6.7 Covalent Cavities: Carcerands and Hemicarcerands

Jasat, A. and Sherman, J.C., 'Carceplexes and Hemicarceplexes', *Chem. Rev.*, 1999, **99**, 931–967.

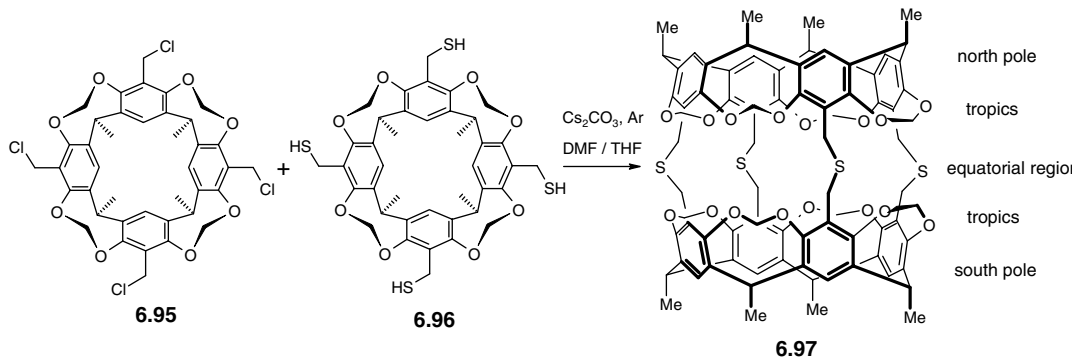
6.7.1 Definitions and Synthesis

A *carcerand* is defined as a closed molecular container or capsule without portals of significant size through which guests can either enter or leave (from the Latin *carcer* meaning 'prison'). Guest molecules within a carcerand are therefore permanently trapped or 'incarcerated' within the internal volume, unless covalent bond breakage within the host occurs. A carcerand that contains a guest giving an incarcerated host–guest complex is termed a *carceplex*. Given this definition, it is necessary also to employ another term, *hemicarcerand*, which describes closed molecular containers from which guests *can* enter and exit with a measurable activation barrier. In the presence of guest species, hemicarcerands form *hemicarceplexes*. Good examples of hemicarcerands are the cryptophanes (Section 6.6), which are able to reversibly entrap relatively small guests such as methane, haloalkanes *etc*. Much of the interest in this kind of three-dimensional inclusion chemistry stems from the possibility of stabilisation of reactive species within the host cavity, drug delivery and intracavity catalysis. All of these applications require the hemicarcerands' ability to (selectively) bind and expel guest species in response to external conditions. Carcerands themselves are not capable of these kinds of applications, although uses in the field of molecular electronics, sensing and molecular devices might be envisaged.

While the cryptophanes are highly successful hosts for binding single molecules, their overall cavity volume (80–90 $Å^3$) is too small to bind simultaneously two guest species in order to admit the possibility of intracavity reactivity and catalysis. Work by Cram *et al*.[68] has focused upon the larger [4]resorcarenes related to **6.3**. Adopting a similar strategy to cryptophane synthesis, Cram was able to couple the upper rims of two resorcarene bowls **6.95** and **6.96** under high-dilution conditions to give a pseudo-spherical cavity-containing capsule (**6.97**, Scheme 6.18).

Carcerand **6.97** was designed by Cram's group, just as they had designed the spherands, with the aid of CPK molecular models. In his Nobel Prize address, writing just two years after the preparation of **6.97**, Cram describes his interest in the host–guest chemistry of this new capsule:

> *The first question to be answered was: what guest compound would be trapped inside during the shell closure? This question is akin to asking whether two soup bowls closed rim-to-rim under the surface of a kettle of stew would net any stew. The answer was that* ***[6.97]*** *'contained' essentially every kind of component of the medium present during ring closure.*[10]



6.95 **6.96** **6.97**

Scheme 6.18 Synthesis of the first carcerand.[68]

