Measuring H-bonding in supramolecular complexes by gas phase ion–molecule reactions†

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H/D and guest-exchange ion–molecule reactions have been used as a new tool to elucidate the operation of multiple hydrogen bonding in gas-phase complexes formed between phosphonate cavitands and ethyl-substituted ammonium ions.

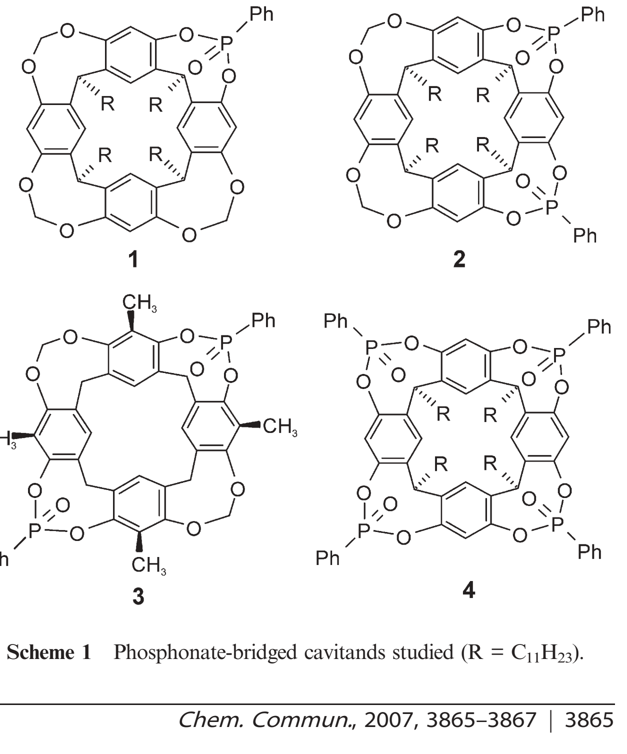
Mastering noncovalent interactions is one of the key issues in supramolecular chemistry.[1] This is particularly true for molecular recognition, where type, number, strength and synergy of noncovalent interactions between host and guest determine the attainable level of selectivity in complexation.[2] Since H-bonding is one of the workhorses of weak interactions, a versatile and efficient methodology capable of assessing the metrics of H-bonding in host–guest complexes is highly desirable. In the past, H-bonding in supramolecular complexes has been mainly elucidated in the solid state.[3] More recently, mass spectrometry has become a valuable tool for the characterization of supramolecular assemblies.[4] However a reliable MS methodology capable of defining number, strength and mode of H-bonding in supramolecular species is still missing. FTICR mass spectrometry allows an elegant way to perform gas-phase ion–molecule reactions.[5] Previously, ion–molecule reactions have been mainly exploited for enantioselectivity,[6] and structural research.[7] Ion–molecule reactions have been sparingly applied for research of H-bonding in supramolecular species,[8] even though H/D-exchange reactions especially bear real potential for studying metrics of H-bonding. During H/D-exchange reactions, the active hydrogens are expected to be exchanged for deuterium. The existence of stable H-bonding interactions would therefore either prevent the exchange or at least slow it down significantly.[9,10]

In this communication we introduce H/D- and guest-exchange ion–molecule reactions as a new tool to elucidate the operation of multiple H-bonding in gas-phase complexes formed between phosphonate cavitands (Scheme 1) and ethyl-substituted ammonium ions. The reactions were performed in an ESI-FTICR mass spectrometer and *n*-PrNH$_2$ was used for guest-exchange reactions and ND$_3$ for H/D-exchange reactions. Phosphonate and phosphate-bridged cavitands are selective receptors for ammonium ions, both in solution,[11] and in the gas phase.[12] Number and positioning of the P=O groups at the upper rim and their relative orientation with respect to the cavity[13] are the key host parameters in defining the multiple H-bonding interactions involved in the recognition process. As reported earlier, the outward orientation of a P=O group with respect to the cavity prevents the complex formation, while the length of the alkyl feet does not influence complexation.[14]

The spectra measured from 1 : 1 cavitand–alkyl ammonium ion solutions showed that cavitands **2** and **4** form the most abundant complexes with all ammonium ions in comparison to cavitands **1** and **3**. Among the guest series, cavitands **2** and **4** formed the most abundant complexes with secondary alkyl ammonium ions. This was not observed with cavitands **1** and **3**.

