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Review

Gas-phase interactions of calixarene- and resorcinarene-cavitands with molecular guests studied by mass spectrometry

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Abstract

The present review examines the limited amount of mass spectrometric literature dealing with the gas-phase formation and stability of host-guest complexes produced by calixarenes and resorcinarene cavitands interacting with molecular guests. The work is presented in the perspective of the specific information that mass spectrometric method are able to provide, as opposed to solution studies. Experimental methods, supramolecular structures, stereochemical and thermodynamic features of host-guest complexes in the gas-phase are discussed. (Int J Mass Spectrom 214 (2002) 23–36) © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Calixarenes; Cavitands; Host-guest complexes; Supramolecular interactions; Gas-phase ion chemistry; Mass spectrometry

1. Introduction

The term "calixarenes" defines a class of concave macrocyclic receptors, formed by the condensation of *p*-substituted phenol and formaldehyde. The extensive development of this important class of molecular receptors in the last two decades has expanded considerably the number and variety of substituents carried by the original calixarene structure, especially for the tetrameric calix[4]arene [1–6]. Both the phenolic hydroxyl and the *para*-substituent were derivatized in many ways, in order to increase the selectivity of the receptor or to modify its flexibility and solubility properties [7,8]. Two or three calixarenes were linked to one another by single bridges between the *p*-substituents [9,10]. Even the two molecules subjected to the initial condensation process were substituted by more functionalized substrates in order to obtain new receptors with specific attributes. For example, formaldehyde was replaced by other alkyl-aldehydes.

More importantly, in many synthetic protocols the *p*-substituted phenol was replaced by 2-substituted resorcinol. The resulting calixarene structures possess four couples of proximal hydroxyls that can be conveniently bridged (frequently by methylene units) leading to receptors with a rigid cavity of molecular dimension [11,12]. These receptors are commonly indicated as resorcinarene cavitands, a new class of compounds capable to trap organic molecules and ions inside their cavity and subsequently release them in a dynamic equilibrium with the solvent. These resorcinarene cavitands opened a new chapter of host-guest chemistry [13].

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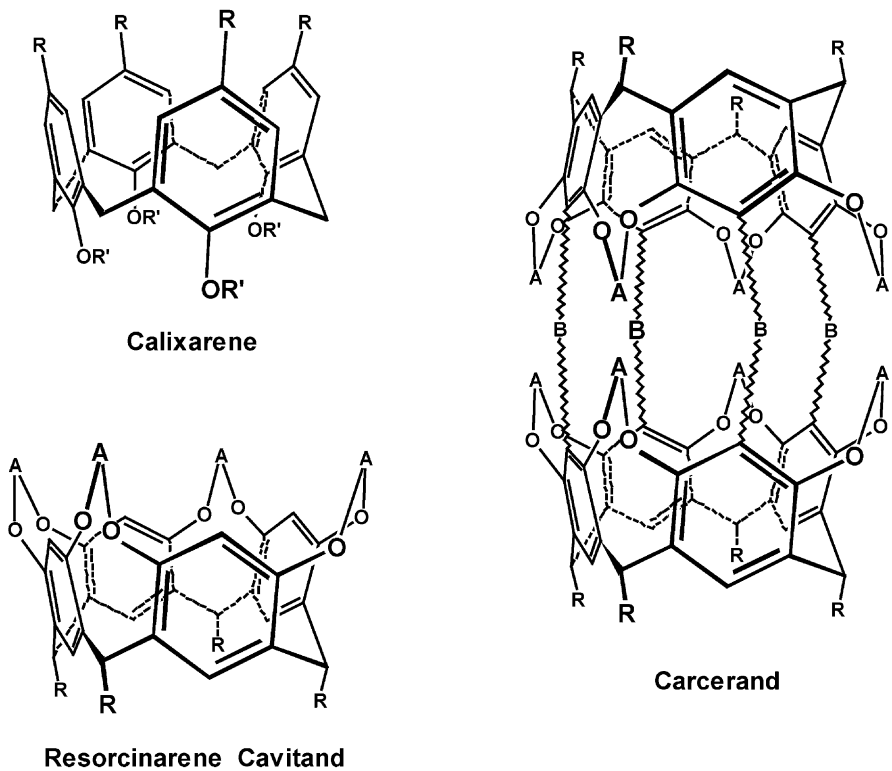


Scheme 1.

Further development of resorcinarene hosts was obtained by chemically binding two cavitand molecules by means of the substituents located in *ortho* (2) position to the original resorcinol hydroxyls. The resulting rigid hollow structures were called either carcerands or hemicarcerands depending on the number of bridges formed between the two cavitands and the consequent absence or presence of openings in the three-dimensional structure through which guest molecules could enter and escape [13–15]. Models of a calixarene, a resorcinarene cavitand and a carcerand are reported in Scheme 1.

Despite the enormous work developed throughout the world to synthesize and characterize all these molecular receptors and to investigate their chemistry in solution, very few studies have been undertaken to date to investigate the interaction between them and organic guest molecules and ions in the gas-phase by means of mass spectrometric methods. This lack of interest for the gas-phase chemistry of calixarene- and resorcinarene-cavitands is difficult to understand: even if the practical applications of host-guest chemistry are likely to be developed for the condensed phase, gas-phase studies nevertheless provide a different and interesting perspective for host-guest interactions. As the solvent is absent, no solvation effects can modify the electronic and thermodynamic properties nor the geometrical constraints of supramolecular binding, so that the pure intrinsic interaction between the two counterparts is uncovered, free from any third-body influence.

The present article overviews the limited body of work addressed to investigate, by mass spectrometric procedures, the gas-phase stability of host-guest complexes formed by calixarenes and resorcinarenes interacting with organic molecular guests. Particular emphasis is given to the work performed in the authors' own laboratory.

Much more extensive literature deals with the gas-phase interaction of alkali metal ions with crown ethers, cryptands and other macrocyclic hosts [16,17]. Another application of mass spectrometry to supramolecular chemistry, quite developed in the past, is the recognition of optically active guests by chiral crown ethers and cyclodextrins [18]. Other recent and rapidly growing fields where mass spectrometry is utilized to characterize complex non-covalent aggregates are, respectively those of organometallic supramolecular architectures [19] and biological protein-substrate and DNA pairing aggregates [20]. All these application in the fields of mass spectrometry have been recently reviewed [16–20] and are out of the range of the present overview.

