# Gas phase molecular recognition of aromatic amino acid and aromatic carboxylic acid guests with a supramolecular [(η$^5$-pentamethylcyclopentadienyl)rhodium(2′-deoxyadenosine)]$_3^{3+}$ cyclic trimer host *via* non-covalent π–π interactions utilizing electrospray ionization mass spectroscopy†

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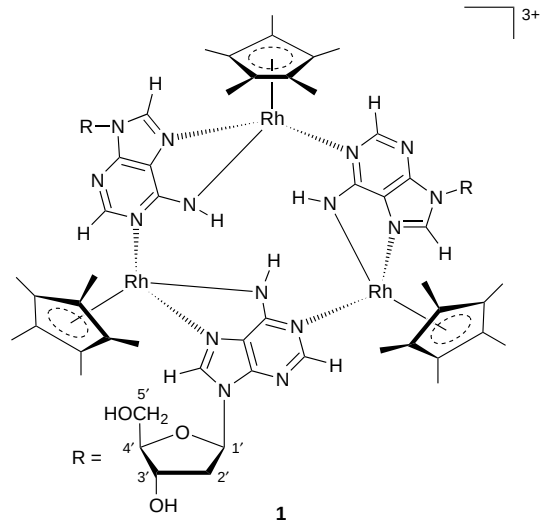
**A novel, gas phase, host–guest molecular recognition process, detected by electrospray ionization mass spectrometry, using guests that encompass aromatic amino acids and aromatic and aliphatic carboxylic acids with a supramolecular, bioorganometallic host, [Cp*Rh(2′-deoxyadenosine)]$_3$[OTf]$_3$ (Cp* = η$^5$-C$_5$Me$_5$), is found to occur predominately *via* non-covalent π–π interactions; non-covalent hydrophobic forces apparently being weak or non-existent.**

Molecular recognition is the cornerstone of many important biological processes; for example, drug and protein interactions with selective DNA sequences.[1–3] Recently, we reported on the molecular recognition of aromatic and aliphatic amino acids, as well as aromatic and aliphatic carboxylic acid guests with supramolecular, bioorganometallic (η$^5$-pentamethylcyclopentadienyl)rhodium (Cp*Rh)–nucleobase/nucleoside/nucleotide cyclic trimer hosts in aqueous solution at pH 7.2.[4] More importantly, in that study, the non-covalent hydrophobic interactions were found to be fully operational in aqueous solution by solvophobic forces that enhanced host–guest complexation, along with the equally important non-covalent π–π interactions.

It was intriguing to extend these above-mentioned aqueous molecular recognition studies to the gas phase, to compare and to better understand the role of water and its effect on the important π–π, hydrophobic, and hydrogen-bonding parameters, including steric, electronic, and conformational effects, that we found controls the host–guest process; to our knowledge, this is the first reported gas phase, host–guest molecular recognition study using a bioorganometallic host. Moreover, it has been clearly demonstrated that the soft electrospray ionization mass spectroscopy (ESIMS) technique was ideally suited for detecting such gas phase host–guest complexes in the absence of solvent.[5–11]

We started our gas phase molecular recognition ESIMS studies with a perusal of the various triangular, bowl-shaped Cp*Rh–nucleobase/nucleoside/nucleotide cyclic trimer molecular receptors we had studied in water, using L-tryptophan (L-Trp) as the guest in all cases.[4] To our surprise, we found that the best host in water, [Cp*Rh(2′-deoxyadenosine)]$_3$(OTf)$_3$ **1**, was also the best host in the gas phase. Thus, when we mixed equimolar amounts of host **1** with guest L-Trp in an aqueous 10 mM $NH_4OAc$ solution at pH 7.0, ions for **1** and the host–guest complex (**1**·L-Trp) were observed at *m/z* 488 (100%) and *m/z* 556 (35%), respectively (Fig. 1). As well, by further increasing the orifice potential from 45 to 80 V, we are able to follow the dissociation of the *m/z* 556 ion for the **1**·L-Trp host–guest complex in the gas phase. From these latter results, we had our first indication of favorable non-covalent π–π interactions in the gas phase between host **1** and L-Trp, as in aqueous solution [association constant, $K_a$ = 607 dm$^3$ mol$^{-1}$; free energy of complexation, $\Delta G^0$ = −3.8 kcal mol$^{-1}$ (1 cal = 4.184 J) in $H_2O$].[4]




