ORGANIC LETTERS

2010
Vol. 12, No. 10
2310−2313

Silver-Promoted Desilylation Catalyzed by Ortho- and Allosteric Cucurbiturils

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Received March 21, 2010

ABSTRACT

Cucurbit[6]-, [7]-, and [8]uril can catalyze the silver(I)-promoted desilylation of trimethylsilylalkynyl-containing pseudorotaxanes by stabilizing a key π-alkynyl silver intermediate through favorable interactions between the metallic cation and the cavitand carbonylated portal.

Recently, the scientific community celebrated the 30th anniversary of the discovery of the famous p53 protein, a tumor suppressor critical to the body's anticancer defense. An issue[1] of *Nature Reviews Cancer* was dedicated to the occasion, which revisited the p53 structure,[1a] its numerous targets,[1b] its effects on apoptosis regulation,[1c] its role in metabolism,[1d] and the various strategies to design p53-binding drugs.[1e] Impressed by the phenomenal efficiency of this 393 amino acid-long choreographer in the cellular ballet, we sought to design a small organic guest, which could interact with different targets (in analogy to p53 interacting with the MDM2 regulator, DNA, etc.) at specific binding sites (similar to p53 transactivation and DNA-binding domains, for example) and which could undergo chemical alteration by a third partner upon such an interaction (in analogy to the interaction with MDM2, which promotes the ubiquitylation of p53,[1a,b] thereby triggering its proteasomal degradation).

Cucurbit[6]-, [7]-, and [8]uril cavitands[2a] (CB[*n*], $n = 6$ 7, 8) were selected as our targets. These macrocycles share a common pumpkin-shaped structure and contain 6, 7, or 8 glycoluril motifs, respectively, linked by methylene bridges.[2] The high degree of similarity between the targets was deliberately intended and adds a level of complexity to the recognition process.

The isobutylammonium cation has been shown to interact strongly with CB[6];[2f] trimethylsilyl groups have proven to fit tightly into the cavity of CB[7] (affinity up to 8.9×10^8 M^{-1}),[2d] and CB[8] can encompass larger or multiple guests due to its wider diameter. In most cases, a positive charge, such as an ammonium or a pyridinium group located close to the CB[*n*] portal, is necessary for strong host−guest affinity through ion-dipole interaction.[2] Consequently, we designed guest **1a**, which was found to display (1) perfect site selectivity toward CB[6] and CB[7] as well as good site

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10.1021/ol100667z
Published on Web 04/26/2010

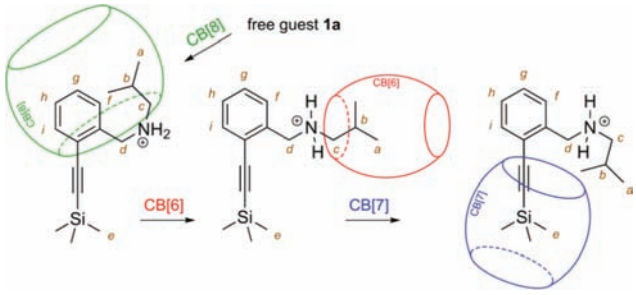

Figure 1. Consecutive site- and host-selective encapsulation of guest **1a** with CB[8], CB[6], and CB[7].

selectivity toward CB[8], (2) strict exclusivity, since only one CB unit at a time can interact with the host, and (3) excellent discrimination between targets: CB[8] can be ejected from guest **1a** upon addition of CB[6], which in turn can be expelled by adding CB[7] (see Figure 1).

Selective recognition could be readily assessed using ^{1}H nuclear magnetic resonance spectroscopy (^{1}H NMR), since (1) hydrogen atoms located near the center of the CB[*n*] cavity undergo a strong upfield shift (up to 1.6 ppm);[3a] (2) decentered hydrogens are affected by a moderate upfield shift, which becomes weaker as hydrogen atoms get closer to the CB[*n*] portals (1.5 → 0.1 ppm);[3b] and (3) hydrogens outside the cavity undergo a significant downfield shift (up to 0.7 ppm) that weakens as the distance between the hydrogens and the portal increases.[3c] The isobutyl unit of guest **1a** interacts strongly with CB[6], since hydrogen atoms at positions *a*, *b*, and *c* undergo a strong upfield shift (0.75, 1.08, and 0.45 ppm, respectively), and hydrogens at position *d* are moderately shifted downfield (0.24 ppm, see Figure 2, spectrum b). Hydrogen atoms *e* are too far from CB[6] and are not affected. The aromatic hydrogen at position *f*, the closest to the CB[6] rim, is significantly shifted downfield (0.54 ppm), and the resolution of *g*−*i* signals improves from a multiplet in the absence of CB[6] to three distinctive signals with readable multiplicities (*i* appears as a doublet and *g* and *h* show two triplet-like signals).