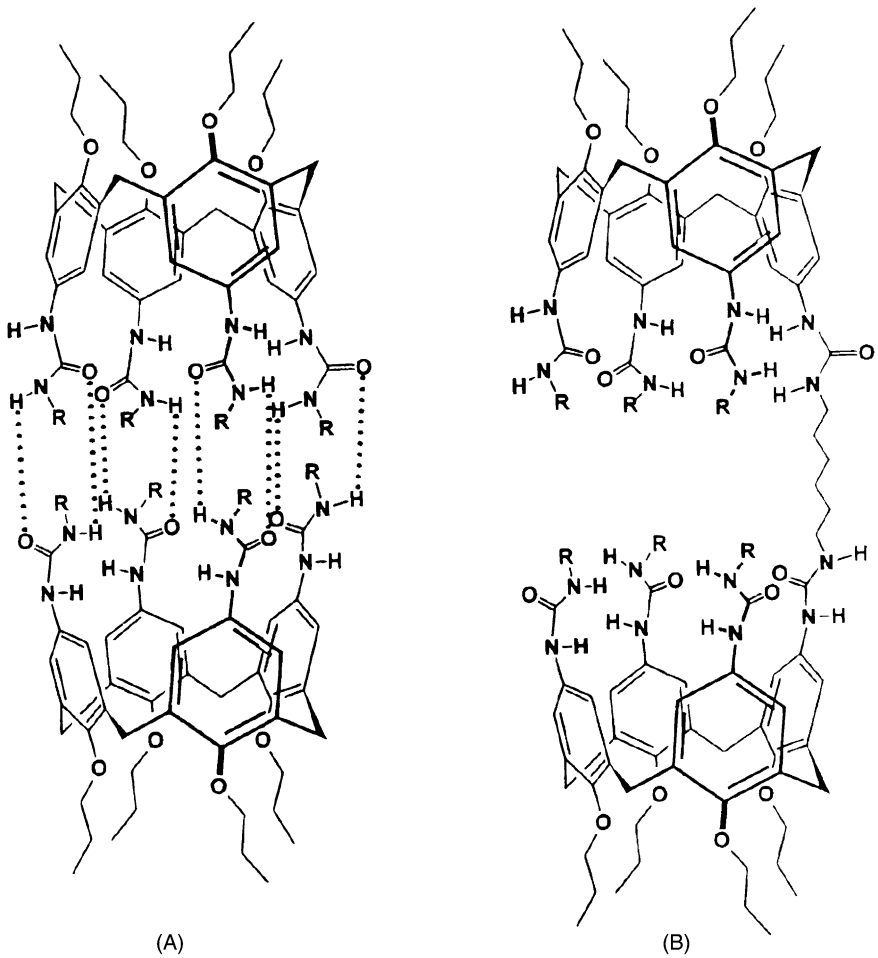
Several factors account for the scarcity of work on the gas-phase reactions of calixarenes and resorcinarenes. One reason is that just the basic structures, not the most interesting derivatives, are readily available by commercial sources. Another reason is that complex host structures can not be maintained with ease in an unexcited state in the vapor phase before they react with a charged or neutral guest. The third and more crucial factor is that the interactions between these hosts and neutral molecular guests, which represent the obvious target, are generally very weak and difficult to occur in the gas-phase. It is generally much simpler to pre-form the complexes in solution and then to ionize and isolate them in the gas-phase, as is performed in electrospray ionization (ESI).

2. Calixarenes and calixarene derivatives

The most simple calixarenes are among the molecular receptors that provide too weak interactions to be observed with ease in the gas-phase. The large flexibility of the calixarene structure is emphasized in the gas-phase, where no solvent molecule limits the free conformational changes of the molecule. Consequently, the constraints associated with the formation of host-guest complexes correspond to a strongly negative entropic contribution, resulting in the weakening of the supramolecular interaction. Then, very little internal energy is sufficient to dissociate the host-guest complex inside the mass spectrometer, preventing its detection. Even in a specific case studied by Wong and coworkers, where the host had considerable steric hindrance to the free conformational change and the guest carried a positive charge, *tert*-butylcalix[4]arene proved to be a less effective ligand than crown ethers toward benzylammonium ions [21].

The formation of host-guest complexes in the gas-phase is favored by any form of derivatization, that reduces the flexibility of the calixarene backbone. This decreases the entropic loss associated to the formation of the host-guest complex, making it energetically feasible. A secondary effect of the reduced flexibility of the ligand is its increased selectivity, as the rigid three-dimensional arrangement of its binding sites should complement those of the guest to produce strong interaction. The stiffening of the calixarene structure has been achieved in several ways. One way is to introduce bulky substituents, especially in the lower rim of the molecule, in order to block its structure in the cone conformation. In such a case, it may happen that the calixarene oxygen become quite inaccessible to the candidate guests, restricting the binding properties of the ligand to the π-electrons of its aromatic rings. Thus, other substituents with target binding properties are frequently introduced at the upper rim of the calixarene structure.

This solution, was successfully demonstrated by Schalley and coworkers, who studied a series of calix[4]arenes functionalized with urea substituents at their upper rim (i.e., the calixarene opening not containing the hydroxyl oxygen) [19,22]. Urea substituents are particularly interesting, since they can act both as donor and acceptor in hydrogen bonding. The consequence is that, under ESI conditions, these calixarenes tend to dimerize, forming a two-valve shell held together by hydrogen bonding, in which guest species of molecular dimension can be trapped (see Scheme 2, structure A). Even if the trapped species described in the original work were typically charged (i.e., tetraalkylammonium ions) [19,22], yielding extremely stable 2:1 complexes, it is not unlikely that also neutral organic molecules capable of hydrogen



Scheme 2.

bonding could be captured inside these supramolecular architectures.

More complex ligands, where two calixarene units are covalently linked by means of an hexyl chain (Scheme 2, structure B), produced 1:1 complexes with tetraalkylammonium ions by self-closure of the ligand halves around the guest ion under ESI conditions [10,22]. When these and other multiple-calixarene ligands were mixed with monomeric urea-substituted calixarenes and alkylammonium salts, the ESI mass spectra showed evidence of stable supramolecular aggregates, containing the three species in specific stoichiometries. These depended on the structure of the coordinating ligand, forming aggregates with up to seven non-covalently bound subunits in a 1:3:3 stoichiometry [22].

