Mass Spectrometric Investigation of Noncovalent Complexation between a Tetratosylated Resorcarene and Alkyl Ammonium Ions

Elina Ventola,[a] Kari Rissanen,[b] and Pirjo Vainiotalo*[a]

Abstract: Noncovalent complexation between tetratosylated tetraethyl resorcarene (**1**) and primary, secondary, and tertiary alkyl ammonium ions (**mMe**, **dMe**, **tMe**, **mEt**, **dEt**, **tEt**, **dBu**, and **dHex**) was studied by electrospray ionization Fourier transform ion cyclotron resonance (ESI-FTICR) mass spectrometry. Interactions of the noncovalent complexes were investigated by means of competition experiments, collision-induced dissociation (CID) experiments, ion–molecule reactions with tripropylamine and gas phase H/D-exchange reactions with deuteroammonia. Gas phase ion–molecule reactions gave especially valuable information about the structure and properties of the complexes. Resorcarene **1** formed relatively stable 1:1 complexes with all aliphatic alkyl ammonium ions. Steric properties of the alkyl ammonium ions and proton affinities of the conjugate amines noticeably affected the complexation properties, indicating the importance of hydrogen bonding in these complexes. According to the competition experiments, the thermodynamically most stable host–guest complexes were formed with alkyl ammonium ions that were most substituted and had the longest alkyl chains. In CID experiments, release of an intact free guest ion or dissociation of the host was observed to depend on the proton affinity of the amine and the strength of the hydrogen bond that was formed. In ion–molecule reactions with tripropylamine, a guest exchange reaction occurred with all alkyl ammonium ion complexes with reaction rates mostly dependent on the steric properties of the original guest ion. In H/D-exchange reactions the N-H hydrogen atoms of the guest ion were exchanged with deuterium, whereas the resorcinol hydrogen atoms remained unchanged.

Keywords: host–guest systems · ion–molecule reactions · mass spectrometry · noncovalent interactions · resorcarenes

Introduction

Weak noncovalent host–guest interactions are vital in many biological systems and, in many cases, they make enzymatic processes highly favorable and efficient. One goal of supramolecular chemistry is to imitate the efficiency and selectivity of biological processes by modeling the noncovalent interactions involved in these systems.[1] Noncovalent interactions include hydrogen bonding, cation–π interactions, CH–π interactions, and hydrophobic interactions.[1a,b] The development of efficient and selective synthetic hosts demands understanding of these interactions and how they work in synthetic hosts.

Resorcarenes are able to form host–guest complexes with a wide variety of guest molecules.[2] Aromatic rings of resorcarenes enable multiple CH–π or cation–π interactions, and polar hydroxy groups and other substituents can participate in hydrogen bonding with suitable guest molecules. Resorcarene complexation has been reported with alkali metal cations,[3] alcohols,[4] various nitrogen compounds,[5] sugars,[6] and steroids.[7]

Mass spectrometry (MS) with a soft ionization technique, such as electrospray ionization (ESI),[8] is challenging the more traditional methods, such as X-ray diffraction methods[9,10] and NMR spectroscopy,[3a,4,7a,11,12] in studies of host–guest complexation. ESI-MS has four benefits in the study of noncovalent complexes: stoichiometry, specificity, sensitivity, and speed. Only a small amount of sample is needed to produce a representative spectrum of an identifiable noncovalent complex in reasonable time. As a technique, ESI-MS is suitable for the region that exists between the solution state and gas phase. Results of titration and competition experiments have been found to correlate relatively well with the results of condensed-phase techniques like NMR spec-

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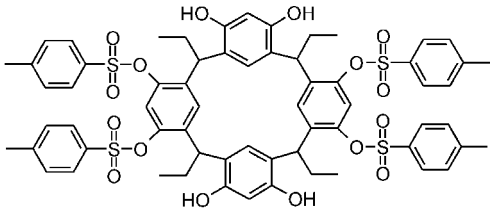
troscopy.[13–15] On the other hand, in-source dissociation, collision-induced dissociation (CID), and ion–molecule reactions reflect the gas-phase properties of the ion under study. Though gas-phase studies are valuable in understanding the interactions in supramolecular complexes without solvent influence, results from gas-phase methods cannot be unambiguously transferred to the solution phase. Some noncovalent interactions are strengthened in the absence of solvent and some become less important. Not only the lack of solvent but also the changes in vibrational modes of the host molecules in the gas phase affect the steric factors of the complex formation.[16] Although mass spectrometric studies of host–guest complexes during the past decade have concentrated on the complexes of crown ethers[13] and cavitands,[17] some studies on resorcarene complexation with alkyl ammonium ions[5d] and alkali metal cations[3b] have also been performed.

Here we report the results from the mass spectrometric study of interactions between tetratosylated tetraethyl resorcarene and eight alkyl ammonium ions differing in degree of substitution and chain length (Scheme 1). Substituted ammonium ions play an important role in chemistry and biology, which makes it of special interest to develop and study host molecules capable of complexing and recognizing them. Additionally, substituted ammonium ions are able to function as hydrogen-bond donors through the protons attached to the nitrogen atom, their alkyl chains are able to engage in CH–π interactions with the host and they appear in ionic form in solution, which is essential for ESI mass spectrometric studies. For their part, tetratosylated resorcarenes are expected to act as hydrogen-bond acceptors by virtue of their S=O and OH groups. In addition, the aromatic rings of the substituents improve the possibility of the resorcarene being able to undergo CH–π interactions with alkyl-chain-containing guests.



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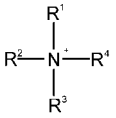


mMe: $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$

dMe: $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$

tMe: $R^1 = R^2 = R^3 = CH_3$, $R^4 = H$

mEt: $R^1 = CH_2CH_3$, $R^2 = R^3 = R^4 = H$

dEt: $R^1 = R^2 = CH_2CH_3$, $R^3 = R^4 = H$

tEt: $R^1 = R^2 = R^3 = CH_2CH_3$, $R^4 = H$

dBu: $R^1 = R^2 = CH_2CH_2CH_2CH_3$, $R^3 = R^4 = H$

dHex: $R^1 = R^2 = CH_2CH_2CH_2CH_2CH_2CH_3$, $R^3 = R^4 = H$

Scheme 1. Systems studied.

Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry, used to detect host–guest complexes produced by electrospray ionization, provides high mass accuracy and resolving power. The ICR cell makes it possible to isolate and store the formed host–guest complexes. After selective ion isolation, various collision-induced dissociation experiments and ion–molecule reactions with neutral reagents can be performed, and valuable information can be obtained on the gas-phase stability, structure, and reactivity of the host–guest complexes. It was also of interest to clarify the comparability of the results obtained by different mass spectrometric techniques.

Results and Discussion

Complex formation with alkyl ammonium ions: All eight alkyl ammonium ions investigated formed 1:1 complexes with resorcarene **1** in acetonitrile. Acetonitrile was chosen as solvent because it is less polar than the more common ESI solvents such as methanol and water. Owing to its aprotic nature it was expected to cause minimum disturbance to the hydrogen bonding between the host and the guest. A fundamental requirement for a mass spectrometric study is charge. Use of charged guests made it possible to observe both the complexes and the free guest ions in acetonitrile.[14] This kind of approach has several advantages: it allows the use of less protic solvents, makes covalent modifications to the host unnecessary, and simplifies the spectrum. The spectra of **1** with alkyl ammonium ions clearly showed the formation of 1:1 complexes. The minor formation of 2:1 dimeric complexes consisting of two host molecules and one guest ion was also observed, but, as the behavior and properties of the dimer have been reported earlier, discussion here is limited to the monomeric 1:1 species.[18] The abundance of the complex ions seemed to depend mostly on the length of the alkyl chain of the ammonium ion and the degree of substitution.