CB[7] targets the trimethylsilyl unit of guest **1a** selectively (see Figure 2, spectrum c), and hydrogen atoms at position *e* undergo a strong upfield shift (0.77 ppm). While the moderate downfield shift of hydrogens *d* is expected (0.25 ppm), the similar behavior of hydrogens *b* (0.26 ppm) is due to the particular conformation of assembly **1a**⊂CB[7], where hydrogens *b* apparently sit at a short distance of the CB[7] rim. In the aromatic region of the spectrum, hydrogen atom *i* interacts with the CB[7] portal and its doublet undergoes an exceptionally high downfield shift (0.90 ppm), while hydrogens *f*−*h* remain unaltered.

As described on numerous occasions, CB[8] can bind to multiple guests[4a−c] or can incite long alkyl chains to curl

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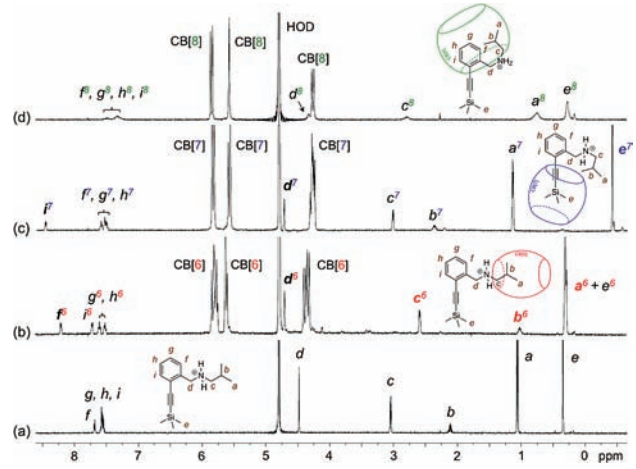

Figure 2. ^{1}H NMR spectra of (a) free guest **1a**, (b) **1a**⊂CB[6], (c) **1a**⊂CB[7], and (d) **1a**⊂CB[8] (500 MHz; 1.0 mM in D_2O, in the presence of 20 mM sodium nitrate).

up into its cavity.[4d] Here we show that CB[8] encapsulates both the aryl and the isobutyl units of guest **1a**, since hydrogens *a*−*d* and *f*−*i* are all shifted upfield (0.15−0.31 ppm). Trimethylsilyl hydrogens *e* are barely affected by CB[8], indicating that they are most probably located at a significant distance from the cavitand. Since (1) upfield shifts are mild and (2) signals undergo significant broadening, we suspect a weak interaction and possibly the presence of a mixture of rapidly equilibrating interlocked assemblies. While CB[6] and CB[7] were found to undergo slow exchange with guest **1a**, in accordance with previous reports,[2d,f] CB[8] and guest **1a** exchange quickly on the NMR time scale.

In order to fulfill the p53 protein analogy, one of the binding sites of guest **1a** must be able to undergo chemical alteration, and the rate of the alteration must be affected by the neighboring binding sites and hosts. The trimethylsilylalkynyl group satisfies these requirements, since it can be desilylated to afford phenylacetylene derivative **2a**. In order to prevent deprotonation of the ammonium unit, we opted for a silver nitrate-promoted desilylation under acidic conditions, as recently described by Pale et al.[5] The following mechanism has been proposed: (1) the silver cation interacts with the trimethylsilylalkynyl unit to form a π-complex intermediate; (2) a σ-alkynyl silver intermediate is obtained upon displacement of the trimethylsilyl group by a nucleophile (such as methanol, subsequently liberating a proton); (3) the alkynyl silver intermediate is hydrolyzed under acidic conditions to afford the desilylated product, and the free silver cation is regenerated.[5a]