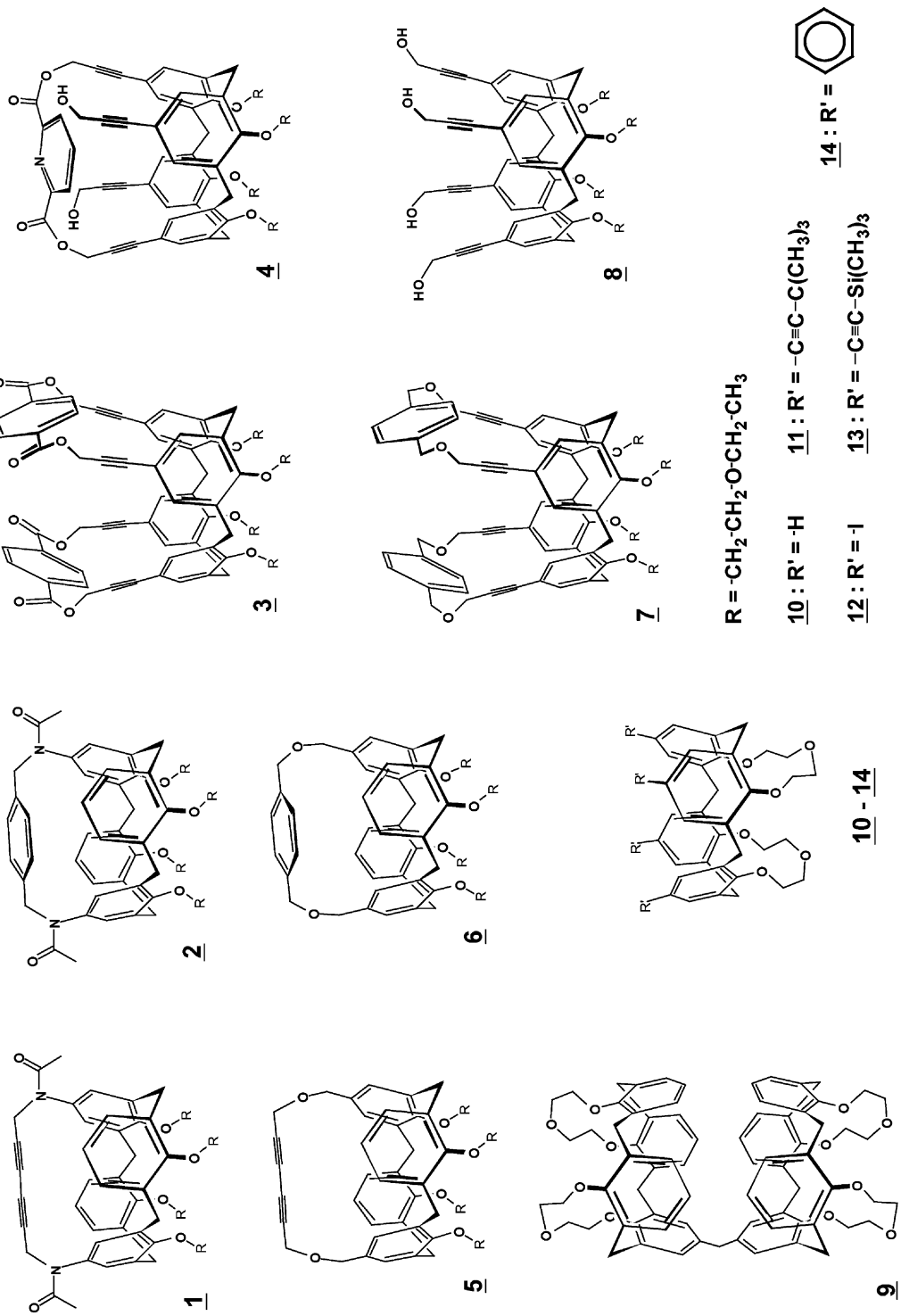
Also melamine substituents were introduced into the calixarene structure to form hydrogen-bonded supramolecular assemblies with diethylbarbituric acid and similar monomers exhibiting concurrent donor and acceptor properties [23]. By covalently bridging three calixarene moieties by means of their melamine substituents, large molecular boxes were obtained [24], capable of forming complex molecular aggregates, that were characterized by MALDI-TOF.

Unless time-resolved experiments are performed after ionization, plain ESI mass spectra represent a chemical system where charged host-guest complexes are either pre-formed in solution or are generated at the high-voltage conditions used in ESI. In both cases, the observation of molecular aggregates in the mass spectrum demonstrate the stability of such complexes in the gas-phase, at least for the time-frame of mass analysis. Due to the rather energetic conditions needed inside the mass spectrometer to isolate the analyte ions, the positive finding of a mass peak corresponding to the host-guest complex in the ESI spectrum is generally accepted as a good demonstration of its existence also in solution. In other words, ESI-MS is supposed to provide a reasonable guess of what chemical reactions may take place in *solution*. Analogous description of mainly the condensed phase chemistry is provided by LSIMS as well as any other technique in which the two counterparts are dissolved together in a liquid matrix and introduced simultaneously inside the ion source of the mass spectrometer.

The investigation of *gas-phase* chemistry requires that the reagents are introduced separately into the mass spectrometer, frequently at different steps of the experiment and using different methods to vaporize them. The most appropriate instruments to perform these studies are time-resolved mass analyzer, capable of trapping ions for long time period, such as Fourier transform ion cyclotron resonance (FTICR) or quadrupole ion-trap mass spectrometers. In these instruments, a substrate ion (for example, the charged host) is first isolated and then allowed to interact with vapors of a neutral reagent species, which is generally pulsed into the reaction chamber. The subsequent mass analysis at various time intervals allows one to determine both the products and the kinetics for their formation.

