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**SPECIAL FEATURE:
PERSPECTIVE****Host–Guest Chemistry in the Mass Spectrometer****Marco Vincenti**

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The study of host–guest chemistry in the gas phase has been pursued systematically only in the last 5 years, after sporadic interest in the 1980s, despite extensive investigation of this chemistry in the condensed phase and the success encountered in several fields of application. Most gas-phase studies have been performed under the controlled conditions that can be achieved inside a mass spectrometer, where solvent effects are not present. At this point, the first evaluation of the achievements and knowledge emerging from these mass spectrometric investigations can be attempted. At the same time, it is possible to evaluate the most promising subjects for future research. This review undertakes these tasks, by presenting (i) applications where mass spectrometry was used to investigate condensed phase equilibria and, more extensively, (ii) experiments where host–guest complexes were formed directly in the gas phase. The latter processes are discussed in detail in relation to the structural and electronic effects, the energetic requirements and the dependence on size, rigidity, spatial geometry and functional groups of both hosts and guests. All these effects combined are likely to contribute to the strength and multiplicity of the non-covalent bonds that allow the complex to be formed. The macro(poly)cyclic hosts considered include crown ethers, cryptands, cyclodextrins, calixarenes, cryptophanes, cavitands, carcerands and macrolides. The guests are either metal cations or organic molecules and ions.

DEFINITIONS

The term ‘host–guest chemistry’ has been used to designate a variety of processes occurring in a number of research fields, such as organic, analytical, biological and organometallic chemistry, and involving molecules and ions with different structures, dimensions and properties. In spite of this apparent vagueness, it is possible to restrict the definition of host–guest chemistry by considering the common elements that these processes possess. In general, host–guest interactions involve the establishment of multiple non-covalent bonds between a large and geometrically concave organic molecule (the host) and a simpler organic or inorganic molecule or ion (the guest). The mere formation of multiple non-covalent bonds between reactants of similar size or geometry is generally referred to as a process of supramolecular chemistry, not host–guest chemistry, because *inclusion* complexes are not formed. Thus, the geometrical requirements are essential to fit the definition of host–guest chemistry. In the gas phase, loosely bound adducts are frequently generated, and many mass spectrometric studies have been directed towards the investigation of charged adducts and clusters. These studies fall outside the range of this survey, which will concentrate on cases where a relatively small guest (neutral or ionic) is embodied within a macrocyclic host. Consequently, the presence of at least one macrocyclic ring is a constant feature of the hosts considered in this review. Almost all these hosts have been produced by

organic synthesis, with the exception of a few naturally occurring macrolides and underivatized cyclodextrins.

INTRODUCTION

The extensive development of host–guest chemistry started in 1967 with the discovery of crown ethers.^{1,2} Soon afterwards several classes of macrocyclic ligands with structures of increasing complexity were synthesized, including cryptands,^{3–5} cyclophanes,⁶ calixarenes,^{7,8} cavitands,⁹ carcerands¹⁰ and many others.^{11–17} An overview of some of these structures is provided in Fig. 1. The involvement of mass spectrometry in this area of chemistry started with the need to characterize these complex molecules with progressively higher molecular masses and lower volatilities. Many analytical problems were solved by using desorption techniques to transfer the largest and most involatile ligands into the gas phase. In particular, soon after its discovery, fast atom bombardment mass spectrometry (FABMS) was extensively utilized to measure the molecular masses of large macro(poly)cycles.

At the same time that FAB was used for analytical purposes, it became evident that the FAB mass spectra of macrocyclic ligands could occasionally show peaks corresponding to the formation of adducts between the ligand and organic or inorganic cations present in the matrix. Later, the interactions occurring between crown ethers and metal cations in the FAB matrix were

exploited to test for the possible correspondence between well established equilibria for host-guest complexation in solution and the data produced by this new mass spectrometric equipment.¹⁸⁻²⁶ Since the FAB spectra proved to represent reasonably the distribution of species present in solution, FAB mass spectrometry became an important investigative tool for studying host-guest chemical equilibria.

A completely different approach is to study host-guest interactions directly in the gas phase, i.e. to vaporize the two (or more) reacting species separately and let them interact in the absence of any other chemical agent (solvent, counter ions, etc.). A mass spectrometer is an especially appropriate instrument to perform such experiments, since (i) the high vacuum conditions typical of a mass spectrometer ion source favour the vaporization of massive hosts, (ii) it is possible to create a reactive atmosphere of controlled composition, where simple bimolecular interactions occur and (iii) the mass analyser and detector allow the interaction products to be identified and quantified.

Obviously, knowledge of these gas-phase processes is still restricted, and many problems have to be solved before these promising mass spectrometric techniques are fully developed. These problems will be considered in detail in the following sections and the various solutions that have been proposed will be reviewed. Just as in the synthetic work and in preliminary practical applications, most mass spectrometric investigations have focused on the simplest systems (namely crown ethers), which can be easily used as model systems, and where the number of parameters to be controlled is reduced and extensive information is available in the literature, covering a variety of experimental conditions. For example, there are numerous studies reporting the selectivity, stability constants and thermodynamic parameters of crown ethers reacting with metal cations in a

variety of solvents. This information can be utilized to draw well supported conclusions on the observed gas-phase processes. In contrast, host-guest interactions occurring between more complex counterparts (calixarenes, cavitands, etc., and organic guests) in the gas phase are not supported by sufficient solution data to allow the specific and precise evaluation of the intrinsic parameters involved in these supramolecular interactions, or to delineate the role of the solvent. However, the results obtained for these complex systems also yield information of increasing refinement and provide support to the synthetic chemist in the search for the most selective host structures.

The reasons for studying host-guest complexation reactions in the gas phase stem from the substantial complexity of the processes occurring in solution and the need to simplify the interaction conditions. The formation of host-guest interactions in the condensed phase implies the solvation of both counterparts and hence the possible modification of a variety of ion-ion, ion-dipole and dipole-dipole interactions. Consequently, both the transition state and the final configuration are strongly influenced by the presence of the solvent, counter-ions and even adventitious species. Stability constants and thermodynamic parameters determined in solution are always influenced by solvent effects, and these tend to mask the intrinsic interaction between the host and the guest. Frequently, the guest interacting with the host has not undergone complete desolvation, so that the size-fit (the well known 'lock-and-key' principle) between the two species is significantly different from that in the gas phase. Elimination of the solvent, by carrying out the reaction in the gas phase, allows host and guest, possibly in an unexcited state, to interact in the absence of any interfering effect caused by other chemical species. The resulting product distribution should, in theory, better reflect the intrinsic affinity of the two reactants, and the thermodynamic quantities (enthalpy, entropy) involved in the host-guest interaction.

INVESTIGATION OF SOLUTION EQUILIBRIA: FAB AND ELECTROSPRAY IONIZATION

In 1983, soon after the introduction of FAB, Johnstone and co-workers¹⁸⁻²⁰ investigated the capability of this new ionization method to reproduce the crown ether selectivity toward metal cations observed in solution. They concluded that the relative abundances of the ions corresponding to the various crown ether-metal ion complexes closely reflected their stability in solution. This allowed them to propose FABMS analysis as a simple and rapid procedure to study such equilibria. The close similarity between solution and FAB data provided interesting support²⁰ for the view that ionization in FAB occurs directly from the solution and reflects solution- and not gas-phase phenomena. The observation that FAB peaks for the complexes increased with increasing the metal ion concentration, in an excess of ligand, induced Vignon and co-workers^{21,22} to elaborate a method to calculate the *absolute* stability constants for complexation. The

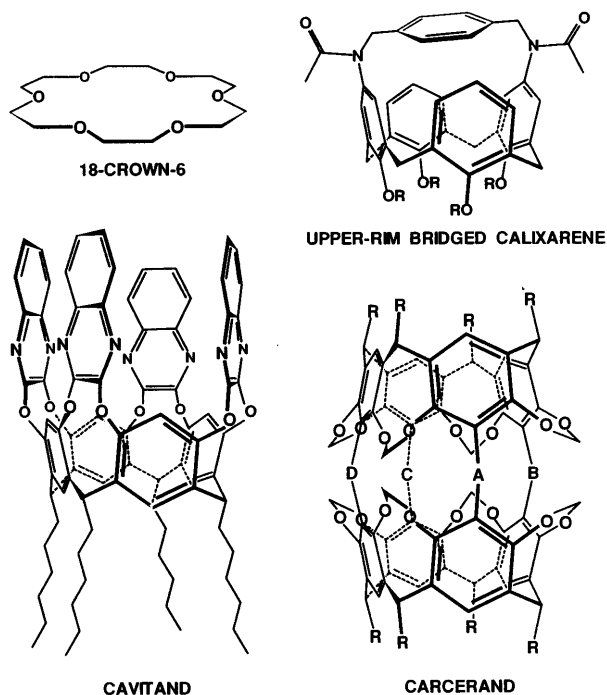


Figure 1. Structures of some macro(poly)cyclic hosts.

experimental curves (complex peak intensity *vs.* alkali metal cation concentration) were matched against the theoretical model by a curve-fitting program, yielding numerical solutions for the stability constants, after successive iterations.²² They found good agreement between these constants measured in glycerol and polyethylene glycol and those obtained from calorimetric techniques in solvents with similar dielectric constants.

