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Supramolecular Control on Chemo- and Regioselectivity via Encapsulation of (NHC)-Au Catalyst within a Hexameric Self-Assembled Host

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Supporting Information

ABSTRACT: The encapsulation of a Au(I) catalyst within a self-assembled, hydrogen bonded, hexameric capsule dramatically changes its catalytic activity, leading to unusual products due to the steric requirements of the host's cavity.

Enzymes are supramolecular catalysts *par excellence* in which supramolecular interactions between the active site and the reagents effect the selection of substrates, facilitate their orientation into the required position for reaction, and promote the subsequent covalent modification, leading to highly selective product formation. As such, enzymes control the selectivity of a reaction dominantly by the second sphere environment, which contrasts with the general mechanism of transition metal catalysis where the substrate interacts only with a limited portion of the catalyst surface, the rest remaining in contact with the bulk solution. Inspired by the efficiency displayed by enzymes, capsular structures as reaction hosts represent an interesting but challenging goal. Recent breakthroughs in supramolecular chemistry have enabled the preparation of a diversity of such capsules, and for several organic reactions, it has been demonstrated that activity and selectivity can indeed be controlled by the second sphere environment provided by the capsule.[1] In contrast, the number of organometallic catalysts enclosed in such systems to control catalytic activity and selectivity is very limited.

Organometallic complexes encapsulated into nanoporous solids have been investigated[2] with observations of improvements in selectivity. Obviously, the creation of such a well-defined environment in solution is much more difficult. Several successful examples of organometallic complexes accommodated in open ended cavitand structures have been reported. Since these supramolecular structures are based on robust interactions, such as metal−ligand interactions[3] or intramolecular hydrogen bonds,[4] the shape of the host is retained, enabling remarkable changes in selectivity for both catalytic hydroformylation and hydrogenation reactions, respectively. The use of capsular hosts in principle allows control of the substrate by selection based on size. Raymond[5] observed substrate size exclusion imparted by the capsule in the Rh(I) catalyzed isomerization of allylic alcohols and ethers to the corresponding carbonyl compounds. These systems operate in aqueous conditions where the hydrophobic effect is a powerful driving force for holding the capsules together and pushing the catalysts and substrates inside the capsule. In contrast, the use of multimeric self-assembled capsules held together by weak intermolecular forces acting as a solvation sphere for an encapsulated organometallic catalyst in order to alter its catalytic activity and selectivity has not thus far been reported.

Herein we report the first Au catalyst that is encapsulated into a capsule[6] which is self-assembled in organic media. Application in the hydration reaction of terminal alkynes yields products of which the chemo- and regioselectivities are strongly affected by the capsule. To this purpose we selected the hexameric assembly obtained by resorcin[4]arene **1** as the largest and, at the same time, simplest self-assembled capsule.[7] The capsule $\mathbf{1}_6$ exists in organic solvents like chloroform-*d* or benzene-d_6 even at concentrations as low as nanomolar,[8,9] but only in water saturated solvents. We found (NHC)-Au complexes to be the most suitable catalyst precursors for encapsulation.

The cavity of $\mathbf{1}_6$ is about 1375 Å^3, and this space is usually filled with six to eight solvent molecules. Suitable guests are usually cationic species[10] such as tetraalkylammonium and phosphonium cations that, depending on their size, are coencapsulated with residual solvent molecules (Scheme 1). The active gold species is monoligated, and the reaction takes place opposite to the ligand position.

The neutral (*i-Pr*-NHC)AuCl complex [chloro[1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)] can be encapsulated within the hexameric host by simple mixing with the resorcin[4]arene in a 1:7 ratio in water saturated chloroform-*d* where self-assembly takes place. Encapsulation of the complex is evidenced by the appearance of a new set of signals in the ^{1}H NMR for the *i*-Pr residue of the Au complex that is significantly upfield shifted compared to the free complex ($\Delta\delta$ = −0.95 ppm; see Supporting Information). A ^{1}H NMR spectrum of the mixture using different stoichiometry shows the coexistence of signals for the free and bound complex, indicative of a slow exchange rate between encapsulated and free species on the NMR time scale.