In our experiments aimed to investigate the gas-phase chemistry of functionalized calixarenes reacting with neutral molecular species, we used a less sophisticated device, namely the chemical ionization (CI) ion-volume of a spectrometer with magnetic mass-analyzer. Some of the functionalized calixarene structures that we studied are reported in Scheme 3. The neutral reacting species (alcohols, esters, nitriles, arenes) were mixed in small percentage with the CI reagent gas (methane) forming a stable atmosphere inside the ion-volume, while the calixarene was pulsed inside it by fast vaporization from a desorption chemical ionization (DCI) probe. The mixture underwent ionization by CI and the products were mass-analyzed and detected. The ion-source temperature was maintained close to ambient and carefully monitored, since the reaction equilibrium exhibited strong dependence from the gas temperature, as should be expected. This instrumental arrangement allowed us to produce host-guest complexation equilibria directly in the gas-phase, but did not provide information on the reaction kinetics nor on the reaction mechanism. For example, it was not clear whether the ionization took place after the host-guest complexes were formed or before. Moreover, the dynamic pumping of the system did not allow us to measure the instantaneous concentration of the reagents and, consequently, to determine the absolute thermodynamic constants for host-guest complexation. However, we performed accurate measurements of the gas-phase relative composition and selected appropriate conditions to compare competitive reactions. For example, one calixarene was allowed to interact with two candidate guests or two different calixarenes were reacted with one candidate guest. In this way, the relative constants for couples of reagents could be measured quite accurately and the relative efficiency and selectivity of the various ligands was revealed very neatly. Examples of competitive complexation experiments are provided in Fig. 1, where **2** (a) and **12** (b) are allowed to react with an excess of a 1:1 mixture of ethyl acetate and *i*-propyl acetate in the gas-phase. Both spectra show evidence of extensive formation of host-guest complexes and preference for *i*-propyl acetate, but the selectivity is much higher for **12** (peak ratio 7:1) than for **2** (peak ratio 2:1)

From the study of the specific gas-phase reactivity of calixarenes with various esters and alcohols, several conclusions of general validity were drawn. (a) The presence of one or more bridges at the upper rim of the cavity dramatically increases the calixarene ability to


1
2
3
4
5
6
7
8
9
10 - 14
R = -CH2-CH2-O-CH2-CH3
10 : R' = -H
11 : R' = –C≡C–C(CH3)3
12 : R' = -I
13 : R' = –C≡C–Si(CH3)3
14 : R' =

Scheme 3.

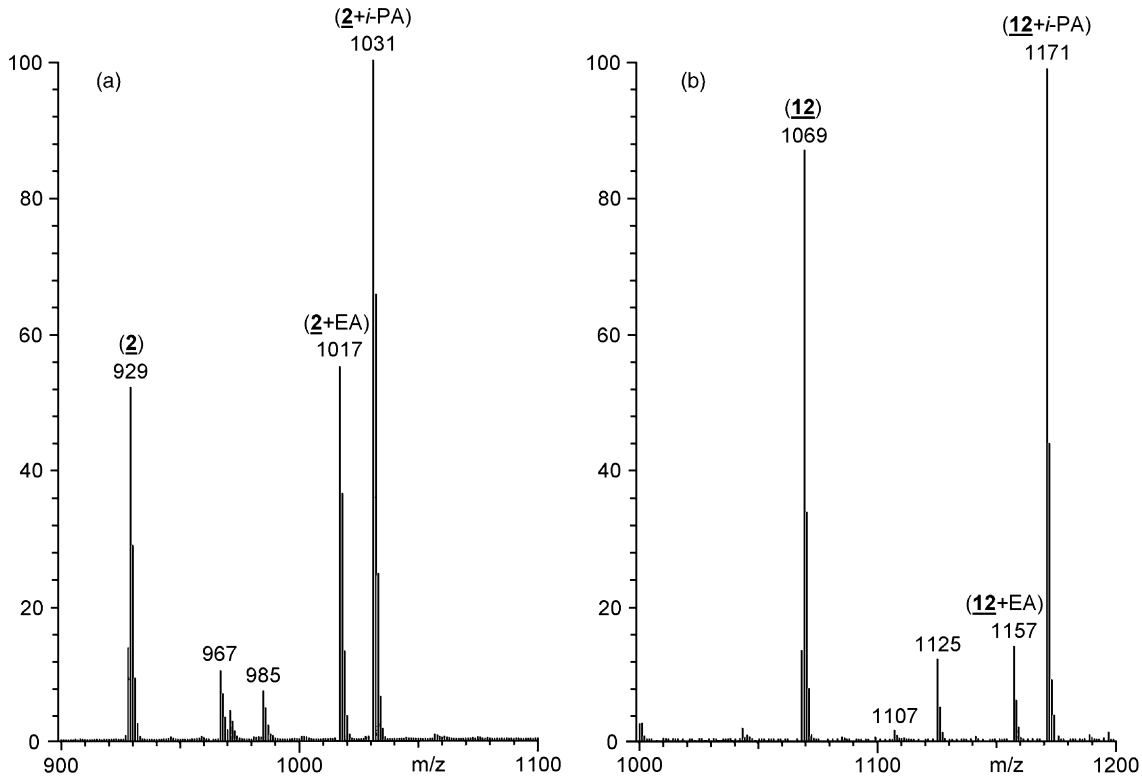


Fig. 1. DCI mass spectra of (a) calixarene **2** (MW 928) and (b) calixarene **12** (MW 1068), reacting in an atmosphere of methane (99%), ethyl acetate (EA, 0.5%), *i*-propyl acetate (*i*-PA, 0.5%), at a total pressure of 30 Pa. All the species identified in the spectra are positively charged by proton attachment $[M + H]^+$.

form inclusion complexes, provided that these bridges are rather rigid, i.e., all the atoms forming the bridge are linked to at least one unsaturated carbon. So, calixarenes **1**, **2**, **3** and **4** form abundant inclusion complexes with a variety of guest molecules, whereas calixarenes **5**, **6** and **7** exhibit scarce binding properties, as a consequence of the bridge flexibility at the upper rim of the cavity. (b) The size of the bridge and the nature of its substituents drives the selectivity of the calixarenes toward different guests [25]. Calixarenes with π-electron donor substituents, such as **1**, **2** and **4**, favor the formation of inclusion complexes with esters over alcohols, whereas **3**, carrying an electron-withdrawing pthalic system, forms more stable complexes with alcohols than with esters. (c) Some extreme forms of selectivity that have been experimentally observed may be peculiar to the mass spectrometric context, where the charge location plays the major role. For example, calixarene **4** forms weak complexes with 1-propanol and 2-propanol and a strong complex with the corresponding acetates, but an even stronger complex with *t*-butanol, whose stability largely surpasses that of the *t*-butyl acetate complex [25]. Evidently, the proton affinity of *t*-butanol is high enough to produce considerable change of the charge distribution in the host-guest complex.

