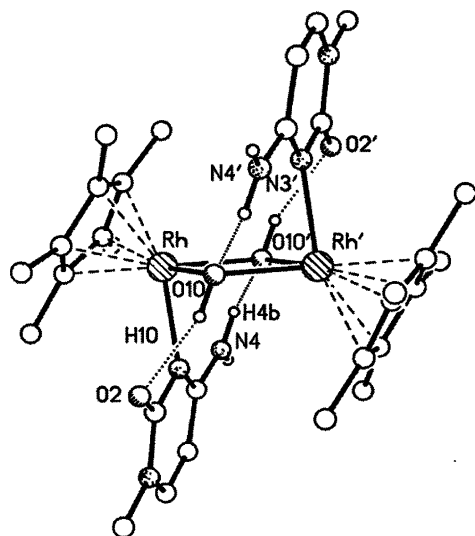*E-mail address:* rhfish@lbl.gov (R.H. Fish).

Fig. 1. X-ray structure of host **1** [4].

and COO$^-$ groups, without seriously disrupting the intramolecular hydrogen bonding regime shown in Fig. 1.

We utilized ^{1}H-NMR techniques to discern the complexation-induced ^{1}H-NMR chemical shifts (CICS) for the host and the guests [3]. Table 1 shows the results with guest L-tryptophan, **2**, in the presence of host **1**. What is dramatically evident for guest **2** are the CICS for H$_d$ ($\Delta\delta = -0.34$); H$_e$ ($\Delta\delta = -0.15$); H$_f$ ($\Delta\delta = -0.07$); and H$_g$ ($\Delta\delta = -0.12$), which were diametrically opposite to the previously reported Cp*Rh-2′-deoxya-denosine cyclic trimer molecular recognition studies with **2**, where no upfield CICS for these designated protons were observed; in that process, the indole phenyl group was found inside the hydrophobic recep-

tor, while the hydrophillic aromatic amino acid NH$_3$$^+$ and COO$^-$ groups were outside in the water media, and the chiral C–H attached to these groups, as well as the adjacent asymmetric CH$_2$, were not affected by the magnetic anisotropy of the inner shell of the host adenosine ligands [3a].
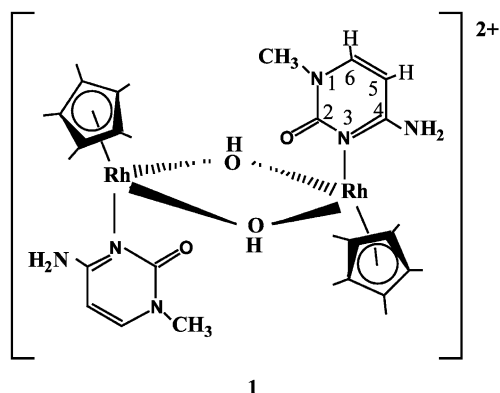
More importantly, we also observed two sets of signals for the host ligand, 1-methylcytosine, bound to Cp*Rh; the N–CH$_3$, H$_5$, and H$_6$ protons. The CICS for one of the now apparently asymmetrical 1-methylcyto-sine ligands (Table 2) was similar to complex **1** alone, while the other had CICS upfield shifts for the N–CH$_3$ ($\Delta\delta = -0.41$); H$_5$ ($\Delta\delta = -0.31$); and H$_6$ ($\Delta\delta = -0.18$). Clearly, the CICS for one of the 1-methylcytosine ligands were affected by the non-covalent interactions with the indole ring of **2** and vice-versa. Thus, it appears plausible that the primary host–guest interaction of **1** with **2** was from a H-bonding process of the NH$_3$$^+$ and COO$^-$ groups with **1**, enhancing non-covalent interac-tions of the 1-methylcytosine ligand with **2**.

