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Melding Caged Compounds with Supramolecular Containers: Photogeneration and Miscreant Behavior of the Coumarylmethyl Carbocation

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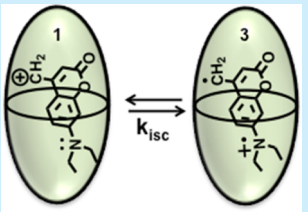
Supporting Information

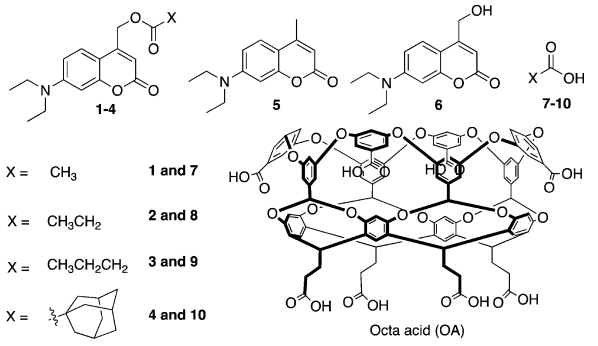
ABSTRACT: By merging well-established concepts of supramolecular chemistry, protecting group strategy, and photochemistry, we have solubilized in water hydrophobic organic molecules consisting of a photoactive protecting group and masked carboxylic acids, released the desired acid, and confined a reactive carbocation intermediate within a capsule. Confinement of the photogenerated carbocation brought out the latent radical-like behavior. This observation is consistent with the recent theoretical prediction of the 7-(diethylamino)coumarinyl-4-methyl carbocation having a triplet diradical ground-state electronic contribution.



Light control of vectorial, spatial, and timely delivery of molecules of chemical and biological interest have attracted intense interest during the past decade.[1−3] The strategy conceals the molecule of interest with a protecting group that releases it upon exposure to light. Since the molecule of interest is released with a photon instead of a chemical agent, the group is termed a photoremovable protecting group (PPG). Thus, a PPG is covalently linked to the molecule to be released, i.e., the leaving group (LG).[2] Ideally, a PPG−LG should undergo rapid, efficient photoreaction, be water soluble, absorb in the visible−near-IR, release the LG at a given location, and discard the spent PPG after the release. Among the various known PPGs, 7-(diethylamino)coumaryl-4-methyl (DEACM) derivatives are currently under intense scrutiny.[3−8] In this paper, we explore the added value of supramolecular concepts to enhance the utility of the PPG strategy.[9,10] As a model, we experiment with the delivery of carboxylic acids of different sizes in an aqueous medium using the DEACM derivative as the PPG and water-soluble octa acid (OA)[11] as the supramolecular host. In this approach, we encapsulate a PPG−LG molecule in the hydrophobic interior of an OA capsule and release the carboxylic acid (LG) therein by exciting the host−guest complex above 400 nm. The supramolecular encapsulation has enabled us to solubilize even hydrophobic PPG−LG molecules in aqueous media, and the host retains the coumarin remains following the release of the carboxylic acid. More importantly, this approach revealed a thus far unobserved property of the DEACM carbocation, namely the triplet diradical.[12] Structures of the octa acid host, the PPG−LGs, the released carboxylic acids, and the coumarin byproducts are shown in Scheme 1.

Procedures for the synthesis of DEACM-LG **1**−**4** (Scheme 1), their spectral data (Figures S1−S16), methods for their host−guest complexation with OA in phosphate/borate buffer, and procedures for irradiation and analyses of photoproducts are

Scheme 1. Structures of Water-Soluble Octa Acid Cavitand, 7-Diethylaminocoumaryl-4-methyl Esters 1−4, Released Carboxylic Acids 7−10, and Photoproducts 5 and 6



provided in the SI. Host−guest complexation was monitored by UV−vis, fluorescence, and ^{1}H NMR spectra. The PPG investigated here, 7-(diethylamino)-4-methylcoumarin (**5**), is well-known to display solvent-dependent emission and absorption spectral features including maxima, lifetimes, and fluorescence efficiencies.[13] Therefore, the PPG linked to the leaving groups in **1**−**4** serves as a sensitive probe for revealing the location and orientation of the ester ensemble prior to, during, and after photolysis.

