Journal of the Iranian Chemical Society, Vol. 1, No. 1, September 2004, pp. 10-19.

JOURNAL OF THE
Iranian
Chemical Society

Conical Cavitands as Second Coordination Spheres and Protecting Environments. Towards Metal-Centred, Intra-Cavity Reactions

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(Received 16 November2003, Accepted 23 December 2003)

Metallocavitands are coordination compounds based on rigidified molecular cavities which possess at least one entry. Those in which the metal centre is rigidly held above the entrance are particularly promising for the study of host-guest interactions between metal-bonded substrates and the internal part of a cavity. Such systems also open the way to highly selective *intra-cavity* reactions. The present review focusses on conical cavities derived from calixarenes and cyclodextrins and examines their possible use as second coordination sphere ligands.

Keywords: Metallocavitands, Calixarenes, Cyclodextrins, Supramolecular catalysis

INTRODUCTION

The synthesis of selective molecular receptors is frequently based upon the rigidification of simpler precursor molecules [1-3]. In a chemical sense, "rigidification" implies the restriction of internal rotations, the freedom to vibrate always defining a limit to the degree of rigidity ultimately achievable. When the internal rotations of a molecule have been largely, if not completely, inhibited, the shape of the molecule may be considered fixed and if this shape is such as to define a three-dimensional cavity sufficiently large to allow both entry and egress of another chemical species (guest), the molecule may be termed a "cavitand". Though this term was first defined in relation to derivatives of the particular polyhydroxy calixarenes derived from resorcinol [4] ("resorcinarenes") and other polyphenols, it is one which might well be applied to a much wider variety of macrocycle derivatives, being both more succinct and more restrictive than the term "container molecules" [5] (which covers encapsulating species). In this variety, many different modes for the introduction of rigidity are possible and many different forms of interaction associated with cavity binding may arise.

Thus, not only resorcinarenes [6,7], but also cyclodextrins [8], urils [9,10] and numerous cyclophanes [11] (including but not limited to calixarenes [12]) can be considered as cavitand precursors and indeed, in some cases, as cavitands themselves. Potentially, this adds much to the subtlety that can be envisaged in cavitand construction and function, an important issue, since it is well known that while extensive rigidification may lead to very high selectivity, this may be associated with extreme kinetic inertness, making the cavitand ill-suited to such applications in catalysis as are discussed in the present article [13]. Thus, the importance of rigidity of a cavitand when used as the binding unit for a metallocatalyst is at least twofold. Firstly, it may engender control of the spatial disposition of the donor atoms to which a metal may be bound and thus can induce selectivity in this binding. This does not necessarily mean that any groups pendent to the donor atoms (and thus to the cavitand) must be rigid, though there may be balance to be struck between the influence of such pendent groups upon the stereochemistry of the catalytic process and their influence upon the rates of substrate entry and product egress from the active site. Secondly, if a reaction substrate is to be included in the

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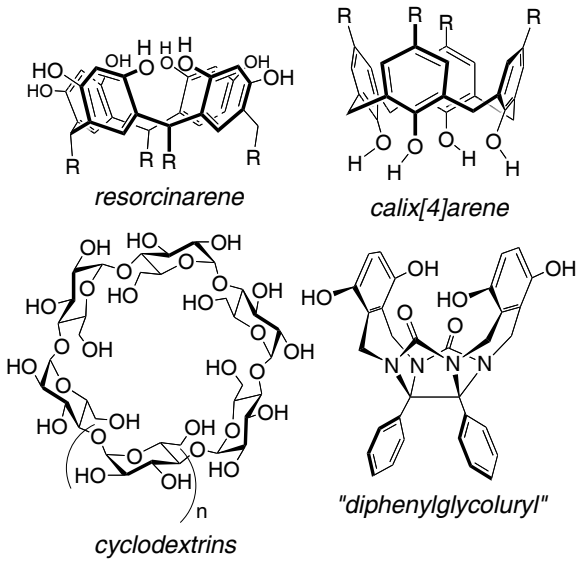
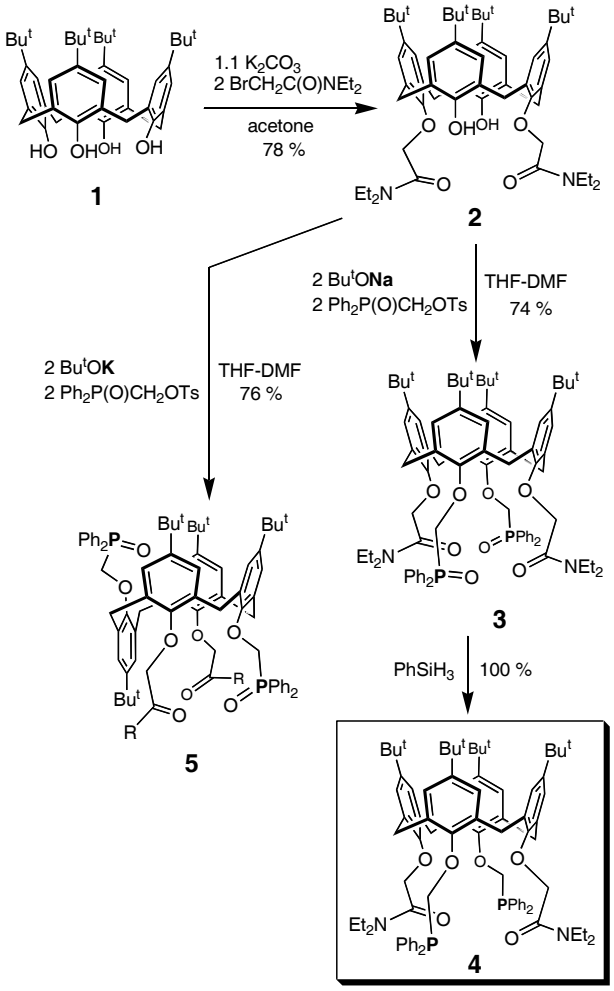


