HETEROCYCLES IN ENCAPSULATION AND ASSEMBLY

(self-assembly/molecular recognition/hydrogen bonding/encapsulation)

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Abstract - Described is the behavior of self-assembled capsules held together by hydrogen bonds. The capsules can be spherical or cylindrical and they reversibly encapsulate suitable guest species in organic solvents. Selectivity to molecular shape and length leads to well-defined complexes of two different guests within the capsule. These lead to their use as catalysts and to the synthesis of multiparticle assemblies. The use of charged guest species for assembly characterization in the gas phase is also described.

INTRODUCTION

Covalent molecule within molecule complexes were introduced by Cram[1] and Collet[2] more than a decade ago and have provided physical organic chemistry with opportunities to stabilize reactive intermediates[3] and observe new forms of stereoisomerism.[4] Hydrogen bonded capsules are newer versions of molecule within molecule complexes. These are formed reversibly and exist for timescales of milliseconds to hours, long enough to effect molecular motions and even reactions of encapsulated species. Capsules large enough to accommodate two or more different molecules are rare as they require cavities of nanoscale dimensions. They permit the exploration of pairwise interactions of molecules isolated from the bulk solution. Here I review four recent developments using such systems in the context of heterocyclic chemistry.

PAIRWISE SELECTION OF GUESTS

The first construct (**1**) (Figure 1) is closely related to Cram's velcrands and demonstrates the enormous effects that seemingly passive methyl groups exert on assembly. The synthesis follows that published earlier with the appropriate changes.[5] The velcrands feature kite-like

shapes that expose large surface areas to solvents. The kite-like shapes are, in turn, favored over other conformations by alkyl groups on the resorcinol rings. Because they also bear methyl groups on the imide nitrogens, the velcrands have no donors for intermolecular hydrogen bonding. Instead, they form dimeric structures featuring face-to-face aryl stacking interactions that minimize their exterior surface areas. Removal of these 8 methyls has two predictable consequences: an alternative vase-like conformation is favored and a self-complementary set of hydrogen bonding sites is exposed on the insides. Consequently, a different dimerization mode can occur to give the large cylindrical capsule (**1•1**). The capsule features dimensions ~ 1.0 x 1.8 nm and is one of the longest self-assembled dimers made to date. The dimer is stabilized by a seam of eight, bifurcated intermolecular hydrogen bonds, with the imide hydrogens of one molecule directed between two carbonyl oxygens of the other.