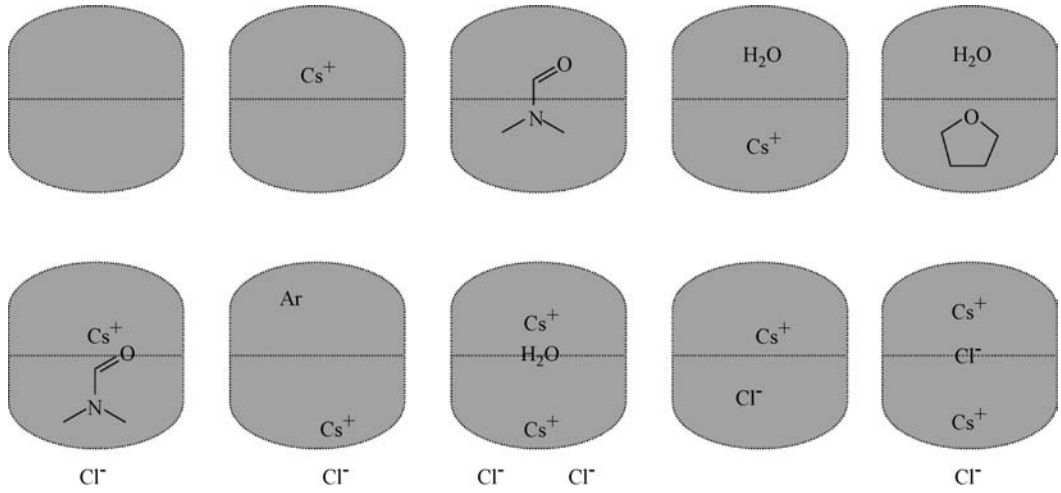
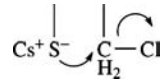


Figure 6.47 Carceplexes formed in the preparation of **6.97** (denoted by grey oval).

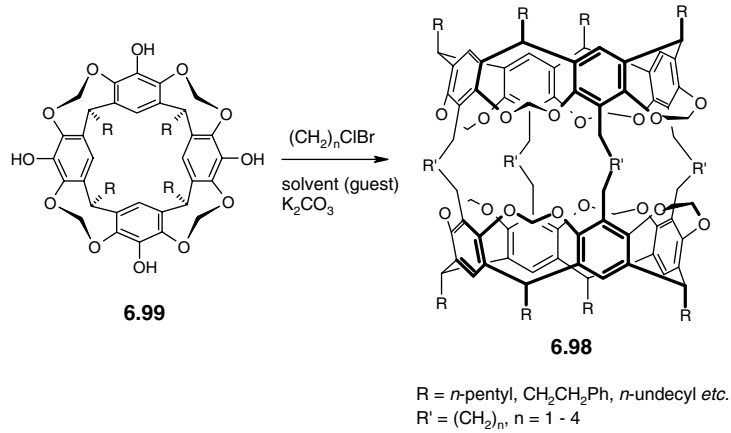
The reaction product from Scheme 6.18 proved to be extremely insoluble in all solvents, and as a result its characterisation was a painstaking procedure. Impurities and unreacted starting materials were extracted by treatment of the product mixture with the most powerful solvents of every type (polar, non-polar, hydrogen bonding, dipolar aprotic *etc.*). The remaining product (various carceplexes – *i.e.* host–guest complexes – of **6.97**) was analysed by elemental analysis for the elements C, H, S, O, N, Cl and Cs, all of which proved to present in varying amounts, the ratio between Cs and Cl being stoichiometric. A solid-state infrared spectrum revealed the presence of the reaction solvent, dimethyl formamide, from observation of the characteristic C=O band. Analysis of the mixture by mass spectrometry (fast-atom bombardment) revealed the presence of all of the carceplexes shown in Figure 6.47. No peaks were found at molecular masses higher than the heaviest carceplex, and no other peaks were observed. Clearly, once ring closure occurs any species present in the inner region of the forming carcerand are completely unable to escape, even argon gas!