Fig. 1. Most employed procavitands.

molecular cavity through weak and labile interactions, a precisely defined size and shape may be essential in ensuring that the interaction is either "all" or "nothing" for different substrates. Obviously, however, the chemical nature of the cavity walls is another important factor to be considered here, in regard both to substrate binding and perhaps more importantly, the way in which inclusion modifies substrate reactivity. The following discussion is an attempt to consider these issues in relation to several transition metal based systems (metallo-cavitands) known at present which may be considered "cavitand catalysts". The analysis itself has close parallels to that of metalloenzyme behaviour, since metals bound to active sites in enzymes are rather frequently found within clefts in the protein structure, and indeed the motivation for many studies of cavitand behaviour has been to find a model for various biological systems.

A great variety of molecules suitable for cavitand formation has become available over the past twenty years (Fig. 1). Most, though certainly not all of these molecules are macrocyclic and it is certainly rare to find a cavity which may be regarded as of uniform cross section. The molecules to which the term cavitand was first applied have a form rather commonly observed in which one end of the cavity is narrower than the other, and this raises various possibilities in regard to metal binding to give a catalyst. Binding to the narrow end to give a "stopper" to the cavity (perhaps



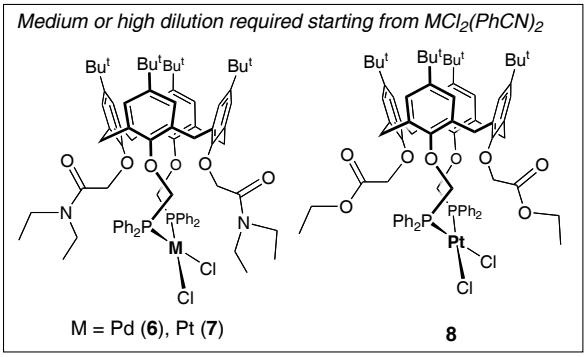
Scheme 1. Synthesis of diphosphine **4**.

being important in rigidification), for example, may allow another ligand to be drawn in through the wide end of the cavity to bind to the metal ion but, if only one coordination site is available, this would require that a substrate to react with the bound ligand would have to be included in the cavity through another mechanism [14]. In contrast, binding of a metal to the edge of the wide entry might more readily allow binding of two species (destined for reaction) in such a way that both would enter the cavity without the action of inclusion forces being crucial for that alone. In studies of functionalised cyclodextrins and calixarenes, we have in fact discovered systems which are illustrative of both these possibilities.

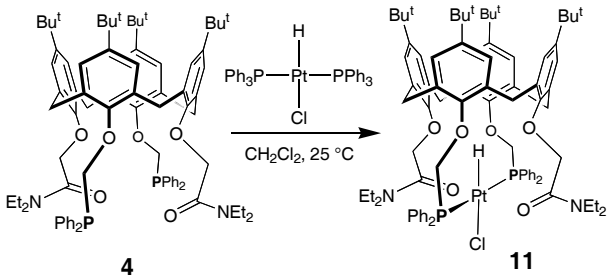
Positioning of Metal Centres at the Entrances to Conical Cavities