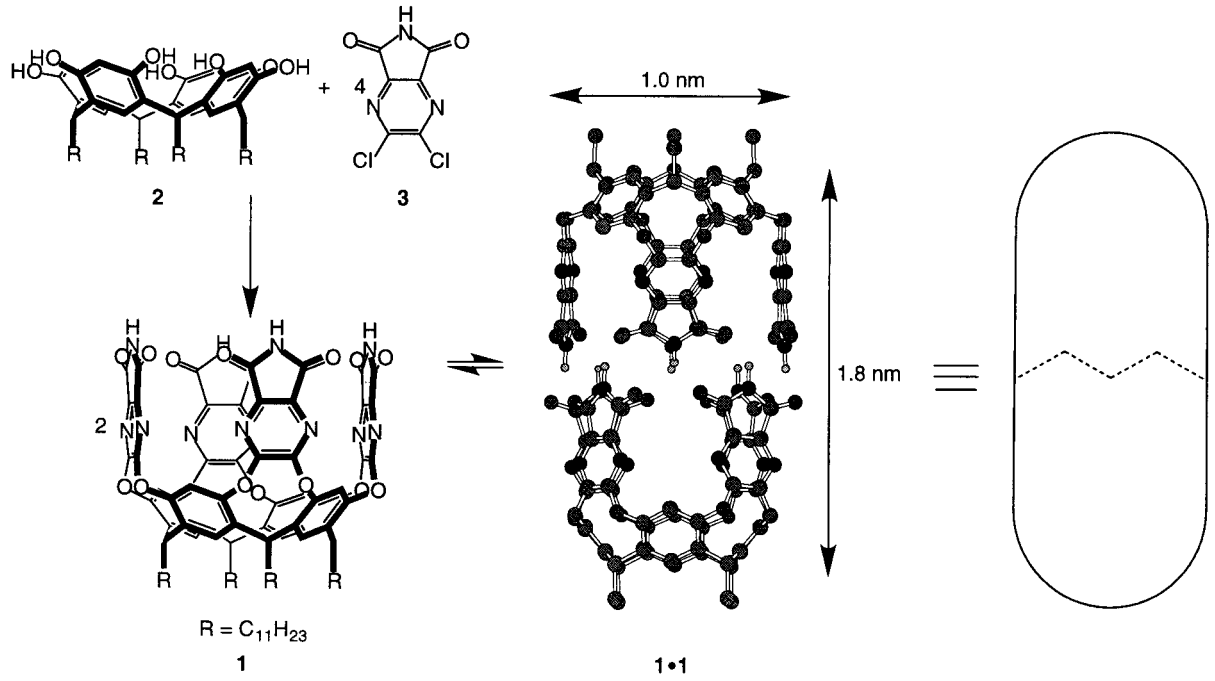


Figure 1

As expected for the assembly of (**1.1**) through hydrogen bonding, its NMR spectra featured N-H signals far downfield in noncompetitive solvents such as $CDCl_3$, benzene-d_6, toluene-d_8 or mesitylene-d_{12}.[6] We found that the addition of suitable guests, such as bibenzyl (**2**), terphenyl (**3**), or dicyclohexylcarbodiimide (**4**) (Figure 2) in mesitylene-d_{12} as solvent, resulted in encapsulation. Specifically, a second set of signals for the guests appeared, and the upfield shifts are characteristic of encapsulated species; integration of these signals established the 1:1 stochiometry of the dimeric host-guest assembly. The encapsulation of unsymmetrical guests (e.g. the amide (**5**) in Figure 2), showed the effect of molecular length on rotational freedom and the symmetry of the complex. The NMR spectrum of the complex showed a doubling of the

capsule's signals: the two ends are different. The guest can spin along the axis of the capsule but is too large to "tumble" and exchange the environments of the two ends on the NMR timescale. This type of restricted motion lies at the heart of the new form of stereoisomerism discovered by Reinhoudt[4] in carceplexes.

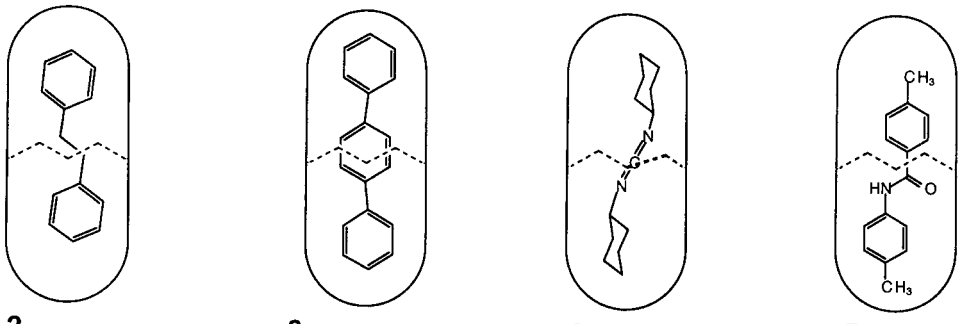


Figure 2

Molecular modelling[7] suggested that two benzene (**6**) or two toluene (**7**) or two *p*-xylene (**8**) molecules can easily be accommodated inside the capsule, and such proved to be the case (Figure 3). Toluene can tumble within the capsule, but the aromatic signals of the xylenes become nonequivalent. Xylene is too long to tumble rapidly enough on the NMR timescale. This peculiar desymmetrization had earlier been observed by Sherman in unsymmetrical hydrogen-bonded capsules containing pyrazine.[8]

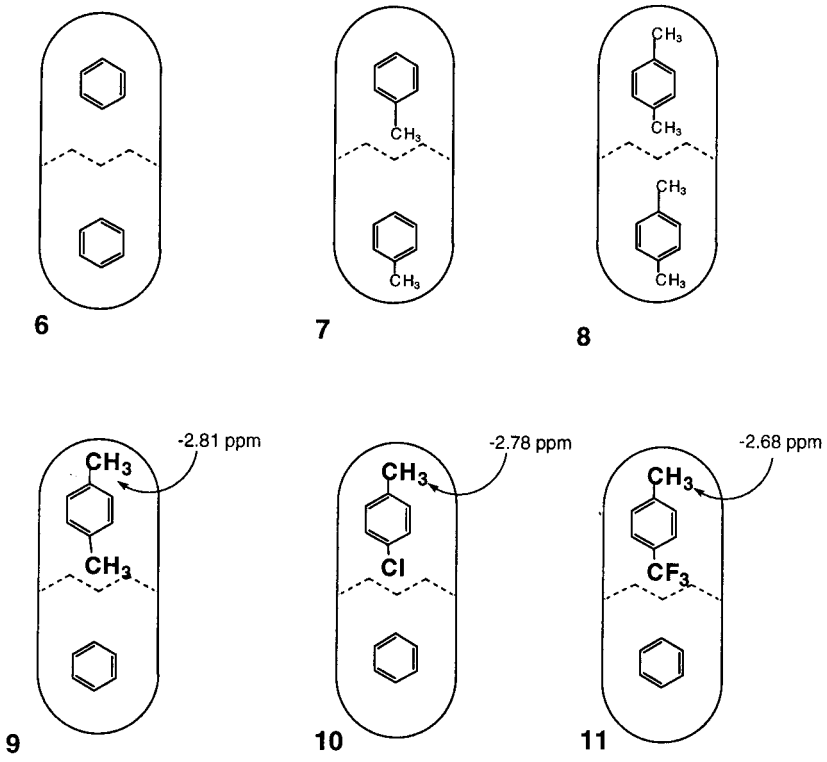
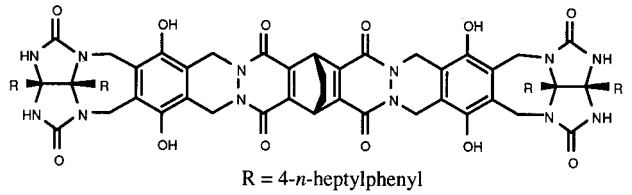