The obvious deduction that stems from the similarity of solution and FAB data for host-guest complexation is that atom bombardment sputters from the matrix the species already formed in solution. In this scenario, gas-phase chemistry would not play any role in such experiments, and FABMS would merely be a method to investigate solution equilibria. This assertion has to be considered in the light of a long-term controversy,^{27,28} not yet fully resolved, on whether direct desorption of preformed ions takes place in FAB or whether significant contributions from processes occurring in the selvedge are present. The distinction is subtle because the ions are sputtered from the liquid phase, but are detected as completely desolvated ions, just as occurs in gas-phase processes. This issue takes particular importance in the study of non-covalently bonded species, such as host-guest complexes, where the specific nature of the non-covalent bond is investigated and the equilibrium strongly depends on the solution (or gas-phase) composition. One wonders whether the desolvated complexes which are determined in FAB reflect the preceding equilibrium of the condensed phase or if they have no memory of the solvent effect and depend uniquely on the gas-phase affinity of the two interacting species. If it were true that selvedge processes were dominant in FAB, then the similarity observed between selectivities measured by FAB and those determined in solution (using different techniques) would be an accidental artifact and one that holds for crown ethers interacting with alkali metal cations, but not necessarily for other systems. In such a case, the value of FAB in probing the formation of host-guest complexes in the condensed phase would be greatly reduced.

The first in-depth inquiry²³ into the host-guest complexation mechanism in a FAB experiment used divided FAB tips (dual targets) to introduce simultaneously yet separately crown ethers and alkali metal cations into the ion source. From the distribution of ionic species formed it was deduced that selvedge processes were likely to contribute to the observed spectra, although the abundance of the crown ether-metal cation complex increased considerably when the two species were mixed together. In a recent and very thorough publication²⁴ it was objected that, upon FAB sputtering, volatile ligands can migrate from one half of the tip to the other and can there generate host-guest complexes (in the condensed phase). These complexes can in turn be sputtered and detected. On the basis of this and other evidence, it was concluded²⁴ that the quantitative contribution of gas-phase processes to the total ion signal is very small compared with the signal generated by direct desorption of complex ions preformed in the condensed phase. It was also observed that the strongly bound crown ether complexes survive the fast atom impact intact. This is possible in complexes with high stability constants. A different result was observed for

carceplexes²⁵ (inclusion complexes between a carcerand and one or more neutral guests), which undergo extensive loss of the guests upon fast atom impact, owing to the much lower interaction energy between the host and guest.

FAB mass spectra of crown ether-metal cation complexes often exhibit cluster ions in fairly high abundance; in these ions, one or two metal cations are associated with more than one crown ether molecule.^{23,24} The most common among these clusters are the 1:2 'sandwich' complexes, in which one metal cation coordinates two molecules of ligand. The abundance of such species is particularly high when the metal cation radius is too large to allow it to fit into the cavity of the crown ether, so that the protruding section of the cation can interact with a second ligand. If the crown ether carries a side-arm with complexing properties,²⁶ the central metal cation is coordinated also from positions out of the crown ether plane and sandwich complexes are no longer formed. The side-arm also provides some steric hindrance that prevents a second ligand from approaching the cation.

FABMS was also utilized to verify the improved selectivity toward some specific metal cations achieved by synthetic ligands with multiple binding sites.^{29,30} These ligands were formed by a central skeleton of one or two metallocenes carrying a crown ether substructure on each cyclopentadienyl moiety. The resulting ligand structure is three-dimensional and can accommodate one^{29,30} or two³⁰ metal cations inside its cavity (see Fig. 2). FAB was able to reveal specific interactions and also the presence of sandwich complexes that were not apparent using other instrumental techniques.

When diazonium ions were used instead of metal cations to form complexes with crown ether ligands,³¹ sandwich complexes could no longer be detected by FABMS analysis. In contrast, significant abundances of 1:2 and even 1:3 complexes were found in field desorption (FD) mass spectra. The origin of such surprising complexes was ascribed to various interaction mechanisms occurring in the gas phase, including insertion complexation, charge transfer and σ - π interactions, each associated with a different interaction energy (see

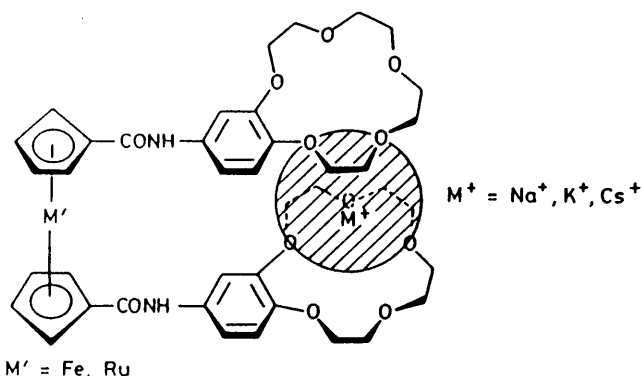


Figure 2. Three-dimensional ligand which binds one or two metal cations. Reprinted by permission of the Royal Society of Chemistry from the *Journal of the Chemical Society Chemical Communications*, P. D. Beer, Synthesis of Novel Metallocene Bis(Crown Ether)s. Potassium Selective Intramolecular Sandwich-type Complexation Observed by Fast Atom Bombardment Mass Spectrometry, p. 1116 (1985).

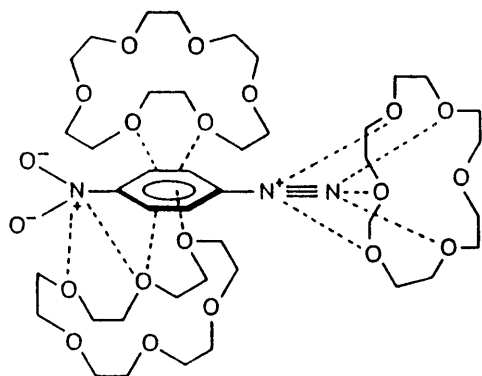


Figure 3. Hypothetical representation of an encapsulated diazonium ion within a 1:3 complex. Reprinted with permission from the *Journal of Organic Chemistry*, **54**, 496 (1989) by K. Laali and R. P. Lattimer. © 1989 American Chemical Society.

Fig. 3). In this sense, FD was found to allow the gas-phase character of the host-guest reaction to be studied. Accordingly, without solvation effects (steric hindrance and solvation energy), the diazonium ions were able to form 1:1 complexes extensively, even in those cases where no solution complexes were observed. FAB tended to reproduce more closely the equilibria typical of the condensed phase, although some host-guest complexes barely formed in solution were clearly evident in FAB mass spectra.³¹

Several recent applications of FAB-MS to the study of host-guest chemistry were devoted to the demonstration of enantioselectivity.^{32,33} The complexation of enantiomeric substituted ammonium ions by means of chiral crown ethers was studied. Moderate enantioselectivity was evident from the relative abundance of the crown ether-substituted ammonium ion complex in an experiment in which each enantiomer was determined relative to a non-chiral internal standard (e.g. 12-crown-4).

Selectivity towards organic anions has been demonstrated for a crown ether cryptand using FABMS.³⁴ The same technique was utilized to test the ability to form inclusion complexes for other classes of macrocyclic hosts, including cyclodextrins¹⁴ and calixarenes.³⁶ The latter compounds appear to be particularly interesting, since the size of the ring can be manipulated, as for crown ethers, and the presence of several aromatic rings imparts three-dimensional structure to the ligand and delimits a π -basic cavity, in which ion- π , π - π and CH- π non-covalent bonds can be formed.^{7,8} Moreover, the aromatic rings can be suitably substituted to introduce functional groups which modify the geometry, size and electronic properties of the ligand. In fact, Shinkai and co-workers³⁶ were able to prove hole-size selectivity, and also the influence of geometrical effects and the role of charge density on complexation. Most interestingly, they observed remarkable differences between solution data and the results of FAB experiments. Especially for the largest host, solvation effects tended to deactivate complexation with aliphatic quaternary ammonium ions, whereas the same ligand yielded the most stable complexes under FAB conditions. Moreover, charge density effects produced the highest binding constants for the smallest guest in FAB, whereas in solution the reverse order of association con-

stants was observed. Thus, this study proved that FABMS cannot be considered merely as an analytical tool for determining host-guest solution equilibria; rather it also provides insights into some gas-phase processes where solvent effects play little or no role. The difference between solution and FAB results is likely to be especially large when the binding constant for host-guest complexes is small, as in the case of ion- π interactions, and when the competing effect of solvation is strong enough to prevent complexation from occurring in the condensed phase.

Besides FAB, other mass spectrometric techniques utilized in recent years to detect host-guest complexes include FD,³¹ desorption chemical ionization (DCI),³⁷ ²⁵²Cf plasma desorption³⁸ and electrohydrodynamic³⁹ mass spectrometry. The extraordinary success of electrospray ionization (ESI) obviously has also had an impact on host-guest complexation studies. Cunniff and Vouras⁴⁰ investigated the formation of crown ether-alkali metal ion adducts by means of ESI-MS and verified a strong correlation between ion abundance and solution concentrations of these complexes. However, this correlation did not hold for sandwich complexes, which were much more abundant in the ESI spectra than in solution. The authors⁴⁰ could not decide whether this discrepancy was the result of gas-phase or charged droplet equilibria; in either case, ESI-MS (and likewise FABMS) did not provide a completely accurate representation of solution equilibria.