As the active species in catalysis is generally cationic in nature, we prepared (*i-Pr*-NHC)Au(OTf) **2** as well and studied its

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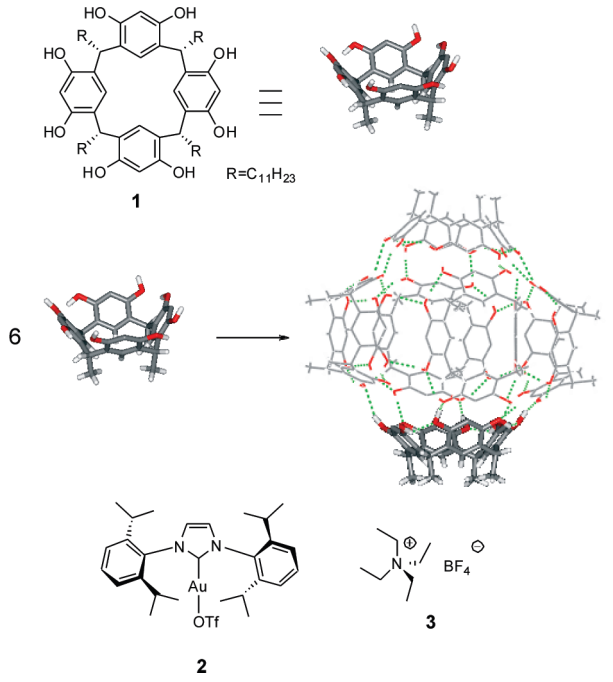
Scheme 1. Resorcin[4]arene 1 Forms a Supramolecular Hexameric Capsule 1_6 Which Encapsulates (NHC)-Au-OTf 2 or Ammonium Guest 3



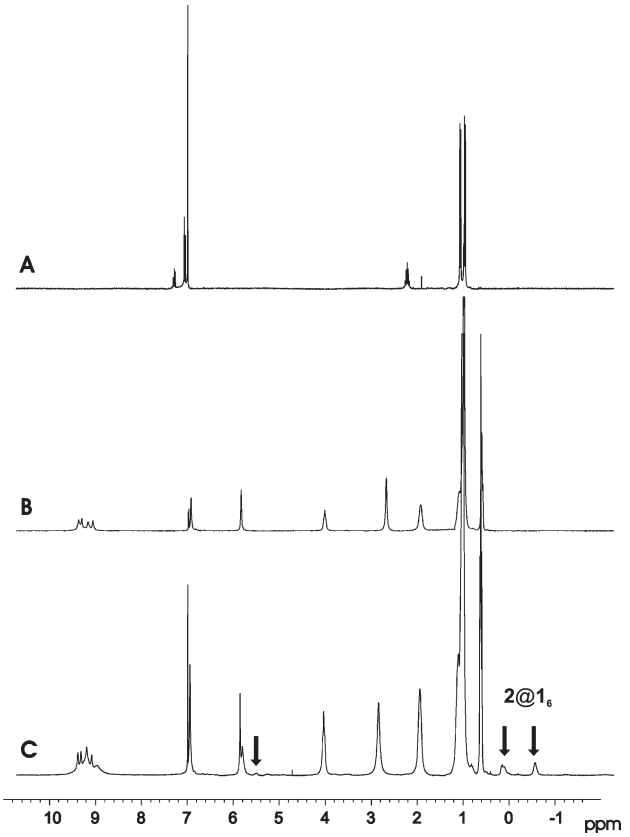


Figure 1. ^{1}H NMR spectra in $CDCl_3$ at 298 K. (A) **2** (3.3 mM); (B) **1** (24 mM); (C) **1** (24 mM), and catalyst **2** (3.3 mM).

binding properties. As shown by the ^{1}H NMR spectra reported in Figure 1, this complex showed quantitative coordination in the capsule when working with the same 1:7 stoichiometry reported above. The ^{1}H NMR spectrum clearly shows the upfield shifted resonances of the *i*-Pr residues of the ligand at −0.26 and 0.37 ppm ($\Delta\delta$ = −0.99 ppm) as broad signals. Analogously, the vinyl resonances of the encapsulated complex appeared between 5 and 7 ppm while the resonances for the free complex in solution completely disappeared.