More recently, the gas-phase reactivity of a new class of calixarenes has been studied (unpublished results). Their structure, reported in Scheme 3 (**9** and **10**–**14**), contains two di(ethylene glycol) units that connect the vicinal aromatic rings at the lower rim of the calixarene. These substituents carry out two functions at the same time: they act as binding groups and block the calixarene cavity in a rigid

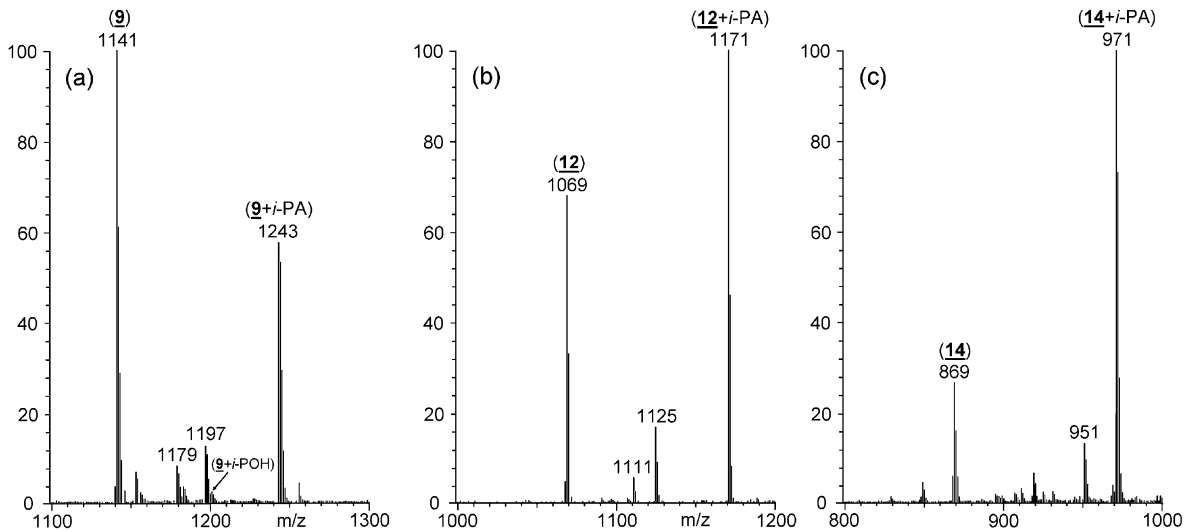


Fig. 2. Positive ion DCI mass spectra of (a) calixarene **9** (MW 1140); (b) calixarene **12** (MW 1068) and (c) calixarene **14** (MW 868), reacting in an atmosphere of methane (99%), *i*-propanol (*i*-POH, 0.5%), *i*-propyl acetate (*i*-PA, 0.5%), at a total pressure of 30 Pa. All the species identified in the spectra are positively charged by proton attachment $[M + H]^+$.

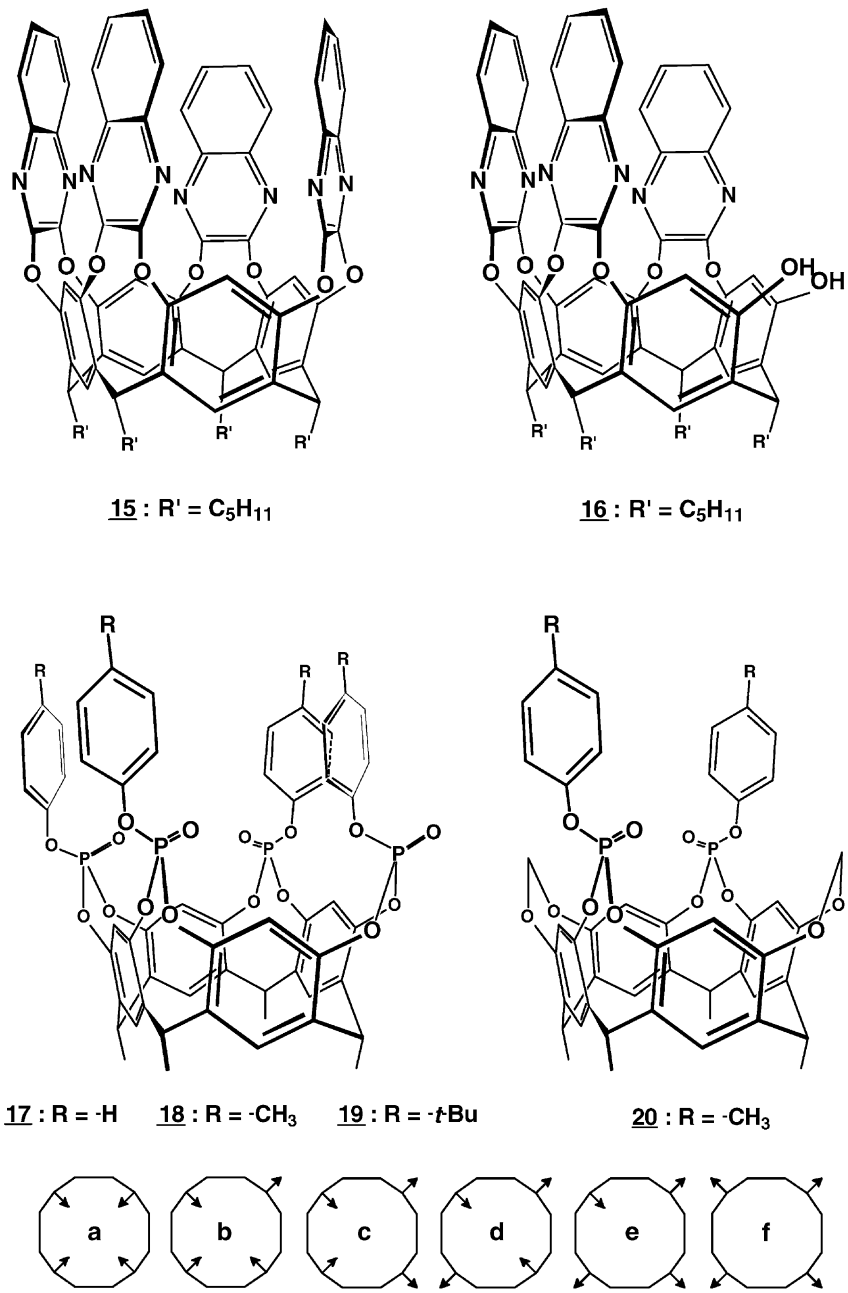
conformation. The other subunits present in the calixarene structure offers the chance of π-electron interaction, but hydrogen bonds can be formed only with the di(ethylene glycol) groups, which have strong electron-donor character. This character imparts distinct selectivity to the calixarenes, as already observed from Fig. 1.