In order to better understand these H-bonding and non-covalent interactions between host and guest, we have conducted computer docking experiments to provide the energy minimized, space-filling/ball and stick model of **1** with a ball and stick model of guest **2**, as shown in Fig. 2. The top view in Fig. 2 demonstrates the H-bonding of the NH$_3$$^+$ group to one μ-O and to the C=O group of one of the 1-methylcytosine ligands, while the COO$^-$ group H-bonds to a NH$_2$ group of the other 1-methylcytosine ligand. This H-bonding scheme of **1** with **2** then provides that the remaining structure of the guest is fixed in relation to the host, as shown in the top and middle views of Fig. 2.

Therefore, the indole group is positioned orthogonal to the plane of the 1-methylcytosine ligands in host **1**, while selectively effecting one of the two 1-methlycyto-sine groups, accounting for this ligand's asymmetry, and the upfield shifts observed in the NMR CICS values (Table 1). Fig. 2 also shows the plausible reason that H$_b$ was appreciably shifted upfield due to its proximity (middle view) to the C=O group of 1-methylcytosine, while also noting the asymmetric CH$_2$ hydrogens, where H$_e$ is more affected by the CICS effects then H$_f$ (Table 1). It is also interesting to note the appreciable upfield shift for H$_d$ ($\Delta\delta = -0.34$), which is shown in Fig. 2, middle, and we attribute this to the proximity to one of the Cp* ligands via a plausible CH-π non-covalent interaction. Moreover, the potentially asymmetric Cp*Rh groups are co-incident in the NMR (only one signal), even though the nitrogen ring of the indole nucleus appears (Fig. 2, middle) in the docking experi-ment to be somewhat orthogonal to one of the Cp* ligands.

We then studied guest **3**, L-phenylalanine, with host **1** (Table 3), and found a striking difference in the CICS for the 1-methylcytosine ligands, as opposed to that with

Table 1
CICS shifts upon host–guest recognition[a]

Free tryptophan (δ)		With host **1** (δ)	$\Delta\delta$
a	7.13	7.02	−0.11
a′	7.05	6.89	−0.16
b	7.58	7.16	−0.42
c	7.39	7.14	−0.25
d	7.16	6.82	−0.34
e	3.15	3.00	−0.15
f	3.34	3.26	−0.07
g	3.90	3.77	−0.12

[a] ^{1}H-NMR shifts at pH 7.0, 300 Hz, 1:1 host–guest ratio.

Table 2
Host **1** ^{1}H-NMR data with guests **2** and **3**[a]

1

Free host **1** (δ)		Guest **2** (δ)				Guest **3** (δ)			
			$\Delta\delta$		$\Delta\delta$		$\Delta\delta$		$\Delta\delta$
N–CH$_3$	3.24	2.83	−0.41	3.22	−0.02	3.23	−0.01	3.13	−0.11
H$_6$	7.44	7.26	−0.18	7.41	−0.03	7.42	−0.02	7.35	−0.09
H$_5$	5.83	5.52	−0.31	5.81	−0.02	5.81	−0.02	5.82	−0.01
Cp*	1.46	1.35	−0.12	1.35	−0.12	1.40	−0.06	1.40	−0.06

[a] 1H-NMR shifts at pH 7.0, 300 MHz, 1:1 host–guest ratio.

guest **2**, L-tryptophan. Relatively, smaller CICS values were observed for the 1-methylcytosine ligands in the presence of **3**; for example, one of the 1-methylcytosine ligands was not greatly effected by the host–guest interaction and showed the N–CH$_3$, H$_5$, and H$_6$ protons with average upfield shift values of $\Delta\delta = \sim 0.017$ for the non-covalent interactions (Table 2). The other 1-methylcytosine ligand had N–CH$_3$, H$_5$, and H$_6$ proton upfield shifts of $\Delta\delta = -0.11$, -0.01, and -0.09, respectively.

