DOI: 10.1002/anie.201005317

Nanoreactors

Transition-Metal-Promoted Chemoselective Photoreactions at the Cucurbituril Rim**

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Supramolecular systems which provide a confined nanospace for the formation of discrete inclusion complexes with reactive guests near active sites are presently of great interest.[1] Supramolecular capsules[2] and coordination cages[3] as well as macrocycles of the cyclodextrin[1] and calixarene[4] types have been intensively investigated for their functionalization with transition metals and the resulting potential to promote the chemoselective and/or catalytic reactions of substrates. Cucurbit[*n*]urils (CB*n*) are synthetic macrocycles with an ever-expanding range of applications.[5] They have already been investigated with respect to their catalytic properties, starting from the early work of Mock on [3+2] cycloadditions catalyzed by CB6[6] and, subsequently, several other examples of photocycloadditions using CB7 and CB8.[7] The hitherto reported catalytic applications have mostly relied, like the elegant examples described for cyclodextrins, particularly the larger γ-cyclodextrin,[7d,e] capsules,[8] and coordination cages,[9] on the ability of sufficiently large hosts to accommodate two reactants within their inner hydrophobic cavity and thereby facilitate stoichiometric reactions. But cucurbiturils are multifunctional in the sense that they possess not only a hydrophobic cavity, but also two carbonyl rims with a known affinity for metals ions.[10] While such metal ions have previously been regarded as “lids on the barrel”, which could either compete with guest binding[11] or further shield the guest,[12] we thought they could be potentially regarded as self-assembling active sites, possibly allowing catalysis in water. In fact, such ternary guest/cucurbituril/metal-ion complexes have been implicated in solution,[11–13] and they are documented in the solid state,[12a,14] suggesting that the required proximity between a substrate as a guest and the desired metal ion would be readily ensured.

We now report a chemoselective transformation of included guests promoted by transition-metal ions coordinated to the cucurbituril rim. Building on our conceptual work with *p*-sulfonatocalix[4]arenes as macrocycles,[15] we have realized a two-phase system (Figure 1), in which the host acts formally as an inverse phase-transfer catalyst to bind a photoreactive substrate by hydrophobic interactions in the aqueous phase and allows the subsequent docking of metal ions to the carbonyl rim through ion–dipole interactions. The resulting ternary self-assembly is synergistically reinforced by weak metal–ligand bonding interactions, which affect the chemoselectivity in the spatially resolved laser photolysis of the aqueous phase. The reaction is designed to afford a photoproduct with reduced affinity to the macrocycle, which accumulates in the organic phase, where the reaction mixture is analyzed.

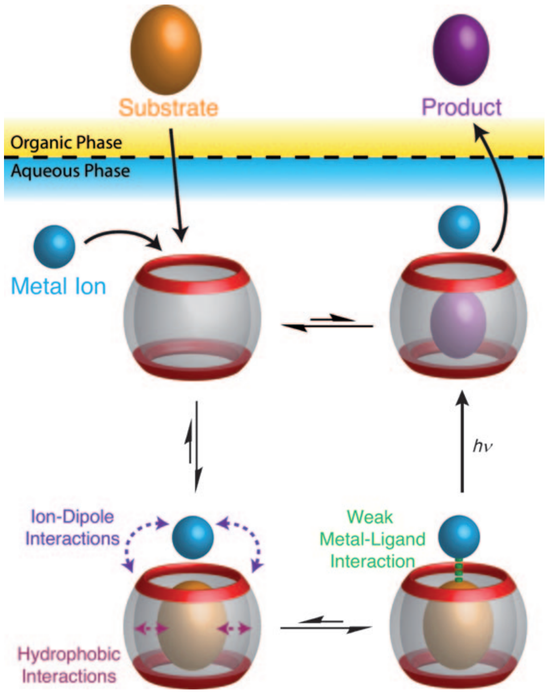

Figure 1. Dynamic self-assembly of a ternary guest/host/metal-ion complex and the transition-metal-promoted photoreaction.

Specifically, we have investigated the influence of metal–ligand bonding on the photodeazetation of the bicyclic azoalkanes 2,3-diazabicylo[2.2.2]oct-2-ene (DBO) and 2,3-diazabicylo[2.2.1]hept-2-ene (DBH) in the presence of CB7 (Figure 2). Addition of CB7 to aqueous solutions of DBO and DBH causes characteristic bathochromic and hypochromic shift in their UV spectra[16] as well as characteristic upfield shifts in their ^{1}H NMR spectra (see Figures S1–S3 and Tables S1–S2 in the Supporting Information), which are

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[**] This work was supported by the DFG (NA-686/5-1), AGAUR (2009 PIV 00107, Visiting Professorship at ICIQ, Tarragona, Spain), and the Fonds der Chemischen Industrie. We thank V. D. Uzunova for the ITC measurements and R. Dsouza and A. Hennig for help with graphics and photography.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201005317.