As illustrated in Figure 1 and Figures S17−S24, the extent of the shift in absorption and fluorescence maxima in an aqueous solution between OA complexed and free **1**−**4** depends on the structure of PPG−LG. ^{1}H NMR spectral titrations (Figure S32) as well as DOSY data (Figure S33) suggested that trigger **1**, similar to **5**, formed a 1:2 capsuleplex with OA.[14] The signals due

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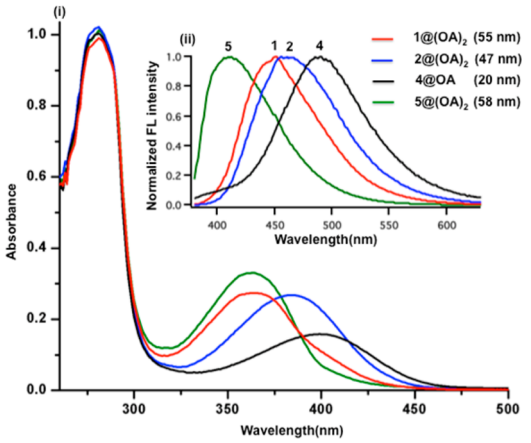

Figure 1. (i) Absorption spectra of **1**@$(OA)_2$ (red), **2**@$(OA)_2$ (blue), **4**@OA (black), and **5**@$(OA)_2$ (green); ([guest] = 2.5×10^{-5} M, [OA] = 5×10^{-5} M in phosphate buffer/H_2O, pH = 7.4). (ii) Representative normalized emission spectra of **1**@$(OA)_2$, **2**@$(OA)_2$), **4**@OA, and **5**@$(OA)_2$. Observed shifts with respect to aqueous media absent the OA are included in parentheses. For spectra of all four triggers, see Figure S27.

to the methyl groups of $OCOCH_3$ and NCH_2CH_3 are shifted upfield (δ ~1.0 to −2.5 ppm) (Figure 2, see the dotted red lines

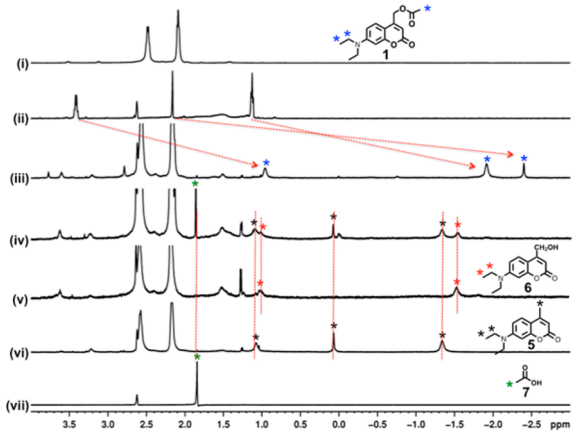

Figure 2. ^{1}H NMR spectra (500 MHz, in 10 mM phosphate buffer/D_2O, pH = 8.7) of (i) OA ([OA] = 1 mM), (ii) **1** ([**1**] = 0.5 mM), (iii) **1**@$(OA)_2$ ([OA] = 1 mM and [**1**] = 0.5 mM), (iv) 5 h irradiation of (iii), (v) **6**@$(OA)_2$ ([OA] = 1 mM and [**6**] = 0.5 mM), (vi) **5**@$(OA)_2$ ([OA] = 1 mM and [**5**] = 0.5 mM), and (vii) acetic acid. The colored stars "***" indicate the upfield-shifted signals due to the guests included within OA. The green star "*" indicates the methyl signal due to free acetic acid in aqueous medium.

connecting (ii) and (iii)), suggesting that these two groups are deeply submerged in the OA cavities, extending end to end between the two interior poles of the capsule through C−H---π interactions.[15] Interestingly, the absorption and emission maxima for OA complexes of **1**−**4** are not the same (Figure 1 and Figures S17−S24). Had the emitting chromophore in **1**−**4** been located in the same environment within the OA capsule, one would expect the absorption and emission maxima to be the same for all guests. The difference in the maxima is a consequence of the exposure of the PPG's fluorophores to differing populations of water molecules. As the size and length of the ester group increases (methyl, ethyl and propyl) in **1**−**3**, the emission maxima shift to longer wavelengths, closer to those observed in solvent water. It is further possible that longer guests exceed the OA capsule capacity, as in the case of **4**, and expose the 7-(diethylamino)coumaryl group, the less hydrophobic part of the guest, to external water molecules (for a cartoon visualization see Figure S48).

