Host–guest complexation in the gas phase. Investigation of the mechanism of interaction between cavitands and neutral guest molecules

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Host–guest complexes are formed in the gas phase by vaporizing cavitand **1** within a mass spectrometer ion-source filled with a mixture of a buffer gas (methane) and one or more candidate guests in known relative concentration. The main purpose of this study was to investigate the inherent mechanism for the process. From experimental data, it was deduced that the complexation is strongly influenced by the geometric and electronic properties of the host as well as on the guest structure and functional groups. The occurrence of this high selectivity, together with the evaluation of reactive species, led us to conclude that the observed supramolecular interactions involve undoubtedly neutral guests, whereas the host might either be a charged or a neutral reactant. To distinguish between these two cases, various experimental observations have been made: (i) the data obtained in the positive- and the negative-ion modes are generally very similar; (ii) the extent to which complexation occurs depends on the residence time of ionic species in the mass spectrometer reaction chamber; (iii) the mass-selected charged host is capable of forming complexes with neutral guests in the octapole collision cell of a tandem mass spectrometer, and their relative abundances are similar to those observed in the experiments conducted in the ion source. It is concluded that the mechanism involving the preliminary ionization of the host and its subsequent interaction with a neutral guest is predominant, but a simultaneous interaction mechanism between neutral species might also occur to some extent. Another conclusion of this study is that CH-π interactions are the dominant interactions between cavitand **1** and aromatic guests.

Introduction

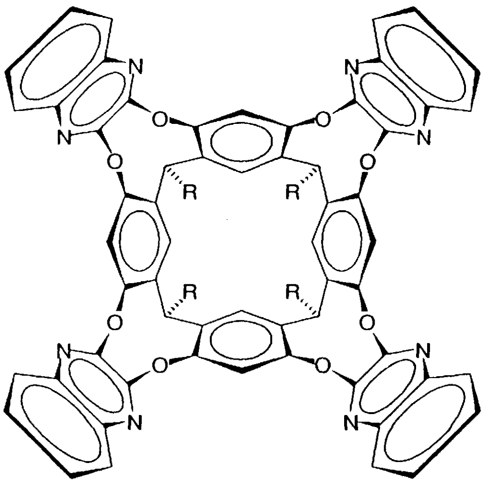
Host–guest chemistry[1–4] has been mainly investigated in the condensed phase, but in the last few years the opportunity of studying host–guest interaction processes in the gas phase has received increasing consideration.[5–23] One of the main reasons for such interest has been the possibility of studying the host–guest complexation without the influence of solvation effects, allowing better understanding of the *intrinsic* phenomena responsible for molecular recognition.

Most of the work reported so far has been focused on the complexes formed between crown ethers and alkali metal ions[8–11,13–17] or ammonium cations,[12,17–20] or between tribenzocyclotriyne and metal ions,[21,22] where in all cases a positive charge is present on the guest before its interaction with the host. Other inclusion complexes have been observed and investigated in the gas phase, using fast atom bombardment (FAB)[24–28] and electrospray ionization mass spectrometry (EIMS),[29–31] although the interaction process leading to the formation of the host–guest complex had presumably taken place in solution, before the mass spectrometric analysis.

We addressed our studies to the gas-phase complexation of neutral guests[5–7] by macropolycyclic receptors, such as cavitands. This work was intended to provide a general tool for investigating the fundamental details of molecular recognition phenomena, when neutral guests are involved. The complexation of neutral guests, provided by charged hemicarcerands, was also studied by C. L. Wilkins and co-workers, using laser desorption Fourier transform mass spectrometry (FTMS).[23]

In previous work[5–7] we have observed that host–guest complexes could be extensively formed in the gas phase where cavitand **1** was vaporized from a desorption chemical ionization (DCI) probe within an ion source containing a mixture of a buffer gas (methane) and small amounts of specific aromatic[5–7] or functionalized aliphatic[7] molecules. The high selectivity achieved in the reaction, due to shape complementarity and the formation of multiple non-covalent interactions, allowed us to claim that the first examples of molecular recognition in the gas phase had been uncovered.[6] A specific feature of these supramolecular interactions is that they take place to a very similar extent when the reaction products are detected either as positive or as negative ions. The fact that the reaction products do not vary with the ion polarity is in sharp contrast with experimental findings from most ion–molecule reactions, where the adducts observed strongly depend on the charge state.[32,33] Further conclusions drawn from previous work were the following: (i) the complexation strongly depends on the ion-source temperature;[5] (ii) the reacting system reaches a condition of thermodynamic equilibrium;[6,7] (iii) when mixtures of candidate guests are present in the gaseous atmosphere, their relative complexation constants can be measured.[6,7]

Although a reaction mechanism has been proposed,[7] we did not have clear evidence of whether host–guest complexation was an ion–molecule or a neutral–neutral reaction. Since extensive complexation and similar selectivity were observed in both positive- and negative-ion modes, it was inferred that the charge does not influence significantly the host–guest interaction and, consequently, we deduced that a neutral–neutral mechanism is more likely to occur.[7] Before attempting to compare gas-phase with solution reactions, it is important to clarify this point. It may also bear on gas–solid interactions.[34–36] Three different sequences of events can be formulated, as shown in Scheme 1 for positive and negative ions.