In addition to alkyl ammonium complexes, $[\mathbf{1} + NH_4]^+$, $[\mathbf{1} + Na]^+$, $[\mathbf{1} + K]^+$, and $[\mathbf{1} + Cu^I]^+$ adduct ions at *m/z* values of 1234, 1239, 1255, and 1279 (most abundant isotope) were often observed, as can be seen in the typical spectrum of **1** with **dHex** presented in Figure 1. These ions arise from unavoidable impurities in the system; the intensities of the adduct ions vary over time, mostly depending on external factors. Complex formation with alkali metal ions

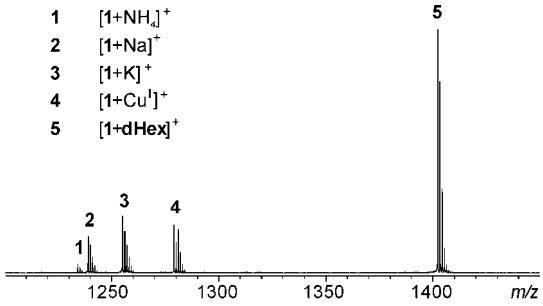


Figure 1. Basic ESI-spectrum of **1** (4.1 μM) with **dHex**, 1:1 in CH_3CN.

such as sodium and potassium is not surprising considering the arrangement and number of oxygen atoms on the upper rim of the host.

The composition of the alkyl ammonium ion complexes was confirmed by comparing the experimental monoisotopic *m/z* values and isotopic patterns with theoretical values calculated on the basis of natural abundances. All ions were singly charged according to their isotopic distributions. The mass differences between the experimental and theoretical values were less than 0.05 Da, which means that experimental values are in good agreement with theoretical values. The studied ions can therefore be considered as true noncovalent alkyl ammonium complexes.

Competing alkyl ammonium ions: Competition experiments were performed to estimate preferences in complex formation between different guest ions. Experiments were carried out between two guests at a time to avoid nonspecific complexation, which could arise with a greater number of charged species in solution.

The mean values of the measurements and calculated overall variances are presented in Figure 2. The results show

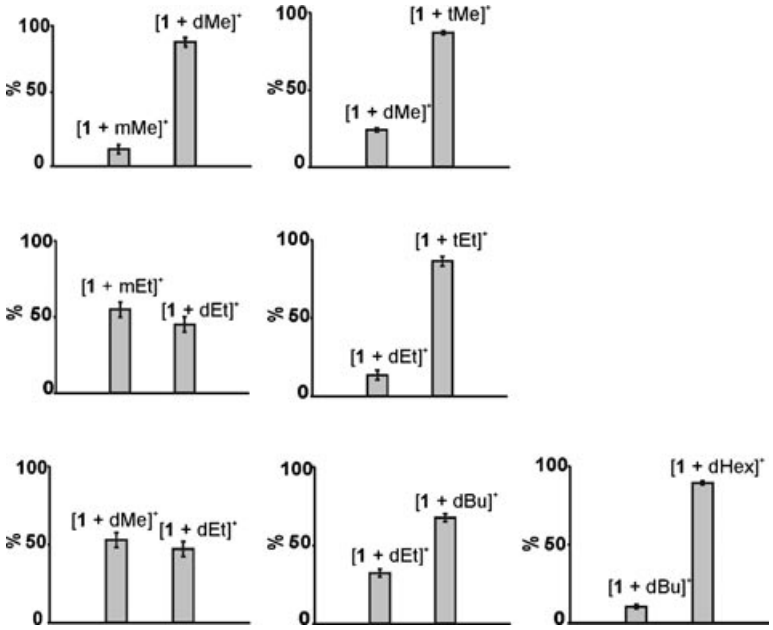


Figure 2. Results of competition experiments involving different alkyl ammonium ions.

the same kind of behavior as was observed earlier; the complex formation depends on the degree of substitution and the length of the alkyl chain attached to the nitrogen atom. With methyl-substituted ammonium ions the complex formation increases in the order **mMe** $\ll$ **dMe** $<$ **tMe**. The order with ethyl-substituted ammonium ions is similar, **mEt** $\approx$**dEt** $\ll$**tEt**. The complexation efficiency of **mEt** and **dEt** is so similar that there is no difference between the two ions within the limits of accuracy. Complex formation with tertiary alkyl ammonium ions is preferred in both groups, although the difference in complexation between **dEt** and **tEt** is greater than the difference between **dMe** and **tMe**. The length of the alkyl chain also seems to have a great effect on complexation. Comparison of **dMe**, **dEt**, **dBu**, and **dHex** shows increasing complex formation as the length of the alkyl chain increases. Although no difference can be seen between **dMe** and **dEt** within the limits of accuracy, **dBu** and especially **dHex** clearly show increased complex formation as the length of the alkyl chain increases. Large enough differences in response factors of alkyl ammonium ions were not observed to explain the trend in complexation. A lower degree of solvation may, in part, be responsible for the enhanced complex formation with alkyl ammonium ions that are more highly substituted and have longer alkyl chains. Also, as the degree of substitution and alkyl chain length increase, the possibility of conformations that are able to form favorable CH–π interactions between guest and host increases. A greater number of favorable interactions between the host and guest improve the thermodynamic stability of the complex. Assuming that hydrogen bonding is one of these interactions, the question concerning the number of hydrogen bonds involved in these interactions arises. Primary and secondary alkyl ammonium ions are theoretically capable of forming more than one hydrogen bond with the host. However, nothing in the competition results points to that.

Collision-induced dissociation: CID experiments were performed with all alkyl ammonium ion complexes to estimate and compare the strength of the complexation with different guest ions. Single-frequency excitation shots were observed to bring a variable amount of additional energy to the complexes, and for that reason their use was avoided and monoisotopic isolations were not pursued.

CID spectra of the alkyl ammonium complexes showed three types of behavior. 1) The fragment ions from the dissociation of the host were observed in the spectra of $[\mathbf{1 + mMe}]^+$. The ions were similar to those formed in dissociation of the $[\mathbf{1 + H}]^+$ ion. 2) Ions $[\mathbf{1 + dMe}]^+$ and $[\mathbf{1 + mEt}]^+$ showed fragment ions from dissociation of the host and the intact free alkyl ammonium ion. 3) In the case of ions $[\mathbf{1 + dEt}]^+$, $[\mathbf{1 + tMe}]^+$, $[\mathbf{1 + tEt}]^+$, $[\mathbf{1 + dBu}]^+$, and $[\mathbf{1 + dHex}]^+$, only the released intact alkyl ammonium ion was observed. Figure 3 presents typical spectra of these three types of dissociation and, for comparison, the dissociation of $[\mathbf{1 + H}]^+$. The dissociation behavior appears to follow the order of the proton affinity of the alkyl amine corresponding to the alkyl ammonium ion used as guest. The lower the proton affinity of the conjugate amine the easier the donation of the proton to the host is,

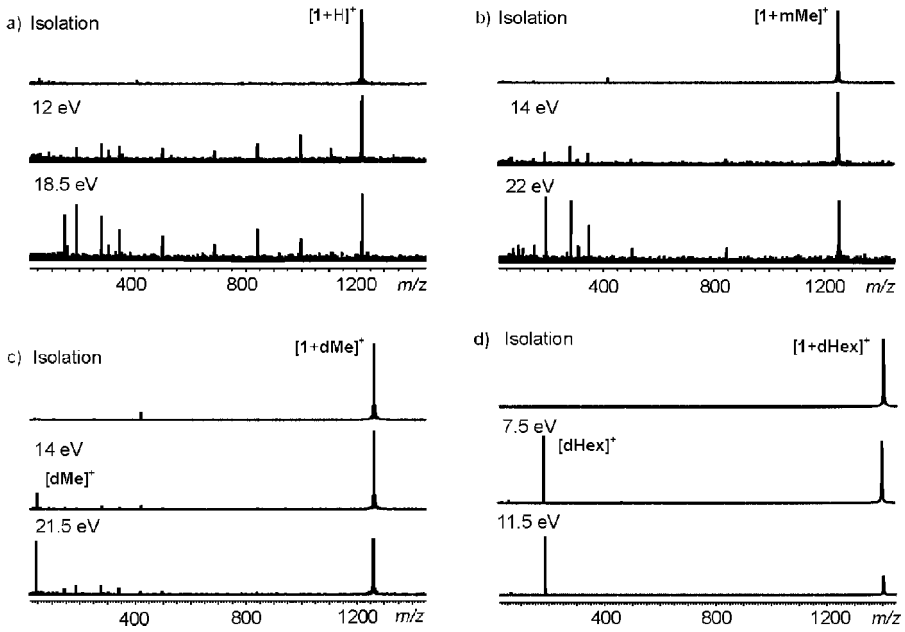


Figure 3. Three types of behavior in dissociation. Isolation and CID spectra of a) $[\mathbf{1} + \mathrm{H}]^+$, b) $[\mathbf{1} + \mathbf{mMe}]^+$, c) $[\mathbf{1} + \mathbf{dMe}]^+$ and d) $[\mathbf{1} + \mathbf{dHex}]^+$.

and the greater the tendency for dissociation of the host. Alkyl ammonium ions, whose conjugate amines possess higher proton affinities, hold the proton tighter and release of the intact alkyl ammonium is observed.