Whether at the wide or narrow entrance to a cavitand or procavitand cone, a possible strategy for fixing a metal ion coordination centre is the attachment of multiple donor atoms, arranged in a manner suitable for chelation, about the wide or narrow edge. It may be the metal binding which converts a partly flexible procavitand into a true cavitand and examples of this are provided in the coordination chemistry of the calixarene **4,** which has two phosphine units attached to the lower rim (Scheme 1) [15]. This compound can be obtained straightforwardly in three steps starting from *p-tert*-butylcalix[4]arene (**1**): (*i*) 1,3-dialkylation with $K_2CO_3/BrCH_2C(O)NEt_2$ leading to **2**; (*ii*) alkylation of the two remaining hydroxy functions with $Bu^tONa/Ph_2P(O)CH_2OTs$ (Ts = *p*-Me-$C_6H_4SO_2$); (*iii*) reduction of the phosphine oxide **3** with phenyl silane. The final calixarene adopts a cone conformation. Note that when the phosphorylation step (*ii*) was achieved with Bu^tOK instead of the corresponding sodium salt, the partial cone isomer **5** was formed selectively, giving a ligand which of course is unsuited to chelation. In view of the rather large separation (14 bonds) between the two phosphorus atoms in **5**, we first anticipated that this ligand would not readily give *chelate* complexes and this is indeed the case. In order to avoid oligomer formation during complexation (and hence to favor chelating behaviour), the reactions are best performed under medium or high dilution conditions. The complexes **6-8** for example (Scheme 2) were obtained in good yields from 10^{-4} M solutions of the corresponding $[MCl_2(PhCN)_2]$ complexes [16]. As shown by several X-ray diffraction studies, the metal centre sits well below the cavity in these complexes, although it possesses a certain degree of mobility. A more powerful method for forming chelate complexes, which does not require high dilution techniques, consists of reacting the diphosphine with cationic complexes coordinated by very labile ligands, such as [RuCl(*p*-cymene)(CH_2Cl_2)]BF_4, [Pd(η^3-allyl)$(THF)_2$]BF_4 or [Rh(COD)$(THF)_2$]BF_4 [17]. Applying this methodology to calix[4]arenes with $–CH_2PPh_2$ units anchored on distal phenolic oxygen atoms gave the corresponding chelate complexes, *e. g.* **9** and **10**. The strategy was also successfully applied to other cavities, notably cyclodextrins, and to longer diphosphines as well [18,19].

The chelate complex **11** was obtained quantitatively by reacting calixarene **4** with $[PtHCl(PPh_3)_2]$ (Scheme 3) [16]. In this case high dilution conditions are not essential. It

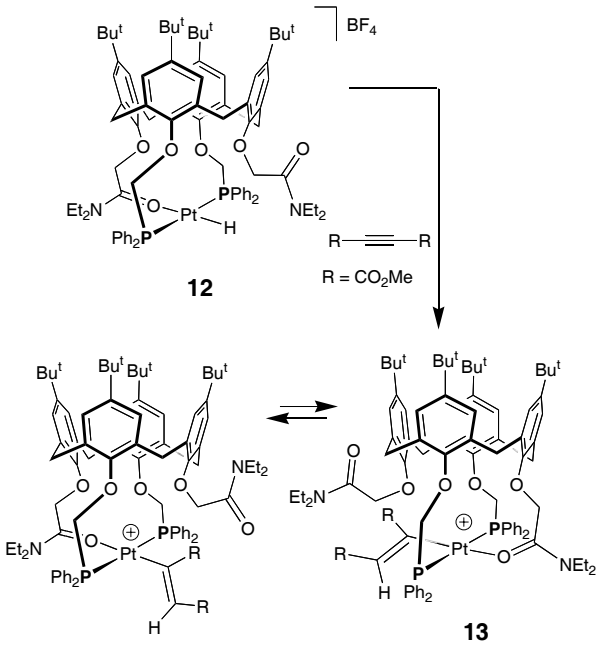


Scheme 2. Calix[4]arene chelate complexes in which the metal centre is positioned at the lower rim.

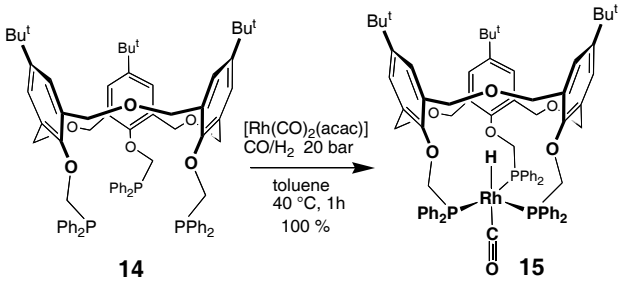


Scheme 3. Confinement of a Pt-H bond at the narrow entrance of a calix[4]arene.

turned out that for this reaction chelate formation is assisted by the two amide side functions which, due to their smaller size, are the only donors of **4** able to initiate the PPh_3 substitution. Related calixarene-diphosphines in which the amide functions have been replaced by non-bonding ligands do not substitute the triphenylphosphine ligands. The most interesting feature of complex **11** concerns

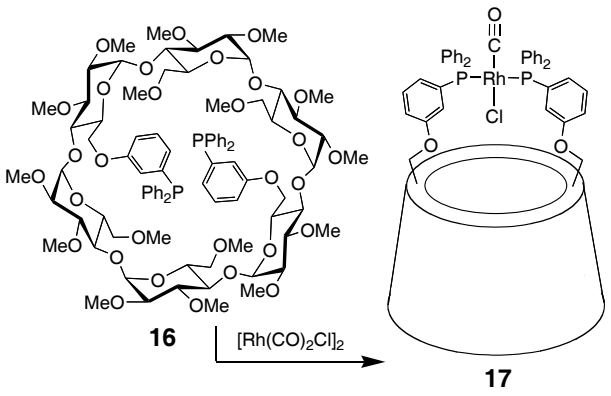


Scheme 4. Reactivity of a semi-encapsulated platinum hydride.



Scheme 5. Controlling the orientation of a "H-Rh-CO" rod.