ESI-MS was also utilized to ascertain the formation of host-guest complexes involving calixarenes⁴¹ and β -cyclodextrin derivatives.^{42,43} In the latter study,⁴³ chiral selectivity was observed toward *d*-propranolol and *l*-tryptophan methyl ester enantiomers. Both guests proved to be strongly associated with the host, as demonstrated by the fact that application of a high declustering voltage within the ESI source did not result in decomposition of the host-guest complexes.

Remarkable examples of host-guest interactions involving biologically active macrolides were uncovered by Ganem and co-workers.^{44,45} using ionspray MS. In the most comprehensive of their studies,⁴⁵ the various mechanisms of interaction were surveyed, together with the possibility of using the relative abundances for the non-covalent complex ions to deduce their solution binding constants. They concluded that ionspray mass spectra might not reflect accurately the solution binding affinities, particularly when hydrophobic effects play an important role in host-guest complex formation. While this difference prevents the binding constants from being measured accurately, ionspray data proved nevertheless to provide important information on host-guest complexes and the nature of their interaction.

The group of publications reviewed in this section demonstrate that MS techniques in which the liquid matrix is present during the ionization process produce data that basically maintain the fingerprint of solution equilibria, but are not completely representative of it. Partial contributions, from gas-phase processes are imparted by elimination of the solvent from the ionic host-guest complexes that are analysed and detected. These desolvated species are likely to arise from intermediate states (strongly dependent on the ionization technique and the experimental conditions chosen)

where solvent effects are still present, yet fast reaction kinetics, such as ligand exchange, might modify the equilibria with respect to the condensed phase condition. Thus, all these mass spectrometric techniques maintain some gas-phase character, which contributes to reducing the solvation effects typical of the condensed phase.

GAS-PHASE REACTIVITY: CROWN ETHERS

The first experiments in which host-guest complexes were formed directly in the gas phase date back to the mid-1980s. Allison and co-workers^{46,47} produced crown ether-transition metal ion complexes in an ion cyclotron resonance mass spectrometer, while Bose *et al.*⁴⁸ published a note reporting the synthesis of inclusion complexes between crown ethers and a variety of substituted ammonium ions within the chemical ionization source of a conventional mass spectrometer. More complete investigations on related subjects were undertaken almost simultaneously by two different groups, namely by Meot-Ner^{49,50} and by Kebarle and co-workers.^{51,52} Both used high-pressure mass spectrometers to measure the proton affinity of a series of polyethers and crown ethers^{49,51} and to determine the stabilities of complexes of aliphatic and aromatic substituted ammonium ions,⁵⁰ H_3O^+ ⁵² and CH_3OH_2^+ ⁵² with crown ethers. The instrumentation used was specifically designed to measure accurately the partial pressure of the gaseous reagents, the reaction chamber temperature and the relative abundances of the ionic products formed. Under such circumstances, both groups could obtain precise and comparable thermodynamic values for the complexation equilibria. It turns out that the formation of ionic inclusion complexes in the gas phase is driven by a large and favourable enthalpic contribution, which is associated with the formation of multiple hydrogen bonds. This large exothermicity is partly compensated for by a large entropy loss, due to the considerable rigidity induced by multiple coordination of the central guest. However, the entropy loss in crown ether complexation is lower than that associated with the coordination of ionic guests by acyclic polyethers.⁵⁰ In fact, the free crown ethers are already more rigid than the corresponding acyclic polyethers, owing to the restrictions imposed by cyclization. Consequently, the crown ethers are more efficient ligands than the corresponding acyclic polyethers for ammonium ions.⁵⁰ The exothermicity for the complexation between primary ammonium ions and 18-crown-6 was found to be only half of that associated with the formation of the crown ether- H_3O^+ ion complex, although in both cases three hydrogen bonds possibly can be formed.⁵² This difference was attributed to the greater acidity of H_3O^+ , which allows more extensive sharing of acidic hydrogens between the central guest and the ether oxygens of the host, resulting in stronger hydrogen bonds. It is interesting that the reverse order of affinity constants is observed in aqueous solution, where crown ethers form much weaker complexes with H_3O^+ than with alkyl-ammonium ions, owing to the higher solvation energy of H_3O^+ with respect to RNH_3^+ . This is a typical

solvent effect, masking the actual host-guest interaction energy, which is revealed in gas-phase studies.

After a period in which systematic investigations on host-guest complexation in the gas phase appears to have lapsed, research in this field exhibited new vitality in the 1990s. A subject that was suited to detailed study was the gas-phase interaction between crown ethers and alkali metal ions,⁵³⁻⁶² given the extensive knowledge existing for these reactions in solution and the availability of suitable mass spectrometric methods. A variety of different techniques were utilized to clarify the nature of the interaction between the two counterparts and the factors regulating the strength of these non-covalent bonds (mainly ion-dipole) in the absence of solvation effects. The kinetics of host-guest reactions yielding 1:1 and 1:2 complexes were measured by Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS).⁵³⁻⁵⁶ The rate constants obtained by assuming pseudo-first-order kinetics were divided by the ion-molecule collision rates, calculated using Langevin theory,⁶³ to give the reaction efficiencies for complexation. Another way to measure directly the relative affinity for metal ions of two competing hosts was to exploit ligand-exchange reactions (ion-molecule 'bracketing' methods^{63,64}), performed by either FTICR-MS⁵⁵ or ion-trap mass spectrometry (ITMS).^{61,62} An example of a ligand-exchange reaction performed in an ITMS instrument is shown in Fig. 4.

From the use of all the cited techniques, several conclusions can be drawn on crown ether-alkali metal ion

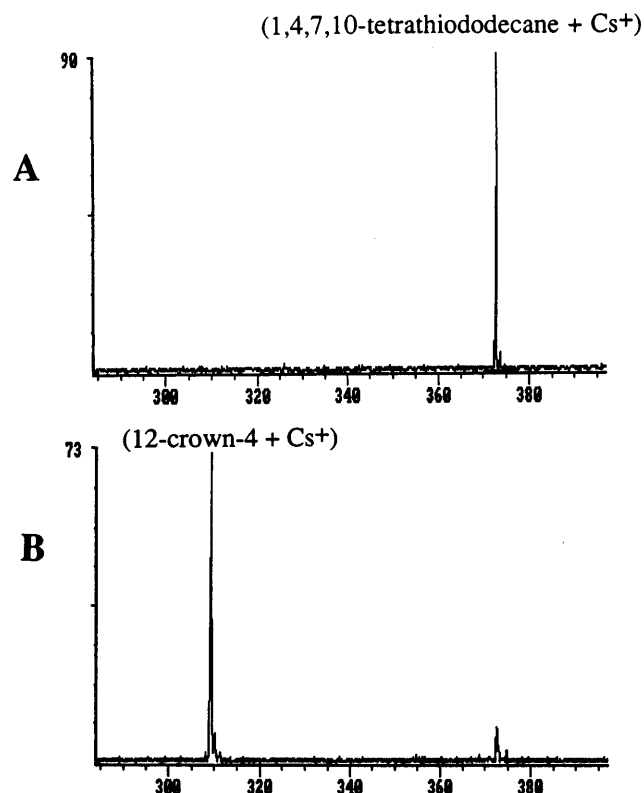


Figure 4. Ligand-exchange experiment showing (A) the isolation of (1,4,7,10-tetrathiadodecane- Cs)⁺ inclusion complex and (B) transfer of the Cs^+ ion to 12-crown-4 during a 100 ms reaction period. Reprinted with permission of Kluwer Academic Publishers from the *Journal of Inclusion Phenomena and Molecular Recognition in Chemistry*, **18**, 37 (1994) by H.-F. Wu and J. S. Brodbelt.

complexation. The non-covalent host-guest interactions occur on a short time-scale, close to the ion-molecule collision rate limit. The subsequent interaction between the host-guest complex and a second ligand to give 1:2 'sandwich' complexes is much slower and is markedly influenced (both in the kinetics and complex stability) by the nature of the hosts and the guest.⁵⁵ In general, metal ions that are small enough to be completely embodied within the crown ether cavity are unable to form sandwich complexes.⁵³⁻⁵⁶ The reaction efficiency for 1:1 complexation increases with decreasing metal ion size, i.e. high charge densities favour the structural and electronic rearrangement of the host and, consequently, its reaction efficiency. Moreover, when two hosts compete for metal ion coordination, complexation by the larger crown ether is always preferred.^{55,56} The two preceding conclusions sharply contrast with the 'best-fit' principle observed in solution, according to which more stable complexes should be formed when the metal ion radius best matches the cavity size of the crown ether. This best-fit rule is possibly an artifact due to the opposing effects of host-guest interaction energy (higher for small cations) and solvation (also more extensive for cations with high charge density). In the gas phase, solvent effects are suppressed and the pure interaction energy is uncovered, without interferences.