Figure 4 presents the dissociation curves of alkyl ammonium complexes. As can be seen, the stability of methyl-substituted ammonium ions follows the order **dMe** > **mMe** > **tMe**, although differences between these three are relatively small. The $E_{\mathrm{com}}^{50\%}$ values, which represent the activation energy where half of the isolated complex has dissociated (Table 1), show the same pattern. Within the ethyl ammonium group (Figure 4b) the order of stability appears to be **mEt** > **dEt** > **tEt**, although differences, especially between **mEt** and **dEt**, are small. The dissociation of $[\mathbf{1} + \mathbf{tEt}]^+$ clearly occurs at lower activation energy than for any of the above-mentioned ions. Comparison of complexes where the guest is a secondary alkyl ammonium ion reveals a clear dependence between the length of alkyl chain and the stability of the complex ion. The comparison is presented in Figure 4c) and, according to this, the stability of complexes with secondary alkyl

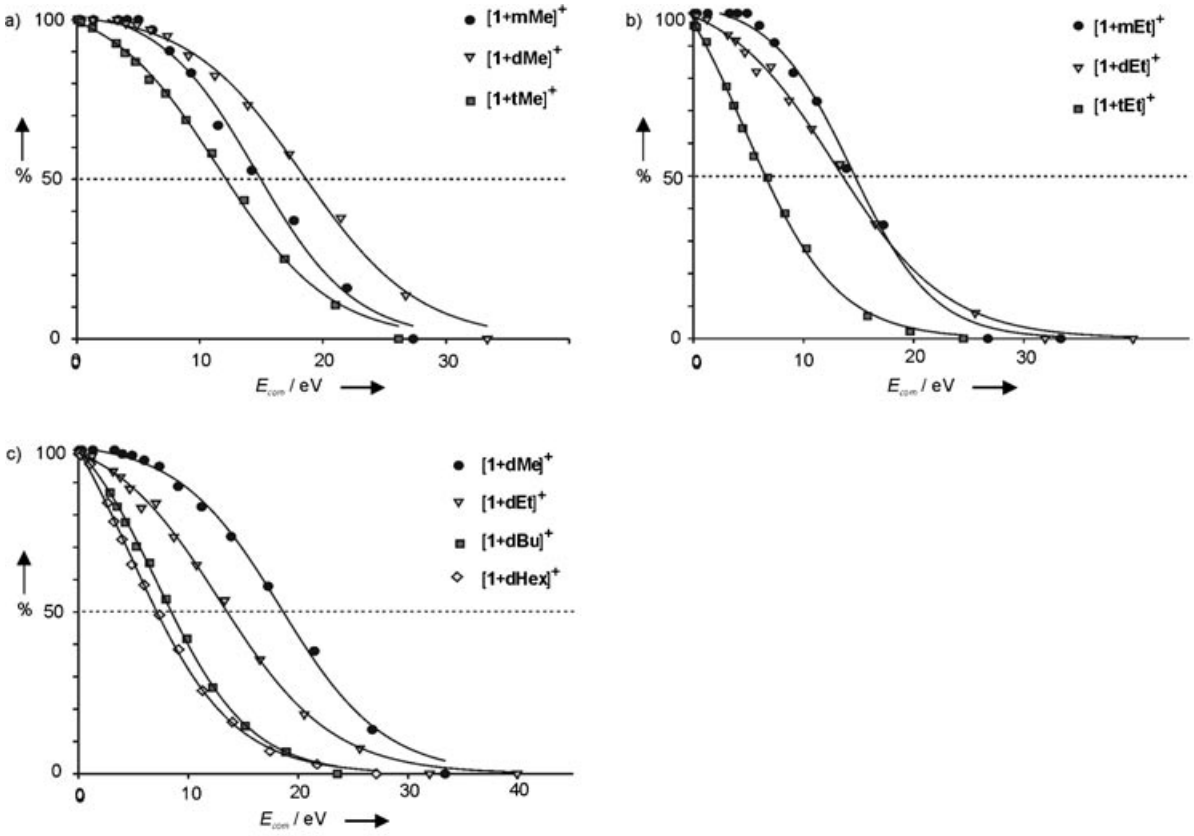


Figure 4. Dissociation curves of alkyl ammonium complexes. a) Methylammonium complexes, b) ethylammonium complexes, c) dialkyl ammonium complexes.

Table 1. Comparison of dissociation curves of alkyl ammonium complexes.

Ion	$E_{com}^{50\%}$ [a]	R^2[b]	PA[c]	Proton donation
$[\mathbf{1}+H]^+$	8.84	0.9988	***	yes
$[\mathbf{1}+\mathbf{mMe}]^+$	14.95	0.9932	899.0	yes
$[\mathbf{1}+\mathbf{mEt}]^+$	14.67	0.9967	912.0	yes
$[\mathbf{1}+\mathbf{dMe}]^+$	18.64	0.9976	929.5	yes
$[\mathbf{1}+\mathbf{tMe}]^+$	12.13	0.9981	948.9	no
$[\mathbf{1}+\mathbf{dEt}]^+$	13.54	0.9983	952.4	no
$[\mathbf{1}+\mathbf{dBu}]^+$	8.46	0.9991	968.5	no
$[\mathbf{1}+\mathbf{dHex}]^+$	7.15	0.9991	–[d]	no
$[\mathbf{1}+\mathbf{tEt}]^+$	6.54	0.9991	981.8	no

[a] Activation energy where half of the complex is dissociated (eV). [b] Correlation of fitting curve, R^2. [c] Proton affinity (PA) of the corresponding amine[19] (kJ mol^{-1}). [d] Value not available.