Figure 3

The pairwise selectivity of the capsule was explored through direct competition experiments involving two solvents. When both benzene and *p*-xylene were added in a 1:1 ratio to a mesitylene-d_{12} solution of (**1**), the unsymmetrically filled capsule was observed almost exclusively! (Figure 3). One benzene and one xylene molecule were found inside (**9**). Apparently, a comfortable occupancy is reached with one of each guest in the capsule, in a behavior that is, to our knowledge, unprecedented (Figure 2). Benzene also paired with *p*-trifluorotoluene (**10**) and *p*-chlorotoluene (**11**) to give new species with one of each guest inside. This selectivity appears to involve matching the overall length of two guests with the dimensions of the capsule. These results suggest using the capsules as selective reaction chambers for bimolecular processes.

CATALYSIS OF A DIELS-ALDER REACTION

Earlier work had established that the multiring structure (**12**) (Figure 4) exists as an hydrogen bonded dimer (**12•12**) , a notional "softball" in organic solvents.[1] (The peripheral R groups of (**12**) have been removed in the energy-minimized structure of the dimer (**12•12**). Unusual thermodynamics[9] were observed for species encapsulated within it and even kinetic behavior - the acceleration of a Diels-Alder reaction[10] – was evident. A **catalytic** application has now been found in this context.



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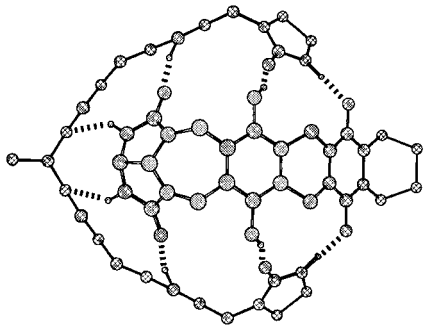
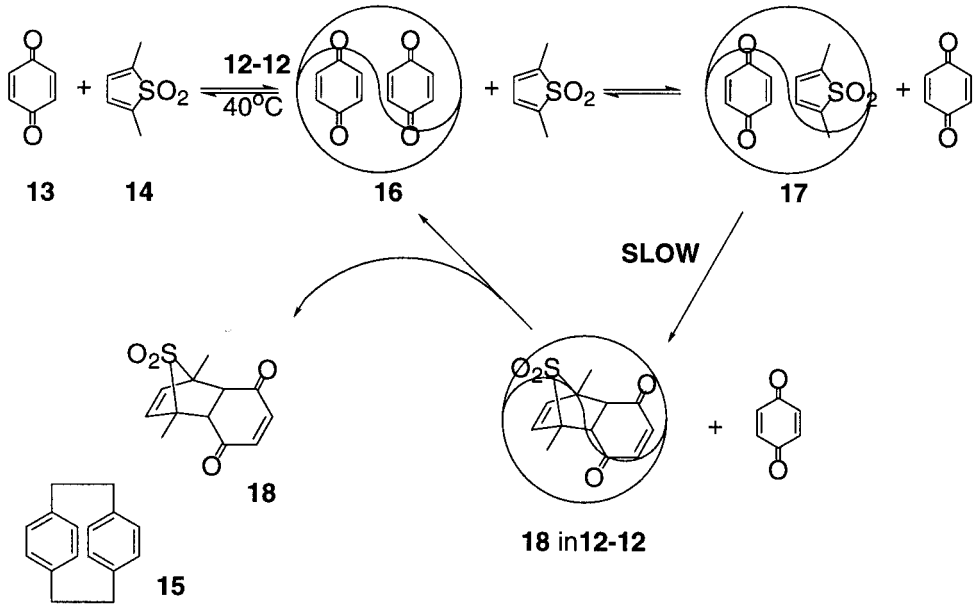