Fig. 2 (bottom) shows the docking experiment results with **1** and **3**, and clearly a similar H-bonding process of the NH$_3^+$ group to one of the oxygen atoms of the Rh(μ-OH) assembly, and the C=O group of one of the 1-methylcytosine ligands, while that of the COO$^-$ group to a NH$_2$ group, was deemed appropriate from the energy minimized structure found in Fig. 2, Top. The critical aspect about this host–guest interaction is that, in analogy to the nitrogen ring proton, H$_d$, in L-tryptophan, the H$_p$, H$_m$, and H$_o$ protons at 7.273, 7.271, and 7.19 δ were upfield shifted, $\Delta\delta = -0.28$, -0.36 and -0.35, respectively (Table 3). Clearly, the aromatic protons of guest **3** were upfield shifted by the proximity to both the C=O of one of the 1-methylcytosine ligands, and one of the Cp* ligands. It is also important to notice that the asymmetric CH$_2$ protons are also substantially shifted upfield with values of $\Delta\delta = -0.29$ and -0.42, respectively. We also observe only one Cp* signal that was shifted upfield with $\Delta\delta =$

−0.06, as was the case with the host–guest complex of **1** with **2**.

In summary, we have demonstrated a new bioorganometallic recognition process with host **1** and several examples of aromatic amino acid guests that depends on selective H-bonding of the NH$_3^+$ and COO$^-$ groups of the aromatic amino acids, **2** and **3**, to an oxygen of one of the Rh(μ-OH) assemblies, and C=O and NH$_2$ groups of the Rh bound 1-methylcytosine ligands, in water at pH 7.0. The significance of this new, highly selective, host–guest process is that it can be thought of as a model for H-bonding of biologically significant guests to metalloenzymes and DNA/RNA [5]. The scope of this new recognition process will be elaborated on in future studies with a variety of biologically significant guests, all in water.

2. Experimental

2.1. NMR sample preparation for host–guest experiments

A pH 7.0 buffer solution was prepared with Na$_2$HPO$_4$·12H$_2$O (35.79 mg, 0.1 mmol), NaH$_2$PO$_4$·2H$_2$O (15.59 mg, 0.1 mmol), and D$_2$O (10 ml).

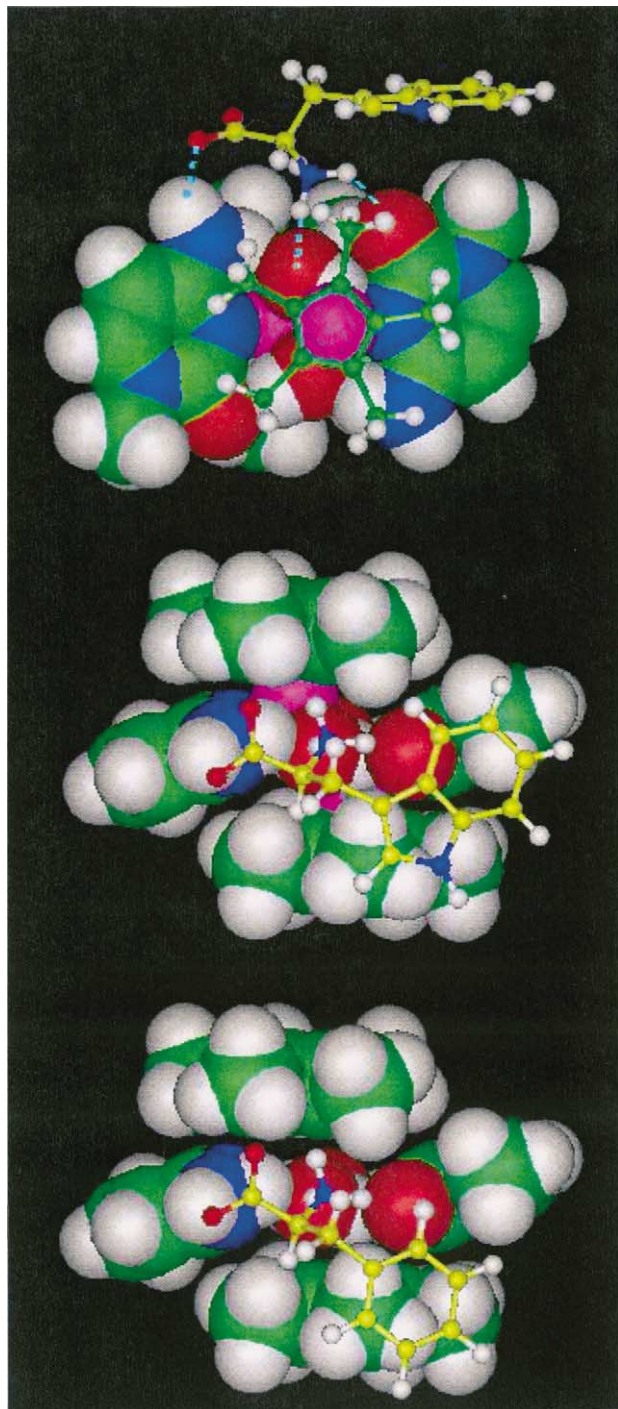A typical NMR sample preparation ([host **1**]–[guest **2**–**3**] ratios = 1:1) is described as follows: Host **1** (17.74