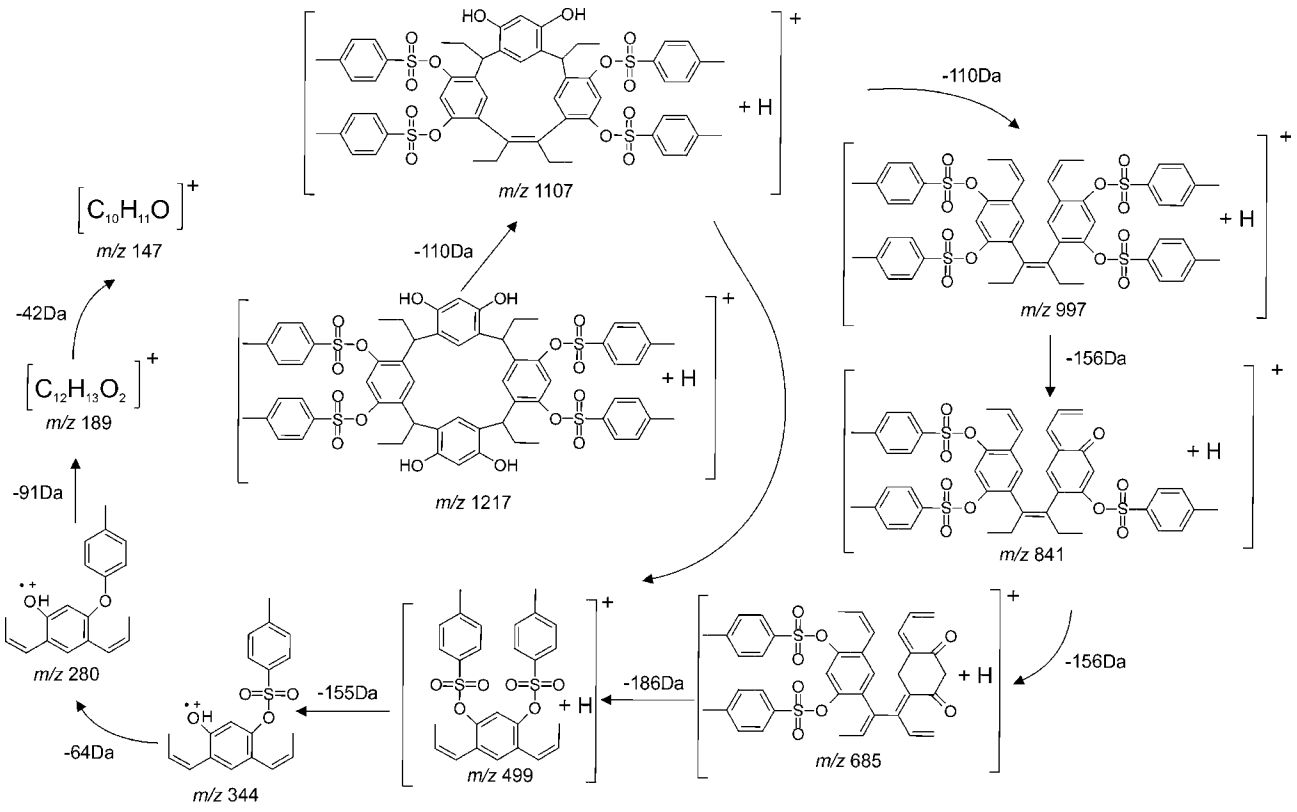
ammonium ion follows the order $[\mathbf{1}+\mathbf{dMe}]^+ > [\mathbf{1}+\mathbf{dEt}]^+ > [\mathbf{1}+\mathbf{dBu}]^+ > [\mathbf{1}+\mathbf{dHex}]^+$.

Since the main binding interaction is assumed to be hydrogen bonding, the effect of the proton affinity must not be overlooked. As the host is assumed to function as a hydrogen-bond acceptor and the guest as a donor, the difference in proton affinities between the host **1** and the amine may be significant for the stability of the complexes. The larger the difference in proton affinities of interacting species is, the longer the hydrogen bond length, the weaker the formed hydrogen bond, and the more unstable the formed complex. Overall, the tendency in stability of the alkyl ammonium complexes in the CID experiment seems to be dependent on the differences between the proton affinities of the host and the corresponding alkylamines. From the dissociation behavior of the complexes it can also be inferred that the proton affinity of the host is higher than the proton affinity of methylamine, but lower than the proton affinity of trimethylamine; the dissociation of $[\mathbf{1}+\mathbf{mMe}]^+$ produces only the protonated host and its fragments, whereas the $[\mathbf{1}+\mathbf{tMe}]^+$ ion releases only the intact alkyl ammonium ion.

Possible dissociation routes and structures of fragment ions formed in the dissociation of $[\mathbf{1}+H]^+$ are shown in Scheme 2. It must be stated that the pathway and the structures presented are only speculative; no MS^n experiments were performed due to low intensity of the fragment ions.

Ion–molecule reactions with tripropylamine: Ion–molecule reactions with tripropylamine were carried out to obtain additional information about the structure of alkyl ammonium complexes and their formation in the gas phase. Tripropylamine was chosen as neutral reagent for two reasons: 1) it has a higher proton affinity (991.0 kJ mol^{-1})[19] than any amine corresponding to the alkyl ammonium ions investigated and 2) the *m/z* value of $[\mathbf{1}+Pr_3NH]^+$ does not overlap with the value of any of the alkyl ammonium complexes investigated. In ion–molecule reactions with tripropylamine, all alkyl ammonium ion complexes exchanged the original guest ion for tripropylammonium, and all of the reactions went to completion. Spectra from ion–molecule reactions between $[\mathbf{1}+\mathbf{tEt}]^+$ and tripropylamine are presented in Figure 5.

There are few feasible reaction pathways for this kind of guest-exchange reaction to happen through dissociation of



Scheme 2. Dissociation of $[\mathbf{1}+H]^+$ in a CID experiment.

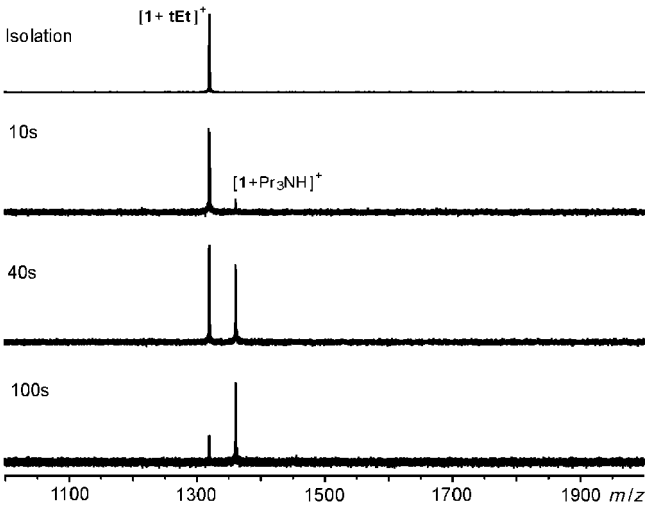


Figure 5. Spectra recorded from the ion–molecule reaction between **[1 + tEt]**$^+$ and tripropylamine.

the complex. Since no traces of ions ([**1** + H]$^+$ or [R_3NH]$^+$) were observed, it must be assumed that the reaction pathway includes a short-lived collision complex where transfer of a proton from the original guest to tripropylamine occurs. Guest-exchange reactions were observed as a function of time and the reaction rate constants and efficiencies were calculated (Figure 6 and Table 2). Comparison of the

Table 2. Experimental rate constants and reaction efficiencies for guest-exchange reactions with tripropylamine

	k_{obs}[a]	k_{eff}[b]
[1+mMe]$^+$	5.50	0.57
[1+dMe]$^+$	0.619	0.06
[1+tMe]$^+$	0.271	0.03
[1+mEt]$^+$	2.31	0.24
[1+dEt]$^+$	0.581	0.06
[1+tEt]$^+$	0.491	0.05
[1+dBu]$^+$	0.595	0.06
[1+dHex]$^+$	0.109	0.01
[**1**+H]$^+$	12.8	0.85

[a] Experimental rate constants in units 10^{-10} cm^{3}s^{-1} mol^{-1}. [b] Relative reaction efficiencies K_{eff} calculated as a ratio k_{obs}/k_{theor}.

methyl-substituted alkyl ammonium complexes (Figure 6a) shows a clear decrease in the reaction rate constants in the order **[1 + mMe]**$^+$ > **[1 + dMe]**$^+$ > **[1 + tMe]**$^+$. Comparison of the ethyl-substituted alkyl ammonium complexes (Figure 6b) shows the same order, but the difference between **[1 + dEt]**$^+$ and **[1 + tEt]**$^+$ is slight. In the case of the secondary alkyl ammonium complexes (Figure 6c), the reaction of **[1 + dHex]**$^+$ is clearly the slowest. There is vir-