12-12

Figure 4

The Diels-Alder reaction is that of *p*-benzoquinone (**13**) with the thiophene dioxide derivative (**14**) (Scheme 1) in *p*-xylene-d_{10}. The release of the product from (**18**) follows pseudo first order kinetics over more than two half-lives (there is no product inhibition). That true catalysis takes place is shown by turnover: over 7 times as much adduct as softball is obtained after 4 days. Furthermore, the excellent guest [2,2]paracyclophane (**15**) competes with the reaction components for encapsulation and inhibits the reaction. The rate enhancement is only 10-fold and is calculated by comparing the half-life for the background reaction at these concentrations with that of the reaction inside the softball.[11]

We had expected that the loss of SO_2 from the adduct would force turnover in the same way that Hilvert's system forced turnover in catalysis by antibodies.[12] The softball catalyzes the reaction for quite different reasons: The initial adduct is an unwelcome guest and it is driven out of the cavity by *p*-benzoquinone. This permits the completion of the catalytic cycle as proposed in Scheme 1.



Scheme 1

The resting state of the capsule contains two quinones.[16] When one quinone is occasionally displaced by the thiophene dioxide, a "Michaelis" complex (**17**) is generated. A moderately enhanced cycloaddition ensues, followed by displacement of the adduct (**18**) from the softball by two molecules of *p*-benzoquinone. The exchange of the encapsulated species in and out of the softball is fast compared to the chemical step, and turnover occurs.

The catalysis is admittedly modest and many better ways of catalyzing Diels-Alder reactions exist;[13] Even so, the use of molecular capsules as catalytic reaction chambers has taken its first step.

ASSEMBLY WITH FOUR IDENTICAL COMPONENTS

Assembly expresses information written in a molecular structure and structure (**19**) (Figure 5) has a wealth of information: the presence of both hydrogen bond donors and acceptors, the curvature imparted by the seven-membered ring adjacent to the glycoluril ring system, and the paired acidic sites (the sulfamide N-H's) available to basic sites (the glycoluril carbonyl oxygens). These features predict a head-to-tail arrangement of four subunits in a macrocycle such as $(\mathbf{19})_4$, in which all of the hydrogen bond donors find their complements to create a closed-shell surface.

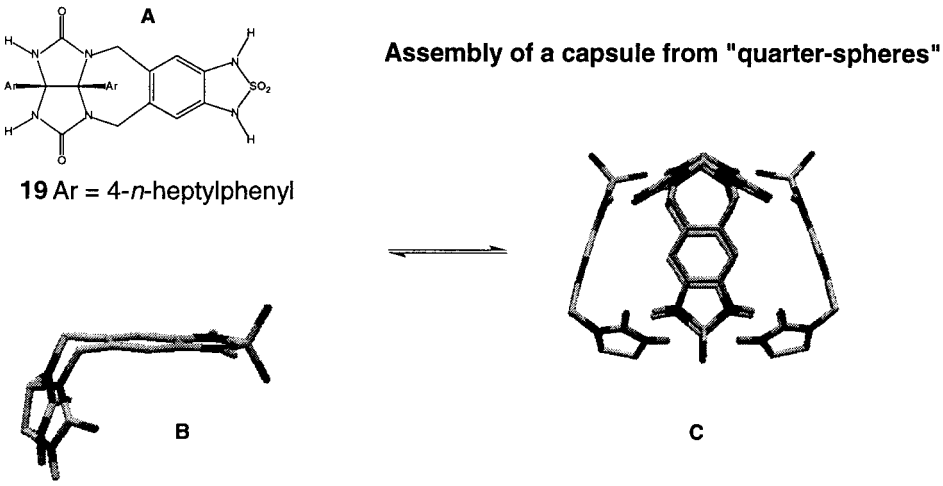


Figure 5

The synthesis of **19** was reported elsewhere.[14] The product is nearly insoluble in CD_2Cl_2 but the addition of adamantane derivatives (**20**) through (**24**) (Figure 6) to suspensions of compound (**19**) caused the solid to dissolve. The ^1H NMR data show the N-H resonances for the sulfamide and the glycoluril shifted downfield, the signals are sharp and concentration independent, and new signals for encapsulated adamantane are evident, widely separated from those of free adamantane. The exchange of guests in and out of the capsule is slow on the NMR timescale, but fast on the human timescale. The stoichiometry shows 4 molecules of compound (**19**) per adamantane. The origins of the intermolecular forces, e.g., the weak van der Waals interactions

that hold the guests in the highly ordered system are not well understood, and it is unlikely that such weak forces alone overcome the entropic problem of bringing five molecules together.