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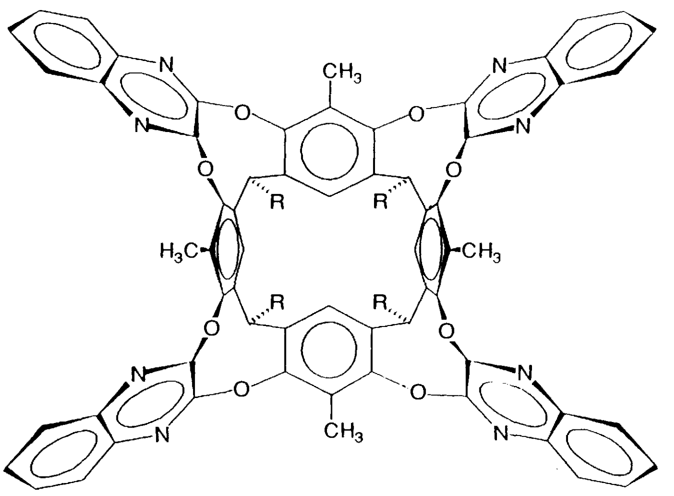
R = C_6H_{13}



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Mechanism (1): reaction of two neutral species

$$\begin{aligned} &\mathrm{Ho} + \mathrm{G} \longrightarrow \mathrm{HoG} \xrightarrow{\mathrm{H}^+} [\mathrm{HoGH}]^+ \\ &\mathrm{Ho} + \mathrm{G} \longrightarrow \mathrm{HoG} \xrightarrow{e^-} [\mathrm{HoG}]^- \end{aligned} \tag{1}$$

Mechanism (2): ion formed from the host

$$\begin{aligned} &\mathrm{Ho} \xrightarrow{\mathrm{H}^+} [\mathrm{HoH}]^+ + \mathrm{G} \longrightarrow [\mathrm{HoGH}]^+ \\ &\mathrm{Ho} \xrightarrow{e} [\mathrm{Ho}]^- + \mathrm{G} \longrightarrow [\mathrm{HoG}]^- \end{aligned} \tag{2}$$

Mechanism (3): ion formed from the guest

$$\begin{aligned} &\mathrm{G} \xrightarrow{\mathrm{H}^+} [\mathrm{GH}]^+ + \mathrm{Ho} \longrightarrow [\mathrm{HoGH}]^+ \\ &\mathrm{G} \xrightarrow{e^-} [\mathrm{G}]^- + \mathrm{Ho} \longrightarrow [\mathrm{HoG}]^- \end{aligned} \tag{3}$$

Scheme 1 Possible reaction mechanisms for host–guest (Ho–G) complexation

According to mechanism (1), upon vaporization, the host (Ho) will reach thermal equilibrium with the chamber walls by multiple collisions with the buffer gas (methane) and interacts with the candidate guest (G) to give a neutral host–guest complex (HoG), before the latter is ionized either by proton transfer (to give positive ions) or electron capture (to give negative ions). In contrast, mechanism (2) assumes that ionization of the host precedes its interaction with the neutral candidate guest to produce the charged host–guest complex ($[\mathrm{HoGH}]^+$ or $[\mathrm{HoG}]^-$).

The case of mechanism (3) closely reproduces a quite conventional reaction of adduct-ion formation, where the charged guest present in the CI reagent gas readily interacts with the host, as it is vaporized into the gas phase.

Experimental

All experiments were performed using a Finnigan-MAT 95 Q hybrid tandem mass spectrometer, in which magnetic, electrostatic and quadrupole analysers are mounted in series (BEQ geometry). Between E and Q sectors, an octapole collision cell is located, which is preceded by an ion-optics system, designed to decelerate ions to low kinetic energies. In the experiments where host–guest interactions were established in the mass spectrometer ion source, the latter was first filled with a gas mixture composed mainly of methane (~99%) and two candidate guests, whose relative pressure was determined by headspace-gas chromatography, as described in a previous publication.[7] Relative and total (~30 Pa, 0.3 mBar) pressures were adjusted using regulating valves. The ion-source temperature was maintained between 45 and 50 °C. In order to prevent additional heating from the electron emission filament, this was turned on only for the few seconds needed to complete the experiment. When a stable composition of the ion-source atmosphere was reached, a small amount (*i.e.* 30–50 ng) of the host (cavitand **1**) was introduced into it by fast vaporization from a DCI probe. The high pressure of cold methane in the ion source ensures constant conditions for thermal deexcitation and ionization of the host (and the host–guest complex), independently from the specific candidate guests selected in each experiment. The interaction products between the gaseous host and guests were mass-analysed and revealed either as positive or as negative ions. From the relative partial pressures of the candidate guest within the ion source and from the relative abundance of the ions corresponding to each of the two host–guest complexes, it was possible to determine the thermodynamic relative complexation constant, as discussed in detail elsewhere.[7]

For the experiments where the voltage of the repeller lens had to be varied, the standard CI source was not adequate, since it contained neither the repeller nor the extraction lenses. Therefore, a new ion source was expressly built, based on the EI source body on which external plates were mounted either without holes or with holes of reduced size, in order to minimize gas outflow, while admitting the probe and the electron beam. With such an ion source, the experiments were conducted according to the usual procedure, except for the fact that the repeller voltage was increased in increments of 10 V, while keeping all the other lens voltages fixed.†

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† The use of a variable repeller voltage causes some defocusing of the ion beam. However, this defocusing cannot be compensated by adjusting the voltages of the other lenses, since this would affect also the residence time of ions in the ion source. On the other hand, the defocusing effects are very similar for ions of similar mass, such as the host and the host–guest complex. Therefore, the peak ratio between these two ions is not modified significantly.