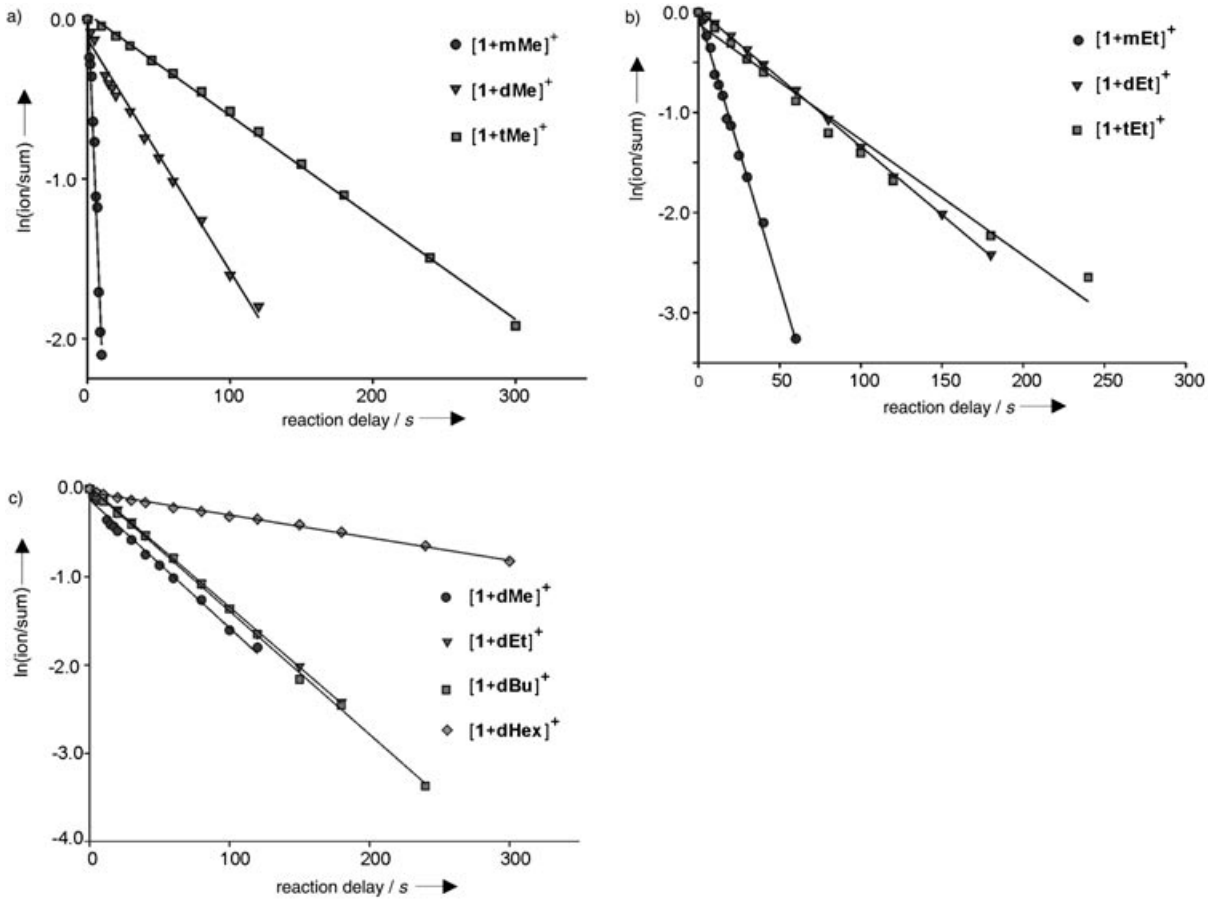


Figure 6. Decay of the relative abundance of the isolated ion as a function of time (s). a) Methylammonium complexes, b) ethyl ammonium complexes and c) secondary alkyl ammonium complexes.

tually no difference between $[\mathbf{1} + \mathbf{dEt}]^+$ and $[\mathbf{1} + \mathbf{dBu}]^+$, while the reaction of $[\mathbf{1} + \mathbf{dMe}]^+$ is slightly faster than the reactions of $[\mathbf{1} + \mathbf{dEt}]^+$ and $[\mathbf{1} + \mathbf{dBu}]^+$. Table 2 also includes the reaction rate constant of the $[\mathbf{1} + H]^+$ ion, which is much higher than the reaction rate constants of the alkyl ammonium complexes.

Table 3. Charge distribution and estimated volume of alkyl ammonium ions according to ab initio calculations (rhf/6–31G(d)).

Ion	Charge of N [a]	Charge of CH[b]	Charge of NH[c]	Volume [Å^3][d]
mMe	−0.85	0.27	0.47	10.76
dMe	−0.74	0.26	0.46	29.93
tMe	−0.64	0.25	0.45	42.02
mEt	−0.85	0.25	0.47	31.34
mEt	−0.76	0.25	0.45	63.13
tEt	−0.68	0.24	0.44	118.5
dBu	−0.77	0.20	0.45	146.9
dHex	−0.77	0.18	0.45	274.8
tPr	−0.70	0.20	0.44	188.7

[a] Mulliken atomic charge of the ammonium nitrogen atom. [b] Mulliken atomic charge of the last CH hydrogen atoms in the alkyl chain. [c] Mulliken atomic charge of the hydrogen atoms attached to the ammonium nitrogen atom. [d] Volume of the ion estimated from the optimized structure.

If all three species were connected by the same proton in the collision complex (Figure 7a), a competition situation would exist among the three species and their proton affinities would likely control the formation of the products. However, since the proton affinity of the host lies somewhere between the proton affinities of methylamine and trimethylamine, one would expect, especially with larger alkyl ammonium ions, that the product ion would then be $[NR_3 + Pr_3NH]^+$, and not the $[\mathbf{1} + Pr3NH]^+$ ion that was seen.

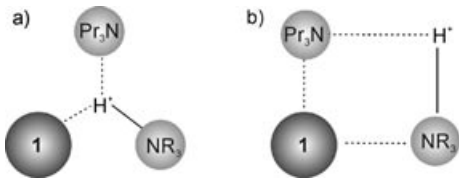


Figure 7. Possible collision complexes formed in the reaction of tripropylamine.

Judging from the reaction rates, there more likely exists a competition between the original guest and tripropylammonium, and the collision complex more resembles the one presented in Figure 7b. In this situation the difference in proton affinities of the competing guests would largely determine the reaction rate of the guest-exchange reaction. The greater the difference in proton affinities, the easier the transfer of the proton from the original guest to tripropylamine and the faster the reaction. Besides the proton affinity, the reaction rates are evidently affected by the sterical properties of the original guest ions. When two or more alkyl groups surround the proton to be exchanged, it is difficult for the neutral amine to get close enough to initiate the reaction. Reaction rates are clearly highest with $[\mathbf{1} + \mathbf{mMe}]^+$ and $[\mathbf{1} + \mathbf{mEt}]^+$ complexes, which have three easily available protons for the reaction. Reaction rates of the sterically most-hindered complexes, $[\mathbf{1} + \mathbf{tEt}]^+$, $[\mathbf{1} + \mathbf{tMe}]^+$ and $[\mathbf{1} + \mathbf{dHex}]^+$, are the slowest.

Gas-phase H/D-exchange reactions: To clarify the importance of hydrogen bonding in alkyl ammonium complexes, gas-phase H/D-exchange reactions were performed on complexes $[\mathbf{1} + \mathbf{mEt}]^+$, $[\mathbf{1} + \mathbf{dEt}]^+$ and $[\mathbf{1} + \mathbf{tEt}]^+$ using ND_3 as reactant gas. Monoisotopic isolations were used to simplify interpretation of the H/D-exchange spectra despite the additional energy that single-frequency excitation shots were observed to bring to complexes. With $[\mathbf{1} + \mathbf{mEt}]^+$ (d_0), three H/D-exchanges (d_1, d_2, and d_3) were observed within a reaction time of 5 minutes (Figure 8a). Correspondingly, with $[\mathbf{1} + \mathbf{dEt}]^+$ and $[\mathbf{1} + \mathbf{tEt}]^+$, two and one H/D-exchanges were observed (Figure 8b,c) within similar reaction times. H/D-experiments were simultaneously performed on the $[\mathbf{1} + H]^+$ and $[\mathbf{1} + Na]^+$ ions to clarify the location of the exchanged hydrogen atoms. In the reaction of $[\mathbf{1} + H]^+$, only peaks corresponding to adduct ions $[\mathbf{1} + ND_3 + H]^+$ and $[\mathbf{1} + ND_3 + D]^+$ were observed in the spectra. Spectra from the reaction of $[\mathbf{1} + Na]^+$ with neutral ND_3 showed no traces of hydrogen exchange (Figure 8d). From this it seems clear that the exchanged hydrogen atoms are the hydrogen atoms of the guest ions. This also implies that the resorcinol hydrogen atoms participate in intramolecular hydrogen bonding in the gas-phase structure. Similar behavior in H/D-exchange reactions has been observed with unsubstituted resorcarene.[3b,20]