Figure 6

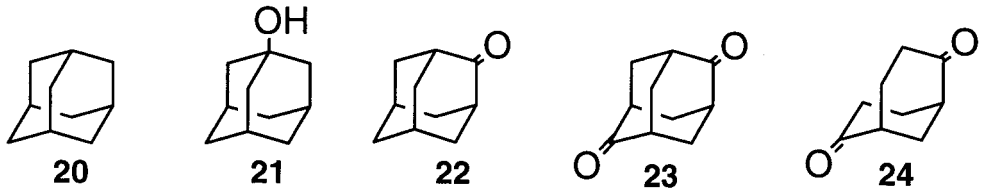


Table 1. Apparent association constants K_a(app), stoichiometries and free energies of formation (ΔG^0) in CD_2Cl_2 at 295 K for the encapsulation of adamantane guests in the tetramer $(\mathbf{19})_4$.

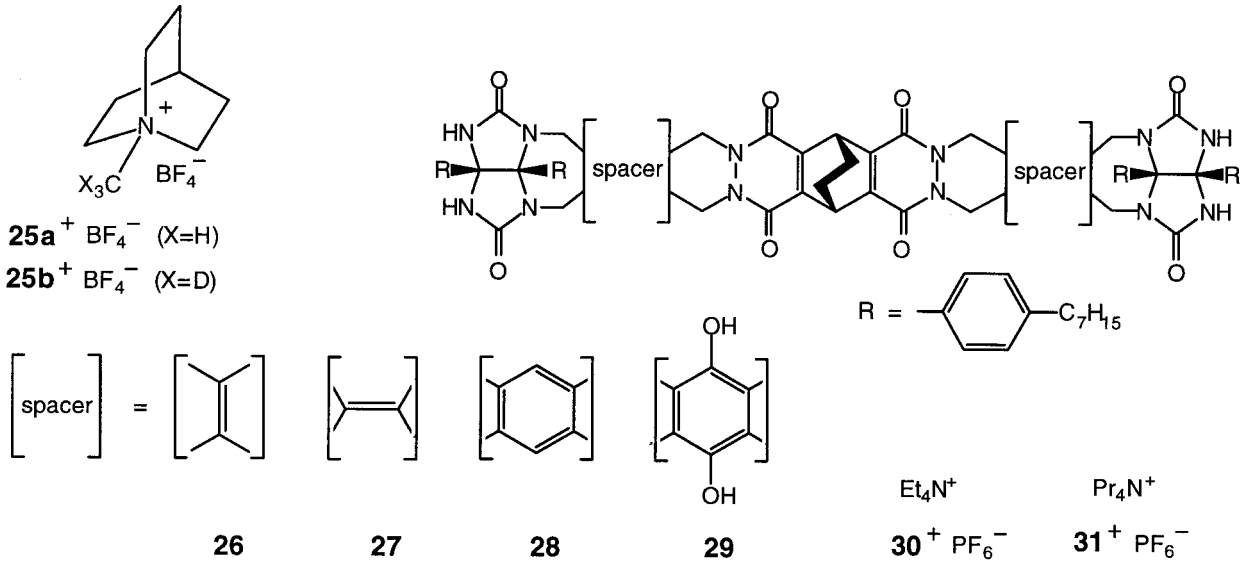
Guest	Stoichiometry*	K_a (M^{-1})**	$-\Delta G^0$ (kcal mol^{-1})
20	1	19 [b]	1.7
21	1.1	48 [b]	2.3
22	1	160 [b]	3.0
23	1	3200 [c]	4.7
24	—[a]	37 [b]	2.1

As shown in Table 1, guests which can further stabilize the tetrameric assembly through hydrogen bonding, such as adamantane-2,6-dione (**24**) are excellent, but the best guest offered both cation-π interactions and charge dipole interactions: it is > 100 times better bound that a neutral guest of comparable size and shape. This was the quinuclidinium species (**25**) (Figure 7) and this molecule has found much use in characterizing our assemblies in the gas phase, a subject to which we now turn.