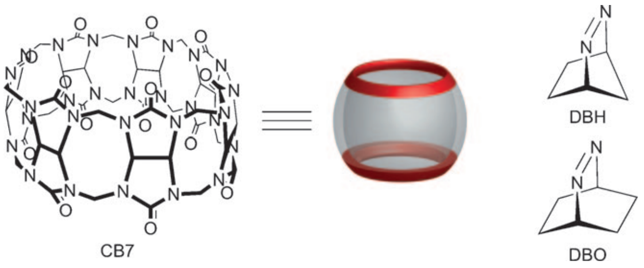


Figure 2. The host CB7 and the reactive guest molecules.

attributed to the formation of inclusion complexes driven by hydrophobic interactions. The corresponding UV and independent isothermal calorimetric titrations can be fitted according to a 1:1 complexation model and afford high binding constants of $(5.8 \pm 0.2) \times 10^6\,\text{M}^{-1}$ for DBO and $(3.8 \pm 0.2) \times 10^5\,\text{M}^{-1}$ for DBH.

The subsequent docking of the metal ions on the carbonyl rim, driven by ion–dipole interactions, can be again monitored by optical titrations (see Figures S4–S8 in the Supporting Information). For this purpose, solutions with the respective metal salt are added to the azoalkane·CB7 binary complexes (excess host). The docking of alkali ions, for example, results in increased protection of the chromophore from the aqueous solution, which is readily monitored through an increase in the fluorescence intensity of DBO (and fluorescence lifetime, see Figure S5a in the Supporting Information). The docking of most multivalent transition-metal ions such as Co^{2+}, Ni^{2+}, and Zn^{2+} results in a hypsochromic shift of the UV absorption band, which is diagnostic for the involvement of the azo group as a monodentate ligand (see Figure S6 in the Supporting Information).[15a] For Ag^+ (and Tl^+), hyper- and bathochromic UV shifts as well as downfield ^{1}H NMR shifts are observed (see Figures S2, S3, and S7 in the Supporting Information). For Ag^+, these are assigned, bolstered by the precise binding mode in the crystal structure of the DBO·CB7·Ag^+ complex (Figure 3), to the predominant involvement of the azo group as a bidentate bridging ligand between two metal ions. In all cases in which coordinative bonds between the azo group and the metal ion are formed, the fluorescence of DBO is quenched, which provides another means of directly following the docking process (see Figure S5b in the Supporting Information).

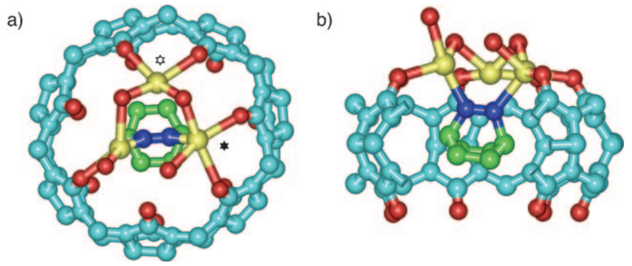
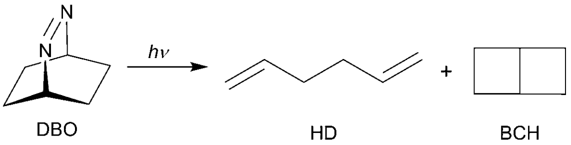


Figure 3. a) Top view and b) dissected side view of the crystal structure of the ternary complex CB7·DBO·Ag^+ showing one of three distinct host–guest complexes in the asymmetric unit (magenta: cucurbituril skeleton, green: guest carbon atoms, red: oxygen atoms, blue: azoalkane nitrogen atoms, yellow: silver ions). Disordered silver atoms are marked with a black (position with major occupancy) or white star (minor occupancy). See the Supporting Information for all ternary complexes.