More striking selectivity is observed in Fig. 2, reporting the DCI mass spectra obtained by reacting, respectively **9**, **12** and **14** with a 1:1 mixture of *i*-propyl acetate and *i*-propanol in an excess of methane. While the ligand efficiency varies along the series, none of the spectra show evidence of the gas-phase formation of host-guest complexes with *i*-propanol, unlike calixarenes **1**–**4**, all interacting with alcohols to some extent [25,26]. Upon CI, the acquired proton is coordinated by the two di(ethylene glycol) units, while the alcohols are likely not to compete for the charge, resulting in poor hydrogen bonding.

Another interesting point is the remarkable differences among calixarenes **9**–**14** to form host-guest complexes. These differences can be partly attributed to the electronic properties of the substituents at the upper rim of the host, which may provide supplemental interaction with the alkyl moiety of the guest. However, the inability of **11** and **13** to form host-guest complexes, even in the gas-phase, cannot be due to electronic factors, but rather to the steric hindrance produced when the entrance of the guest tends to distort the cone conformation of the calixarene, drawing the four bulky *t*-butyl groups too close to one another. In order to compare the reactivity observed in the gas-phase for this new class of calixarenes with that in a liquid phase, we are now recording LSIMS spectra for a variety of host-guest mixtures, using tetra(ethylene glycol) as the liquid matrix (unpublished results). This work is in progress.

3. Resorcinarene cavitands

Resorcinarenes are synthesized by condensation of resorcinol and aldehydes, which form a cyclic tetramer under the appropriate conditions. Just as calixarenes were derivatized either at the upper or at the lower rim to obtain a rigid three-dimensional cavity capable of molecular recognition, the easiest way to achieve the same result with resorcinarenes is to form chemical



Scheme 4.

bridges between the hydroxyl groups of vicinal aromatic rings (see Scheme 1). Unlike calixarenes, the upper rim of these resorcinarene cavitands is defined as the one bearing the oxygen atoms. Generally, the binding properties of the cavitands are imparted by the substituents on the bridges. These bridges can either be two or more, and may be all identical or different from one another, depending on the specific

features that the chemist wants to obtain. An example of these possibilities is shown in Scheme 4, reporting four typical structures among the ones that we have extensively studied by mass spectrometric methods. The substituents of the lower rim are frequently used to modify the solubility properties of the cavitands or to chemically bind these molecules to a solid surface.

The gas-phase reactivity of compound **15**, together with some of its derivatives, has been studied in detail, mostly using the same DCI-MS technique described in the preceding chapter [27–29]. The peculiar feature of cavitand **15**, as a molecular receptor, is that it does not interact with its guests by hydrogen-bonding, but rather by CH–π and π–π stacking. Although, these interactions are generally regarded as weaker than hydrogen bonds, **15** forms extremely stable complexes with aromatic compounds (including benzene) and chloroalkanes in the gas-phase. These are important target compounds and justify the need of deep investigation of the host binding properties, in view of the possible applications.

The DCI mass spectrum of **15** using pure methane as the reagent gas exhibits either the protonated molecular ion (positive ion mode) or the molecular ion (negative ion mode) without fragmentation. When methane was substituted by benzene, toluene or other aromatic compounds, the formation of host-guest complexes was evidenced in the DCI mass spectra (both polarities) by the virtual disappearance of the host molecular ion and the simultaneous appearance of the peak corresponding to the 1:1 aggregate [27]. In the subsequent experiments, the percentage of the candidate guest within the reacting atmosphere was dropped to only 1%, with 99% methane, resulting in minor change of the mass spectra. In fact, the mass signal relative to the host-guest aggregate remained the base peak of the spectrum, while a small abundance (5–10%) of the empty host molecular ion showed up [28]. Quite surprisingly, positive and negative ion mass spectra turned out very similar, providing the same estimate of the extent of host-guest complex formation. Even more surprising was the fact that almost identical mass spectra were obtained in the positive and negative ion polarities also when mixtures of candidate guests were employed in the reacting atmosphere, yielding relative complexation constant estimations close to one another [29]. This finding is extremely unusual in mass spectrometric studies of ion-molecule reactions, since the charge state and location determines the electronic state of the reacting species and drives their reactivity. In order to better understand this finding, deep investigation of the reaction mechanism was undertaken [29].

It is evident that, for molecular receptors interacting with their guest by hydrogen bonding, both geometry and electronic configuration are strongly modified by the presence of a proton. For example, this is the case for calixarene **10** and cavitand **17**, which interact with basic guests by sharing a proton. Upon ionization of the host by DCI, ESI or LSIMS, followed by gas-phase reaction with a neutral guest (in a time-resolved instrument), the host-guest interaction takes place at the same site where the proton is located. For cavitand **15**, the DCI process may occur differently, and the charge carrier, either a proton in the positive mode or an electron in the negative mode, may be delocalized in the cavitand structure, not located inside the cavity where the guest is accommodated. In such a case, both the geometry and the electronic configuration of the interacting functional groups should not be significantly affected by the ionization process, thus explaining the similarity of positive and negative ion mass spectra. An alternative possibility is that the host-guest complexation equilibrium was established before the ionization of the complex takes place. Then, the ionization process should not modify significantly this equilibrium in the time scale of ion extraction and mass analysis [29].