In the case of EtNH$_3^+$ complexes, [M + PrNH$_3$]$^+$ was detected as a product (Fig. 1). However, among complexes formed with Et$_2$NH$_2^+$, the guest exchange was only observed with complexes of **1** and **3** (Table 1). Among the triethyl ammonium complexes, only the complex formed with **2** exchanged the original guest.

It is notable that the guest exchange was also observed in those cases where the conjugate amine of the original inbound ammonium ion had higher proton affinity than the *n*-propylamine. This behavior implies that the guest-exchange reaction proceeds through the formation of a protonated cavitand. The proton affinities of the cavitands are not known, but earlier studies have implied that they are relatively high.[8b] Consequently, it is



Scheme 1 Phosphonate-bridged cavitands studied (R = C$_{11}$H$_{23}$).

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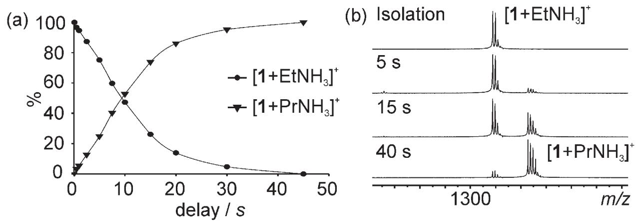

Fig. 1 Reaction of $[\mathbf{1} + EtNH_3]^+$ complex with $PrNH_2$. (a) Relative abundances of the ions as a function of reaction delay (s). (b) Isolation spectrum and the spectra measured at 5, 15, and 40 s delays.

Table 1 Observed reaction rate constants for $PrNH_2$ (k_{PrNH2}) and ND_3 ($k_{H/D}$) reactions and the number of observed H/D exchanges

	$EtNH_3^+$			$Et_2NH_2^+$			Et_3NH^+	
	$PrNH_2$	ND_3		$PrNH_2$	ND_3		$PrNH_2$	ND_3
	k_{PrNH2}[a]	H/D	$k_{H/D}$	k_{PrNH2}[a]	H/D	$k_{H/D}$[a]	k_{PrNH2}[a]	H/D
1	1.97	3	0.22	0.14	2	0.02	—	—
2	0.93	2	0.01	—	—	—	0.002	—
3	1.85	3	1.02	0.09	2	0.43	—	—
4	2.44	3	0.14	—	—	—	—	—

[a] 10^{-10} cm^3s^{-1} mol^{-1}.

reasonable to assume that the proton is not directly transferred from an inbound ammonium ion to *n*-propylamine. However, the life-time of the transition state, which involves the formation of a protonated cavitand is short, since only negligible peaks corresponding to protonated cavitands were occasionally observed.

The decay of the relative abundances of the ions as a function of time was used to deduce the reaction rate constants for the guest-exchange reactions (Table 1). The rate constants show an expected trend, dropping upon moving towards more substituted ammonium ions. This is likely caused by the differences in the proton affinities of the conjugate amines, as well as the steric factors. Nevertheless, the differences between the rate constants for the $EtNH_3^+$ complexes of the cavitands were negligible.

The H/D exchange reactions occurred relatively fast for all the complexes formed with primary ethyl ammonium ion (Fig. 2, Table 1). The complexes of **1**, **3**, and **4** formed with $EtNH_3^+$ exchanged three hydrogens. Within a reaction delay of 300 s, the $EtNH_3^+$ complex of **2** exchanged only two hydrogens, but the elevation of the base line and the reaction rate implied that the third hydrogen would have also been exchanged if a longer delay would have been used. During the reactions with $EtNH_3^+$ complexes a minor formation of $[M + ND_3 + H]^+$ and $[M + ND_3 + D]^+$ was also occasionally observed.

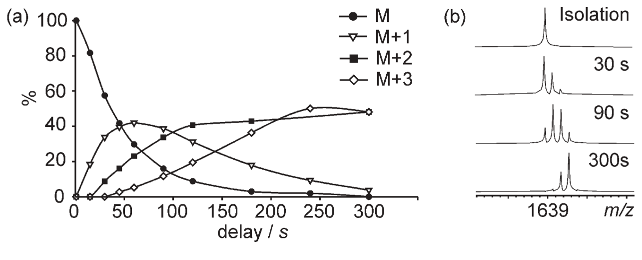

Fig. 2 Reaction of $[\mathbf{4} + EtNH_3]^+$ with ND_3. (a) Relative abundances as a function of the delay (s). (b) Isolation and the reaction spectra measured at 30 s, 90 s, and 300 s delays.