We also conducted additional gas phase, ESIMS host–guest experiments with L-Phe and G1–G5 (see Guest structures) in the presence of host **1**. Table 1 contains the results, and what was very interesting, was the fact that G4, which had an association constant, $K_a$ = 760 dm$^3$ mol$^{-1}$, and a free energy of complexation, $\Delta G^0$ = −3.9 kcal mol$^{-1}$, with **1** in water, provided no detectable host–guest complex in the gas phase. Thus, initial indications clearly show that non-covalent hydrophobic interactions between G4 and **1** appear to be weak in the gas phase, and opposite to what occurred in water.[4,9,10]

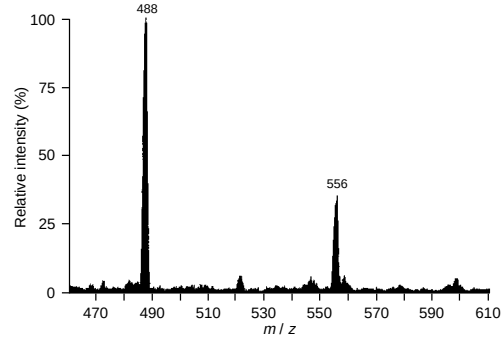
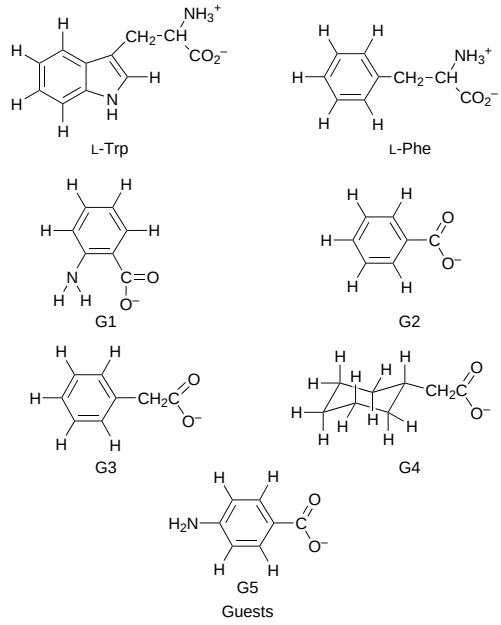



**Fig. 1** ESIMS of host **1** (*m/z* = 488) and host–guest, **1**·LTrp (*m/z* = 556) (experimental conditions, Table 1 footnotes)




Additionally, guest L-Phe, an aromatic amino acid that had a $K_a$ value of 456 dm$^3$ mol$^{-1}$ ($\Delta G^0$ = −2.8 kcal mol$^{-1}$) with **1** in aqueous solution, provided no corresponding detectable gas phase host–guest complex. Therefore, in water, L-Phe is in the prevalent zwitterion form at pH 7, and is more soluble in water and has a favorable Hansch partition coefficient, log $P_{octanol}$, in comparison to L-Trp; these factors appear to further demonstrate the solvophobic effect of water on the ability of L-Phe to form a strong host–guest complex in the aqueous phase.[4] Interestingly, in the gas phase, the water desolvated zwitterion form of L-Phe must inhibit host–guest complexation, apparently for reasons associated with its pronounced hydrophilicity.

In contrast, *o*-aminobenzoic acid ($K_a$ = 810 dm$^3$ mol$^{-1}$; $\Delta G^0$ = −4.0 kcal mol$^{-1}$, in $H_2O$ with **1**), G1, provides a detectable host–guest complex with **1** in the gas phase, since the free $NH_2$ group, in this instance, provides electron-donation to the aromatic ring thereby increasing π-electron density, and further facilitating non-covalent π–π interactions in the absence of solvent. Moreover, a positional isomer of G1, G5, which was found in the aqueous phase to sterically inhibit π–π interactions with host **1**, also did not provide a detectable host–guest complex in the gas phase, thus verifying a similar inhibition with the desolvated guest. Furthermore, aromatic carboxylic acids, G2 and G3, also readily provide detectable host–guest complexes in the gas phase with **1**, and again, dramatizes the dominance of the aromatic π electron effect in the gas phase molecular recognition process with the electron deficient host **1**.