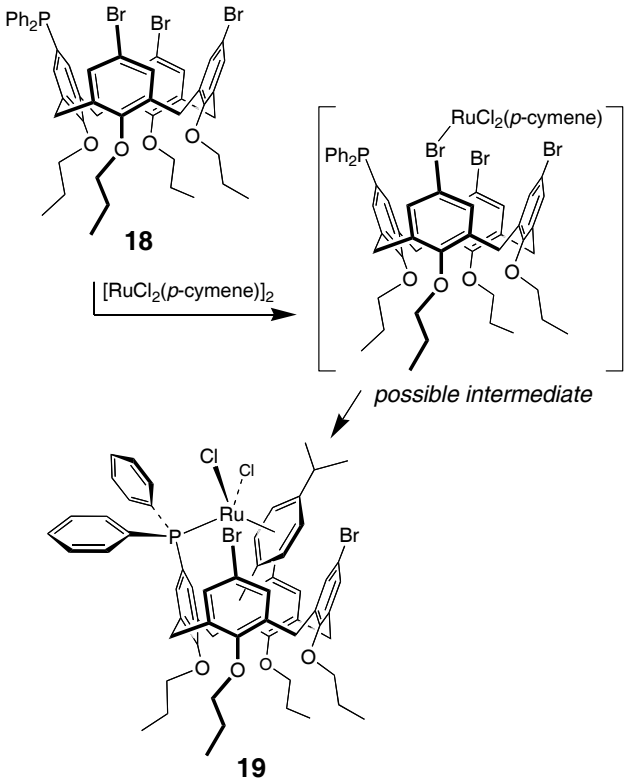
the orientation of the Pt-H bondwhich points to the centre of the cavity. As suggested by an X-ray diffraction study, this could arise from weak hydrogen bonds involving two of the phenolic oxygen atoms. Due to the steric protection provided by the two pendant amide groups which result in partial encapsulation of the hydride, complex **11** does not react with electrophiles, unlike other platinum hydrides. The situation is different with complex **12** where the hydride bond lies perpendicular to the calixarene axis (Scheme 4). Indeed, this



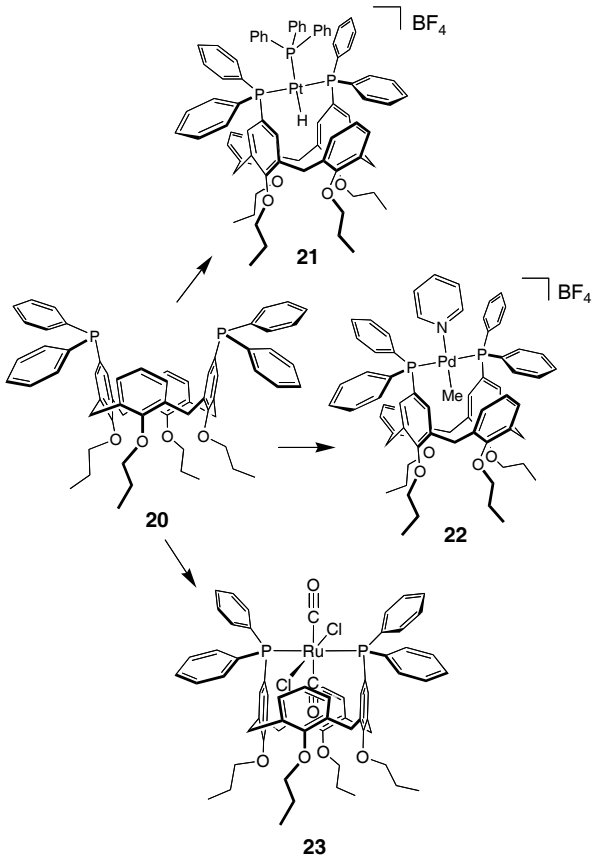
Scheme 6. Synthesis of a hydroformylation catalyst based on a cyclodextrin-modified diphosphine.

complex reacts readily with $MeO_2CC{\equiv}CCO_2Me$ to afford the fluxional insertion product **13**.

Metallo-cavitands may also be obtained from tripodal claws, *e.g.* the triphosphine **14**, constructed on a C_{3v}-symmetrical homotrioxacalix[3]arene building block [20]. This particular cavity is somewhat larger than that of a generic calix[4]arene, the separation between two phenol centroids being close to 6.5 Å. Reaction under CO/H_2 (20 bar) of **14** with $Rh(acac)(CO)_2$ results in the quantitative formation of the rhodium carbonyl hydride **15** (Scheme 5). As inferred from ROESY experiments, the Rh-H bond is directed towards the interior of the cavity. This means that **14** is able to control the orientation of the entrapped H–Rh–CO rod, possibly by allowing weak interactions to occur between the hydridic H and phenolic O atoms. Complex **15** is extremely stable, indicating that precursor **14** is ideally suited for the stabilisation of trigonal bipyramidal structures. This may also explain why its activity in the hydroformylation of styrene (in toluene) is *ca.* 10 times lower than that of conventional Wilkinson-type catalysts. The aldehyde selectivity of this reaction is comparable to that of standard catalysts, suggesting that the catalytic process takes place outside the cavity. Higher hydroformylation activity was observed with metallocavitand **17** (Scheme 6), a rhodium complex based on an *a*-cyclodextrin *A,D*-substituted by two phosphine ligands (**16**) [21]. When this procatalyst was used for octene hydroformylation in a methanol-water mixture, the aldehyde selectivities were again close to those observed with Wilkinson type catalysts. Clearly, the reaction medium used does not force the catalytic process to occur inside the



Scheme 7. Filling the calixarene basket with an organometallic ruthenium unit.