Fig. 2. The top view of **1·2**: H-bonding of the NH_3^+ group to one μ-OH and to the C=O group of one of the 1-methylcytosine ligands, while the COO^- group H-bonds to a NH_2 group of the other 1-methylcytosine ligand. Middle view of **1·2**: bottom view of **1·3**. N (blue); O (red); H (white) Rh (magenta).

mg, 0.01mmol) and an appropriate amount of guest molecules (0.01 mmol), in a 5-mm NMR tube, were dissolved in 1.0 ml of D_2O. To this preparation, 50 μl of

Table 3
CICS shifts upon host–guest recognition[a]

Free L-phenylalanine (δ)		Interaction with host **1** (δ)	$\Delta\delta$
a	3.85	3.79	−0.07
b	2.98	2.69	−0.29
c	3.15	2.73	−0.42
o,o′	7.19	6.84	−0.35
m,m′	7.271	6.91	−0.36
p	7.273	7.00	−0.28

[a] 1H-NMR shifts at pH 7.0, 300 MHz, 1:1 host–guest ratio.

pH 7.0 buffer solution was added to the NMR tube and the NMR spectra recorded.

2.2. COSY experiments

1H-NMR assignments for all protons were based on previous NMR correlation studies with Guest **2** and **3**. See Refs. [3a,3b] in text for details.

2.3. Docking of L-Trp, 2, and L-Phe, 3, to the host, complex 1

2.3.1. Protocol and procedures

An initial structure of the host–guest complex was obtained via rigid-body docking of several conformers of L-Trp, **2**, to the organometallic host complex, **1** [4]. We used the program Molfit employing a small grid interval of 0.78 Å, which is appropriate for small molecule docking experiments. The docking results for the several conformers were combined and sorted by the complementarity score. All the results were statistically analyzed [6,7] and provided uniqueness values for all the solutions. The best docking solutions were energy minimized, restricting the host complex **1** to its′ initial X-ray structure [4] (the Rh atoms were omitted) and allowing free movement only of the guest molecules, **2** and **3**. We used the CVFF force field in the Discover module of the MSI package. The model for the host–guest complex with L-Phe, **3**, interactions was obtained by replacing the L-Trp, **2**, by L-Phe, **3**, and repeating the restrained energy minimization.

2.4. Computer docking results

The rigid-body, computer docking experiment produced an interesting model structure, which was statistically unique. In this structure, the carboxyl group of L-

Trp, **2**, was at hydrogen bonding distances from the amino group of one of the 1-methylcytosine ligands in the host–guest complex, while the amino group of **2** was at hydrogen bonding distances from the carbonyl group of the second 1-methylcytosine ligand in the host–guest complex. A hydrogen bond could also be formed between the amino group of **2** and the μ-OH moiety in the host complex, **1**. The preservation of these hydrogen bond interactions, during computer docking, produced several host–guest complexes with different conformers of **2**, which were then energy minimized. The structure presented in Fig. 2 (top and middle) was one of two similar lowest-energy structures that were found.

Acknowledgements

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