Another method^{58,59} utilized to test the relative metal ion affinity of two ligands, and an alternative to the ligand-exchange ('bracketing') method, is the so-called 'kinetic' method. The kinetic method was initially developed^{65,66} to measure the relative gas-phase proton affinities of organic compounds; one measures the relative abundance of the two protonated monomers resulting from collision-induced dissociation (CID) of a proton-bound dimer generated from the corresponding monomeric bases. The proton tends to remain on the base with the higher proton affinity, provided that the transition states for the two possible dissociations are similar and no reverse activation barrier is present. A similar approach can be used for crown ether-alkali metal ion bound dimers ($L_1-M^+-L_2$), which can dissociate upon CID to give the corresponding 1:1 complexes. For example, in Fig. 5 the 1:1:1 complex between 15-crown-5 (15-C-5), potassium (K^+) and pentaethylene glycol (5-GLYCOL) was initially formed, isolated (Fig. 5(a)) and subsequently dissociated (Fig. 5(b)). The relative abundance of the two $L-M^+$ complexes, measured from the CID mass spectrum (Fig. 5(b)), should correlate with the relative metal ion affinity of the two ligands. The results obtained by this method were similar to those obtained by the bracketing method in many respects (for example, it was confirmed that larger crowns achieve stronger interactions), but substantial differences were found for the metal ion selectivity of the larger crown ethers,⁵⁹ which apparently formed more stable complexes with alkali metal cations other than Li^+ . The results were interpreted in terms of a 'maximum contact point' model.⁵⁹ The kinetic method present advantages and drawbacks⁵⁵ with respect to the bracketing method, which are mainly associated with the preliminary assumptions and might account for some of the discrepancies observed. For example, in the kinetic method dissociation occurs from the 1:2 complex, where binding energies may be different from

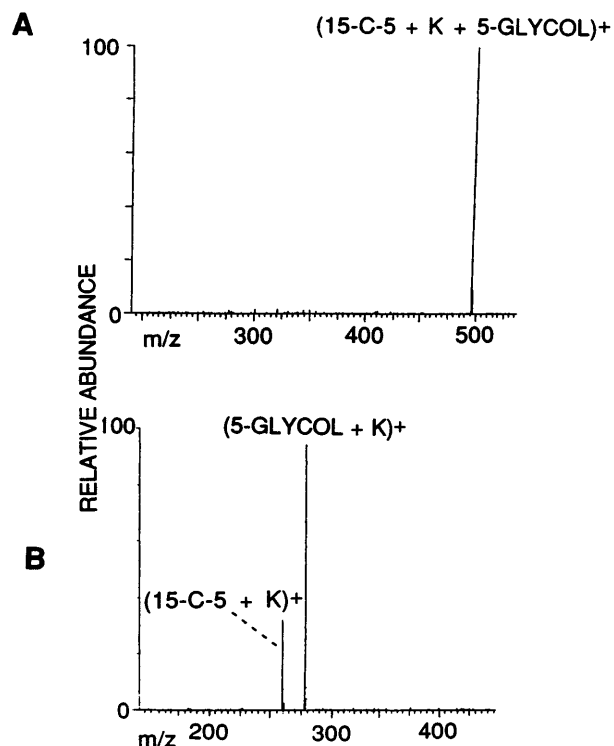


Figure 5. Kinetic method for determining relative metal ion affinity. (a) Mass-selected spectrum of the (15-crown-5 + K + pentaethylene glycol)⁺ adduct. (b) Collision-induced dissociation of the (15-crown-5 + K + pentaethylene glycol)⁺ adduct. 15-crown-5 = 15-C-5; pentaethylene glycol = 5-GLYCOL. Reprinted by permission of Elsevier Science Inc. from Determination of Orders of Relative Alkali Metal Ion Affinities of Crown Ethers and Acyclic Analogs by the Kinetic Method by C.-C. Liou and J. S. Brodbelt, *Journal of the American Society for Mass Spectrometry*, 3, 543. © 1992 by the American Society for Mass Spectrometry.

the ones present in 1:1 complexes. On the other hand, the two competing dissociation pathways might have different transition states and different reverse energy barriers, since the establishing of multiple metal ion-ligand interactions require substantial rearrangement of the crown ether conformation.

Important extensions of the results obtained for alkali metal ions and crown ethers were reported in two recent publications^{61,62} describing the reactivity of Mg^{2+} , Ca^{2+} and Al^{3+} towards crown ethers⁶¹ and nitrogen and sulphur analogues of 12-crown-4.⁶² Alkaline earth metal ions formed mixed complexes, where both an OH group and the crown ether were coordinated to the central metal ion, so that the latter acquires the favoured (+2) oxidation state on charge transfer. The OH ligand presumably arises from preliminary binding of a water molecule. From ligand-exchange experiments where the stabilities of 12-crown-4 complexes and its nitrogen and sulphur analogues were comparatively tested, it turned out that oxygenated 12-crown-4 compounds have the highest affinity for alkali metal ions, whereas cyclen (the nitrogen analogue of 12-crown-4) formed the most stable complexes with Mg^{2+} , Al^{3+} , Ni^{2+} and Cu^{2+} .

Another class of complexation reactions that has been extensively studied in the gas phase is that occurring between crown ethers and (substituted) ammonium ions.⁶⁷⁻⁷² Confirmation of multiple hydro-

gen bonding between host and guest was obtained, as previously observed by Meot-Ner.⁵⁰ The multiplicity of interactions is likely to determine the order of ammonium ion affinity, which increases with increasing number of oxygen donors.⁶⁷ Selectivities, structural factors and interaction energies were investigated by low-^{67,69} and high-energy⁶⁸ CID carried out either on 1:2 sandwich complexes or, more frequently, on 1:1 crown ether–ammonium ion complexes. It was deduced that for the most strongly bound complexes (where multiple hydrogen bonds are present) fragmentation by cleavage of the crown ether skeleton is energetically favoured with respect to the dissociation of the host–guest complex, resulting in fragments that still include the substituted ammonium ion moiety.^{68,69,71} At the other extreme, weakly bound complexes dissociate to form the unfragmented but protonated ligand on the one hand, or the initial (substituted) ammonium ion on the other. For example, 12-crown-4 forms a weakly bound complex with NH_4^+ and, consequently, the complex dissociates simply by releasing the ammonia molecule (Fig. 6(a)), whereas 15-crown-5 and particularly 18-crown-6 forms such a stable complex with ammonium ion that surpassing the high-energy barrier for dissociating the complex also promotes the cleavage of the crown ether skeleton (Fig. 6(b) and (c)). In this way, the CID fragment profile becomes a convenient method to evaluate the nature and strength of the hydrogen-bonding interactions that regulate host–guest affinity.⁷¹ This evaluation method may lead to erroneous conclusions when kinetic factors are predominant in determining the dissociation pathway. In fact, fast homolytic cleavage of covalent bonds may occur more extensively than the slow dissociation of multiple hydrogen bonds, even if the latter process is thermodynamically favoured. The relative influence of thermodynamic and kinetic factors determining the CID of crown ether–alkylammonium ion complexes was investigated in detail using energy-, time- and pressure-resolved collisional activation experiments.⁷¹ These experiments, performed with several different ligands and substituted ammonium ions, revealed a variety of interaction modes, possibly involving functional groups of the guest unconnected with the charge location. Another important conclusion was that a large difference in gas-phase basicities of host and guest weakens the hydrogen bonding between them, resulting in less stable inclusion complexes.

As for alkali metal ions, for ammonium ion complexation it has been debated whether the ligand-exchange technique or the kinetic method better defines the actual order of ammonium ion affinity for a series of ligands.⁷⁰ It was concluded that both methods are consistent with the temperature-dependent equilibrium measurement, which remains the method of choice whenever the reagents are volatile enough that their partial pressures can be accurately controlled. However, the kinetic method might fail when entropic factors become important, while the bracketing technique may provide ambiguous results whenever the gas-phase concentrations of the two ligands are not stable or cannot be estimated correctly.⁷⁰

The ligand-exchange method was skilfully exploited to verify enantioselectivity in host–guest complex-