For adamantyl ester **4**, the emission maximum appears at 490 nm (λ_{max} in water 470 nm), suggesting that the coumaryl chromophore is in the most highly polar environment compared with the other three. Consistent with this, the ^{1}H NMR spectrum revealed **4** to form a 1:1 host−guest cavitandplex with the adamantyl portion fully within the OA and the chromophore portion exposed to the solvent H_2O (Figure 3).[16] Adamantyl

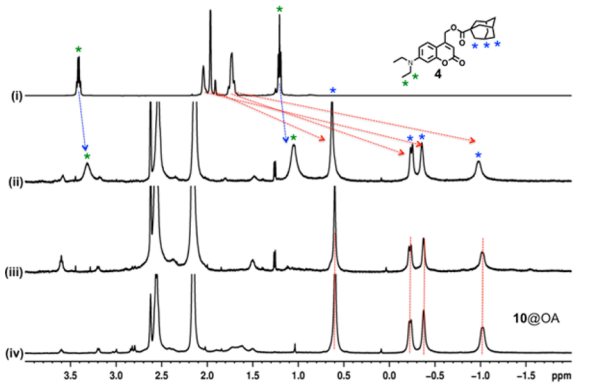

Figure 3. ^{1}H NMR spectra (500 MHz) of (i) **4** in $CDCl_3$, (ii) **4**@OA ([OA] = 1 mM and [**4**] = 1.0 mM in 10 mM phosphate buffer buffer/D_2O, pH = 8.7), (iii) 20 min irradiation of (ii), (iv) **10**@OA ([OA] = 1 mM and [**10**] = 1.0 mM in 10 mM $Na_2B_4O_7$ buffer/D_2O, pH = 8.7). The colored stars "***" indicate the upfield shifted signals due to the guests included within OA. The green star "*" in (ii) indicates the signals due to NCH_2CH_3 exposed to water.

hydrogens were shifted upfield (δ 0.8 to −1 ppm), whereas the diethylamino hydrogens at δ 3.3 and 1.1, were similar to their positions in $CDCl_3$ (see the dotted red and blue lines connecting i and ii). Excess OA had little effect on the positions of the NCH_2CH_3 signals, but did broaden them due to the dynamic equilibria from capping-decapping of the OA cover on the diethylamino end. Among the four esters, the adamantyl ester **4** is unusual: (a) The extended length of the adamantyl carboxylate exceeds the length of the capsule and (b) the more hydrophobic adamantyl group prefers the OA and exposes the less hydrophobic DEACM group to water (Figure 3 and Figure S37).

Based on absorption, emission and ^{1}H NMR spectra (Figure 1 and Figures S18, S19, S22, S23, S35, and S36) we conclude that **2** and **3** formed 1:2 elongated capsuleplexes less compact than **1**. In these cases, the emitting DEACM group is partially exposed to the aqueous media at the middle of the capsule. The dynamic nature of the varying exposure of these two complexes is revealed through the broadening of the ^{1}H NMR signals when excess OA is present (Figures S35 and S36). Thus, the OA complexes of **1**-**4** provided ample opportunity for irradiation and thus examination of the photochemistry of DEACM-LG in a confined space while monitoring the systematic variation of the polarity of their environment. The effects of these variations on the photochemistry of **1**@OA_2 (1:2 complex) and **4**@OA (1:1 complex) are described below, whereas that of **2**@OA_2 and **3**@OA_2 are only briefly mentioned (for spectral details, see the SI).

Progress of the photoreactions of **1**-**4** was followed by ^{1}H NMR, LC-DAD-MS and fluorescence. ^{1}H NMR provided the product identities and quantitative estimate of released

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carboxylic acids, LC-DAD-MS permitted quantitative estimates of the two coumarin derived products **5** and **6** and fluorescence monitored the change in the environment around the coumarin moiety. Although carboxylic acids were quantitatively released, we were concerned with our inability to obtain a good mass balance with respect to the coumarin PPG. Early literature dealing with **5** as a laser dye had identified at least five photoproducts of dimerization, oxidation and radical reactions.[17−19] We suggest that the poor mass balances could be due to side reactions resulting from **5** and **6** that, as they are formed, begin to compete for incident light with **1**. Although several small peaks were observed by LC-DAD-MS, sufficient amounts for spectral identification could not be isolated or characterized.