Although, the structure of cavitand **16** contains two phenolic hydroxyls capable of hydrogen bonding, a second synergic interation (possibly, CH–π with the opposing quinoxaline) is necessary to complement the hydrogen bond between host and guest; otherwise the formation of complexes in the gas-phase is not observed. As a matter of fact, ethanol and metyl acetate can not be trapped inside the cavity of **16**, whereas *n*-butanol, ethyl acetate and *n*-butylamine form strong inclusion complexes, as is evident from

the abundance of the corresponding peaks in the DCI mass spectra [28]. Notably, these fine structural aspects of host-guest chemistry were neatly detected by gas-phase MS experiments, but did not appear from solution experiments, where solvent effects covered the pure one-to-one interaction. It is also worth noting the different selectivity with respect to **15** toward entire classes of target guests [28]. In fact, **15** forms strong complexes with aromatic compounds and halometanes, while **16** reacts more selectively with aliphatic esters, ketones, alcohols and amines.

Unlike cavitand **15**, phosphate-bridged cavitands **17**–**19** interact with their guest essentially by hydrogen bonding, as the aryl-substituents of the phosphate groups are not rigid, being free to rotate along their axis and the P–O bond and making their contribution to non-covalent binding negligible. The formation of hydrogen bonds is made possible by the four P=O groups present in **17**–**19**, which possess considerable donor character. All these cavitands exist in six diastereomeric species, that cannot interconvert into one another and have different chemical and chromatographic properties, allowing their separation. The six diastereomers, indicated with **a**, **b**, **c**, **d**, **e**, and **f** in Scheme 4, are different in the orientation of the four P=O binding groups, each one pointing either toward the inside or the outside of the cavity. The interactions between these cavitands and aliphatic and aromatic amines (or ammonium ions) have been extensively investigated by ESI-FTICR-MS [30] and LSIMS [31,32]. Due to the synergic effect of multiple hydrogen bonding and the steric hindrance of the aryl-substituents protruding atop the cavity, isomers **a** and **b** proved to be strong supramolecular ligands, whereas isomers **e** and **f** did not form any inclusion complex with amines. For example, Fig. 3 shows the LSI mass spectra obtained by mixing *p*-toluidinium ion with, respectively, (a) **19b** and (b) **19e** in 200:1 concentration ratio. In the first spectrum the dominant signal is relative to the host-guest complex, whereas in the second spectrum the base peak corresponds to the protonated cavitand. Actually, extensive formation of adducts between protonated **e** and **f** isomers and several amines was induced in the FTICR mass spectrometer, and this formation proved to occur at the collision rate [30]. However, these adducts did not

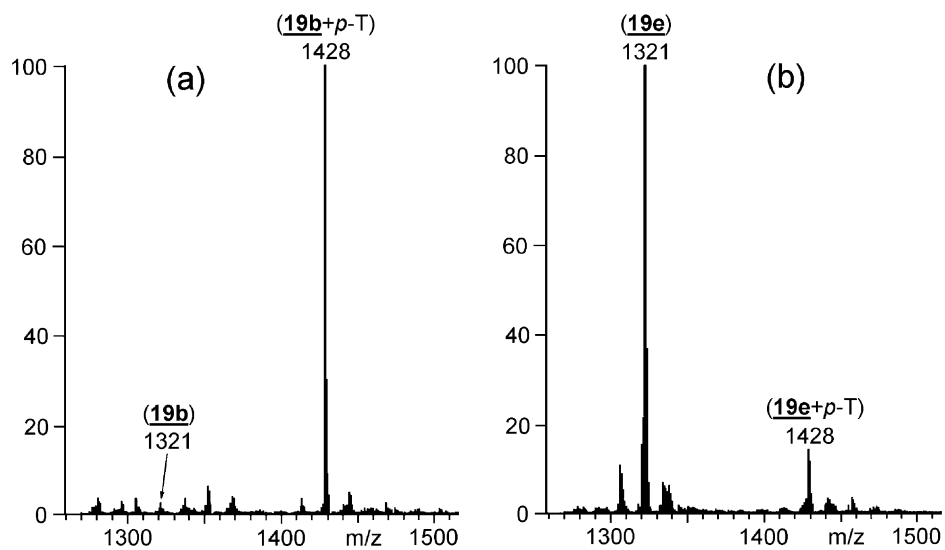


Fig. 3. Liquid secondary ion mass spectra of mixtures of (a) cavitand **19b** or (b) cavitand **19e** (MW 1320, concentration: 1.4×10^{-3} M for both) and *p*-toluidinium (*p*-T) chloride 0.28 M in 3-nitrobenzyl alcohol. The peaks at *m*/*z* 1321 represent the protonated molecular ion $[M + H]^+$.

involve the cavity and proved to be weakly-bound, as shown by collision-induced dissociation (CID) experiments. In contrast, protonated **17b**, **18b** and **19b** reacted much slower and to a lower extent than isomers **e** and **f**, due to geometrical constraints associated with the entrance of the amine into the cavity and the unfavorable entropic contribution. Once formed, these host-guest complexes proved to be much more strongly bound than the simple external adducts [30].

From a thermodynamic point of view, the initial charge transfer from the bulk solution to the inside of the cavity (isomers **a**, **b** and, to a minor extent, **c** and **d**) is highly exothermic, as multiple hydrogen bonds are formed at once. The charge carrier could either be an ammonium ion [31], an alkali metal ion, a protonated solvent molecule or a simple proton [30]. For example, the gas-phase proton affinity of **18b** turned out to be as high as 945 kJ mol^{-1} [31], as measured by the CID "kinetic method" [33,34]. This explains why extensive formation of host-guest complexes for **18b** is observed in ESI-MS [30], LSIMS and CI-MS [31], but considerably less in the FTICR gas-phase reaction of *protonated* **18b** and *neutral* amines, as this second step involves the formation of a single hydrogen bond between the neutral amine and the proton already coordinated by the cavitand. Adducts are virtually not formed for isomers **18e** and **18f** under ESI-MS and LSIMS conditions, even in the presence of high concentrations of amine or ammonium ion.