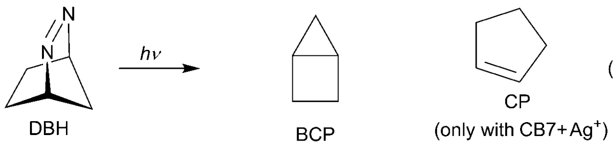
It is important to note that metal–ligand bonds between azoalkanes and transition metals are generally very weak.[15a,17] The addition of the respective metal ions in low millimolar concentrations does therefore not cause any UV-spectral changes when CB7 is absent (insets in Figures S6 and S7 in the Supporting Information). Only at very high metal-ion concentrations and for very few metal ions[17] is it at all possible to obtain evidence for the formation of metal–ligand bonds to the free azoalkanes and to quantify the very low binding constants; for example, values of $(20 \pm 3)\,\text{M}^{-1}$ for DBH and $(10 \pm 5)\,\text{M}^{-1}$ for DBO were estimated from the appearance of weak charge-transfer bands for Ag^+. As can be projected from all accessible binding constants (see the Supporting Information), the ternary complexes form with positive cooperativity, because the three types of supramolecular interactions (Figure 1) add up: the ligation affinity of the metal ion to the complexed azoalkane increases by about three orders of magnitude as a consequence of the added ion–dipole interactions to the host. In essence, CB7 serves as a template for the formation of the metal–ligand bond to the azoalkanes, and it is this positioning of the chromophore right next to the metal ion which can be exploited to alter the chemical reactivity of the encapsulated guest. The ternary assemblies can in fact be viewed as simplistic but functional metalloenzyme models, because they possess both an active site and a hydrophobic pocket for selective substrate binding. They differ conceptually from designed metallomacrocycles, in which the transition metal is irreversibly incorporated through the attachment of nitrogeneous ligands to the macrocycle.[4]

Bicyclic azoalkanes are photoreactive and eliminate nitrogen upon irradiation in their near-UV n,π* absorption bands.[18] With the self-assembly of the ternary complexes firmly established, we took advantage of the rapid supramolecular exchange dynamics and proceeded to screen the photoreactivity of the encapsulated azoalkanes in the presence of different metal ions. Note that the photolysis of DBO [Eq. (1)] is known to afford, with very low quantum yield, a mixture of bicyclo[2.2.0]hexane and 1,5-hexadiene derived from ring closure and opening of the intermediate 1,4-cyclohexadiyl biradical, respectively.[18] The ring-opened product arises preferably from the triplet excited state.[18b,19] Photolysis of DBH [Eq. (2)], on the other hand, proceeds with unit quantum efficiency and leads, from both the singlet and triplet excited state, to the clean formation of bicyclo[2.1.0]pentane (housane) as the exclusive photoproduct.[18a]

In experimental detail, the reaction was performed in a two-phase system[20] consisting of an aqueous solution con-



(1)



(2)

taining the water-soluble macrocyclic host and the metal salt, and an organic layer (*n*-pentane for DBO and toluene for DBH) containing the bicyclic azoalkane. The photolysis was preferably conducted by phase-selective laser irradiation (355 nm, Nd-YAG laser; Figure 4). Owing to the high solubility of the azoalkanes in water[21] we used an excess (two equivalents) of the macrocycle to ensure quantitative complexation and to avoid photolysis of residual uncomplexed azoalkane in the aqueous phase. We analyzed the photoproduct distributions by GC analysis by drawing aliquots from the upper organic phase. To exclude a preferential complexation of one of the reaction products with CB7, we added an excess of cadaverine (1,5-diaminopentane), a strong competitive binder,[5d] to the reaction mixture after complete photolysis.[5d]

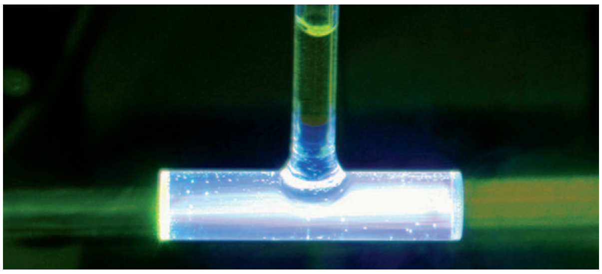


Figure 4. Photograph of the phase-selective laser irradiation ($\lambda_{exc}=355$ nm, third harmonic Nd-YAG laser, incident from the right) of the DBO·CB7 complex in aqueous solution. The upper phase in the cuvette neck contains *n*-pentane colorized with a trace amount of β-carotene. Note the N_2 bubbles resulting from photodeazetation.