Plots of product yields vs time as monitored by LC-DAD-MS are provided in Figure 4 and Figures S40 and S41. Analysis of

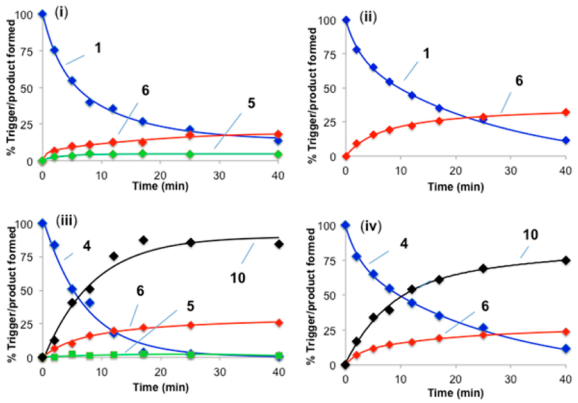

Figure 4. Solvolysis of **1** and **4** under different conditions: (i) photosolvolysis of **1** in aqueous buffer with OA (λ > 300 nm), N_2 atmosphere; (ii) photosolvolysis of **1** in aqueous buffer with OA (λ > 300 nm), under air; (iii) photosolvolysis of **4** in aqueous buffer with OA (λ > 300 nm), N_2 atmosphere; (iv) photosolvolysis of **4** in aqueous buffer with OA (λ > 300 nm), air equilibrated. [**1**] = 100 μM, [OA] = 200 μM in 10 mM $Na_2B_4O_7$).

these results as well as ^{1}H NMR spectra leads to the following conclusions: (a) The DEACM-LG **1** thermally hydrolyzes very slowly resulting in the release of acetic acid and formation of **6** in the buffer solution; ∼ 50% conversion in 10 h (Figure S45(i)). (b) In contrast, OA protects **1** from thermal hydrolysis and release of **6** and acetic acid are reduced to ∼5% conversion in 10 h in the dark (Figure S45(ii)). This confirmed that access of water to the encapsulated **1** is restricted by OA. (c) According to ^{1}H NMR, irradiation of **1**@OA_2 quantitatively releases acetic acid within 5 h (Figure 2(iv)). (d) ^{1}H NMR spectra of irradiated **1**@OA_2 under nitrogen saturated conditions surprisingly revealed an unexpected photoreduction product **5** along with the expected PPG hydrolysis product **6** and acetic acid (Figure 2(iv), (v), (vi) and (vii)). (e) It is clear from the fluorescence maxima (Figure S43 and S44) and ^{1}H NMR spectra (Figure 2(iv), (v), (vi), and (vii)) that **5** and **6** formed from the photolysis of **1**@OA_2 had remained within the capsule. (f) ^{1}H NMR spectra, and product analyses by LC-DAD-MS of irradiation of **2** and **3** (Figures S39, S40 and S46) further confirmed reactivity similar to **1**@OA_2.

The photochemistry literature on DEACM-LG esters in aqueous media report hydrolysis to **6** is the major or exclusive photoproduct.[6,7,20−22] In contrast, as illustrated in Figure S47(i), excitation of **1**@OA_2 under nitrogen-saturated conditions resulted in **5** as well as **6** along with many other undetermined products in small amounts. Surprisingly, formation of **5** is suppressed when the irradiation was conducted under air-saturated conditions (Figure S42(ii)). We conclude that formation of **5** only occurs within OA and must be ascribed to the influence of the capsule on the photochemical divergence observed.

The photochemical outcome of the 1:1 OA complex of **4** is clearly different from the 1:2 complexes of **1**−**3** with OA. A comparison of the ^{1}H NMR spectrum of the irradiated sample with that of the authentic **10**@OA confirmed that, following the release, the more hydrophobic adamantyl carboxylic acid still prefers the hydrophobic OA cavity rather than water (Figure 3(iii) and (iv); see the dotted red lines connecting (iii) and (iv)). Interestingly, in this case even under nitrogen-saturated conditions, **6** continues to be the preferred product (Figure 4(iii) and Table S1). Since **4** forms an open OA cavitandplex (Figure S43) the trigger is exposed to water and probably undergoes the same reaction as when it is in aqueous media. This is consistent with our postulate that **5** is formed only within a hydrophobic closed capsule. Thus, the photobehaviors of **1** and **4** within OA bring out two extremes of the influence of confinement on the photorelease process.