For **17b**, **18b**, **19b** and **18c** the more basic the amine is, the stronger is the host-guest complex formed, since more equal distribution of hydrogen bonds between host and guest is accomplished. However, trimethylammonium ion interacts more weakly than methyl- and dimethylammonium ion, as only one hydrogen can be shared with the triple converging P=O bonds of the cavitands. Less difference is observed for **18c**, as shown in Fig. 4, and almost no difference for **18d**, because these cavitands have decreasing ability to form multiple hydrogen bonds [31]. Competitive reaction experiments, in which mixtures of candidate guests were mixed with a much lower concentration of cavitand, allowed us to compare the relative stability of the complexes (Fig. 4d) and to order them in scales of decreasing affinity.

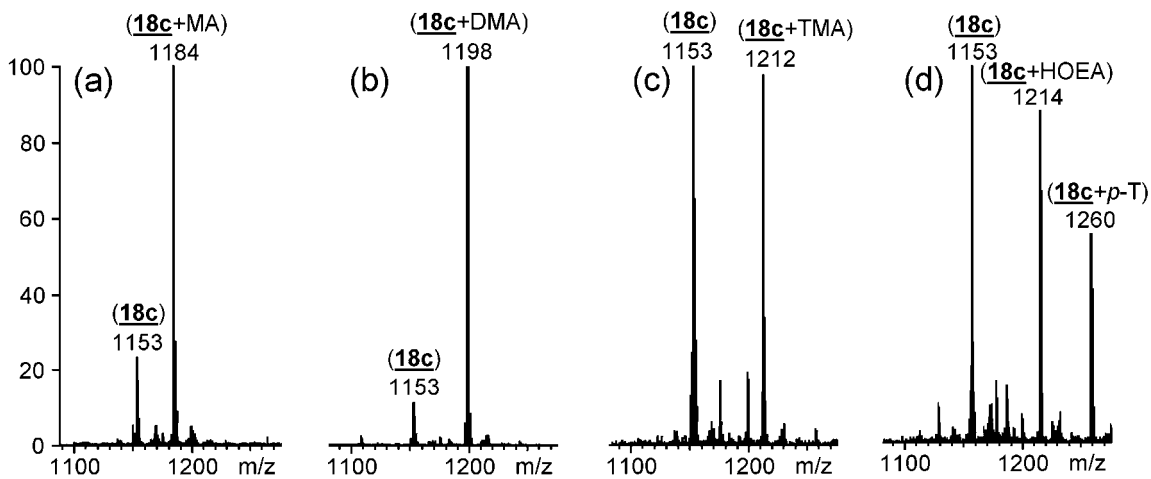


Fig. 4. Liquid secondary ion mass spectra of mixtures of cavitand **18c** (MW 1152, concentration: 1.4×10^{-3} M) and (a) methylammonium (MA) chloride; (b) dimethylammonium (DMA) chloride; (c) trimethylammonium (TMA) chloride and (d) ethanolammonium (HOEA) chloride plus *p*-toluidinium (*p*-T) chloride. The LSIMS matrix was 3-nitrobenzyl alcohol. The concentration for all alkyl chloride was 0.28 M. The peaks at *m*/*z* 1153 represent the protonated molecular ion $[M + H]^+$.

4. Carcerands and hemicarcerands

Carcerands are formed by coupling two cavitand units by means of chemical bridges, usually in the number of four. As the name of the class suggests, carcerands imprison guest molecules inside their cavity, that cannot escape, due to the modest size of their cavity portals. The imprisoned guests are generally one or two molecules of the solvent used in the final step of the carcerand synthesis. The small dimensions of the cavity pores make the steric hindrance for the guest egress too strong to be overcome at the limited internal energy available in solution chemistry. When crystals of these inclusion complexes (called carceplexes) are dissolved in a different solvent, the carcerand retains the original guest, without exchange. Thus, the steric stability of their complexes represents the characteristic feature of carcerands.

Carceplexes are more readily dissociated in the gas-phase than in solution. Quite often, the analytical problem is just the opposite, viz. to obtain a clear mass spectrometric evidence of the carceplexes. This goal was accomplished by DCI-MS, using isobutane as the reagent gas at a temperature close to ambient [35,36]. More extensive dissociation was promoted by laser desorption [37] and also in DCI-MS by increasing the ion-source temperature. Also CID at low collision energy was able to dissociate the carceplex, suggesting that a modest increment of the carcerand internal energy was sufficient to activate the vibrational modes that enlarged the cavity portals, allowing the guest egress [32]. A different mechanism [37], that implies the CID breaking of one of the bridges, should be excluded in this case, as no evidence of carcerand fragmentation is present in CID and DCI mass spectra, contrarily to what is observed in LD [32,37].

Hemicarcerands, in which one or more bridges of the carcerand structure are missing, allow the dynamic exchange of guests in solution. Therefore, hemicarcerands have chemical properties more similar to cavitands than to carcerands. The same proved to occur in the gas-phase [37]. Sodium-attached hemicarcerand ions, with one and two missing bridges, released their guests when transferred in the ultra-high vacuum cell of a dual-cell FTICR mass spectrometer. On the other hand, empty hemicarcerand ions formed 1:1 and 1:2 host-guest complexes with dimethylacetamide, when they were allowed to interact for variable time periods with 10^{-7} Torr pressure of dimethylacetamide [37].

5. Conclusions

More than two decades after their introduction, calixarene and resorcinarene cavitands are nowadays investigated for their possible practical applications. To this respect, gas-phase interaction studies have limited direct impact on applications, and should still be regarded chiefly as fundamental studies. However, they provide a unique perspective and information, since the dynamic character of the gas-phase interaction makes the attractive forces established between host and guest depend uniquely on their relative structures and the intrinsic energy of the system. Moreover, the major source of interference, that is the solvent, is absent in gas-phase studies. The simplicity of the reacting system has the potential of revealing the specific nature and strength of each supramolecular binding. Thus, the thermodynamic parameters associated to subtle structural attributes such as, for example, synergic multiple binding, conformational dynamics and steric constraints can be measured.

In order to undertake these studies, it is convenient to establish strong cooperation between synthetic chemists and mass spectroscopists, and to have access to instruments capable of time-resolved experiments, particularly FTICR mass spectrometers. But, above all, it is essential that the scientist investigating supramolecular architectures become aware of the significance of gas-phase studies in elucidating the intrinsic nature of supramolecular interactions.

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