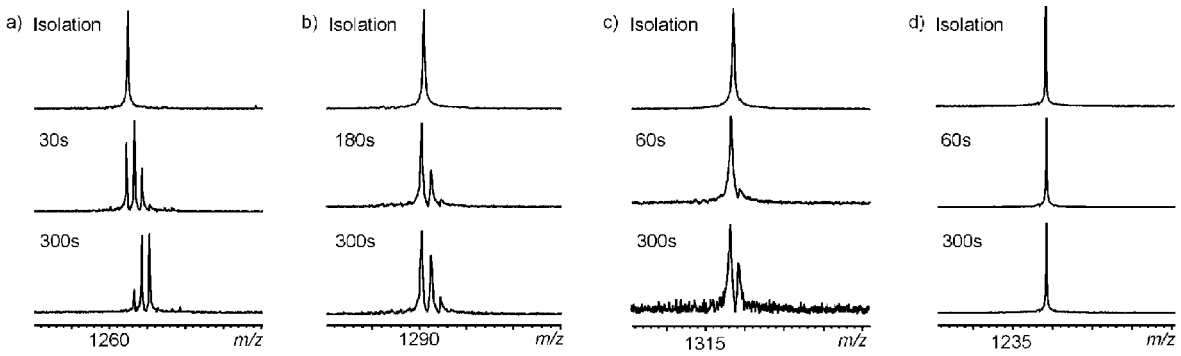


Figure 8. H/D-exchange spectra. a) $[\mathbf{1} + \mathbf{mEt}]^+$, b) $[\mathbf{1} + \mathbf{dEt}]^+$, c) $[\mathbf{1} + \mathbf{tEt}]^+$, and d) $[\mathbf{1} + Na]^+$.

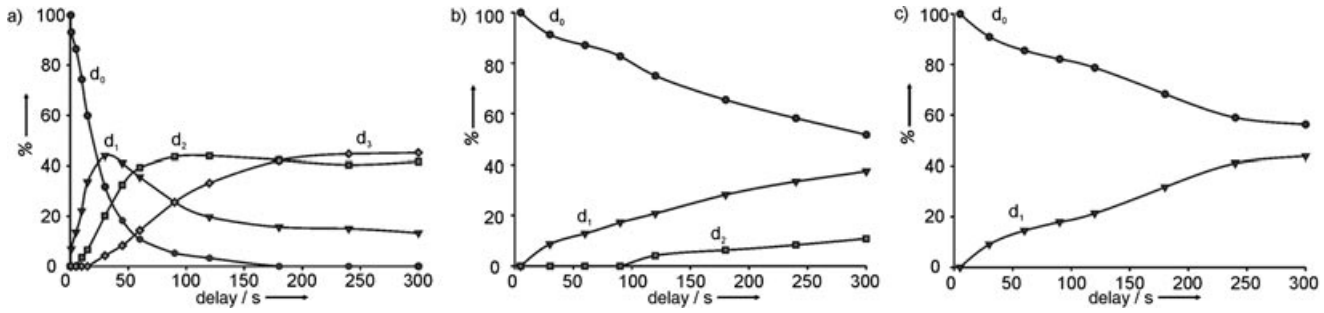


Figure 9. Relative intensities in an H/D-exchange experiment as a function of reaction time (s). a) $[\mathbf{1} + \mathbf{mEt}]^+$, b) $[\mathbf{1} + \mathbf{dEt}]^+$, and c) $[\mathbf{1} + \mathbf{tEt}]^+$.

The reaction of $[\mathbf{1} + \mathbf{mEt}]^+$ reached equilibrium after 240 s. At the equilibrium stage the d_3 ion was predominant, although the d_2 ion had almost the same abundancy (Figure 9a). The reaction rate constant for the first exchange (k_1) was calculated from the slope of the disappearance of the reactant ion and it was found to be 2.36×10^{-11} cm^3 molecule^{-1} s^{-1}. The reaction rate constants for the second and third exchanges of the hydrogen atom of $[\mathbf{1} + \mathbf{mEt}]^+$ were 1.71×10^{-11} and 7.66×10^{-12} cm^3 molecule^{-1} s^{-1}. Reactions of $[\mathbf{1} + \mathbf{dEt}]^+$ and $[\mathbf{1} + \mathbf{tEt}]^+$ did not reach equilibrium within the reaction time of 5 min (Figure 9b,c). For these reactions the reaction rate constants (k_1) for the first exchange were calculated to be 1.53×10^{-12} and 1.35×10^{-12} cm^3 molecule^{-1} s^{-1}, respectively. Exchange reactions for the last H/D-exchange were so slow in all three cases that hydrogen bonding must play a role in these complexes, particularly, when single-frequency excitation shots were used and it could be assumed that isolated complexes gained additional energy, which presumably further accelerated the reaction. Similar results were obtained with the failure of the H/D-exchange reaction with $[\mathbf{1} + \mathbf{mEt}]^+$ to reach termination and the continued presence of forms d_1 and d_2 at equilibrium stage.

Comparison of results obtained by different methods: At first glance, the different mass spectrometric techniques appear to give confusing and contradictory results. However, closer examination of the results shows them to be quite logical and each technique offers information that is a relevant piece of the puzzle.

Competition experiments are often considered to describe the solution-state properties of complexes.[14,15] Before a complex is formed in solution, desolvation of both species must take place. In addition, desolvation of the ions must occur when they are transferred to the gas phase in an electrospray ionization process. Thus, the different solvation properties of the species not only affect the formation of the complexes, but also affect the ion yield obtained in electrospray ionization and the ionization efficiency of the species.

Earlier it was stated that systems with similar energetic and structural features can safely be compared.[14,20,21] The alkyl ammonium ions used in this study differ only in a minor way in their charge distribution, as can be seen from Table 3 in which the results of ab initio optimizations of the alkyl ammonium ions are presented. The differences in their energetic features can therefore be considered small. The number and length of the alkyl chains, on the other hand, significantly alter the steric properties of the ions. The alkyl ammonium ion is presumably solvated at the nitrogen atom. Nonpolar alkyl chains are likely to be less solvated, especially in the presence of a fairly aprotic solvent such as acetonitrile. As the number and length of the alkyl chains increase, their ability to shield the nitrogen center from solvation increases as well. The alkyl ammonium ions bearing long alkyl chains or having a higher degree of substitution are likely to be less solvated than smaller alkyl ammonium ions. Owing to the lower degree of solvation, the formation of complexes with larger alkyl ammonium ions could be expected to be an enthalpically more favorable process. Furthermore, the formed complex ion could be assumed to be less solvated; production of gas-phase ions from the complex ions with larger alkyl ammonium guests would thereby be enhanced. It is the thermodynamic stability that determines if a complex is formed in solution or not and, if it is formed, to what extent it is formed. As noted above, the increased substitution and length of the alkyl chains are likely to increase the thermodynamic stability of the complex owing to the increased amount of favorable CH–π contacts. These two factors arising from the sterical properties of the alkyl ammonium ions can be considered responsible for the trend observed in competition experiments.

Proton affinities seemed to be a more important factor than the steric properties of the guest ions in the CID experiments. The larger the proton affinity difference between the host and the guest, the longer and weaker the hydrogen bond that existed between them was, and the faster their dissociation took place. Results from the CID experiments showed almost the opposite trend in the stability of the ions compared with the results from competition measurements. However, in comparing these results, it must be remembered that results from competition measurements are more indicative of solution-phase properties, and CID results indicative of the properties of gas-phase ions. In addition, CID measures the kinetic stability of the ions. Since the results from the competition experiments and the CID experiments show almost opposite trends, the complexes can be assumed to have different thermodynamic and kinetic stabilities.