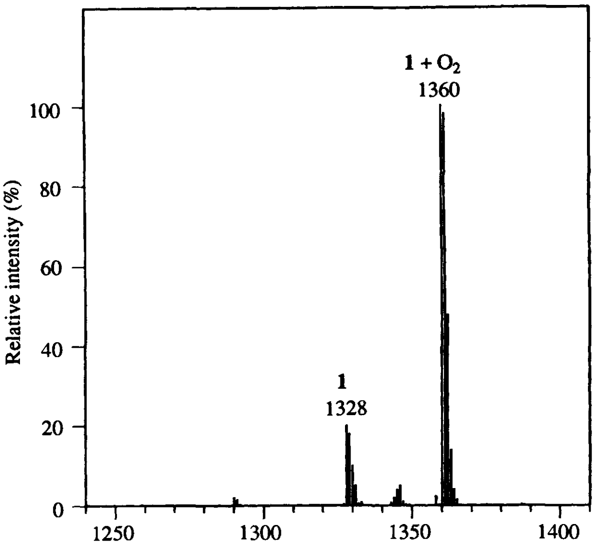

Fig. 1 Negative-ion DCI mass spectrum of cavitand **1**, vaporized within an atmosphere of methane containing a small amount of oxygen (~0.5%)

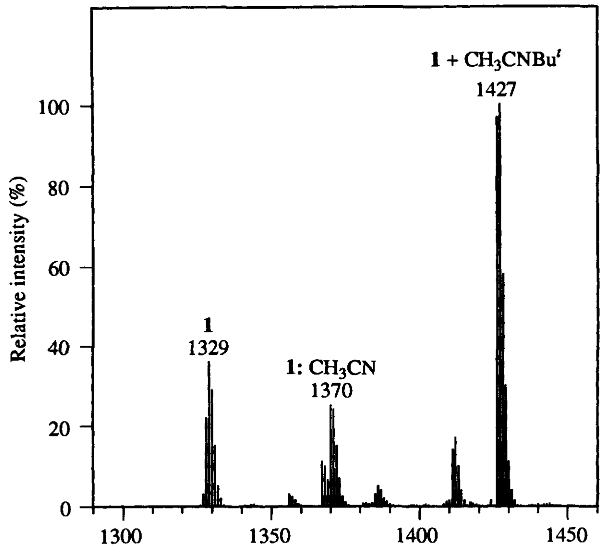

Fig. 2 Positive-ion DCI mass spectrum of cavitand **1**, obtained using a mixture of isobutane (99%) and acetonitrile (1%) as the reagent gas

In collision-induced dissociation (CID) experiments, the molecular ion corresponding to the host–guest complex was mass-selected by the magnetic analyser, decelerated to 0.3–30 eV kinetic energy, and allowed to collide several times with argon (0.15 Pa, 1.5 × 10^{-3} mBar) in the octapole collision cell of the mass spectrometer. The decomposition products were detected by scanning of the quadrupole mass analyser. Metastable spectra were recorded in the same way, without argon in the collision cell.

In order to perform ion–molecule reactions in the octapole collision cell, the molecular ion of the free host was produced in the ion source, where the reagent gas consisted of pure methane. This molecular ion (either positive or negative) was mass-selected and then decelerated to 0.5 or 1 eV kinetic energy. As it passed through the octapole cell, it was allowed to collide, and possibly react, with a gaseous mixture of two candidate guests, at a total pressure of ~0.2 Pa. The interaction products were detected by scanning of the quadrupole mass analyser located at the octapole cell exit. The use of 20 kV dynode-electron multiplier detectors avoided mass-discrimination effects in the mass spectra.

Cavitands were synthesized in the laboratory, according to published procedures.[37] All other compounds were obtained from Aldrich and were used without further purification. High-purity methane and argon were obtained from SIAD (Bergamo, Italy).

Results and discussion

In a few selected experiments, it is possible to induce a reaction of cavitand **1** with a charged species, which most likely occurs through mechanism (3). For example, when a small amount (*i.e.*, 0.1–1%) of oxygen (or air) is mixed with the CI buffer gas (methane) and the cavitand Ho is vaporized in the ion source, then extensive formation of $[\mathrm{Ho} + 32]^-$ ions is observed in the negative-ion mode, to give the most abundant ion in the mass spectrum (Fig. 1). In contrast, no $[\mathrm{Ho} + 32]^+$ or $[\mathrm{Ho} + 33]^+$ ion can be detected in the positive-ion mode under identical experimental conditions. According to the high electron affinity of oxygen, the following reaction mechanism [eqn. (4)] is proposed

$$\mathrm{O_2} \xrightarrow{e^-} [\mathrm{O_2}]^- + \mathrm{Ho} \longrightarrow [\mathrm{HoO_2}]^- \qquad (4)$$

The base peak in the background negative-ion mass spectrum is $[\mathrm{O_2}]^-$, while no peak is present at *m/z* 32 ($\mathrm{O_2}^+$) or 33 ($\mathrm{O_2H^+}$) in the positive-ion spectrum.