Formation of the photoproducts **5** and **6** from the photo-triggers of **1**−**3** within OA under nitrogen suggests that both radical and carbonium ion intermediates are generated during their photochemistry. But in aqueous solution in the absence of OA as outlined above only **6** is produced (Figure S45(iii) and (iv)). To identify whether the triplet (T_1) is involved in the photorelease, the fluorescence intensities were compared under nitrogen and oxygen saturated conditions (Figure S31). Oxygen had no effect on the fluorescence intensity of **1**@OA_2 nor on the production of the carboxylic acid. However, unexpectedly the oxygen altered the ratio of **1**@OA_2 conversion to **5** and **6**. LC-DAD-MS analysis under aerated and nitrogen-saturated conditions confirmed that **5** is not formed in the presence of oxygen (Figure S47(ii)). Thus, it is clear that the presence of oxygen selectively favors the formation of **6**. At low conversions, the initial degradation rates are the same within the experimental error (Tables S2 and S3). However, at higher conversions, secondary products formed in the presence of oxygen in small amounts could not be identified.

The differences in photobehavior of DEACM-LG between isotropic and confined media resembles the chemistry of diradical and carbene intermediates in solution and within OA.[23,24] Assuming that the ion pair resulting from DEACM-LG would also show a difference in behavior between a confined capsule and an isotropic aqueous solution, we sought the origin of the unusual formation of **5** on the basis of the confinement effect. Albright and Winter, through UB3LYP calculations, proposed that the disjointed DEAC−CH_2 cation exists as a closed-shell singlet in equilibrium with its open-shell triplet.[12] They calculated that the open-shell triplet diradical is, in fact, 9 kcal/mol more stable than its closed-shell singlet. In our hands and as suggested,[12] the closed-shell singlet cation in isotropic aqueous solution is more rapidly trapped by the solvent to give **6**. However, when confined within the hydrophobic OA capsule and in the absence of nucleophilic agents, the singlet has sufficient time to intersystem cross to the lower energy open shell triplet (Scheme 2 and Figure S49).[12] While reactions of the ground-state triplet DEACM carbocation have not been reported, reduction and hydrogen abstraction are possible processes that would lead to **5**. The absence of this product in the presence of oxygen could be due to trapping of the triplet

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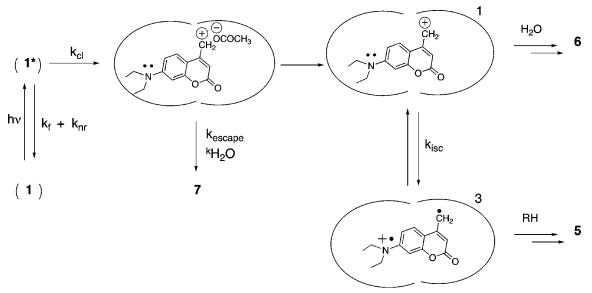
Scheme 2. Suggested Mechanism for the Photorelease of Carboxylic Acids from DEACM Acetate within the Octa Acid Capsule[a]



[a]For a detailed scheme, see Figure S44.

diradical by oxygen. Further support for the above rationale comes from the photobehavior of **4**@OA. In this case, **6** is the major product and **5** is formed only in very minor amounts (Figure 4(iii) and (iv)), consistent with the model that the DEACM carbocation is exposed to the aqueous environment outside the open end of the cavitand. While it is quite possible that **5** could be formed by a homolytic process, especially within a nonpolar cavity, our earlier studies with 4-methoxyphenacyl[10] and 7-methoxycoumaryl-4-methyl[25] derivatives, which are known to include homolytic components (or intermediates), formed OA adducts. The absence of such products in the current system suggested that the cleavage occurs preferentially, if not exclusively, by a heterolytic process as observed with 4-hydroxyphenacyl esters.[26] The triplet radical most likely abstracts the benzylic hydrogen present in the interior of the capsule to yield **5**.

By incorporating supramolecular chemistry concepts, we have been able to expand the utility of the photoprotecting group strategy to hydrophobic systems and provide a unique method for removing the remains following the delivery of the desired molecular target. Our ability to enclose and isolate the PPG−LG and photogenerate carbocation within a "dry" capsule has created a miniature single molecule hydrophobic "laboratory" for us to probe the computational predictions[12] regarding the electronic nature of the DEACM carbocation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01572.

Experimental procedures; ^{1}H NMR, ^{13}C NMR, UV, and ESI-MS spectra for all new compounds; irradiation procedures; COSY, DOSY, and ^{1}H NMR titration spectra of host−guest complexes; progress of photoreactions as monitored by ^{1}H NMR, LC-DAD-MS, and fluorescence (PDF)

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Notes

The authors declare no competing financial interest.

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