MASS SPECTROMETRIC CHARACTERIZATION USING CHARGED GUESTS

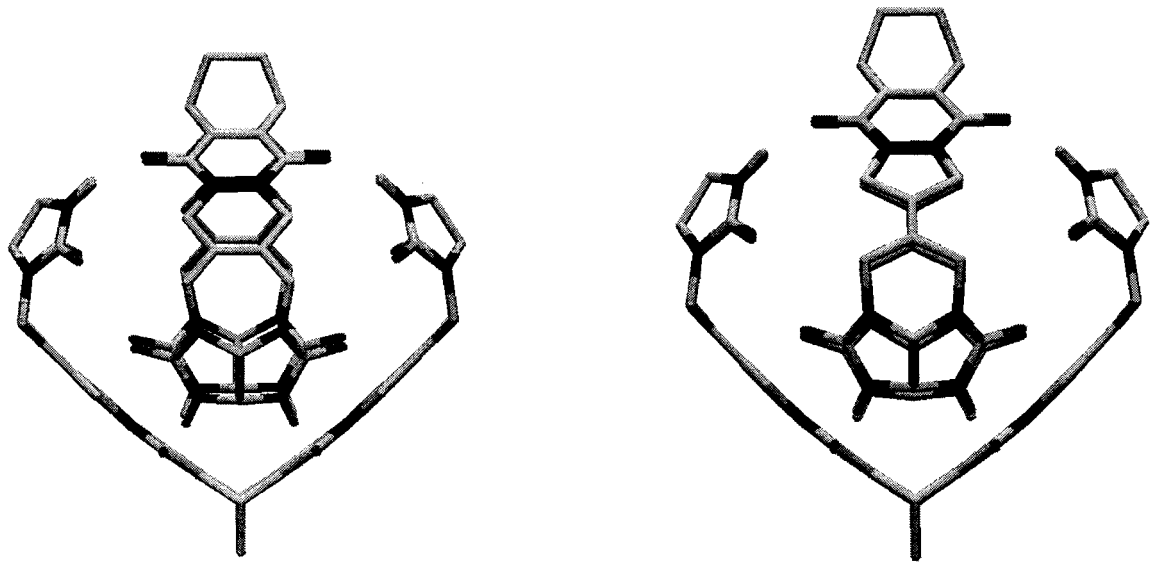
Extensive NMR studies have revealed details about the encapsulation process in solution, but the detection of our complexes by mass spectrometry had until recently been disappointing. The ion labeling methods such as attaching crown ether-Na^+ complexes,[15] metal ions[16] or anions[17] have proven useful in characterizing aggregates without guest species,[18] but are not applicable to our capsules. Rather, we use charged guests directly to characterize capsules of various sizes in the gas phase.

Figure 7

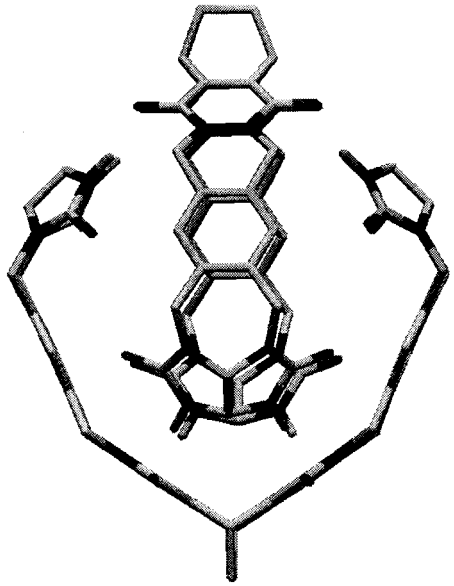


The spectra were obtained by electrospray ionization[19] of chloroform solutions of **25a**$^{+}BF_4$ and samples of the softballs (**26-29**) (Their line formulas are given in Figure 7 and their energy-minimized structures are shown in Figure 8).