Another reaction occurring through mechanism (3) is observed when cavitand **1** is vaporized within an atmosphere containing isobutane (99%) and acetonitrile (1%). In the background positive-ion spectrum an abundant *m/z* 98 ion is present, with the possible structure $[\mathrm{CH_3C{\equiv}NC(CH_3)_3}]^+$. This ion extensively interacts with the cavitand to form the adduct ion $[\mathrm{Ho} + 98]^+$ (Fig. 2). As for reactions with $[\mathrm{O_2}]^-$, this interaction is non-specific, *i.e.* it is commonly observed with a variety of molecules, independent of their shape and dimensions.

In our experiments, which were designed so as to form host–guest interactions, mechanism (3) occurs only in a few specific cases that can easily be recognized. It is rare when methane is used as the main component of the gas phase, and may occur only with more reactive ionizing gases. It should also be noted that cavitand **1** has both higher proton and electron affinities than do most guest molecules studied and, therefore, it should favourably compete with them for the charge.

The interactions referred to as host–guest complexations have a very different mechanism. Typical features of these interactions are the following:

(i) They are highly specific and depend mostly on the host conformation, structure, shape and dimensions. To observe host–guest complexation in the gas phase the host must have a rigid pre-organized cavity. A wide variety of molecular receptors (cavitands, bridged calixarenes, cryptophanes) with different structures were tested and it was found that those having non-rigid cavities were unable to undergo host–guest complexation in the gas phase.[38,39] Another demonstration relevant to the significance of the cavity is provided by kite-like compound **2**, which is structurally similar to vessel-like cavitand **1** but is geometrically different, *viz.* it adopts a different overall shape and therefore presents no cavity.[40] Unlike cavitand **1**, this compound does not undergo host–guest complexation with any of the guests tested, demonstrating that the guest must be located inside the host cavity.

(ii) Positive- and negative-ion spectra generally provide

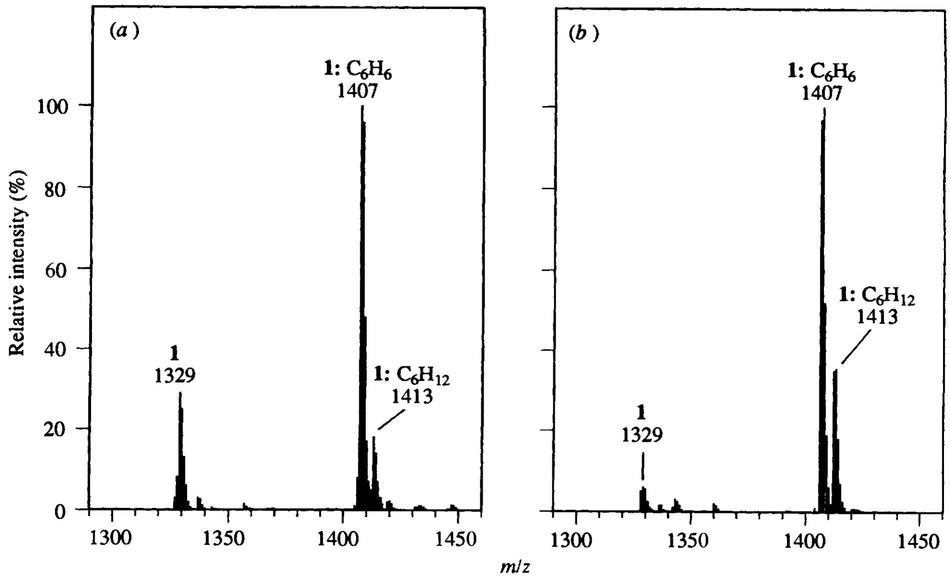

Fig. 3 Comparison of the DCI mass spectra obtained from vaporizing cavitand 1 within a gas mixture composed of methane (~99%), benzene (0.53%) and cyclohexane (0.47%); (*a*) positive ions; (*b*) negative ions. The relative complexation constants of benzene and cyclohexane are 4.6 and 2.6, respectively.

almost the same results; namely the extent of complex formation is about the same whether they are detected in the positive- or in the negative-ion mode. Moreover, when mixtures of candidate guests are employed, similar relative complexation constants can be determined for the two polarities, as shown in Figs. 3(*a*) and 3(*b*) for C_6H_6 and C_6H_{12}.

(iii) In many cases, the guest interacting with the cavitand to form the host–guest complex is not present as an ion in the background mass spectrum. For example, in the negative-ion spectrum arising from the reaction of cavitand **1** with benzene (M_w 78), the base peak is $[Ho + 78]^-$, but no peak is present at *m*/*z* 78, demonstrating that it is the neutral benzene which reacts, not the charged species.