Results from the gas-phase ion–molecule reactions with tripropylamine showed the importance of the steric properties of different guest ions. The rate of the guest exchange reaction was observed to depend mainly on the accessibility of the proton attached to the nitrogen atom of the original

guest ion. The more the NH protons of the guest ion were shielded by the alkyl chains, the slower the proton transfer from the alkyl ammonium to the neutral tripropylamine, and the slower the guest exchange reaction took place. In addition to steric properties of the alkyl ammonium ions, the proton affinities of the conjugate amines were also observed to affect the reaction rates of the guest exchange reaction.

According to the gas-phase H/D-exchange experiments, alkyl ammonium complexes partly exchanged the NH hydrogen atoms of the guest. The fact that the reaction did not reach termination and that the exchange of the last hydrogen atom was extremely slow, suggests that the complex has a hydrogen-bonded nature. Although a definite conclusion for or against hydrogen bonding cannot be drawn on the basis of these results alone, the host nevertheless showed no sign of being able to exchange resorcinol hydrogen atoms. The failure to exchange them could be due to intramolecular hydrogen bonds between the resorcinol hydroxyl groups and the S=O oxygen atoms of the substituents.

Conformations of related compounds have been reported. Lukin et al.,[22] for example, performed molecular mechanics calculations on tetratosylated resorcarene, which has methyl or propyl substituents on the lower rim. According to their study, the lowest energy conformation of this resorcarene would be a boat conformation with horizontal diacylated resorcinol rings and a C_2-symmetric propeller-like orientation of the four sulfonyl fragments. This conformation allows the formation of two pairs of intramolecular S=O···H–O hydrogen bonds. According to the reported crystal structure,[23] resorcarene tetramesitylsulfonate exists in the boat conformation in the solid state as well, which allows the formation of two intramolecular hydrogen bonds. In addition to the intramolecular hydrogen bonds, the boat conformation would also allow the complexation of relatively large guest ions, as was also observed in the present study. In the boat conformation the guest ion would be located more at the stern of the boat than in the middle. The tosylate substituents are located at the ends of the boat conformation. This location offers multiple CH–π sites for interaction between the alkyl chains of the guest ion and the aromatic rings of the substituents of the host.

Conclusion

As demonstrated in this study, mass spectrometry is a valuable tool for studying the gas-phase properties of, in particular, supramolecular assemblies. However, liquid-phase properties can also be elucidated. The usefulness of ion–molecule reactions will increase as they are more frequently applied to supramolecular complexes. At best, ion–molecule reactions with convenient reagents can offer diverse information about the energetics of complexes and the factors affecting their formation. However, as we have shown, the results from different mass spectrometric techniques must be interpreted with care, given the many factors that influence the formation and stability of these kinds of complexes.

Resorcarene **1** was found to form a singly charged noncovalent complex with all investigated alkyl ammonium ions, which were stable enough to survive the electrospray ionization process and isolation for MS/MS experiments. The following observations were made during the study: 1) resorcarene **1** has a relatively wide conformation in the complex structure and the complexation site is most likely at the stern of the boat conformation, whereas guest ions as large as dihexylammonium are able to from complexes with resorcarene **1**. 2) According to the competition experiments, the thermodynamically most stable host–guest complexes were formed with alkyl ammonium ions that were most substituted and had the longest alkyl chains. This is most likely caused by decreased solvation of the alkyl ammonium ions and increased possibility to form stabilizing CH–π interactions with the substituents of the host. 3) In CID experiments, release of an intact free guest ion or dissociation of the host was observed to depend on the proton affinity of the conjugated amine and the strength of the hydrogen bond that was formed. 4) In ion–molecule reactions with tripropylamine, a guest exchange reaction occurred with all alkyl ammonium ion complexes, with reaction rates mostly dependent on the steric properties of the original guest ion. In H/D-exchange reactions the NH hydrogen atoms of the guest ion were exchanged with deuterium, whereas the resorcinol hydrogen atoms remained unchanged. The fact that the exchange reactions did not reach termination and that the exchange of the last hydrogen was extremely slow suggests that the complex has a hydrogen-bonded nature, although a definite conclusion cannot be drawn.

Experimental Section

All mass spectrometry experiments were performed with the BioApex 47e Fourier transform ion cyclotron resonance mass spectrometer, equipped with an Infinity cell, a passively shielded 4.7 T 160-mm bore superconducting magnet and an external Apollo electrospray ionization source manufactured by Bruker Daltonics. The required 1×10^{-9} Torr vacuum was maintained by rotary vacuum pumps and turbomolecular pumps supplied by Edwards (Edwards High Vacuum International, Crawley, UK). The sample was introduced to a 70° off-axis sprayer through a syringe infusion pump (Cole-Parmer 74900 series, Cole-Parmer Instrument Company, Vernon Hills, IL) at a flow rate of 90 $\mu L\,h^{-1}$. Room-temperature nitrogen gas was used as nebulization and counter-current drying gas. Experimental parameters were kept as constant as possible to maintain comparable conditions. Ion-source voltages were mostly adjusted between −3.8 and −4.0 kV to end plate and between −4.0 and −4.4 kV to capillary. The capillary exit voltage was adjusted between 100 V and 350 V. The measurements and data handling were accomplished with Bruker XMASS software version 6.0.2.

Synthesis and characterization of resorcarene **1** were reported earlier.[23] Resorcarene **1** was dissolved in $CHCl_3$. All alkyl ammonium ions were used as ammonium chlorides and they were first dissolved in methanol and then diluted in acetonitrile. The sample for measurement was prepared in acetonitrile with a concentration of 4.1 μM and a host–guest ratio of 1:1 to avoid nonspecific complexation. For ion–molecule reactions, a host–guest ratio of 1:3 was used to produce adequate intensity for isolation in the higher cell pressure. Protonated host $[\mathbf{1}+H]^+$ was produced from a 1% trifluoroethanol (TFA)/methanol (v/v) solution.

Competition experiments were performed with a host–guest1-guest2 ratio of 1:1:1. The spectrum of a competition measurement consisted of 16 summed scans. Each experiment was carried out on five different samples and each sample was measured five times. The overall variance was

calculated from the standard deviation of sampling and the standard deviation of the measurement ($s^2 = s_1^2 + s_2^2$). Measurements or samples were rejected if the average deviation of a suspect value from the mean was at least four times the average deviation of the retained values.[24]

In collision-induced dissociation (CID) experiments, collisionally cooled precursor ions were isolated by the CHEF procedure.[25] Isolated ions were thermalized during a 3.0 s delay, translationally activated by an on-resonance radio frequency (RF) pulse, and allowed to collide with pulsed argon background gas. Each spectrum was a collection of 32 scans. To maintain comparable conditions, the parameters of the pulse program were kept constant.

In ion–molecule reactions with tripropylamine the neutral reagent was introduced to the cell through a variable leak inlet valve. The pressure was allowed to rise to 5×10^{-8} Torr where it was kept constant. Ions were isolated as in CID experiments and allowed to react with the neutral reagent with delay times from 0.1 up to 300 s. The spectra consisted of 2, 4, 8, or 16 scans. The number of scans was varied according to the reaction delay needed, while keeping the time of the experiment convenient. Variation in the number of scans did not influence the resulting spectrum. All the spectra were background-corrected. The decay of the relative abundance of the reactant ion as a function of time was used to deduce the reaction rate constant (k_{obs}). The pressure readings for the neutral reagent were corrected with the measured geometrical correction factor of propylamine. Theoretical reaction rate constants (k_{theor}) were calculated by using the average dipole orientation (ADO) theory proposed by Bowers et al.[26] The dipole moment for tripropylamine measured at room temperature and in liquid was used in calculations.[27] Relative reaction efficiencies (K_{eff}) were calculated as the ratio k_{obs}/k_{theor}.