Scheme 8. Confinement of metal-organic fragments in the calix[4]arene **20**.

CD cavity. A complex soluble in pure water (**17** does not fulfil this condition) probably would be helpful to reach this goal.

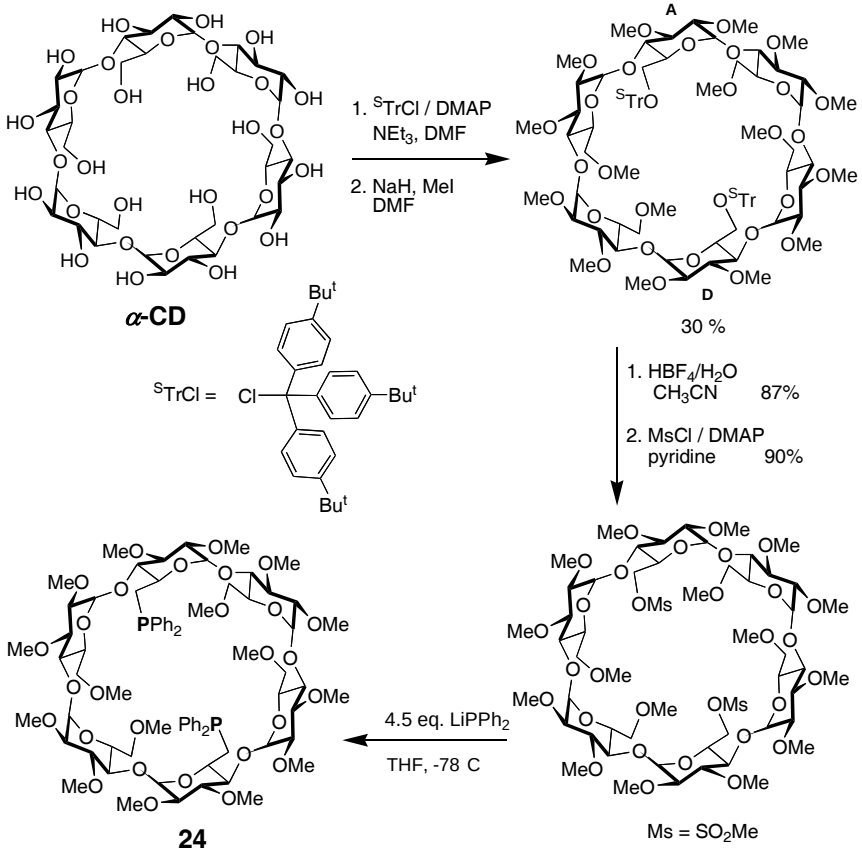
It is worth mentioning here that the use of cavities equipped with non-chelating ligands may also lead to complexes having a partially included ligand sphere. Thus, reaction of monophosphine **18** with $[RuCl_2(p\text{-cymene})]_2$ gave a quantitative yield of complex **19** where the *p*-cymene unit fills the calixarene basket (Scheme 7) [22]. Obviously, owing to the presence of bulky bromine atoms that increase the cavity depth and hence maintain the metal fragment inside the calixarene core, rotation about the P–C(phenol) is restricted. Why the Ru(*p*-cymene) unit sits in the calixarene interior rather than outside could be due to the fact that the first reaction step during complexation is coordination of a bromide atom to a $RuCl_2$(*p*-cymene) fragment, thus forming a transient Ru•••Br bond which then guides the "$RuCl_2$(*p*-cymene)" unit to the neighbouring phosphorus atom. Clearly, only those ruthenium fragments maintained inside the calix can be brought into contact with the phosphorus lone pair. However steric effects that orientate the phosphorus lone pair towards the calixarene axis prior to coordination could also account for the observed phenomenon.

Transition Metal Chemistry Inside the Cavity

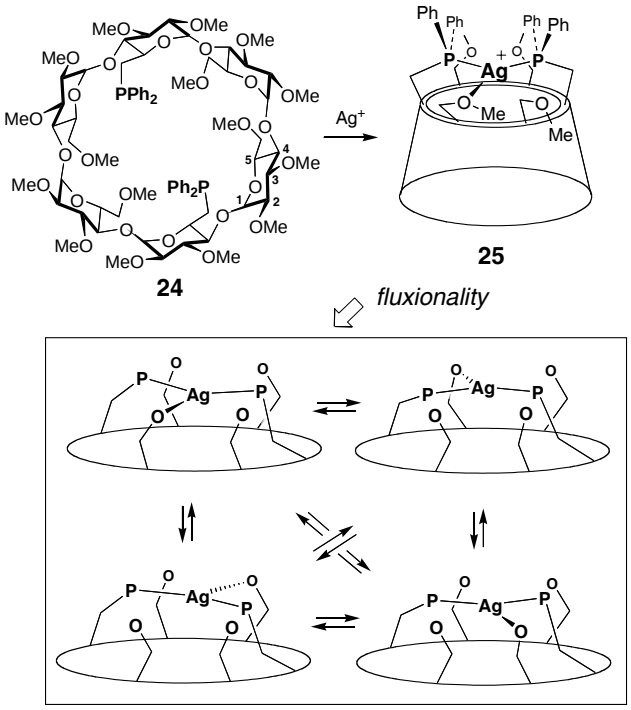
Once a transition metal is immobilized through chelation at the mouth of a conical cavity, the cavity can wrap around the endo-oriented ligands so as to partly protect the metal centre or to behave as a second sphere ligand. Should the whole system be designed for a catalytic reaction that takes place inside the cavity, then it becomes desirable that the cavity size fits with the encapsulation of two substrates located on adjacent coordination sites and also that *intra-cavity* ligand exchange processes become feasible.