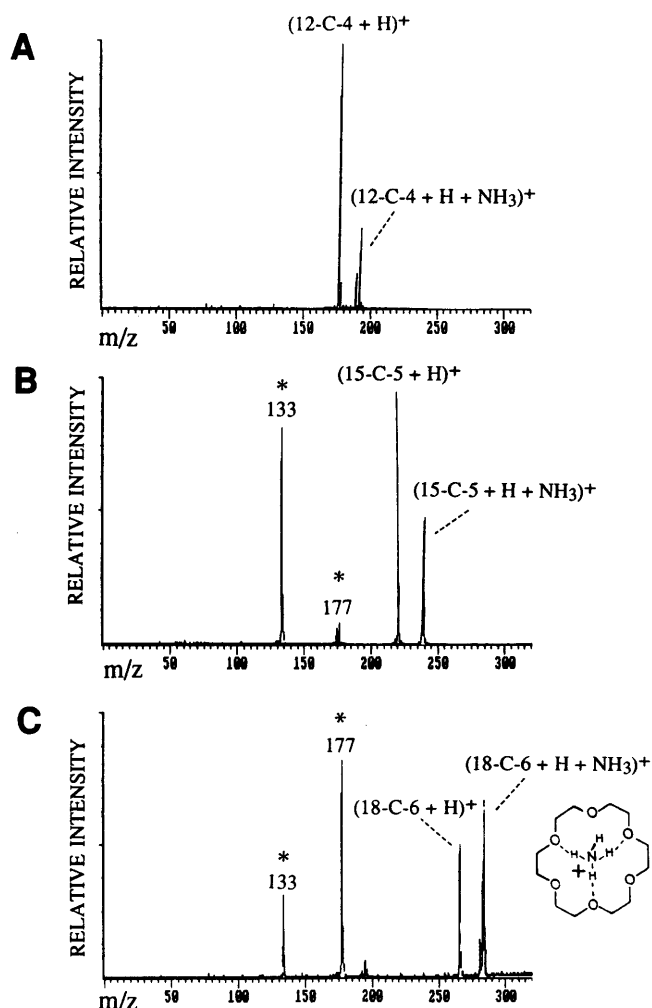


Figure 6. Collision-induced dissociation spectra for the complexes (a) mass spectrum of the isolated $(12\text{-crown-4} + \text{H} + \text{NH}_3)^+$, (b) $(15\text{-crown-5} + \text{H} + \text{NH}_3)^+$ and (c) $(18\text{-crown-6} + \text{H} + \text{NH}_3)^+$ recorded using an ITMS instrument. The peaks labelled with asterisks are crown ether fragment ions. Reprinted by permission of Elsevier Science Inc. from Hydrogen-bonding Interactions in Gas-Phase Polyether/Ammonium Ion Complexes by C.-C. Liou, H.-F. Wu and J. S. Brodbelt, *Journal of the American Society for Mass Spectrometry*, 5, 260. © 1994 by the American Society for Mass Spectrometry.

ation.⁷² The exchange equilibria of two enantiomeric guests, occurring between a chiral crown ether and 18-crown-6 were measured comparatively, yielding an energy difference of $4.2 \pm 0.4 \text{ kJ mol}^{-1}$. This value is close to that measured in a non-polar solvent, but about double that found in methanol, demonstrating that solvation is unfavourable to chiral recognition.⁷²

Complexation of negative ions has also been studied, although much less extensively than for metal and ammonium cations. In general, negative ions are more weakly bound to crown ethers than positive ions, because they possess more basic character. Therefore, they need acidic groups on the ligand in order to be strongly coordinated. For example, chloride, bromide and iodide ions are able to form host–guest complexes with crown ethers in the gas phase, but their binding energy is low ($< 1 \text{ eV} \approx 96 \text{ kJ mol}^{-1}$).⁷³ However, if the basic character of the guest is enhanced, as in the case of fluoride ion, then the host–guest interaction is stronger, especially for the large and highly polarizable crown

ethers and their sulphur analogues. The ability to form complexes with negative ions is considerably enhanced when perfluoro crown ethers are used instead of their hydrogenated analogues. For example, perfluorinated crown ethers,^{74,75} and perfluorinated cryptands⁷⁶ exhibit very strong ligand-fluoride and ligand-O₂⁻ binding interactions.

GAS-PHASE REACTIVITY: OTHER MACRO(POLY)CYCLES

Crown ethers proved to be extremely efficient ligands for acidic guests, such as alkylammonium ions, and in cases where the formation of multiple hydrogen or ion-dipole bonding is possible. However, host-guest chemistry encompasses many applications in biological, organic and analytical research, where either the interaction mechanisms are different from those that are operative for crown ethers, or where much more selective interactions with the possible guests are required in order to achieve highly specific chemical responses. The synthesis of progressively more complicated chemical structures that could fulfil these requirements, particularly towards neutral target guests, has not so far been accompanied by detailed study of the possible host-guest interaction processes in the gas phase. Very few gas-phase studies have been reported that endeavour to elucidate, in a solvent-free environment, the non-covalent interaction mechanisms occurring in the complexes formed by macropolycyclic hosts, such as calixarenes, cryptands, cavitands and carcerands (see Fig. 1). Obviously, the more complicated the ligand, the more difficult it is to single out clearly the specific structural, geometric or electronic elements that promote the chemical reactivity towards particular guests. Just as the understanding of the factors determining crown ether reactivity proved not to be straightforward, so more uncertainty and, possibly, incorrect interpretation is expected for more complicated hosts. However, the synthetic effort necessary to generate the hosts should always be complemented by an equally deep characterization of the reactivities of these hosts, including those exhibited in the gas phase.

A few publications have expanded the study of ligand-metal ion interactions to more unusual hosts than crown ethers, including porphyrins,⁷⁷ cyclotriynes,^{78,79} valinomycin⁸⁰ and calixarenes.⁸¹ All these studies utilized FTICR-MS to synthesize organometallic complexes both in 1:1 and 1:2 (sandwich stoichiometry. High reaction efficiency was always found for 1:1 complexation (about one reactive collision in two or three) and a slightly lower efficiency for further ligand coordination, indicating a high interaction energy. Cyclotriynes proved to react promptly with 22 different cations,⁷⁹ including alkali and first-, second- and third-row transition metal ions. Co²⁺, Ni²⁺ and Cu²⁺ did not form sandwich complexes, possibly because their size was small enough to allow the metal cation to be embedded inside the ligand cavity, preventing the second ligand from interacting. This explanation parallels that given to account for the lack of sandwich complexes between Li⁺ and large crown ethers.⁵⁵

Valinomycin reacts rapidly with alkali metal ions in the gas phase,⁸⁰ particularly with those having high charge density. Ligand transfer from crown ether- and cryptand-alkali metal ion complexes occurs promptly, yielding valinomycin complexes, whereas the reverse reaction is not observed. Since kinetic factors proved not to account for these ligand-exchange results, it was deduced that valinomycin has a much higher intrinsic affinity for alkali metal cations than either crown ethers or cryptands.⁸⁰ These results strongly contrast with solution experiments, where (i) remarkable selectivity toward K⁺ is observed and (ii) crown ether and cryptand complexes are more stable than the corresponding valinomycin complexes. It is worth noting that the cavity of valinomycin is extremely wide, greatly exceeding that required for the 'best-fit' model, but it can be reorganized by multiple intramolecular hydrogen bonding, so that the metal cation can be locked deep inside the large enveloping ligand structure. In agreement with this model, no 1:2 sandwich complexes have been reported. This 'preorganization' of the ligand possibly plays a role in most host-guest complexation, but in this case the noticeable differences between solution and gas phase results are most likely due to solvation effects.⁸⁰ The extensive solvation of valinomycin is unfavourable to the formation of metal ion complexes in the condensed phase, while strong and multiple ion-dipole interactions can be established in the absence of the solvent between the highly polarizable structure of valinomycin and charged guests.

Calixarenes with blocked conformation are ligands with toroidal cone geometry which have two different binding sites. The '*exo*' site is located at the lower (narrower) rim of the ligand and preferentially binds metal cations by its phenolic hydroxyls (see the structure in Fig. 1, where R = H).^{7,8} The '*endo*' site is delimited by four aromatic rings capable of π - π and CH- π interactions with organic guests. FTICR-MS experiments were performed to synthesize calixarene 1:1 complexes with both singly and doubly charged metal cations.⁸¹ For divalent cations, complexation was associated with proton loss from the host, yielding singly charged products. Both *exo* and *endo* sites are likely to be occupied in 1:2 complexes, in which two alkali metal ions are coordinated.⁸¹ The interaction of such calixarenes with organic ammonium ions should, in theory, give rise to ditopic bonding, where the charged nitrogen occupies the *exo* site and the organic moiety of the guest interacts with the aromatic rings of the *endo* site.⁸¹ While crystal structure analysis supports this assumption, more extensive investigation is needed to confirm the occurrence of ditopic binding in the gas phase.

A rapidly expanding area of host-guest chemistry is the synthesis of ligands capable of selectively binding neutral organic molecules. Verification and measurement of host-guest affinities in solution are affected by the contribution of solvation, which on the one hand is necessary to solubilize both reagents, and on the other may prevent the complexation from occurring. Complicating solvent effects are excluded by study these non-covalent interactions in a mass spectrometer, but the interaction products have to be mass analysed and detected as ionic species, which obviously have a differ-

ent electronic configuration than the corresponding neutral-neutral complexes. Since the donor-acceptor properties of both host and guest stem directly from their electronic configuration, considerable risk exists that the experimental findings derived from MS data are not applicable to solution chemistry. The limitation is critical in that multiple yet weak interactions (π - π , CH- π , dipole-dipole, etc.) are likely to be responsible for complex formation and the nature of these interactions can be radically modified by the presence of a positive or negative charge. For example, a weak dipole-dipole interaction can be replaced by a much stronger ion-dipole interaction.