(4) For a set of very recent publications, see: (a) Andersson, S.; Zou, D.; Zhang, R.; Sun, S.; Aakermark, B.; Sun, L. *Eur. J. Org. Chem.* **2009**, *8*, 1163. (b) Hwang, I.; Ziganshina, A. Y.; Ko, Y. H.; Yun, G.; Kim, K. *Chem. Commun.* **2009**, *4*, 416. (c) Rajgariah, P.; Urbach, A. R. *J. Incl. Phenom. Macrocyclic Chem.* **2008**, *62*, 251. (d) Ko, Y. H.; Kim, H.; Kim, Y.; Kim, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4106.

(5) (a) Halbes-Letinois, U.; Weibel, J. M.; Pale, P. *Chem. Soc. Rev.* **2007**, *36*, 759. (b) Viterisi, A.; Orsini, A.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 2779.

The effect of CB[6], CB[7], and CB[8] on the desilylation of guest **1a** in deuterated water was consequently studied. While desilylation in the presence of a catalytic amount of silver nitrate has been reported,[5] we opted for a large excess of the metallic cation (5.0 equiv) in order to avoid an additional level of complexity when evaluating the effect of CB[*n*] units on the desilylation kinetics. The reaction was found to be quantitative, and the concentration of byproduct trimethylsilanol-d^1 (**5**; see Figure 4) could be readily monitored by ^{1}H NMR in the presence of a known amount of an inert reference compound for quantification (*N*,*N*-dimethylformamide). Due to the bulkiness of the CB[*n*] cavitands, we expected that CB[6] and CB[7] would shield the alkynyl unit from silver attack and that the remote CB[8] would barely prevent desilylation. Amazingly, the exact opposite effect was observed (see Figure 3a), and these

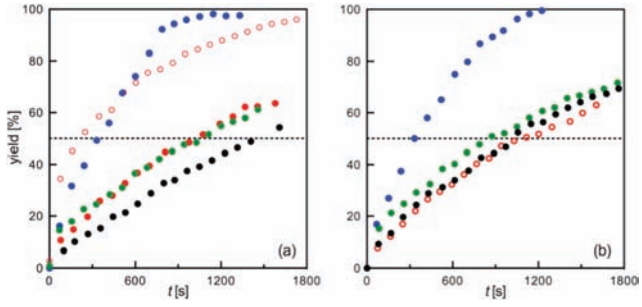

Figure 3. Yield of the Ag(I)-promoted desilylation of (a) guest **1a** and (b) guest **1b**, as a function of time (s), in the absence of CB[*n*] cavitands (black dot), as well as in the presence of 10% CB[6] (red dot), 50% CB[6] (red open dot), 10% CB[7] (blue dot), and 10% CB[8] (green dot). The yield is derived from the amount of trimethylsilanol-d^1 formed during the reaction.

experiments constitute the first rationalized examples of an organometallic reaction *catalyzed* by CB[*n*] cavitands.[6] A 10% catalytic amount of CB[7] was found to increase the rate of desilylation by 4.3 times (half-life of guest **1a** in the absence of CB[*n*] $t_{1/2} = 1.5 \times 10^3$ and 3.4×10^2 s in the presence of 10% equiv CB[7]), allosteric CB[6] increased it by a factor of 1.5 ($t_{1/2} = 1.0 \times 10^3$ s) when 10% CB[6] was used, and by a factor of 6.6 in the presence of 50% CB[6] ($t_{1/2} = 2.2 \times 10^2$ s); a similar enhancement is observed when CB[6] is replaced by CB[8] ($t_{1/2} = 1.1 \times 10^3$ s when 10% CB[8] is present, a 1.4-time rate increase).

We propose the following mechanism for the catalytic process in the presence of CB[7] (see Figure 4): (1) a fraction of guest **1a** interacts with CB[7]; (2) silver cations form π-complex **3**⊂CB[7] with assembly **1**⊂CB[7]; favorable interactions between silver and the oxygen lone pairs of the CB[*n*] portal stabilize the complex; (3) assembly **3**⊂CB[7] undergoes a nucleophilic substitution, when water displaces

(6) Catalytic hydrogenation of 1-hexanal and 1-octanal in the presence of CB[6] and ruthenium(II) has been reported; however, the role of CB[6] has not been described. See: Karakhanov, E. A.; Karapetyan, L. M.; Kardasheva, Y. S.; Maksimov, A. L.; Runova, E. A.; Terenina, M. V.; Filippova, T. Y. *Macromol. Symp.* **2008**, *270*, 106.

