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Release of Guests from Encapsulated Masked Hydrophobic Precursors by a Phototrigger

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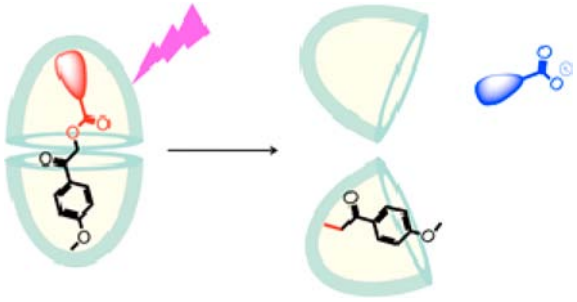
ABSTRACT



Examples of release of organic acids from encapsulated *p*-methoxyphenacyl esters provided here demonstrate the value of a phototrigger strategy to release chemicals of interest in water from hydrophobic precursors. In this study, a photochemical β-cleavage process centered on the *p*-methoxyphenacyl group is exploited to release the acid of interest from a water-soluble capsule made up of octa acid.

Interest in synthesizing new hosts and exploring the structure and characteristics of natural and synthetic supramolecular hosts has continued unabated for over five decades. Elegant examples where the excited-state chemistry and physics of a guest have been altered by the confinement and weak interactions provided by the hosts have been reported.[1−5] In this context, we have been exploring a new host, commonly known as octa acid (OA; Figure 1), to control the excited-state processes of organic guest molecules.[6]

A distinct feature of the OA capsuleplex is its dynamic character that assembles−disassembles in the time scale of a second. When containing pyrene, the capsuleplex disassembles in 2.7 s,[7] and partial opening in microsecond time scale has been established in several examples.[8] The dynamic capsuleplexes are thus suited to store and release molecules of interest.

In this study, by exploiting the light activated β-cleavage of a carbonyl compound (photorelease), we have explored the feasibility of opening a capsuleplex "at will" and releasing the contents to an aqueous exterior.[9] We have achieved this via a "phototrigger" mechanism utilizing the *p*-methoxyphenacyl group as the "trigger" and the masked acid the "load" to be released.[10,11] Molecules **1**−**6** that we

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have investigated in this context are listed in Figure 1. β-Cleavage (−CO−; with respect to the photoactive carbonyl chromophore) in all these cases where the *p*-methoxyphenacyl group is linked via an ester linkage results in the release of the carboxylic acid. Although the mechanism of the triggering process is yet to be deciphered, we have established that acids can be released from OA capsule to the aqueous medium by a light initiated process. Results of this study are presented below.

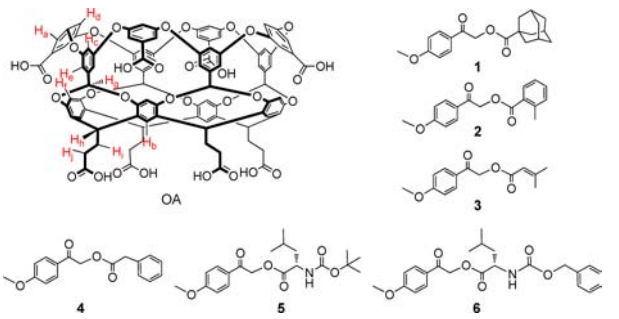

Figure 1. Structures of water-soluble cavitand, octa acid (OA), and guests.

Capsular host−guest complexes (2:1) of OA and **1**−**6** (see the Supporting Information for synthesis and spectral data) were prepared by stirring an aliquot of DMSO stock solution (5 μL) of **1**−**6** with OA in a 2:1 (host to guest) ratio in borate buffer solution (0.6 mL; pH ~ 9). In Figure 2, ^{1}H NMR spectra of OA and **1**−**6** present in D_2O in the ratio of 2:1 are displayed. Inclusion of guests within OA host was assumed from the evident upfield shift (note in Figure 2 between δ 1 and −3 ppm and see Figure S1, Supporting Information) of all methyl and methylene signals of the guests with respect to that in $CDCl_3$.[12,13] ^{1}H NMR titration data (Figures S2−S5 in the Supporting Information) as well as the diffusion constants measured by DOSY (diffusion-ordered spectroscopy) experiments (Figures S6−S11 and Table S1, Supporting Information) suggested the formation of 2:1 host−guest complexes (capsuleplexes). 2D-COSY and NOESY spectra (Figures S12−S23, Supporting Information) supported the conclusion that the methoxy group anchored the guest molecules at one tapered end of the capsule. The single set of upfield shifted signals for the guest molecules in ^{1}H NMR titration experiments suggested there were no free molecules in solution. The above studies established that guests **1**−**6** formed stable capsuleplexes in aqueous solution.