From the above observations it can be concluded that the specific reactions occurring between cavitand **1** and some small organic molecules with appropriate shape and structure, namely host–guest complexations, can take place only *via* mechanism (1) or (2), both involving a neutral guest.

In most gas-phase reactions within a mass spectrometer ion source, when a covalent bond is formed it is so by an ion–molecule reaction, because ions are more reactive than neutral species (in terms of kinetic and thermodynamic constants). Neutral species, of course, reside longer in the ion source than do charged species, but this does not compensate for their much lower reactivity.[33] In the case of host–guest complexes, several supramolecular interactions occur (CH-π, dipole–dipole) at the expense of covalent-bond formation,[41] and steric factors are extremely important. Ion–dipole interactions can still be important in the case of mechanism (2), but not in mechanism (1) where two neutrals interact. All in all, the competition between mechanisms (1) and (2) depends on the relative reactivity of $[HoH]^+$ (or $[Ho]^-$) and Ho (in terms of thermodynamic and possibly kinetic constants) towards G to form a supramolecular complex.

One possible way to discriminate between mechanisms (1) and (2) is to vary the residence time of the ions in the mass spectrometer ion source. This effect can be obtained by varying the 'repeller' voltage (the repeller is a plate mounted at the rear wall of the ion source that has the function of repelling ions) with respect to the voltages of the other lenses, particularly the extraction plates. Variation of this differential voltage produces a change in the initial kinetic energy of ions and, consequently, on their residence time in the ion chamber. Quite certainly, also the focusing of the ion beam is affected by this voltage variation, but the effects on ions of similar mass (*i.e.* the empty host and the host–guest complex) are almost identical. Neutrals are obviously unaffected by this voltage variation. Since the standard CI source has neither a repeller nor extraction lenses, we modified the EI volume so as to minimize the gas outflow from it (see Experimental section).

If host–guest interaction is established between two neutral species, and their reaction product is subsequently ionized [mechanism (1)], the relative abundance of this ion with respect to the ionized empty host should not depend on how much time has elapsed before both ions are extracted from the reaction chamber. If it is the charged host which interacts with the neutral guest [mechanism (2)], then it should be possible to make the reaction run under kinetic control by appropriately decreasing the time allowed for the interaction. Beyond this limit, formation of the host–guest complex should be progressively inhibited, as the residence time of the charged host in the reaction chamber is too short for complexation to occur.

The reaction of cavitand **1** with benzene was studied in both the positive- and the negative-ion mode. The repeller voltage could be varied over a wide range (ΔV = 150 V for positive ions, and ΔV = 190 V for negative ions), still allowing for easy detection of the reaction products. The results are reported in Fig. 4(*a*) and (*b*), where the percentage of host–guest complex formed is plotted against the differential repeller voltage. In the same diagrams, the results obtained for typical ion–molecule reactions are also presented for comparison, namely the reactions of cavitand **1** with $[O_2]^-$ (negative-ion mode) and with $[CH_3C{\equiv}NC(CH_3)_3]^+$ (positive-ion mode), already mentioned above.

Fig. 4(*a*) and (*b*) show that host–guest complexation can be almost totally inhibited in both ion polarities by shortening the residence time of the ions in the reaction volume. As the residence time is increased, the extent of complexation also increases rapidly, up to a point where a plateau is reached (70% for positive ions, 85% for negative ions). It should be noted that maximum ion transmission is achieved in the plateau region. These results suggest that mechanism (2) is operating. When the reaction is under kinetic control, the longer the charged host