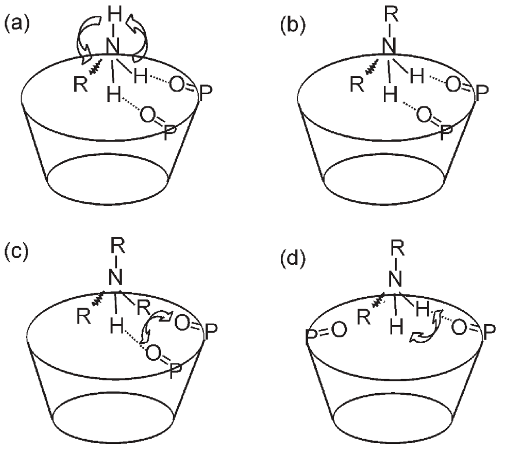

Fig. 3 (a) Gyroscopic interaction between **2** and RNH_3^+, (b) stable interaction between **2** and $R_2NH_2^+$, (c) pendulum-interaction between **2** and R_3NH^+, and (d) pendulum-interaction between **3** and $R_2NH_2^+$.

In the case of $Et_2NH_2^+$ complexes, no H/D-exchanges were observed with complexes of **2** and **4**, but the $Et_2NH_2^+$ complexes of cavitands **1** and **3** exchanged the two possible hydrogens. Among the Et_3NH^+ complexes, no H/D-exchanges were observed. This might be caused by the proton affinity difference between the triethylamine and ND_3 and is not necessarily related to a particularly strong single H-bond of the complexes.

According to the results, the interaction of the $EtNH_3^+$ with all cavitands resembles a gyroscope (Fig. 3a), which leaves at least one hydrogen at a time open for reaction. However, in the $Et_2NH_2^+$ complexes of cavitands **2** and **4**, both of the NH protons are involved in hydrogen bonding with adjacent P=O groups (Fig. 3b) and exchange reactions are not observed. Cavitands **1** and **3** can employ only a single available hydrogen bonding site and the interaction with diethyl ammonium ion is reminiscent of a pendulum, which enables the occurrence of reactions. This implies that the distance between the opposing P=O groups in cavitand **3** is too large for synergistic H-bonding with the distal P=O groups (Fig. 3d).[15] Similarly, Et_3NH^+ forms a stable hydrogen bond with cavitands **1** and **3**, but the Et_3NH^+ complex of cavitand **2** resembles a pendulum (Fig. 3c), which enables the guest-exchange reaction.

In the case of tetraphosphonate-cavitand **4**, the H-bonding takes place with two adjacent P=O groups at a time.[16] This is clearly shown by the most abundant formation of the $Et_2NH_2^+$ complex. However, the ring arrangement of the four P=O groups enables the guest to rapidly change its H-bonding pattern with the host over time. This possibility most likely increases the proton affinity of the cavitand and also stabilizes the complexes formed, as in the case of the $[\mathbf{4} + Et_3NH]^+$ complex, which was not observed to undergo guest-exchange reaction although the reaction was observed in the case of $[\mathbf{2} + Et_3NH]^+$ complex.

In conclusion, gas-phase ion–molecule reactions have revealed the structure and dynamics of the H-bonding interactions of the studied complexes. Structurally, the cavitands are able to utilize only two adjacent phosphonate groups simultaneously for interaction with alkyl ammonium ions. In the case of primary and secondary ethyl ammonium ions a kinetically stable hydrogen bonding interaction pattern is formed only if the available hydrogen bond acceptor sites of the cavitand equal the hydrogen bond donor sites of the ammonium ion in number and simultaneous availability. When this is not the case, the interaction resembles either a pendulum or a gyroscope, both compatible with the gas-phase H/D exchange. In addition, hoop arrangement of the four P=O groups in tetraphosphonate cavitand **4** offer an extra stabilization for its complexes. In general, we believe that this experimental methodology is unique in defining multiple H-bonding interactions in terms of geometry, strength and synergy of interaction. Similar behavior has been recently observed also in the case of complexes of carboxylated crown.[17] This innovative MS tool can be applied to the investigation of a wide variety of supramolecular systems (tweezers, base-pairing, dynamic polymers *etc.*), provided that the complexes can be analyzed by mass spectrometric methods on either polarization. Utilization of ion–molecule reactions is mainly limited by volatility of the neutral reagent and proton affinity difference between the interacting species. However, in the case of H/D-exchange reactions several deuterated reagents have successfully been used (D_2O, CD_3OD, CD_3COOD, ND_3), broadening the applicable proton affinity area.[18]

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