^{1}H NMR spectral recordings of the progress of the reaction from irradiation of capsuleplexes of **1**−**6** included within OA indicated complete conversion within 90 min in all cases except **3** which took ~8 h (for details see the Supporting Information). ^{1}H NMR spectra of the irradiated **1**@OA_2, **2**@OA_2, and **3**@OA_2 presented in Figures 3 and 4 confirmed the formation of acids as one of the main products. Figure 3 also provides ^{1}H NMR spectra of **1**@OA_2 before (a) and after irradiation (b) and that of independently prepared 1-adamantane carboxylic acid@OA complex (c). We have established 1-adamantane carboxylic acid forms a 1:1 cavitandplex in water.[13] The identical spectra shown in parts b and c of Figure 3 suggest that upon irradiation the capsuleplex of **1** resulted in cavitandplex of 1-adamantanecarboxylic acid. It is quite likely that 1-adamantanecarboxylic acid released to the aqueous exterior led to the formation of a 1:1 cavitandplex. Observations made with **2**@OA_2 and **3**@OA_2 establish the potential of the "supramolecular photorelease" technique. As illustrated in Figure 4b, d, independent experiments suggested that *o*-toluic acid (product from **2**) and 3,3-dimethylacrylic acid (product from **3**) preferred to reside in water even in the presence of OA. They do not form complexes with OA, for example, at δ 2.19 ppm (*o*-toluic acid) and at δ 1.62 and in the absence of OA. Comparison of the ^{1}H NMR spectra of the irradiated samples (Figure 4a, c) and signal at 1.76 due to 3,3-dimethylacrylic acid both in the presence of OA and with independently prepared samples of [acid + OA] (Figure 4b, d) revealed that upon irradiation of *p*-methoxyphenacyl esters **2** and **3** the corresponding product acids were released to aqueous exterior. Products obtained (see the Supporting Information for isolation procedures of products) and their yields as estimated by GC and HPLC (with respect to the reacted material)

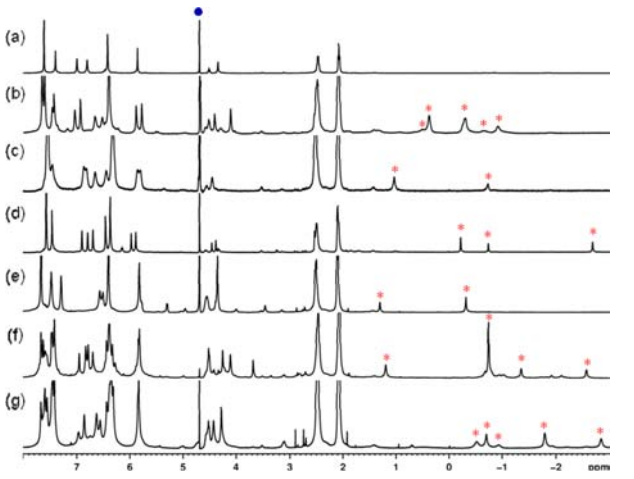

Figure 2. ^{1}H NMR (500 MHz) spectra of (a) OA ([OA] = 1 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (b) **1**@$(OA)_2$ ([OA] = 1 mM, [**1**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (c) **2**@$(OA)_2$ ([OA] = 1 mM, [**2**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (d) **3**@$(OA)_2$ ([OA] = 1 mM, [**3**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (e) **4**@$(OA)_2$ ([OA] = 1 mM, [**4**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O, (f) **5**@$(OA)_2$ ([OA] = 1 mM, [**5**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O and (g) **6**@$(OA)_2$ ([OA] = 1 mM, [**6**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O. (* indicates the bound guest proton peaks; ● indicates the residual solvent peak of water.)