The encapsulated and free complex **2** showed very different diffusion coefficients (7.9×10^{-10} vs 1.4×10^{-9} m^2 s^{-1} respectively) as evidenced by DOSY experiments. On the other hand, the similar diffusion coefficients observed for encapsulated **2** and the hexameric host indicate that complex **2** indeed resides inside the capsule (see Supporting Information). The ^{19}F NMR signal of the triflate anion of the complex did not change upon encapsulation which means that it probably remains excluded by the encapsulation process.

Further evidence for the encapsulation was provided by the ^{1}H NOESY spectra; in addition to the expected intramolecular contacts between different resonances of **2**, the NOESY spectrum of the encapsulated complex showed clear cross peaks between the *i*-Pr residues of the Au complex and both the hydroxyl residues of the capsule and the aryl proton between the OH groups of the aromatic moieties, confirming the presence of the Au complex within the self-assembled capsule (see Supporting Information). Similar spectra indicating both binding and close contacts were obtained if the experiments were performed in benzene-d_6 instead of $CDCl_3$ as solvent.

The process can be reversed, as the encapsulated catalyst can be displaced by a guest with better binding capabilities, such as cationic tetraethyl ammonium tetrafluoroborate **3**. In fact, addition of 10 equiv of **3** to a solution of the encapsulated **2** led to complete displacement of the latter and encapsulation of the organic cation (see Supporting Information).

Complex **2** has a molecular volume of about 400 Å^3 and consequently occupies about 30% of the volume of the cavity. This means that two to four extra solvent molecules are coencapsulated to ensure stable complexation, in agreement with the general 55% occupancy rule proposed by Rebek.[11] Such solvent molecules can be easily exchanged with substrate molecules of comparable size and shape, suggesting the possibility that the encapsulated complex is able to convert substrates while in the cavity. NHC-Au complexes are known to efficiently catalyze a variety of organic transformations.[12] For these initial experiments, we selected the hydration of alkynes as a test reaction to investigate the supramolecular effect of the capsule on the activity and selectivity of the catalyst, also because the presence of water is required for capsule formation. 4-Phenyl-1-butyne **4** was chosen as a substrate yielding two possible hydration products, 4-phenyl-2-butanone **5** and 4-phenyl-butanal **6**.

Recent literature has demonstrated that Au catalysts usually give Markovnikov addition of water to terminal alkynes[13] leading to the almost exclusive formation of methyl ketones.[14] Under anhydrous conditions the same catalyst transforms this substrate into 1,2-dihydronaphthalene **7** via an intramolecular rearrangement.[15] Therefore, Au catalyst **2** was evaluated, in both its free and encapsulated form, in the hydration of 4-phenyl-butyne in benzene-d_6 under identical experimental conditions (Scheme 2).

As expected the reaction carried out with free **2** in water saturated benzene-d_6 at 70 °C led to the almost exclusive and quantitative formation of **5** as hydration product within 30 min, with only traces of **6** and **7**. As expected, once encapsulated in the

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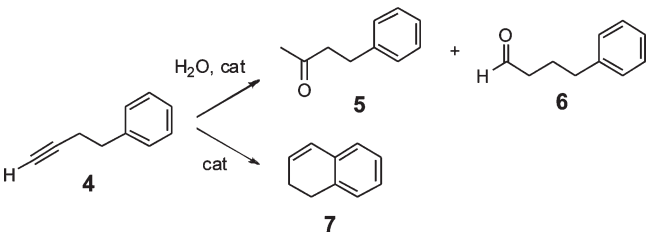
Scheme 2. 4-Phenyl-butyne 4 Provides Two Possible Hydration Products 5 and 6 and One Cyclization Product 7 under Anhydrous Conditions