Despite the cited and unavoidable limitations, mass spectrometric investigations on the interactions between

large and structurally organized hosts and non-polar organic guests have been undertaken since 1990.⁸² Extensive formation of complexes between small organic molecules and stabilized macrocyclic hosts was observed for cavitands,⁸²⁻⁸⁴ carcerands,^{37,85} tightly bridged calixarenes^{86,87} (Fig. 1) and cryptophanes,⁸⁸ but not for simple⁸⁹ and loosely bridged⁸⁷ calixarenes. The inability of simple calixarenes to form inclusion complexes with neutral organic species is not surprising. In fact, the formation of such complexes in the gas phase is rare and represents an exception rather than the rule, although the widespread custom of publishing only positive and not negative results, tends to support the opposite impression. During our own investigations, the ability to form inclusion complexes with neutral

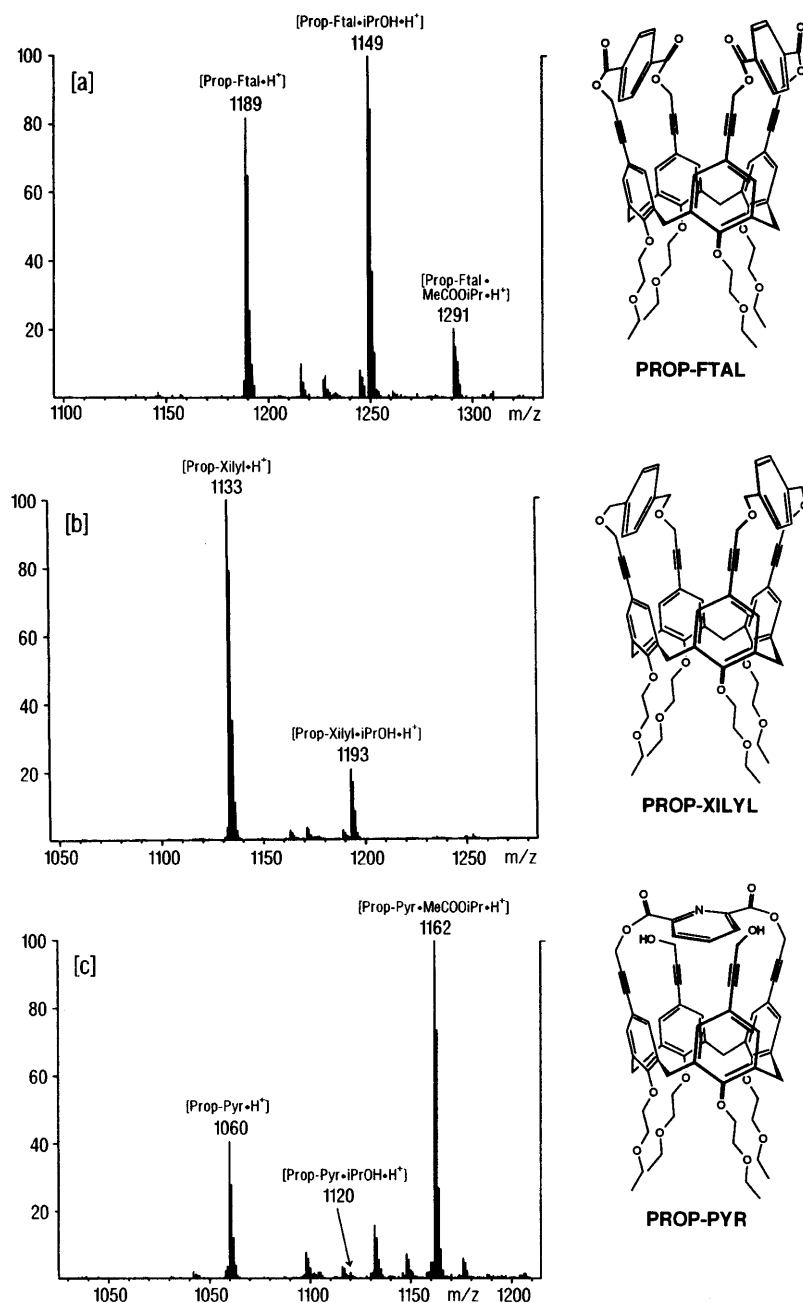


Figure 7. Host-guest complexation processes during DCI-MS experiments performed by using three different bridged calixarene hosts, but identical candidate guests and conditions. The reagent gas was formed by an equimolar mixture of propan-2-ol and isopropyl acetate in an excess of methane. The ion source was maintained at low temperature (about 50 °C). (a) Prop-Ftal; (b) Prop-Xilyl; (c) Prop-Pyr.

guests was tested for almost 100 macropolycyclic hosts, with different structures, geometries and substituents, and only a few of them yielded complexes.⁹⁰ Particularly striking is the case of upper-rim bridged calixarenes, where small structural or geometrical differences in the bridge produced dramatic variations in their affinity toward neutral guests.^{86,87} For example, in Fig. 7(a), Prop-Ftal proves to undergo extensive complexation with propan-2-ol and, to a smaller extent, also with isopropyl acetate, under chemical ionization (CI) conditions. In contrast, Prop-Xilyl, which is structurally similar to Prop-Ftal except for the substitution of four CO and CH₂ groups, only forms a complex with propan-2-ol and then in low abundance (Fig. 7(b)). The bridged chemical structure proved also to affect the host selectivity toward either acetates or alcohols. In fact, Prop-Pyr selectively forms a complex with isopropyl acetate, while the corresponding complex with propan-2-ol is barely visible in the DCI mass spectrum (Fig. 7(c)), unlike Prop-Ftal, which form a more stable complex with propan-2-ol than with isopropyl acetate (Fig. 7(a)). Some of these reactivity differences were

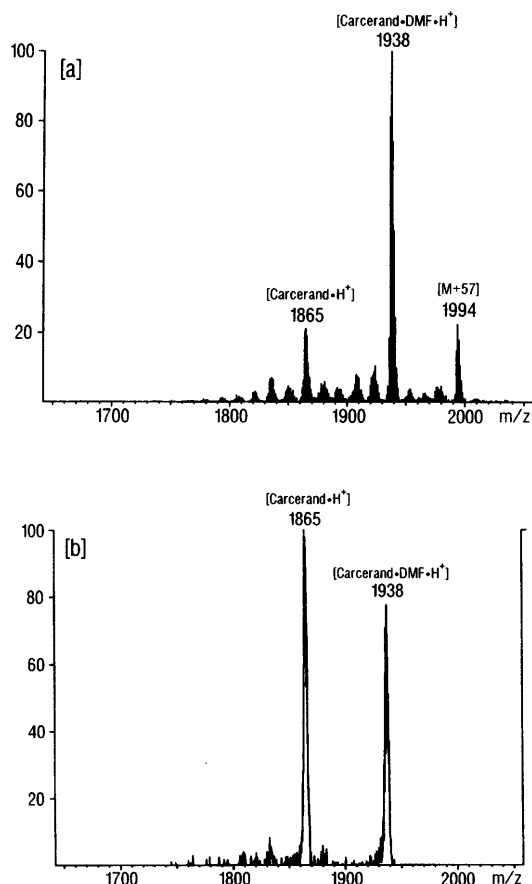


Figure 8. (a) Positive-ion DCI mass spectrum of the inclusion complex formed by the carcerand depicted in Fig. 1, where A = B = C = D = —CH₂SCH₂— and R = *n*-C₅H₁₁, and by dimethylformamide (DMF) as the guest. Isobutane was used as the reagent gas at a pressure of 30 Pa. The ion-source temperature was kept at 50 °C. The ion at *m/z* 1994 is the adduct formed by attachment of the *tert*-butyl ion (from isobutane) to the carceplex. (b) Collision-induced dissociation fragment ion spectrum of the parent ion at *m/z* 1938 arising from the preceding experiment. Loss of the guest was activated by multiple collisions with argon atoms (pressure 0.2 Pa) at 1.6 eV centre-of-mass kinetic energy in the octopole collision cell of a hybrid BEQ mass spectrometer.

attributed to the relative rigidity of the hosts. From preliminary experiments with these calixarenes and from data obtained with several other classes of ligands, it was deduced that the presence of a rigid, well defined three-dimensional cavity, with portals of constant size, is essential for forming stable inclusion complexes with neutral molecules in the gas phase.^{87,88} This conclusion contrasts with the results obtained for crown ether–alkylammonium ion complexes, where a flexible structure enabled the host to adopt the most favourable conformation for binding the guest.⁷² While maximization of hydrogen bonding accounts for the latter results, the rigidity requirements for three-dimensional hosts interacting with neutral organics are possibly associated with the need to deactivate the vibrational modes that can overcome the weak attractive forces in the complex, leading to its dissociation. In any case, many more in-depth investigations on bridged calixarene complexes need to be carried out to confirm these concepts.