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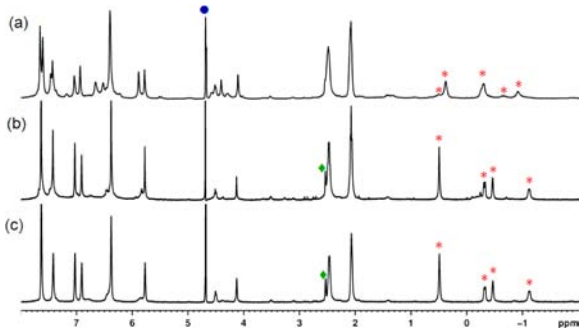

Figure 3. ^{1}H NMR (500 MHz) spectra of (a) **1**@$(OA)_2$ ([OA] = 1 mM, [**1**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (b) After 30 min irradiation (λ > 280 nm) and (c) **8**@OA ([OA] = 1 mM, [**8**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O. (* indicates the bound guest proton peaks; ● and ◆ indicate the residual solvent peak of water and DMSO-d_6, respectively.)

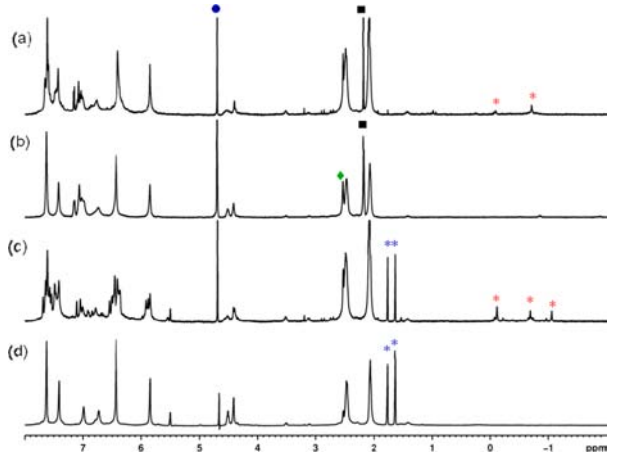

Figure 4. ^{1}H NMR (500 MHz) spectra of (a) Irradiated (λ > 280 nm, 1 h) sample of **2**@$(OA)_2$ ([OA] = 1 mM, [**2**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (b) Mixture of **11** and OA ([OA] = 1 mM, [**11**] = 1 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (c) Irradiated (λ > 280 nm, 8 h) sample of **3**@$(OA)_2$ ([OA] = 1 mM, [**3**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O; (d) Mixture of **12** and OA ([OA] = 1 mM, [**12**] = 1 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O. ("*" indicates the photoproducts). (■ and * indicate the unbound proton peaks of o-toluic acid and 3, 3′-dimethylacrylic acid, respectively; ● and ◆ indicate the residual solvent peak of water and DMSO-d_6 respectively.)

are listed in Figure 5. Conversion-independent product distribution suggests the possibility of 100% conversion of the guest without complications. *p*-Methoxyacetophenone and the corresponding acid were consistently formed upon irradiation of **1**–**6** included in OA. *p*-Methoxyphenacyl-appended OA, one of several minor products identified by ESI–MS and LC–MS, was isolated in the case of **1**–**3**. This product is readily seen under positive or negative polarity (Figures S24 and S25, Supporting Information), showing the first peak of the isotope series at *m*/*z* 1877.4

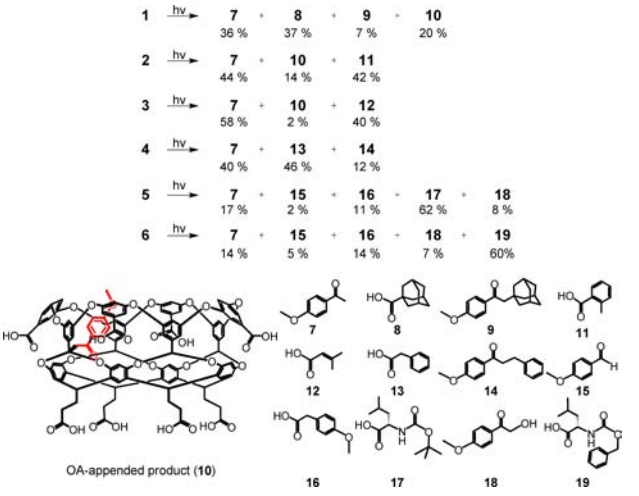

Figure 5. Product distribution upon photolysis of guests **1**–**6**@OA. Structure of products shown below equations.

and 1875.4, respectively. The fragmentation behavior is similar to the one observed for OA[14] (Figure S26, Supporting Information), while the isotope pattern simulation indicates a singly charged ion with molecular formula $C_{105}H_{73}O_{34}$ under positive polarity. On the basis of the *m*/*z* values, fragmentation behavior, and isotope distributions, we assign this product to a *p*-methoxyphenacyl-OA adduct. Although ESI–MS confirmed the formation of an adduct, the ^{1}H NMR spectra were not clean and did not permit identification of the exact structure of the adduct. Based on the abstractable hydrogen present in the interior of OA (H_g, Figure 1), we tentatively assign the structure as shown in Figure 5. No attempt was made to look for OA adducts from **4**–**6**.