The calix[4]arene diphosphine **20** is perfectly suited for forming chelate complexes in which the P-donor atoms are *trans* [23]. By forming such complexes the geometry of the calixarene core flattens and becomes rigid (*i.e.*, a cavitand is formed), leaving a separation of about 5.5 Å between the two phenol rings bearing the phosphine units. This space is sufficient for encapsulating small ligands like a hydride (**21**), a methyl group (**22**), or a carbonyl unit as found in **23** (Scheme 8). In view of the short distance between the encapsulated guest and the cavity walls in this latter complex, weak CO/phenol interactions are very likely to occur, but these could not be detected spectroscopically.

A somewhat larger trans-spanning diphosphine built on a molecular cavity is the *A,D*-substituted cyclodextrin **24** [24]. This ligand has been prepared in three steps from α-cyclodextrin via a methodology that relies on the use of the supertrityl group (Scheme 9). Molecular models show that this cyclodextrin displays some flexibility, allowing the ligand's bite angle to range from 180° to ca. 145°. Reaction of **24** with $AgBF_4$ in non coordinating solvents afforded the silver complex **25**. The precise coordination geometry of **25**, T-shaped or trigonal, is not known, but the complex was shown to have a fluxional structure in solution, the third coordination site being alternatively occupied by each of the four primary methoxy groups (Scheme 10). Addition of acetonitrile in excess to a $CDCl_3$ solution of **25** displaces in a reversible manner the coordinated methoxy function, affording a mixture of the two equilibrating complexes **26** and **27** in which the coordinated nitriles occupy the interior of the cavity (Scheme 11). This unprecedented observation of a (*bis*-nitrile, *bis*-phosphine) cationic silver complex, **27**, possibly arises from the stabilizing effect exerted by the cavity walls which favor recombination of **26** once a nitrile ligand dissociates. The included ligands of **26** and **27** can be exchanged with other nitriles, *e.g.* with PhCN (in excess) which results in the formation of the mononitrile complex **28**. Another interesting property of diphosphine **24** relates to its marked tendency to form chelate complexes

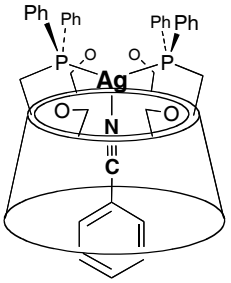


Scheme 9. Synthesis of the cyclodextrin diphosphine **24**.



Scheme 10. Synthesis and fluxional behaviour of the silver complex **25**.

with square planar or octahedral metal ions [25]. Thus, reacting this ligand with d8-metal chlorides gave only complexes in which the ligand behaves as a trans-chelator, as in **29**-**32**. More interestingly, in all the chloro complexes obtained with this ligand, a metal-chloride bond points towards the centre of the cavity. X-ray studies indicate that weak bonding occurs between the included chloride and the inwardly-oriented H-5 atoms connected to the phosphine-substituted glucose units (Fig. 2). This hypothesis is

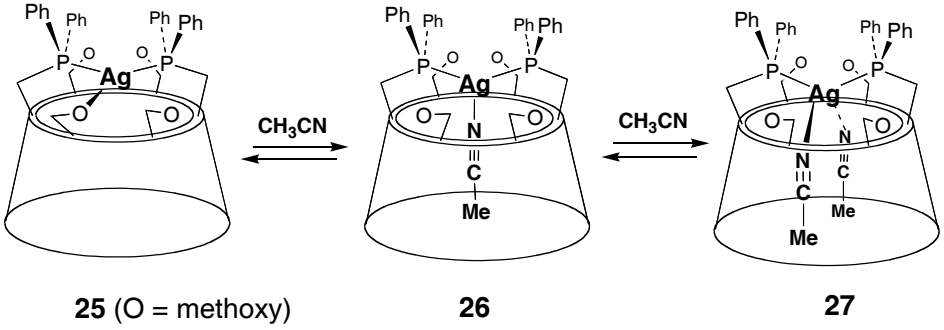


28 (O = methoxy)

corroborated by the ^{1}H NMR spectra, where the corresponding H-5 signals have undergone a significant low-filed shift (*ca*. 1ppm). Chloride entrapment is favored over that of smaller ligands, such as CO, or the less polarized metal-Me bonds. Thus, supramolecular forces appear to be responsible for guest selection. Note that the nature of these complexes shows for the first time that cyclodextrins may form weak bonds with metal-bonded chloride atoms.