The photolysis of DBO in water as well as in organic solvents (*n*-pentane), in the presence of only CB7, in the presence of only metal ions, and in the presence of both CB7 and most metal ions produced about a two- to threefold excess of 1,5-hexadiene (70 ± 5 %) over the bicyclic product (Table 1 or Table S3 in the Supporting Information). But for very few metal ions (Tl^+, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ag^+) and for these only when CB7 was present, the chemoselectivity increased strongly and afforded a five- to tenfold excess of the diene (83–90 %). Since actually the ternary DBO·CB7·metal-ion complexes are being irradiated under these conditions, and since the photoreactivity is unaffected by the macrocycle complexation as such (see numerous control experiments in the Supporting Information), we interpret the photoproduct distributions as arising from an altered photoreactivity when particular metal ions are coordinated to the cucurbituril rim. The preferential formation of the diene is indicative of a preferred reaction from the triplet excited state, presumably caused by heavy-atom-induced intersystem crossing. Such heavy-atom effects are reminiscent of (but much more pronounced than) the effects observed in the DBO photolysis in heavy-atom-doped zeolites.[19]

Table 1: Photoproducts of DBO under different conditions with and without CB7 and metal ions[a]

Host	Metal ion	HD[b]	BCH[b]
–	–	65	35
CB7	–	65	35
–	alkaline (earth) metal ions, Fe^{3+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Ag^+	65–75	25–35
CB7	alkaline (earth) metal ions, Cr^{3+}, Mn^{2+}, Zn^{2+}, Pb^{2+}	65–75	25–35
CB7	Tl^+, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ag^+	83–90	10–17

[a] Concentrations: 2 mM DBO, 4 mM CB7, and 10 mM metal ion. [b] Products correspond to 1,5-hexadiene and bicyclo[2.2.0]hexane, see Equation (1).

The results for the photolysis of DBH were even more revealing (Table 2). DBH affords invariably 100 % bicyclo[2.1.0]pentane in aqueous solution, in organic solution, and in the presence of metal ions, CB7, and both—with one single exception: This hit was found for the DBH·CB7·Ag^+ ternary complex, for which the significant formation of a new photoproduct, cyclopentene, was observed [41 %, Eq. (2)]. The presence of the macrocycle is, indeed, essential to produce cyclopentene, since even the photolysis of DBH in the presence of 1 M $AgNO_3$ did not lead to this unexpected product. Even though our example lacks catalytic turnover because excess CB7 and Ag^+ ions are required, it is evident that Ag^+ ions promote the photochemical formation of cyclopentene inside CB7.

Table 2: Photoproducts of DBH under different conditions with and without CB7 and metal ions[a]

Host	Metal ion	BCP[b]	CP[b]
-	–	100	0
CB7	–	100	0
–	alkaline (earth) metal ions, Fe^{3+}, Co^{2+}, Cu^{2+}, Tl^+, Zn^{2+}, Ag^+	100	0
CB7	alkaline (earth) metal ions, Fe^{3+}, Co^{2+}, Cu^{2+}, Tl^+, Zn^{2+}	100	0
CB7	Ag^+	59[c]	41[c]

[a] Concentrations: 2 mM DBH, 4 mM CB7, and 30 mM metal ion. [b] Products correspond to bicyclo[2.1.0]pentane and cyclopentene, see Equation (2). [c] Unselective irradiation of both phases in a photoreactor afforded a product ratio (BCP/CP) of 73:27.

While cyclopentene has not been observed previously in the direct photolysis of DBH, this product can be formed through the one-electron oxidation of DBH.[22] With this mechanistic background and additional electrochemical considerations (see calculations of Gibbs energies for electron transfer in the Supporting Information), we propose that the silver ions complexed to the portals (Figure 3) facilitate a highly exergonic one-electron oxidation of singlet DBH. Elimination of nitrogen from the resulting azo radical cation affords the 1,3-cyclopentanediyl radical cation,[23] which undergoes a rapid 1,2-H shift to give the cyclopentene radical cation.[22] We presume that the latter is reduced, again in an exergonic reaction, by the (still portal-associated) silver atom to yield cyclopentene and a regenerated silver ion. Note that the singlet excited state of DBH is far too short-lived (ca. 150 ps)[24] to undergo bimolecular electron transfer with additives, which accounts for the fact that cyclopentene is not formed upon direct photolysis. It is likely to do so, however, when firmly held in place in immediate proximity to the oxidizing metal ion within the ternary cucurbituril complex. This is an interesting example of new chemoselectivities created through exposure to a self-assembling active site within a discrete nanospace.[2]

In summary, we have realized a phase-selective photoreaction of a cucurbituril host–guest complex, in which transition-metal ions coordinated to the carbonyl portals of the macrocycle play an active role by affecting, for the first time, the chemoselectivity of product formation. This demonstrates the potential for metal catalysis at the cucurbituril rim and the concomitant exploitation of the same macrocycles as inverse phase-transfer catalysts.

Received: August 25, 2010

Keywords: cucurbiturils · homogeneous catalysis · host–guest complexes · photochemistry · supramolecular chemistry

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