Cram's group found that careful drying of the hydrated complexes followed by reflux in D_2O results in the substantial replacement of the incarcerated water by the deuterated analogue, suggesting that the portals on the sides of the carcerand are large enough to permit the diffusion of small molecules such as water through the cavity walls, although it is possible that even this process involves exchange of D^+ for H^+ ions. The elemental analysis data indicated that about five per cent of the mixture consisted of the free carcerand, 60 per cent encapsulated Cs^+, 45 per cent contained Me_2NCHO, 15 per cent THF and only one to two per cent Cl^-. This distribution is consistent with the affinity of calix[4]arene type molecules for Cs^+ (Section 3.14) and suggests that formation of **6.97** involves an S_N2 linear transition state in which the Cs^+ is coordinated to the sulfur (Equation 6.3).



(6.3)

The problems with carcerand solubility were soon overcome by exchange of the methyl 'feet' for a range of groups such as *n*-pentyl, *n*-undecyl, 2-phenyl ethyl *etc.* to give carceplexes soluble in organic solvents with solvent molecule guests, in yields as high as 32 per cent. Related compounds with acetal bridges (OCH_2O) between the hemispheres such as **6.98**, have been prepared from CH_2Br_2 and tetrol **6.99** (Scheme 6.19). Use of longer alkyl chains up to $(CH_2)_4$ results in elongated capsules whose bridges



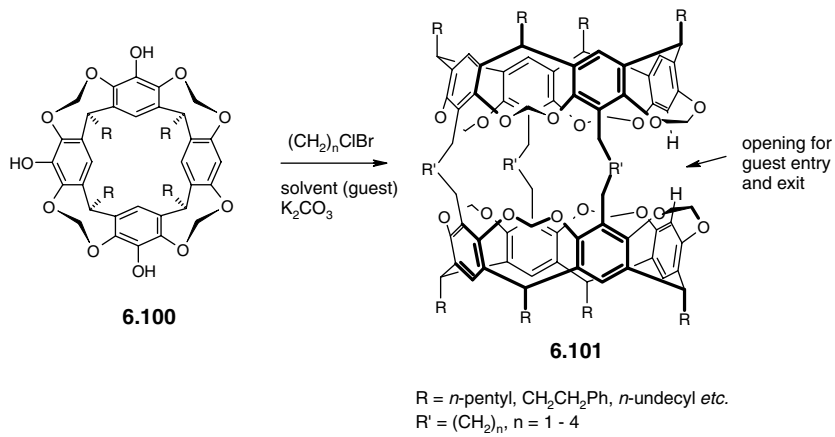
6.99 **6.98**

Scheme 6.19 Preparation of $(CH_2)_n$-bridged carcerands and hemicarcerands from tetrol **6.99**.

are flexible enough to allow the passage of some small guest species under forcing conditions, forming hemicarceplexes. The rigidifying acetal spacers at the upper rim of each bowl (termed the 'tropical' regions by analogy with planetary geography) may also be altered to OCH_2CH_2O groups, giving a wider, shallower curvature to each hemisphere. All of these multiple ring-closure steps involve the simultaneous assembly of seven molecules (including the guest), yet despite this carcerand **6.98** is formed in up to an amazing 87 per cent yield.

Even in the presence of $(CH_2)_4$ bridges, however, complexes **6.98** are still reluctant to allow passage of guest molecules in and out of their cavities. As a result, true hemicarceplexes active for host–guest chemistry involving multiple guest exchange and intracavity reactivity have a specific portal engineered into one side of the compound. Thus, reaction of the triol **6.100** with dihalides $X(CH_2)_nX$ gives the triply bridged hemicarceplex **6.101**, which has one distinct open portal, allowing ready guest access (Scheme 6.20).

Since the preparation of **6.97**, an enormous range of carcerand and hemicarcerand species have been prepared based upon both [n]resorcarenes and calix[n]arenes (n = 4,5), all of which exhibit interesting binding behaviour and intra-cavity reactivity, as we will see in the next sections.



6.100 **6.101**

Scheme 6.20 Reaction of a resorcarene triol with dihaloalkanes to give a hemicarcerand with a portal for guest exchange.