The host–guest complexation mechanism was studied in more detail for some cavitands (see structure in Fig. 1) interacting with aliphatic and aromatic neutral guests.^{82–84} As for bridged calixarenes (see above), most of the experiments entailed vaporization of the free host from a DCI probe within the ion source in an atmosphere containing two candidate guests in known relative abundance and an excess of a CI reagent gas (generally methane) that proved to be inert towards the host. The relative affinity of the cavitand for the two guests was evaluated from the relative abundance of the corresponding charged complexes in the mass spectrum. For similar guest pressures, the absolute affinity was roughly given by the relative abundance of the complex with respect to the free host. Although the cross-section for ion–molecule reactions is generally much higher than that for neutral–neutral processes, the specific nature of host–guest interactions, together with the observation of close similarities between positive- and negative-ion spectra, supported the idea that neutral complexes could be formed in the ion source, and later ionized. From experiments in which the ion residence time in the reaction chamber was varied, and from results of ion–molecule reactions conducted in the octopole collision cell of a tandem mass spectrometer, it was deduced, however, that the interaction of the charged cavitand with the neutral guest is the process occurring with the highest probability, although neutral–neutral interactions may contribute significantly under specific conditions.⁸⁴ The mechanism of complexation of the charged guest by the neutral host is possible only for guests with extremely high proton (positive ions) or electron (negative ions) affinity.

Further conclusions gathered from the gas-phase studies of cavitands, calixarenes and cryptophanes were the following: (i) the vaporized host was stabilized by multiple collisions with the CI reagent gas, present at high pressure, and so acquired the thermal energy imparted by the ion-source temperature; (ii) the extent of neutral guest complexation depended strongly on the reaction chamber temperature, demonstrating the existence of a dynamic equilibrium between the formation and the dissociation of the complexes; (iii) the reacting system reached a condition of thermodynamic equilibrium before the products were mass analysed and

detected. Although the complexation kinetics could not be measured, as a time-resolved mass spectrometer was not available, the reaction efficiency is expected to be considerably lower than that of such ligands as crown ethers, since the steric restraints are much more severe. However, the forward and reverse reactions should be fast enough to allow thermodynamic equilibrium to be reached, at least in the case when the steric constraints are not too great. In this connection, the last interesting feature of the gas-phase reactivity of all these classes of organic ligands was that considerably larger molecular guests could be hosted in the cavity than those observed in solution reactions, yielding host-guest complexes that cannot be formed in the condensed phase. This differential effect is particularly evident for hosts having either a small cavity or a small portal, such as the smallest cryptophanes⁸⁸ and the most tightly bound bridged calixarenes.⁸⁷ Several reasons can account for this behaviour and more detailed study has to be carried out to understand which contribution is most important. The first reason fixes on to the transition state of the host-guest complex. If both reactants are partly solvated in the transition state preceding complexation, the steric hindrance for the guest to access the cavity must be considerably enhanced with respect to the pure geometric requirements. Only these geometric requirements are likely to influence the gas-phase processes. An alternative explanation for the differences between solution- and gas-phase chemistry is that vibrational modes that are active in the gas phase, but not in solution, may allow the large guests to pass even through narrow host portals. This mechanism has already been observed for the reverse reaction, namely complex dissociation. In fact, the release of imprisoned guests from closed-shell carcerands was induced by collisional activation in a

tandem mass spectrometric experiment even at low collision energies.²⁵ Figure 8(a) reports the DCI mass spectrum of the carceplex formed by inclusion of a dimethylformamide solvent molecule during the synthesis of the host. In Fig. 8(b), the carceplex molecular ion extensively releases the guest on collisional activation at moderate collision energy, while no fragmentation of the carcerand skeleton is observed. This dissociation is possibly induced by activating the vibrational modes which allow the guest to escape through enlarged pores. Besides the portals, the cavity itself could be subjected to a 'compression' by the action of the solvent on the vibrational modes of the host.

Wilkins and co-workers⁸⁵ provided a different explanation for the laser photoactivated dissociation of carcerand complexes. In the photodissociation mass spectra they observed that some fragment ions have lost one bridge unit from the host, by cleavage of two covalent bonds, but the guest is intact and remains associated with the fragmented host cavity (Fig. 9). It was deduced that ring opening was a necessary but not sufficient condition for the guest release. The high abundance of unfragmented free host in the spectra can be justified by assuming that this species has only one dissociated bond in the ring, not two, so that a portal is opened in the cavity (allowing guest escape) without fragmentation. The same hypothesis could account for the variations in the relative abundance of the complex *vs.* free carcerand ions in the laser desorption mass spectra. The small dimethyl sulphoxide guest was more extensively retained than the larger dimethylformamide and dimethylacetamide. It was supposed that larger guests could facilitate ring opening through release of steric strain.⁸⁵ In any case, spontaneous dissociation of the stabilized carcerand complexes does not occur,^{25,85}

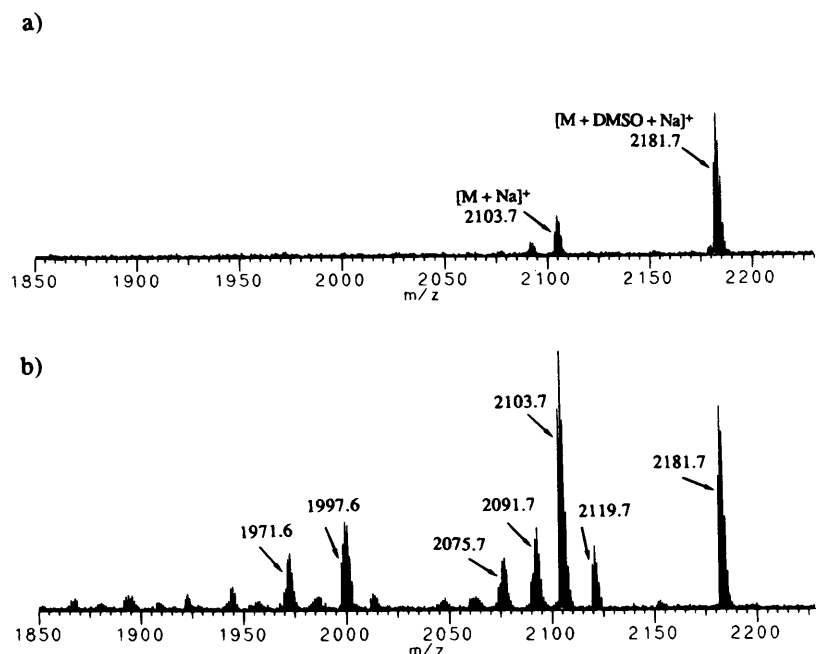


Figure 9. Photodissociation of the inclusion complex formed from dimethyl sulphoxide (DMSO) and the carcerand depicted in Fig. 1, where $A = B = C = D = -OCH_2O-$ and $R = -CH_2CH_2C_6H_5$: (a) CO_2 laser desorption, eject all ions with $m/z < 2090$; (b) same as (a) followed by 308 nm excimer laser photodissociation and measurement of the resulting photodissociation mass spectrum. Spectra (a) and (b) are plotted with the same absolute abundance scale. Reprinted with permission from the *Journal of the American Chemical Society*, **114**, 5748 (1992) by L. M. Nuwaysir, J. A. Castoro, C. L.-C. Yang and C. L. Wilkins. © 1992 American Chemical Society.

because the portals are too small to allow guest egress. A completely different situation was observed for hemicarcerands, where either one or two portals are present. For these hosts, both gas-phase complex formation and dissociation are facile,⁸⁵ as for cavitands, and depend on the internal energy of the host and on the guest partial pressure.

ENERGETICS

Determining the interaction energy between hosts and guests in the gas phase is particularly important because these thermodynamic quantities are then measured without the contribution of the solvation energy, which is always present in solution measurements and cannot be evaluated separately with sufficient accuracy. Therefore, gas-phase measurements reflect uniquely the intrinsic affinity between the host and the guest. However, a number of requirements have to be fulfilled in order to achieve reasonable estimations of these quantities. It must be ascertained that the isolated reacting species and products are not vibrationally excited, when their relative abundances are measured. This thermal stabilization is easily achieved in high-pressure mass spectrometers^{50,52} and under CI conditions in both conventional⁸³ and ion-trap⁷¹ mass spectrometers, where the reagents and complexes experience hundreds of collisions with the CI buffer gas. A different situation is found in FTICR-MS experiments, which require low-pressure conditions. In this case, the isolated ions are allowed to stabilize radiatively,⁵⁵ by emission of infrared photons, before letting them interact with a selected neutral reagent. In all of these experiments, thermal stabilization does not represent a problem and is easily achieved. The second condition that has to be satisfied in order to determine the thermodynamic complexation constants accurately is to measure the vapour pressures of the reagents. This requirement is extremely difficult to fulfil, especially for the involatile hosts, which easily condense before reaching the measuring device. Meot-Ner^{49,50} and Kebarle and co-workers^{51,52} prepared mixtures of the reagent in known composition within a heated chamber and let them flow at controlled flow-rates together with a carrier gas into the ion source. Alternatively, the pressures of more volatile hosts and guests can be determined with calibrated ionization gauges and using known ion-molecule reaction rate constants.⁵⁵ These approaches are not possible for highly involatile hosts (such as cavitands) and guests (such as metals). In these cases, it is convenient to perform competitive reactions, where either two different hosts or guests are involved, and to measure their relative pressures. Relative thermodynamic parameters are obtained thereby (for example, the relative complexation constants), not the absolute values. Both the 'kinetic' method and the 'bracketing' technique typically provide estimates of relative ion affinities for involatile molecule.^{70,55} If the absolute guest affinity is known for a specific host, then this host-guest system can be used as a reference for attributing an absolute value to the other reactive systems. Relative pressure measurements for volatile materials can be made either by using an ion gauge calibrated for each gaseous substance or by inde-

pendent analysis of the gas-phase composition (e.g. headspace gas chromatography⁸³). For involatile materials, the relative pressures can be obtained from the relative rates of highly efficient ion-molecule reactions,⁷² such as proton transfer, or from comparisons of the total electron ionization ion current *vs.* nominal ion gauge reading.⁵⁵