self-assembled capsule $\mathbf{1}_6$, the catalyst was much slower and only 5% conversion was observed after 30 min, indicating that the reaction rate is controlled by the barrier provided by the capsule to the approach of the substrate to the catalyst. The catalyst was, however, sufficiently stable and continued to convert the substrate, and after 400 min 28% of the substrate was converted. Interestingly, the encapsulated catalyst gives rise to a different product distribution than the free catalyst. In addition to product **5** (12%), also significant amounts of linear aldehyde **6** (4%) was formed as the hydration product, which is unprecedented for Au catalysts.[13] This clearly demonstrates that the regioselectivity can be steered to the opposite direction with respect to the natural catalyst selectivity by putting it in a sterically constrained environment. Furthermore, we observed also the formation of 1,2-dihydronaphthalene **7** (12%), a product that is formed after intramolecular rearrangement usually found only in the absence of water. Apparently, the intramolecular reaction is favored when taking place within the cavity due to unusual folding of the substrate. Alternatively, the capsule may impose a barrier for the entrance of water, making the intermolecular reaction relatively slow compared to the intramolecular one.

The ammonium salt **3** binds better than the complex, providing a means to control the reactivity of the encapsulated catalyst and evidence for the reaction taking place inside the capsule. In a typical experiment 10 equiv of **3** were added after the reaction had progressed for 400 min. As displayed in Figure 2, a rapid increase of the yield in **5** was observed, while the amount of **6** and **7** remained almost unchanged, providing clear experimental evidence for the complete displacement of **2** from the capsule. Once released to the bulk solvent, the catalyst exclusively produces **5** as the hydration product.

Substrate **4** did not show affinity for the free caspule $\mathbf{1}_6$ in the absence of catalyst **2**. Addition of **4** to $\mathbf{2@1}_6$ under reaction conditions did not provide new signals directly attributed to the encapsulated substrate, but new weak very broad upfield shifted resonances appeared at 0.20 and −0.39 ppm close to the signals attributed to the *i*-Pr residues of encapsulated catalyst **2** and are attributed to *i*-Pr residues of new Au species derived by the original encapsulated complex **2** (see Supporting Information). No changes on the ^{1}H NMR spectrum were detected for $\mathbf{2@1}_6$ under reaction conditions (70 °C for 5 h) in the absence of **4**. It is therefore likely that the new species observed upon substrate addition represents the resting state of the catalytic cycle formed by interaction with **4**.

In conclusion, herein the first example of an organometallic catalyst encapsulated in a supramolecular self-assembled hexameric capsule of resorcin[4]arene has been presented. Catalyst encapsulation occurs in organic solvents driven by the matching

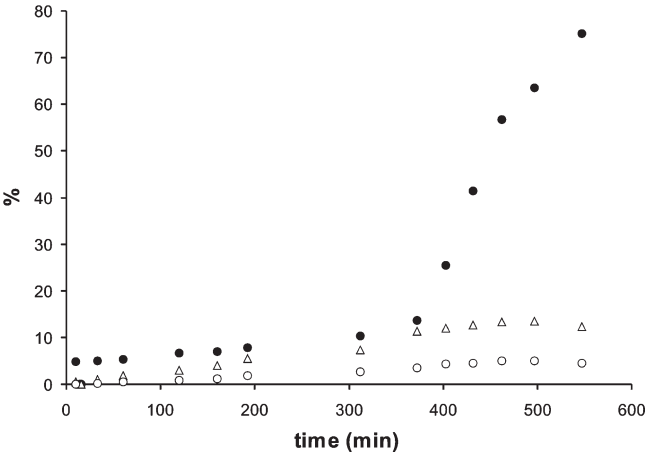


Figure 2. Reaction profiles for **4** (66 mM) with catalyst **2** (3.3 mM) in water saturated benzene-d_6 at 70 °C in the presence of **1** (33 mM) with addition after 400 min of **3** (33 mM). (●) 5, (○) **6**, and (△) **7**.

of size, shape, and attractive weak interactions between the catalyst and capsule. The remaining space is sufficiently large to coencapsulate alkynes that can be subsequently converted into hydration products. The catalytic activity and selectivity of the NHC-Au catalyst is controlled by the nanoenvironment provided by the self-assembled capsule as host, leading to unusual regioselectivity in the hydration of 4-phenyl-butyne together with an unusual cyclization product. Solvation of the catalyst from bulk benzene to the hexameric host alters activity and selectivity mimicking catalysis occurring in the active site of enzymes. Further studies on selectivity aspects for encapsulated complexes in the self-assembled hexamer are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information. Experimental part and procedures for this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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