Are Conical Cavities Suitable for Catalytic Reactions ?

Catalysts that exploit the presence of a cavity located nearby a metal centre have already been reported, the first examples of this type being Breslow's biomimetic systems (Fig. 3) for the hydrolysis of esters such as the copper complex **33** (the catalysts are *β*-CD derivatives) [26]. In these catalysts the cavity essentially acts as a supramolecular receptor that favorably orientates the substrate while the catalytic process itself takes place outside the cavity. The same holds for the rhodium catalyst **34** which hydroformylates 4-allyl-catechol **A** two times



25 (O = methoxy) **26** **27**

Scheme 11. Coordination chemistry inside a cyclodextrin cavitand**.**

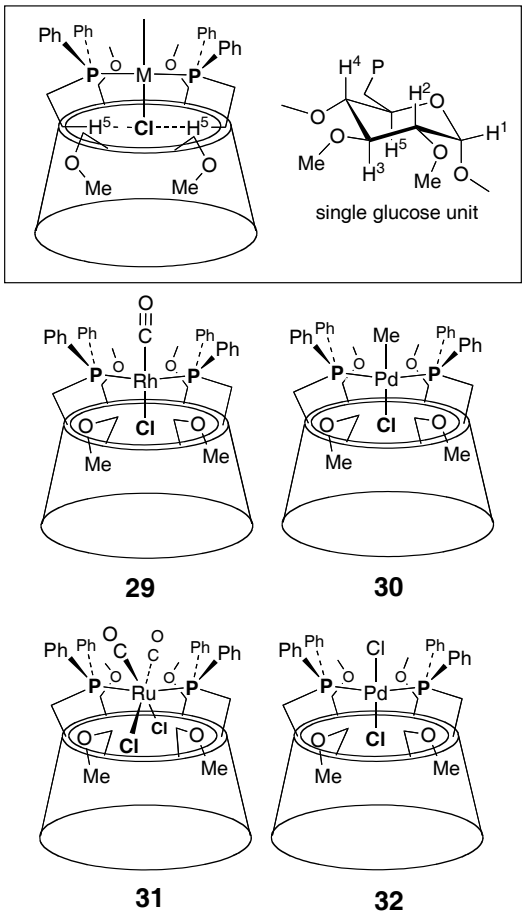


Fig. 2. Weak Cl•••cavity interactions (involving H^5 atoms) in metallo-cyclodextrins.

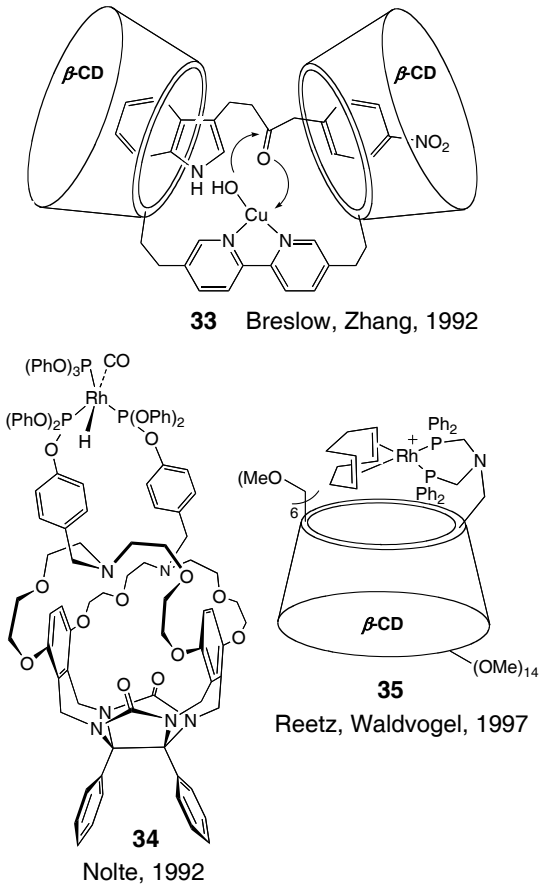
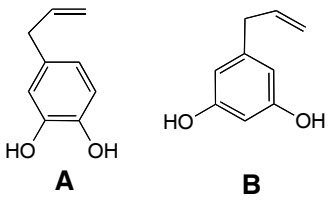
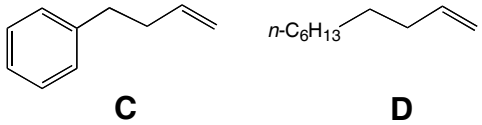