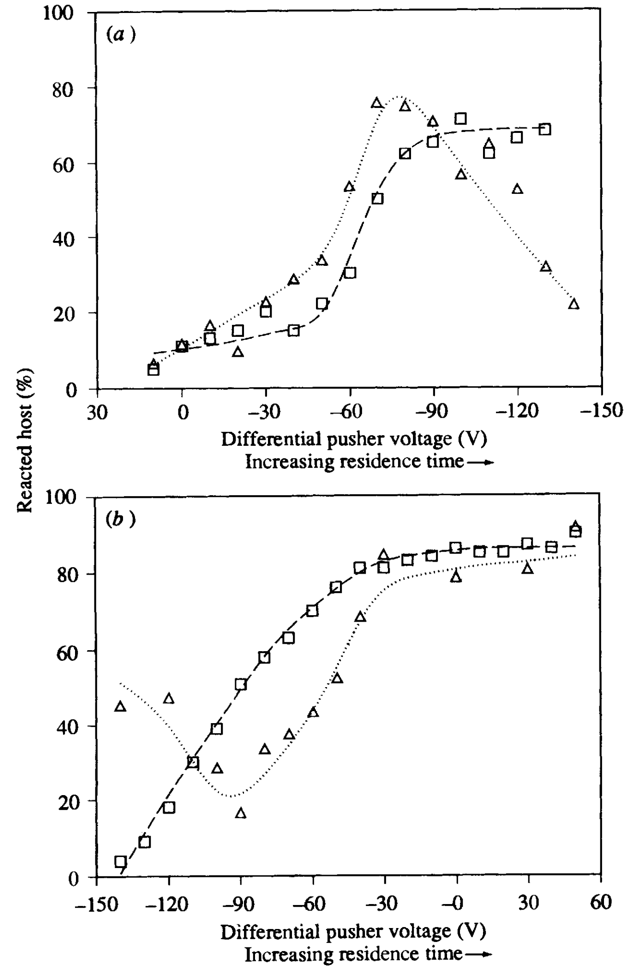

Fig. 4 Diagrams reporting the percentage of the complex (1 : benzene) formed in the ion source (□) as a function of the repeller lens voltage, upon which the residence time of ions in the ion source depends; (*a*) positive ions; the relative abundance of the gas-phase reaction of cavitands **1**, isobutane and acetonitrile, already mentioned above, is reported for comparison (△); (*b*) negative ions; the reaction between cavitands **1** and O_2^- is also reported (△)

remains in the ionization chamber, the greater will be its interaction with the neutral guest. When the residence time in the ion volume is long enough, a state of thermodynamic equilibrium is reached, corresponding to the plateau in the diagrams. Although these trends are similar to those obtained for the ion–molecule reactions also reported in Fig. 4, significant differences between the two plots exist. These are mainly due to different kinetic constants for the two reactions as well as to the remarkable mass difference between the ionic species involved, namely 1328 Da (cavitand **1**) for host–guest complexations and 32 Da (O_2) (or 98 Da for positive ions) in the case of ion–molecule reactions. Smaller masses correspond to higher velocities and hence shorter residence times in the ion source.

Although the data reported in Fig. 4 represent strong evidence in favour of an ionic mechanism for gas-phase host–guest interactions, an alternative explanation for the curves shown in Fig. 4 is possible. If one assumes that the neutral–neutral complexation mechanism (1) takes place and that ionization of the host–guest complex occurs afterwards, it might be that this ionic product decomposes within the ion source by means of CID upon impact with gas-phase constituents, releasing the charged host and the neutral guest. The occurrence of such a process could be consistent with the results of Fig. 4, since CID of the host–guest complex is likely to be more extensive for more energetic collisions, *i.e.* at higher kinetic energy of the impinging ion.

To verify this alternative explanation, a series of CID experiments were run in the octapole collision cell of our hybrid mass spectrometer at various collision energies. Cavitand **1** was allowed to react with benzene in the mass spectrometer ion source under standard conditions; the host–guest complex was extracted from the source as a protonated positive ion, and was selected by the magnetic analyser. Following deceleration of the ion to low kinetic energies, the charged complex was allowed to pass through the octapole with and without argon collision gas present. The intact complex and its decomposition products (the empty host was the only decomposition product) were analysed and detected. The resulting mass spectra, some of which are shown in Fig. 5(*c*)–(*e*), can be compared with the corresponding metastable-ion spectra [Fig. 5(*a*), (*b*)], obtained under the same conditions, but in the absence of the target gas. It is evident that the relative abundance of the dissociation product is considerably increased when the target gas is present. It can be deduced that low-energy collisions are effective in promoting the dissociation of the charged host–guest complex, that the extent of dissociation depends on the collision energy and, most important, that a laboratory collision energy as low as 0.3 eV (*i.e.*, the kinetic energy of the complex) is sufficient to induce this process. This observation also confirms that supramolecular interactions are quite weak in comparison with covalent bonds, although not necessarily as low as 0.3 eV, since CID experiments are run under multiple-collision conditions and energy transfer occurs as a multistep process.

The second method used to distinguish between mechanisms (1) and (2) has been to compare the host–guest interactions observed in the ion source with those produced in the octapole collision cell of the mass spectrometer. In the latter experiment, the host is ionized in the ion source under standard CI conditions, then either its positive or negative molecular ion is extracted and selected by the magnetic analyser. Finally, the host molecular ion is decelerated to very low kinetic energy (*i.e.*, 0.5 eV) and allowed to pass through the octapole cell filled with an atmosphere of mixed candidate guests. These conditions proved to be effective in promoting the formation of host–guest interactions, in which case, of course, only the ionic mechanism (2) is possible. The relative abundances of the mixed interaction products are measured using the quadrupole mass analyser located after the octapole reaction cell. The corresponding results are summarized in Table 1.

In the first experiment, a gaseous mixture of benzonitrile and anisole (gas-phase abundance ratio 1.45 : 1) was allowed to flow into the octapole cell. The choice of these candidate guests carrying, respectively, a strongly electron-withdrawing and a strongly electron-donating substituent on the benzene ring was intended to highlight possible differences in the reactivity of positively and negatively charged hosts. It was observed that: (i) in the octapole cell both benzonitrile and anisole can form inclusion complexes with charged cavitand **1**; (ii) in both the positive- and negative-ion modes stronger host–guest interactions were experienced by benzonitrile than by anisole, demonstrating that the host has a predominant electron-donating character even when it bears a positive charge; (iii) in the negative-ion mode, nearly the same relative complexation constants (4.3 *vs.* 4.7) were measured when the interaction was established in the ion source and when it took place in the octapole cell; the same did not apply to the positive-ion mode, where significant differences exist between the two values.