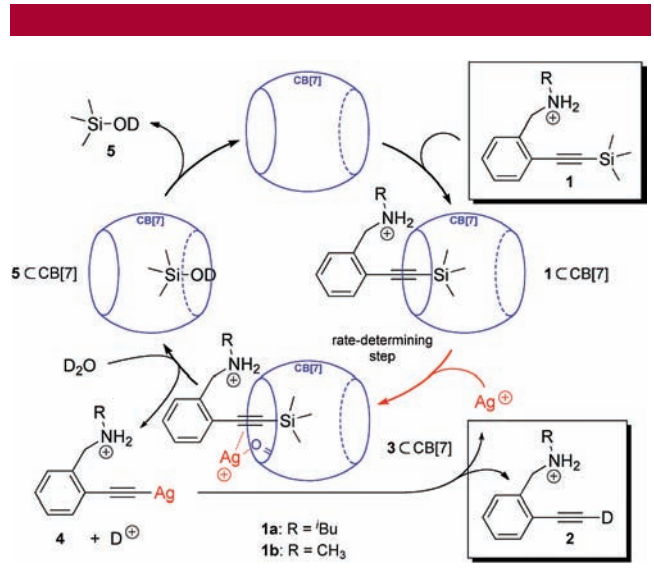

Figure 4. Plausible cycle for CB[*n*]-catalyzed desilylations in the presence of Ag(I) salts in aqueous medium.

the trimethylsilyl unit (water probably crosses the CB[7] portal and reaches the interior of the cavity before displacing the trimethylsilyl group); products of the substitution are CB[7]-bound trimethylsilanol-d_1 **5**⊂CB[7], D^+ cations and presumably alkynylsilver **4**, in analogy with the mechanism proposed by Pale et al.;[5] (4) alkynylsilver **4** is hydrolyzed in the presence of D^+ and phenylacetylene derivative **2a** is obtained quantitatively, while CB[7] liberates trimethylsilanol-d_1 (**5**) and can interact with guest **1a** as a new cycle starts (the affinity of guest **1a** toward CB[7] was found to be at least 10^3 times higher than silanol **5**).

A similar mechanism can take place when CB[7] is replaced with CB[6] or CB[8] at allosteric positions, since in both cases the carbonylated rim of the cavitand can stabilize the ternary guest/CB[*n*]/silver complex which is responsible for the desilylation rate enhancement. In both cases, trimethylsilanol-d_1 does not interact with the cavitands, which become available for the next catalytic cycle immediately after desilylation. One should also note that an additional series of concomitant host−guest interactions dramatically increase the complexity of these catalytic processes: upon desilylation in the presence of CB[6], the latter may subsequently interact with the isobutyl unit of guest **1a** and participate in a next round of catalysis, but it will also bind to the isobutyl unit of product **2a**, which thus acts as a catalyst poison. This effect is particularly damaging at higher concentrations of product **2a**, and it may explain its rapid formation during the first 100−300 s, followed by a noticeable retardation (see Figure 3a). A similar effect could be observed with CB[8], which can encapsulate the phenylacetylene unit of product **2a**, and to a far lesser extent with CB[7], which displays a low affinity toward the isobutyl unit of product **2a**.[2f]

The results described above indicate undoubtedly that CB[*n*] plays a crucial role during the formation of the alkynylsilver π-complexes. However, one may question the existence of assembly **3**⊂CB[*n*] as the key component of

the catalytic cycle and argue that the free fraction of CB[*n*] cavitands, although present at extremely low concentration and possibly coordinated with silver cations, may be responsible for the rate enhancements (i.e., CB[*n*] would not have to interact with guest **1a** in order to catalyze its desilylation).