Meot-Ner⁵⁰ determined the absolute thermodynamic complexation constants for four different alkylammonium ions interacting with crown ethers. On changing the reaction chamber temperature, the variations of these complexation constants were reported in van't Hoff plots, yielding the absolute dissociation enthalpy ΔH and entropy ΔS for each host-guest interaction. The ΔH values ranged from about 125 kJ mol⁻¹ up to 192 kJ mol⁻¹, indicating the existence of multiple hydrogen bonding. The contribution of multiple bonding to the dissociation enthalpy was estimated to be 50–88 kJ mol⁻¹. Very similar instrumentation was utilized by Sharma and Kebarle⁵² to determine enthalpy, entropy and free energy changes for the reaction of crown ethers with H₃O⁺ and CH₃OH₂⁺ ions. Extremely large exothermicities (ΔH up to -368 kJ mol⁻¹) and entropy losses (ΔS up to -56 eu) were recorded, especially for the interactions between large crown ethers and H₃O⁺. The large ΔH value was attributed to multiple hydrogen bonding between counterparts of similar proton affinity, while the large entropy loss was ascribed to the considerable stiffening of soft puckering vibrations that are allowed in the free crown ether. Even the least favourable among these host-guest complexations (i.e. 12-crown-4 interacting with CH₃OH₂⁺) produced enthalpy changes as high as -243 kJ mol⁻¹ and entropy losses exceeding 40 eu.

Ligand-exchange reactions allowed Dearden and co-workers⁵⁵ to determine the free energy change for transfer of alkali metal cations from 18-crown-6 to 21-crown-7. For all the metal ions the transfer proved thermodynamically favourable with energy changes ranging from 3 to over 16 kJ mol⁻¹ (for Cs⁺), demonstrating that complexation by larger crowns is favourable even for the alkali metal cations with the smallest ionic radius (e.g. Li⁺). Other quantitative estimations of the relative reactivities for various metal ions were obtained by converting the rate constant for each 1:1 complexation into the corresponding reaction efficiency.^{55,79}

Large sets of low-energy CID experiments, where laser-desorbed alkali metal ion-crown ether complexes were dissociated in an FTICR mass spectrometer at different centre-of-mass kinetic energies were exploited to obtain the appearance energies for the dissociated metal ions.⁵⁷ These values were corrected by the estimated internal energies of the complexes, yielding approximate evaluations of the absolute interaction energies between hosts and guests. For 18-crown-6 these interaction energies ranged from 134 to 167 kJ mol⁻¹.

A different way to utilize CID data to estimate roughly the interaction energy in crown ether-ammonium ion complexes was to compare the relative abundance of intact protonated crown ether and/or substituted ammonium ions with that of fragments arising from covalent bond cleavage of the crown ether skeleton,^{69,71} as previously discussed (Fig. 6). The fundamental postulate is that, in strongly bound complex-

es, going beyond the high activation barrier for dissociation would release highly excited host ions, which in turn can decompose by skeletal fragmentation. From these data and from appearance energies in energy-resolved breakdown graphs, it was deduced that the strongly bound complexes must have interaction energies of at least 58–146 kJ mol⁻¹.

STRUCTURAL EFFECTS

The formation of stable host–guest complexes generally requires multiple attractive interactions between specific functional groups of the host and the guest, in the form of partial charge transfer, dipole interactions, van der Waals forces, etc. Both electronic and geometric complementarity between these functional groups is needed in order to achieve a strong interaction. Any change in the structure of the reagents modifies both their electronic and geometric properties, resulting in a change in their relative affinity. Electronic effects associated with the introduction of either electron-donating or electron-withdrawing substituents have obvious consequences on the binding facility of convergent ligands. Also, the influence of the relative proton affinity between host and guest on the strength of hydrogen bonds has been presented in the preceding sections and will not be discussed further.

Much more subtle and often elusive are the geometric requirements for host–guest complexation, since the gas-phase structures of the reagents are not known precisely. Macroscopic elements that have been discussed in the foregoing sections include the size of crown ether rings and the rigidity of bridged calixarene cavities. More difficult to understand, even for the relatively simple crown ether structures, is the three-dimensional arrangement of the binding groups responsible for complexation and the fluctuating equilibrium between optimum interaction geometry and steric constraints. Among these complex structural effects, the most extensively considered and analysed is the so-called ‘macro-cyclic effect’. This term refers to the higher selectivity and higher binding capacity exhibited by cyclic ligands with respect to the corresponding acyclic ligands.

The macrocyclic effect, first observed in solution,⁵ has proved to be even more prominent in gas-phase experiments. Higher rate constants, reaction efficiencies and kinetic selectivities are observed for crown ethers interacting with metal ions than for the corresponding polyglyme ligands. For example, in a typical case the relative reaction efficiencies are different by a factor of four.⁵⁵ Also, a larger dependence on the guest charge density was observed for crown ethers, although the polarizabilities of cyclic and acyclic ligands were approximately the same. These effects were attributed to the ‘preorganization’ of the crown cavity, which is associated with a more favourable initial configurational entropy. In other words, a lower entropy loss is endured by the already constrained cyclic ligand than by the flexible acyclic polyglyme during complexation.^{55,67} The formation of 1:2 sandwich complexes in comparative experiments also exhibited considerable macrocyclic effects, which made the crown ether complexes interact more readily and with higher selectivity

than the corresponding polyglyme complexes.⁵⁵ Besides entropic factors, the latter effect is possibly due to a different geometric arrangement of the ligands in 1:1 complexes. Unlike crown ethers, acyclic polyethers are likely to surround the guest extensively by assuming a three-dimensional configuration, which sterically obstructs the channels by which a second ligand could approach the complex. The distinct binding properties between cyclic and acyclic ligands is also evidenced by differences in the CID fragment ion spectra of their corresponding substituted ammonium ion complexes.⁷¹ The difference in entropy loss consequent to complex formation by either a cyclic or acyclic ligand was quantitatively measured by Meot-Ner,⁵⁰ revealing large negative entropies in the latter case. The difference in entropy loss adds up to 37 J mol⁻¹ K⁻¹ for 12-crown-4 *vs.* triglyme.

A major structural effect was observed by comparing the relative reactivities of two cavitand hosts (see Fig. 1) towards a variety of neutral target guests. In the same reaction experiment, two candidate guests were allowed to interact competitively with both cavitands introduced simultaneously into the ion source to ensure identical reaction conditions. The cavitand depicted in Fig. 1 (whose structure is open and accessible only on one face) proved to bind the aromatic guests selectively.^{82,83} By eliminating one quinoxaline ring from the cavitand structure, a new host (the second cavitand) is obtained containing two phenolic hydroxyls capable of hydrogen bonding. This new cavitand exhibited drastically different properties from its precursor and proved to form complexes with aliphatic amines and alcohols fairly selectively.⁸³ The dramatic affinity differences exhibited by the two cavitands, together with the extremely high selectivity toward long-chain aliphatic alcohols (and acetates) with respect to the short-chain analogues, demonstrated the occurrence of ditopic binding on the second cavitand structure. For example, butan-1-ol formed stable complexes by interacting with both the phenolic hydroxyls of the cavitand (hydrogen bonding) and the facing quinoxaline ring (CH– π interaction), whereas ethanol could not undergo complexation with the same cavitand because its short chain length precluded its simultaneous interaction with both binding sites.⁸³

CONCLUSIONS

The cases just presented in the preceding section are just two examples of structural effects, which in general are intrinsic to the concepts of molecular recognition and host–guest chemistry themselves. In fact, no molecular recognition phenomena could be conceived without recalling the need for structurally complementary reactants. In application-oriented research, the design of new host molecules is formulated while keeping in mind the structural requirements necessary to achieve selective complexation of some individual target guests (i.e. pollutants, drugs, explosives, noble metals, etc.), that can be either detected, transported, extracted or removed. A variety of different tools are utilized in host–guest structural studies, including theoretical calculations, model binding, computer graphics

simulation and progressive expertise hatching. For this purpose, model compounds are synthesized and tested. Gas-phase reactivity characterization is one of the most promising characterization methods, since pure one-to-one interaction is achieved, without the intervention of third-body mediators. Thus, gas-phase processes should in theory reveal the underlying causes of host-guest recognition. However, to achieve such a key role, continuous and systematic research work has to be accomplished, where the gas-phase binding properties of the most important classes of macrocyclic ligands are com-

pared and rationalized, and connected with their geometric structure, their conformational dynamics and the nature and location of their binding sites. If this methodical investigation of the principles and energetics regulating host-guest interactions are to be pursued by mass spectrometric methods, and if mass spectrometric investigations are to precede, not follow, solution experiments and become a reference for them, then mass spectrometry will have secured a pre-eminent position in host-guest chemistry.

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