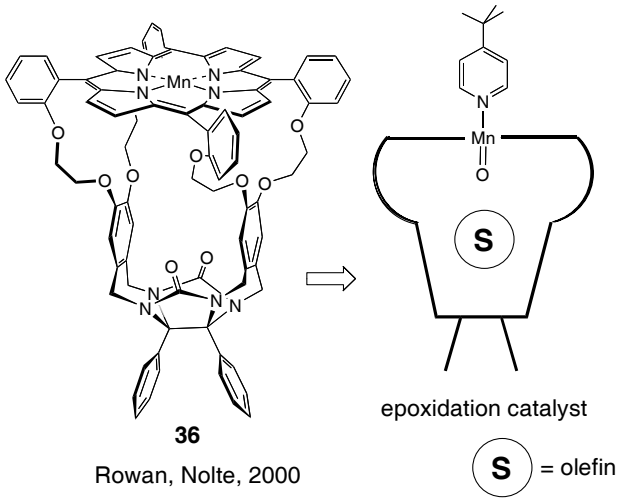
Fig. 3. Supramolecular catalysts based on a cavitand (**33**, **35**) or a molecular clip (**34**).

than the allyl-resorcinol **B** [27]. Substrate selectivity results in this faster case from hydrogen bonding with the two ureido carbonyl functions of the glycoluril pocket. More recently, Reetz and Waldvogel described the cyclodextrin-derived rhodium hydroformylation catalyst **35** [28]. In the presence of a 1:1 mixture of olefins **C** and **D**, this hybrid catalyst preferentially hydroformylates olefin **C** (substrate selectivity 87/13) when operating in water-DMF, a medium which is supposed to force inclusion of the olefin in the cavity during catalysis. The increased activity observed with olefin **C** rests on preferential substrate binding by the cavity in a particular medium. Here again the loosely bound metal centre is located outside the cavity.

The first reported catalyst that operates inside a molecular clip is the glycoluril derivative **36** which is equipped with a Mn-porphyrin roof [29]. Bound to *p-tert*-butyl-pyridine, which activates the Mn centre through exo-coordination, **36** results in a catalyst which epoxidises olefins inside the clip (Scheme 12). As shown by







Scheme 12. Olefin epoxidation catalyst based on a molecular clip.

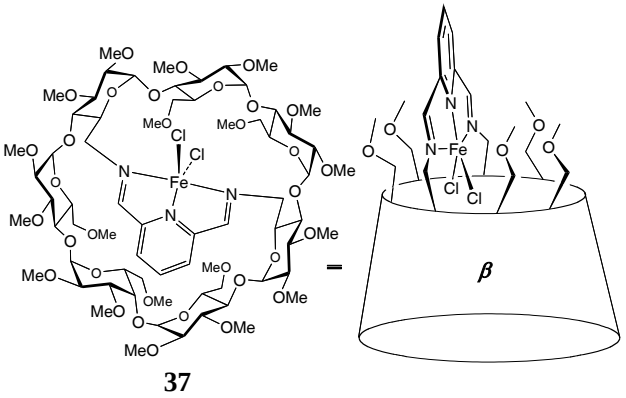


Fig. 4.. The first polymerization catalyst operating in a "tube".

comparative experiments with porphyrins having non-shielded faces, the cavity of **36** provides protection from oxidative decomposition. The only known procatalyst based on a conical cavity is the blue iron complex **37** (Fig. 4) [30]. This compound contains an *endo*-oriented 1,3-diiminopyridine-$FeCl_2$ unit that bridges the entrance of a *β*-cyclodextrin derivative. After activation with MAO, the complex polymerizes ethylene in toluene, producing a PE which in terms of crystallinity and melting point is similar to that obtained from the conventional Brookhart/Gibson iron catalysts [31]. However, the catalytic activity of **37** remains 1000 times lower than that of the latter systems, possibly because the catalytic centre is surrounded by five coordinating methoxy groups. This drawback could possibly be circumvented by using non-coordinating substituents. Note, the smaller α-CD analogue of **37** is not active at all. Overall, complex **37** constitutes a prototype for catalysts operating in a tube. Clearly chemical modification of such systems could lead to novel water-soluble polymerization catalysts.

Outlook

The results discussed above illustrate that conical cavities equipped with chelating units are good precursors for the preparation of partially-encapsulated metal complexes. Metal centres sitting at the entry of a funnel display several advantages over classical complexes. Metal confinement provides protection of organometallic species formed within the cavity against decomposition reactions. Funnel ligands may also enhance the stability of labile complexes by favoring their reformation after inner-ligand dissociation. An emerging chemistry is that of catalytic reactions taking place inside a cavity. To achieve such a reactions, the cavity must meet several conditions: (i) the portals must be sufficiently large to allow substrates to come in and products to escape; (ii) to couple two reaction partners the metal should possess two encapsulated, *cis*-positioned, coordination sites. This is required by many (not all) catalytic reactions, notably in olefin polymerization or co-oligomerization reactions; (iii) finally, the size of the cavity should be compatible with ligand exchange reactions taking place at the metal centre. As outlined above, the latter property has already been achieved in some metallo-cyclodextrins and also in clip-shaped systems. Recent reports show that this is also possible using rigidified calix[6]arenes [32]. Achievement of catalytic reactions inside a cavity is a promising topic that is only at an early stage of development. Realization of this challenging goal is expected to lead to valuable new catalysts, in particular to water-soluble complexes operating in a capsule functioning as a monomolecular solvent, as well as to catalysts in which the cavity walls induce efficiently diastereoselective reactions.

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