From the above observations it could be concluded that, in the gas phase, host–guest complexation predominantly occurs *via* the ionic mechanism (2), in which the charged host interacts with the neutral guest. However, as long as the positively and negatively charged hosts react similarly (*i.e.*, they exhibit the

Table 1 Gas-phase relative complexation constants for couples of candidate guests interacting with cavitand **1**. In the experiments conducted in the octapole cell the gaseous guest mixture was utilized as prepared, while in ion-source reactions the guest mixture was diluted with a large excess of methane (> 99%)

	Benzonitrile/Anisole (pressure ratio 1.45:1)	Butan-1-ol/Toluene (pressure ratio 0.47:1)
Ion source, positive ions	6.0	6.5
Octapole cell, positive ions	1.5	11
Ion source, negative ions	4.3	0.9
Octapole cell, negative ions	4.7	1.1

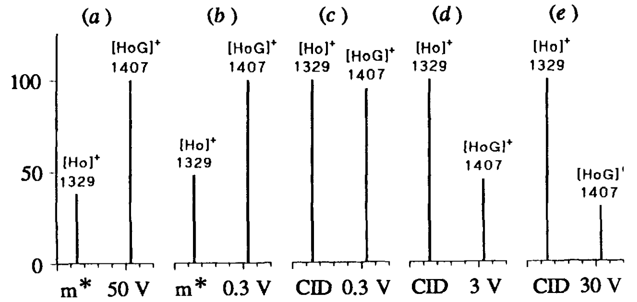

Fig. 5 Spontaneous and collision-induced decomposition (CID) of the charged (**1**:benzene) host–guest complex (*m/z* 1407) in the octapole cell, yielding the empty host (*m/z* 1329). (*a*) Metastable transition at 50 eV kinetic energy; (*b*) metastable transition at 0.3 eV kinetic energy; (*c*) CID at 0.3 eV collision energy; (*d*) CID at 3 eV; (*e*) CID at 30 eV.

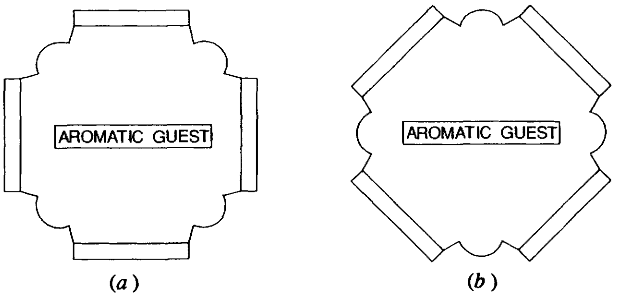

Fig. 6 Schematic representation of interaction geometries between aromatic guests and quinoxaline rings of cavitand **1**. (*a*) T-Shaped geometry; (*b*) 45° inclined geometry.

same selectivity), it cannot be excluded that also the neutral host behaves in the same way, contributing through mechanism (1) to the overall complexation within the ion source.

Similar complexation constants between positive and negative ions were observed for several other couples of candidate guests; for example, benzene–acetonitrile.[6,7] Therefore, no new information on the interaction mechanism could be obtained from these guests. Pentafluorobenzene was tested against benzene to check whether it could be selectively recognized by the positively charged host, but it was not: the substitution of fluorine for hydrogen completely inhibits the supramolecular interaction in both ion polarities. Since the host cavity is large enough to accommodate either guest quite easily,‡ the observed inhibition cannot be ascribed to steric hindrance,[5] but it must be due to the electronic properties of pentafluorobenzene, despite its strongly electron-withdrawing character that should in theory favour its complexation with an electron-donating host, such as cavitand **1**. A reasonable explanation of this behaviour is that the substitution of hydrogen with fluorine eliminates CH-π interactions, which proved to be very important when aromatic molecules are involved in molecular recognition phenomena.[7,37,42,43] The vase-shaped cavity of compound **1** is delimited by four quinoxaline rings, two of which can interact with the methines of aromatic guests in a T-shaped geometry [Fig. 6(*a*)]. From the geometry observed in the crystal structure[44] of [**1**•fluorobenzene] caviplex it is deduced that a 45° inclination of the π-system is also favoured, as already found for other cyclophanes[45] [Fig. 6(*b*)].

In the case of cavitand **1** the guest can rotate around four equivalent CH-π interacting positions, due to the C_{4v} symmetry of the host cavity. The affinity of compound **1** for benzonitrile over anisole, both in the positive- and negative-ion modes, indicates the polar character of CH-π interactions.[46,47] The presence of electron-withdrawing substituents on the guest enhances the strength of the interaction between the 'acidic' CH of the guest and the 'basic' π-system of the host. Even more convincing is the effect of the substitution of the guest hydrogens with fluorine (benzene *vs.* pentafluorobenzene), which leads to complete suppression of CH-π interactions and, consequently, complexation.