For ND_3 (H/D-exchange) ion–molecule reactions, ions were isolated as in CID experiments, but single frequency excitation shots were used to achieve monoisotopic isolations. The rate constant k_1 was calculated as k_{obs}. The pressure readings for the neutral reagent were corrected with the measured geometrical correction factor of ammonia. Rate constants k_2 and k_3 were estimated at the equilibrium state using the calculated k_1 value and the maximum ion abundances.[28]

Gaussian98 or Gaussian03[29,30] software with the Hartree–Fock method was used for ab initio calculations. Geometry optimization and charge distribution of guest ions was calculated by using the 6–31G(d) basis set.

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[1] a) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*; Wiley, Chichester, **2000**; b) H.-J. Schneider, A. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*, Wiley, Chichester, **2000**; c) J.-M. Lehn, *Angew. Chem.* **1988**, *100*, 91–116; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89–112. d) J.-M. Lehn, *Angew. Chem.* **1990**, *102*, 1347–1362; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304–1319.

[2] a) H.-J. Schneider, U. Schneider, *J. Inclusion Chem.* **1994**, *19*, 67–83; b) W. Abraham, *J. Inclusion Phenom. Macrocyclic Chem.* **2002**, *43*, 159–174.

[3] a) Y. Tanaka, Y. Kobuke, M. Sokabe, *Angew. Chem.* **1995**, *107*, 717–718; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 693–694; b) M. Mäkinen, P. Vainiotalo, K. Rissanen, *J. Am. Soc. Mass Spectrom.* **2002**, *13*, 851–861; c) M. Letzel, C. Agena, J. Mattay, *J. Mass Spectrom.* **2002**, *37*, 63–68.

[4] K. Kobayashi, Y. Asakawa, Y. Kikuchi, H. Toi, Y. Aoyama, *J. Am. Chem. Soc.* **1993**, *115*, 2648–2654.

[5] a) H.-J. Schneider, D. Güttes, U. Schneider, *Angew. Chem.* **1986**, *98*, 636–638; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 647–649; b) H. Konishi, O. Morikawa, *Chemistry Express*, **1992**, *7*, 801–804; c) H.-J. Schneider, D. Güttes, U. Schneider, *J. Am. Chem. Soc.* **1988**, *110*, 6449–6454; d) M. Mäkinen, P. Vainiotalo, M. Nissinen, K. Rissanen, *J. Am. Soc. Mass Spectrom.* **2003**, *14*, 143–151; e) H. Mansikkamäki, M. Nissinen, C. A. Schalley, K. Rissanen, *New J. Chem.* **2003**, *27*, 88–97.

[6] a) Y. Aoyama, Y. Tanaka, S. Sugahara, *J. Am. Chem. Soc.* **1989**, *111*, 5404; b) K. Kurihara, K. Ohto, Y. Tanaka, Y. Aoyama, T. Kunitake, *J. Am. Chem. Soc.* **1991**, *113*, 444–450.

[7] a) I. Higler, P. Timmerman, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1996**, *61*, 5920–5931; b) A. Friggeri, F. C. J. M. van Veggel, D. N. Reinhoudt, *Chem. Eur. J.* **1999**, *5*, 3595–3602.

[8] a) M. Yamashita, J. B. Fenn, *J. Phys. Chem.* **1984**, *88*, 4451–4459; b) J. B. Fenn, M. Mann, C. K. Meng, S. F. Wong, C. M. Whitehouse, *Science* **1989**, *246*, 64–70; c) *Electrospray Ionization Mass Spectrometry* (Ed.: R. B. Cole), Wiley, New York, **1997**.

[9] D. J. Cram, H.-J. Choi, J. A. Bryant, C. B. Knobler, *J. Am. Chem. Soc.* **1992**, *114*, 7748–7765.

[10] a) A. Shivanyuk, J. Jr., Rebek, *Chem. Commun.* **2001**, 2374–2375; b) K. Murayama, K. Aoki, *Chem. Commun.* **1998**, 607–608; c) K. N. Rose, L. J. Barbour, G. W. Orr, J. L. Atwood, *Chem. Commun.* **1998**, 407–408.

[11] A. Shivanyuk, J. Jr., Rebek, *Chem. Commun.* **2001**, 2424–2425.

[12] M. H. K. Ebbing, M.-J. Villa, J.-M. Valpuesta, P. Prados, J. de Mendoza, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4962–4966.

[13] J. S. Brodbelt, *Int. J. Mass Spectrom.* **2000**, *200*, 57–69.

[14] C. A. Schalley, *Int. J. Mass Spectrom.* **2000**, *194*, 11–39.

[15] E. Leize, A. Jaffrezic, A. Van Dorsselaer, *J. Mass Spectrom.* **1996**, *31*, 537–544.

[16] a) J. M. Daniel, S. D. Friess, S. Rajagopalan, S. Wendt, R. Zenobi, *Int. J. Mass Spectrom.* **2002**, *216*, 1–27. b) M. Vincenti, A. Irico, E. Dalcanale in *Advances in Mass Spectrometry*, *Vol. 14* (Eds.: E. J. Karjalainen, A. E. Hesso, J. E. Jalonen, U. P. Karjalainen), Elsevier, Amsterdam, **1998**, pp. 129–150.

[17] a) M. Vincenti, C. Minero, E. Pelix'zzetti, A. Secchi, E. Dalcanale, *Pure Appl. Chem.* **1995**, *67*, 1075–1084; b) M. Vincenti, E. Dalcanale, *J. Chem. Soc. Perkin Trans. 2* **1995**, 1069–1076; c) J. M. J. Nuutinen, A. Irico, M. Vincenti, E. Dalcanale, J. M. H. Pakarinen, P. Vainiotalo, *J. Am. Chem. Soc.* **2000**, *122*, 10090–10100; d) M. Vincenti, A. Irico, *Int. J. Mass Spectrom.* **2002**, *214*, 23–36. e) A. Irico, M. Vincenti, E. Dalcanale, *Chem. Eur. J.* **2001**, *7*, 2034–2042.

[18] E. Ventola, K. Rissanen, P. Vainiotalo, *Chem. Commun.* **2002**, 1110–1111.

[19] E. P. Hunter, S. G. Lias, *J. Phys. Chem. Ref. Data* **1998**, *27*, 413–656.

[20] M. Mäkinen, J.-P. Jalkanen, J. Meriläinen, P. Vainiotalo, *Supramol. Chem.* **2004**, *16*, 293–297.

[21] S. M. Blair, E. C. Kempen, J. S. Brodbelt, *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1049–1059.

[22] O. Lukin, A. Shivanyuk, V. I. Kalchenko, *J. Org. Chem.* **1998**, *63*, 9510–9516.

[23] A. Shivanyuk, *Chem. Commun.* **2001**, 1472–1473.

[24] a) B. W. Woodget, D. Cooper, *Samples and Standards*, Wiley, Chichester, **1987**, pp. 40–47; b) L. F. Hamilton, S. G. Simpson, D. W. Ellis, *Calculations of Analytical Chemistry*, McGraw-Hill Inc., New York, **1960**, pp. 2–11; c) D. McCormick, A. Roach, *Measurements, Statistics and Computation*, Wiley, Chichester, **1987**, pp. 24–31.

[25] L. J. de Koning, N. M. M. Nibbering, S. L. Van Orden, F. H. Laukien, *Int. J. Mass Spectrom. Ion Processes* **1997**, *165/166*, 209–219.

[26] T. Su, M. T. Bowers in *Gas-Phase Ion Chemistry*, *Vol. 1* (Ed.: M. T. Bowers), Academic Press, New York, **1979**, pp. 83–118.

[27] A. L. McClellan, *Tables of Experimental Dipole Moments*, *Vol 3*, Rahara Enteprises, El Carrito, **1989**, p. 543.

[28] S. Campbell, M. T. Rodgers, E. M. Marzluff, J. L. Beauchamp, *J. Am. Chem. Soc.* **1995**, *117*, 12840–12854.

[29] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A.

Pople, *Gaussian 98*, *Revision A.9*, Gaussian, Inc., Pittsburgh PA, **1998**.

[30] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, *Gaussian 03*, *Revision B.01*, Gaussian, Inc., Pittsburgh PA, **2003**.

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