**Table 1** Host–guest complexes in the gas phase with host **1**[a]

| Guest | Host ion, *m/z* (%) | Host–guest ion, *m/z* (%) |
|---|---|---|
| L-Trp | 488 (100) | 556 (35) |
| L-Phe | 488 (100) | ND[b] |
| G1 | 488 (100) | 534 (25) |
| G2 | 488 (100) | 528 (36) |
| G3 | 488 (100) | 533 (40) |
| G4 | 488 (100) | ND |
| G5 | 488 (100) | ND |

[a] An API III plus triple quadrapole spectrometer (PE-Sciex), equipped with an ion spray interface, was used for these ESIMS experiments. Host **1** and the guests in equimolar concentrations were dissolved in an 10 mM ammonium acetate solution at pH 7.0 and then delivered at 2.5 μl min$^{-1}$ to the ion-spray tip *via* a 50 μm id fused silica capillary. The ion-spray tip was held at a potential of 4.8 kV and compressed air (45 psi) was employed to assist liquid nebulization. Interface temperature (55 °C); orifice potential (45 V); positive ion detection mode; 5–10 scans summed for each host–guest experiment (±5–10%), which were performed three times. [b] Not detected.

The ESIMS literature with organic hosts and various guests has reported few comparisons of aqueous solution and gas phase molecular recognition chemistry.[5–11] However, the limited reported studies also demonstrate that the aqueous solvent is an important parameter especially for hydrophobic effects.[4,9,10] Thus, in the absence of water; *i.e.* under ESIMS conditions, this solvophobic force is missing, and therefore, non-covalent hydrophobic effects are greatly weakened in the gas phase, as is corroborated in this ESIMS study.

Future ESIMS molecular recognition studies will focus on the gas phase host–guest complexes of substituted aromatic carboxylic acid guests with **1** for a further understanding of steric and electronic effects involving non-covalent π–π interactions. As well, we will also focus on the molecular recognition of peptides containing terminal Trp or Phe groups with host **1**, and a comparison of the gas phase results with similar peptide–host **1** non-covalent π–π interactions in water, as analyzed by $^1$H NMR spectroscopy. In a preliminary experiment in both the gas phase (ESIMS) and in water ($^1$H NMR spectroscopy), it was found that the Trp–Met–Asp–Phe tetrapeptide with host **1** formed a host–guest complex in water that is detected in the gas phase; $^1$H NMR shows π–π interactions with the both terminal Trp or Phe groups.[12] Thus, complex **1** can be thought of as a simplified model DNA host which selectively binds peptides with terminal Trp or Phe groups *via* non-covalent π–π interactions in aqueous solution that are detected in the gas phase.

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## Footnotes and References

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1 J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 90 and references therein.
2 B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts and J. D. Watson, *Molecular Biology of the Cell*, Garland Publishing, New York, 1989, pp. 481–612.
3 H.-J. Bohm and G. Klebe, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2589.
4 H. Chen, S. Ogo and R. H. Fish, *J. Am. Chem. Soc.*, 1996, **118**, 4993.
5 M. Vincenti, *J. Mass Spectrom.*, 1995, **30**, 925 and references therein.
6 M. Przybylski and M. O. Glocker, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 807 and references therein.
7 E. Lamcharfi, S. Chuilon, A. Kerbal, G. Kunesch, F. Libot and H. Virelizier, *J. Mass Spectrom.*, 1996, **31**, 982.
8 M. Sawada, Y. Takai, T. Kaneda, R. Arakawa, M. Okamoto, H. Doe, T. Matsuo, K. Naemura, K. Hirose and Y. Tobe, *Chem. Commun.*, 1996, 1735.
9 Y.-T. Li, Y.-L. Hsieh, J. D. Henion, T. D. Ocian, G. A. Schiehser and B. Ganem, *J. Am. Chem. Soc.*, 1994, **116**, 7487.
10 Q. Wu, J. Gao, D. Joseph-McCarthy, G. B. Sigal, J. E. Bruce, G. M. Whitesides and R. D. Smith, *J. Am. Chem. Soc.*, 1997, **119**, 1157.
11 D. V. Dearden, C. Dejsupa, Y. Liang, J. S. Bradshaw and R. M. Izatt, *J. Am. Chem. Soc.*, 1997, **119**, 353.
12 S. Ogo, S. Nakamura, R. Bakhtiar, Y. Watanabe and R. H. Fish, unpublished work.

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