Remarkable differences between the positive- and negative-host reactivity was found using butan-1-ol and toluene as competing guests. The protonated host exhibits much higher affinity for butan-1-ol than for toluene, whereas in the negative-ion mode almost no discrimination between the two guests is evident (Table 1). In the corresponding mass spectra [Fig. 7(*a*)–(*d*)] the peak ratio between the two complexes inverted when the polarity was switched from positive to negative. Butanol has a more pronounced electron-donating character in CH-π interactions than does toluene and is stabilized by the positive charge of the host. From the spectra reported in Fig. 7, it can be noted that the complexation occurring in the ion source is almost identical with that observed in the octapole cell, where the charged host interacts with the neutral guest. In fact, the same selectivity and even closely similar ion abundances were found.§ Consequently, the interaction mechanisms must be identical, at least in this case. Further support for the occurrence of the ionic mechanism (2), also in ion-source reactions, is provided by the effect of ion polarity: no such effect should be observed in the neutral–neutral reaction (1).

Conclusions

Discovery and exploitation of gas-phase host–guest complexation has preceded our comprehension of the inherent interaction mechanism. This puzzling issue has been partially clarified in this paper, at least in the specific case of a cavitand

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‡ In ref. 5 host–guest complexation was observed for 2-fluorotoluene and also for such a large guest as 1,3-bis(trifluoromethyl)benzene. The absence of steric hindrance for pentafluorobenzene was also confirmed by CPK models.

§ In general, much more extensive complexation is observed in the ion source than in the octapole reaction cell; however, in the case of Fig. 6(*a*) and (*c*), the relative pressures of the two candidate guests with respect to the buffer gas were deliberately lowered much below the usual value, in order to best match the data obtained from octapole experiments.

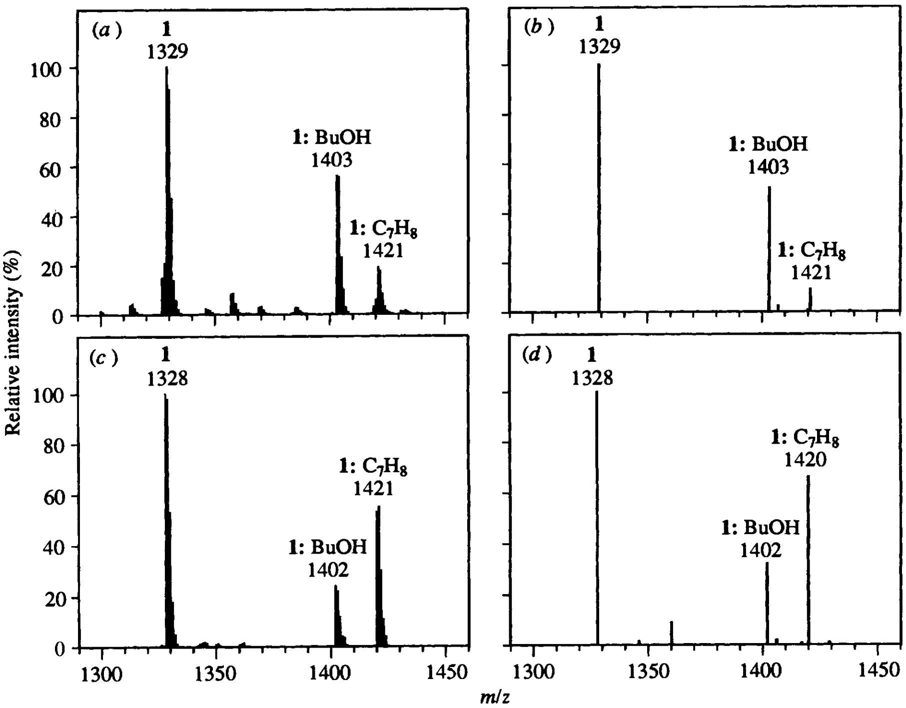

Fig. 7 DCI mass spectra obtained from cavitand **1** reacting with a mixture of butan-1-ol and toluene (abundance ratio 0.47 : 1). The guest pressures in the ion source were lowered with respect to methane as much as necessary to make the free-host relative abundance in spectra (*a*) and (*c*) similar to that observed in spectra (*b*) and (*d*). (*a*) Positive ions, reaction conducted in the ion source; (*b*) positive ions, reaction conducted in the octapole cell with the selected host molecular ion moving at a kinetic energy of 0.5 eV; (*c*) negative ions, ion source; (*d*) negative ions, conditions as for Fig. 7(*b*).

interacting with small (M_w 70–150 Da) organic molecules. The use of various mass spectrometric techniques, allowing the time and conditions of interaction to be varied, confirmed that a mechanism envisaging the preliminary ionization of the host and its subsequent interaction with a neutral guest is coherent with experimental findings. However, confirmatory evidence was obtained that the host charge plays only a limited role in these complexation equilibria. This observation and theoretical considerations suggest that the occurrence of a second simultaneous interaction mechanism between neutral host and guest is possible, depending on the nature of the interacting species.

We believe that the results obtained with a variety of neutral guests can still be exploited to deduce information about the host cavity, geometry, dynamics and binding sites, as well as on the modes of interaction in supramolecular chemistry, in the absence of interfering solvent effects. For example, the role of CH-π interactions in host–guest complexation has been evidenced. The predictive value of these results has already been exploited in the generation of both selective gas sensors for organic molecules[35–36] and selective trapping materials in chromatographic devices,[34] where solid–gas interactions are present.

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