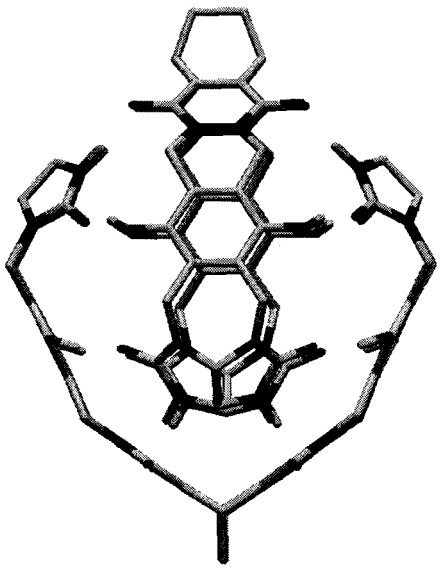
Figure 8



26•26 **27•27**



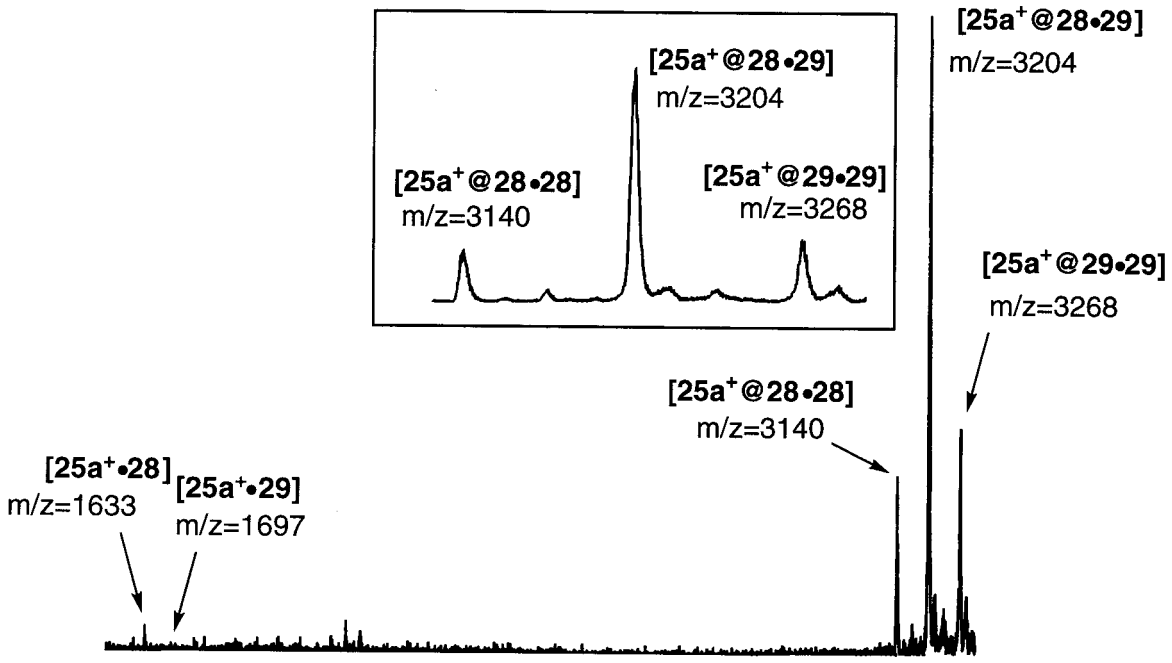
28•28



29•29

The *m/z* ratios of the base peaks correspond to **25a** attached to the homodimers (**26•26**) through **29•29**. The elemental compositions of these ions were confirmed by the analysis of the isotope patterns, which are calculated from natural isotope abundances. Further, mass shifts of $\Delta m = 3$ upon use of $[D_3]$-labeled $\mathbf{25b}^+$ in the capsules clearly indicate that the ions consist of two softball monomers and one guest cation.[20]

Figure 9



The observation of heterodimers by NMR has also been used as a criterion for the formation of capsule assemblies,[21] and indeed, the ESI ms spectrum of an equimolar mixture of **28** and **29** with $\mathbf{25a}^+$ shows a presence of a heterodimer [$\mathbf{25a}^+$@**28•29**] (Figure 9).

The relative intensity of the heterodimer is clearly larger than expected from a statistical 1:2:1 pattern of **[25a$^+$@28•28] : [25a$^+$@28•29] : [25a$^+$@29•29]**. Interactions of a charged species with the inherent dipole of the heterodimer may favor these capsules in the gas phase.
Control experiments with non-assembling (S-shaped) isomers and other related molecules (known from previous studies not to form capsules) failed to give signals in the ESI ms spectra. Competition experiments with **28** and the guests (**30**$^+$) and (**31**$^+$), which offer only non-specific binding showed that both **25a**$^+$ and **30**$^+$ are guests of the softball (**28•28**), but **31** fails in this regard. The implication is of selectivity: the ions require molecular recognition between host molecule and guest rather than mere charge.

The encapsulation of cations in the gas phase provides a method of characterization which is independent from and complementary to NMR studies in solution. The ESI results are far more sensitive for the detection of these complexes since encapsulation of **25a**$^+$ could be detected by NMR only for **27•27** and **29•29** in chloroform solution. For our neutral complexes, only rarely[22] have they been observed in the ESI spectra.[23]

In conclusion, heterocyclic compounds offer the moderately acidic and basic sites which lead to their assembly through hydrogen bonding. The capsules emerge through coupling the heterocycles with carbocyclic frameworks that provide the curvature. The seemingly limitless combinations are likely to hold our attention for some time.