In order to discriminate between both mechanisms, we prepared guest **1b**, which lacks the CB[6] binding site, and we subsequently determined the effect of CB[6], CB[7], and CB[8] on its desilylation rate. As expected, CB[6] does not interact with guest **1b** (see Figure 5, spectrum b), and CB[7]

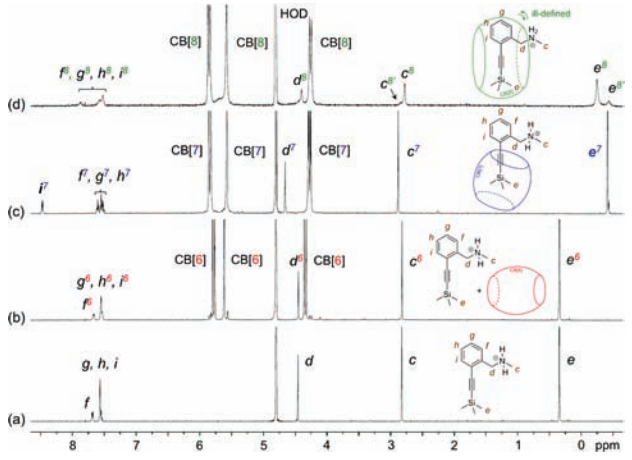

Figure 5. ^{1}H NMR spectra of (a) free guest **1b**, (b) **1b**⊂CB[6], (c) **1b**⊂CB[7], and (d) **1b**⊂CB[8] (500 MHz; 1.0 mM in D_2O, in the presence of 20 mM sodium nitrate).

displays strong affinity toward its trimethylsilyl unit; hydrogens *e* are shifted upfield by 0.77 ppm, and hydrogens *c*, *d* and *i*, close to the CB[7] rim, undergo downfield shifts (0.06, 0.20, and 0.79 ppm, respectively). The interaction between CB[8] and guest **1b** is ill-defined; the trimethylsilyl singlet *e* of free guest **1b** splits into two shielded and broad signals upon interaction with CB[8] (upfield shifts of 0.61 and 0.88 ppm; 8:1 ratio), indicating the presence of at least two slowly interconverting assemblies, in which the trimethylsilyl unit is encapsulated; hydrogens *c* undergo a similarly distributed split, and a very weak upfield shift. Hydrogens *d* are shifted upfield by 0.06 ppm (an unusual value, which suggests neither encapsulation, nor localization at the CB[*n*] portal, or possibly a rapidly equilibrating mixture at both locations); aromatic hydrogens undergo mild upfield and downfield shifts, and their location cannot be attributed with any degree of certainty.

While desilylation of guest **1a** was enhanced by a factor of 6.6 with 50% CB[6], no effect was observed in the desilylation of guest **1b** ($t_{1/2} = (1.0-1.1) \times 10^3$ in the absence or presence of CB[6]), thereby indicating that CB[6] must be bound to the guest in order to catalyze its desilylation. As expected, 10% CB[7] catalyzes the reaction (by a factor of 3.1; $t_{1/2} = 3.3 \times 10^2$ s vs 1.0×10^3 s in the absence of cavitand). CB[8] was found to have almost no effect on the desilylation rate of guest **1b** ($t_{1/2} = 8.5 \times 10^2$ s in the presence of 10% CB[8]); since several **1b**⊂CB[8] assemblies are present in the reaction mixture, we suspect that some of them favor the desilylation reaction, and others inhibit it, especially if the alkynyl unit is trapped inside the cavitand.

The structure of the key intermediates **3**⊂CB[n] is also supported by the fact that the asymmetric coordination of silver to the CB[6] portal has been reported once.[7] In addition, CB[*n*] cavitands do interact in a similar way with other metallic cations, including cesium,[8a] calcium,[8b] zinc,[8b] strontium,[8b] cadmium,[8c] and some lanthanides.[8d−f] While this study was intended as a proof of concept, we think that it will trigger the development of new CB[*n*]-containing catalytic systems, in particular for metal-catalyzed coupling reactions in aqueous medium.

Acknowledgment. This work was supported by the Department of Chemistry and Biochemistry, the College of Arts and Sciences and the Vice President for Research at Ohio University, Athens, OH.

Supporting Information Available: Preparation and characterization of CB[*n*] guests **1a**, **1b**, **2a**, and **2b**, detailed characterization of interlocked assemblies, and procedures for kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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