The UV absorption spectra of guests **1**–**3**, *p*-methoxyacetophenone and OA shown in Figure S27 (Supporting Information) suggested that under our irradiation conditions (450 W medium pressure mercury lamp; Pyrex filter) both OA and the guests would be excited. We have shown previously OA to be an excellent triplet sensitizer with triplet energy close to 73 kcal mol^{-1}.[15] Thus, independent of which one absorbs light, we believe only the resulting triplet of the guest would be the reactive species. On the basis of the known characteristics of *p*-methoxyacetophenone,[16,17] we expect the lowest reactive triplet of **1**–**6** within the nonpolar capsule to have the $\pi\pi^*$ configuration.

Several mechanisms have been proposed for the photorelease of acids from phenacyl derivatives in organic

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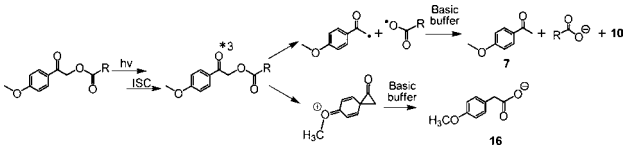
solvents which depend on polarity and hydrogen atom and electron-donating ability of the medium.[9,11,18−25] We speculate on the basis of the minor products isolated from the encapsulated **1**−**6** that the primary process triggering the release of acid depends on the structure of the guest. Lack of formation of *p*-methoxyphenylacetic acid **13** (Figure 5) from OA-encapsulated **1**−**4** suggested that the reaction did not proceed via *p*-methoxy-assisted Favosrskii rearrangement (Scheme 1).[18,22] However, this process seemed to occur to some degree in the case of **5** and **6** where *p*-methoxyphenylacetic acid was isolated in small amounts (11 and 14%). The difference in behavior between these two sets of molecules (**1**−**4** and **5** and **6**) could be attributed to the nature of their complexes with OA.

We speculate that with elongated guests, **5** and **6** cause the capsule to be slightly expanded, generating some space between the two caps. Consistent with this notion the diffusion constants for **1**−**4** were slightly larger than for **5** or **6** suggesting that the latter capsuleplexes are slightly larger. This expanded structure most likely allows the reactant guest molecule to experience leakage of the polar aqueous environment into the space and this is enough to influence the formation of *p*-methoxyphenylacetic acid via a polar intermediate.

Formation of *p*-methoxyacetophenone in all cases (**1**−**6**) could be accounted for by a homolytic β-cleavage process to yield *p*-methoxyphenylacyl and acyloxy radical intermediates (Scheme 1); isolation of small amounts of coupling products **9** and **14** resulting from the loss of CO_2 (to yield stable adamantyl radical and benzyl radical, respectively) in the case of **1** and **4** is consistent with involvement of radical intermediates.[19,21,26] Most likely, *p*-methoxyphenacyl-appended OA isolated in the case of **1**−**3** derive via the homolytic β-cleavage process followed by acyloxy radical abstracting the hydrogen (H_g) from the host OA and the cage partner *p*-methoxyphenylacyl radical coupling to the radical site resulting from the hydrogen abstraction process. Given that OA is a good hydrogen donor, we cannot rule out the possibility of hydrogen abstraction by triplet ketone followed by homolytic cleavage of the ester group to give the enol of the acetophenone. Further work is needed to fully understand the mechanism of the phototriggering process within the above supramolecular capsule.

Scheme 1. Possible Reaction Pathways for the Photolysis of Guests **1**−**6**@OA



This presentation has brought to light that an OA capsuleplex could be photochemically disassembled to release the contents. We have established "proof of principle" of a supramolecular photorelease strategy that has the potential to release chemicals of interest in water from hydrophobic precursors. It is important to recognize that without the aid of OA, these hydrophobic precursors could not be solubilized in water. Further studies with phenacyl and related systems as triggering agents[9] within organic capsules are currently underway in our laboratory. These along with planned time-resolved studies, we hope, would provide a better understanding of the mechanism of photorelease of OA encapsulated guest molecules.

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Supporting Information Available. Sample preparation and irradiation procedures, isolation and characterization of products, and additional NMR and absorption spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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