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REFERENCES

1. For relevant behavior of covalently-bound molecule-within molecule capsules see R.C. Helgeson, K. Paek, C.B. Knobler, E.B. Maverick, and D.J. Cram, *J. Am. Chem. Soc.*, 1996, **118**, 5590.
2. A. Collet, J.P. Dutasta, B. Lozach, and J. Canceill, 'Topics in Current Chemistry, 165: Chemistry I-Directed Synthesis and Molecular Recognition,' ed. by E. Weber, Springer Verlag, Berlin, 1993, pp. 104.

3. For related processes that occur in covalently bound hosts see: D.J. Cram, M.E. Tanner, and R. Thomas, *Angew. Chem., Int. Int. Ed. Engl.*, 1991, **30**, 1024; R. Warmuth, *Chem. Commun.*, 1998, **59**.

4. P. Timmerman, W. Verboom, F.C.J.M. van Veggel, W.P. van Hoorn, and D.N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1994 **33**, 1292.

5. L.M. Tunstad, J.A. Tucker, E. Dalcanale, J. Weiser, J.A. Bryant, J.C. Sherman, R.C. Helgeson, C.B. Knobler, and D.J. Cram, *J. Org. Chem.*, 1989, **54**, 1305; D.J. Cram, H-J. Choi, J.A. Bryant, and C.B. Knobler, *J. Am. Chem. Soc.*, 1992, **114**, 7748; J.R. Moran, J.L. Ericson, E. Dalcanale, J.A. Bryant, C.B. Knobler, and D.J. Cram, *J. Am. Chem. Soc.*, 1991, **113**, 5707.

6. T. Heinz and D.M. Rudkevich, *Nature*, 1998, **394**, 764.

7. F. Mohamadi, N. G. Richards, W. C. Guida, R. Liskamp, C. Caufield, G. Chang, T. Hendrickson, and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440; D. Q. McDonald and W. C. Still, *Tetrahedron Lett.*, 1992, **33**, 7743.

8. R.G. Chapman and J.C. Sherman, *J. Am. Chem. Soc.*, 1995, **117**, 9081.

9. J. Kang and J. Rebek, Jr., *Nature*, 1996, **382**, 239.

10. J. Kang and J. Rebek, Jr., *Nature*, 1997, **385**, 50.

11. J. Kang, G. Hilmersson, J. Santamaría, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 3650.

12. D. Hilvert, K.W. Hill, and M.T.M. Auditor, *J. Am. Chem. Soc.*, 1989, **111**, 9261.

13. For cycloaddition inside a cucurbituril see: W.L. Mock, T.A. Irra, J.P. Wepsiec, and M. Adhya, *J. Org. Chem.*, 1989, **54**, 5302.

14. T. Martin, U. Obst, and J. Rebek, Jr., *Science*, 1998, **281**, 1842.

15. K. C. Russell, E. Leize, A. Van Dorsselaer, and J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 209.

16. K.A. Jolliffe, M.C. Calama, R. Fokkens, N.M.M. Nibbering, P. Timmerman, and D.N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1247.

17. X. Cheng, Q. Gao, R.D. Smith, E.E. Simanek, M. Mammen, and G.M. Whitesides, *J. Org. Chem.*, 1996, **61**, 2204.

18. For reviews of MS applications in supramolecular chemistry see: M. Vicenti, E. Pelizzetti, E. Dalcanale, and P. Soncini, *Pure Appl. Chem.*, 1993, **65**, 1507; M. Vicenti, C. Minero, E. Pelizzetti, A. Secchi, and E. Dalcanale, *Pure Appl. Chem.*, 1995, **67**, 1075; M. Vicenti, *J. Mass Spectrom.*, 1995, **30**, 925; M. Przybylski and M.O. Glocker, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 806.

19. *Electrospray Ionization Mass Spectrometry*, R.B. Cole, Ed., Wiley, New York, 1997.

20. C.A. Schalley, T. Martin, U. Obst, and J. Rebek, Jr., "Characterization of Encapsulation complexes in the Gas Phase and Solution", *J. Am. Chem. Soc.*, 1999, in press.

21. O. Mogck, V. Böhmer, and W. Vogt, *Tetrahedron*, 1996, **52**, 8489; J.M. Rivera, T. Martin, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 819.
22. R.K. Castellano, D.M. Rudkevich, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1996, **118**, 10002.
23. J.C. Ma and D.A. Dougherty, *Chem. Rev.*, 1997, **97**, 1303; J.B. Fenn, M. Mann, C.K. Meng, S.F. Wong, and C.M. Whitehouse, *Mass Spectrom. Rev.*, 1990, **9**, 37; P. Kebarle and L. Tang, *Anal. Chem.*, 1993, **65**, 972A; S.J. Gaskell, *J. Mass Spectrom.*, 1997, **32**, 677.

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