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Photorelease of Incarcerated Caged Acids from Hydrophobic Coumaryl Esters into Aqueous Solution

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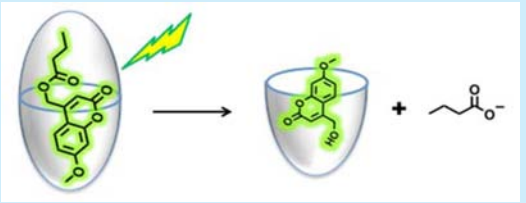
Supporting Information

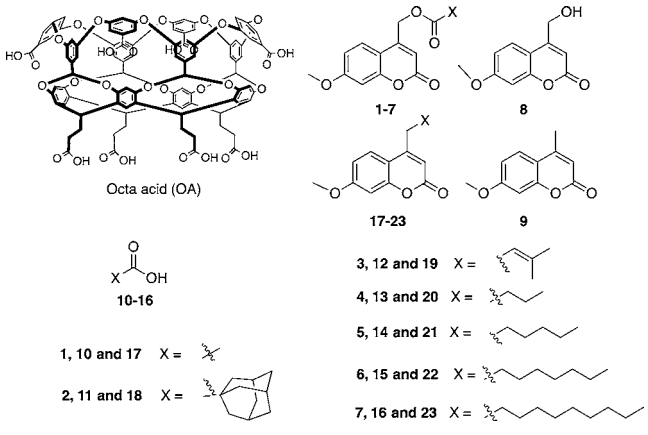
ABSTRACT: Photolysis of aqueous solutions of carboxylic acid esters of 7-(methoxycoumaryl)-4-methanol included within the capsule made up of two molecules of octaacid released the acids in water. The trigger 7-(methoxycoumaryl)-4-methyl chromophore remains within octaacid either as the alcohol or as an adduct with the host octaacid through a hydrogen abstraction process. The method established here offers a procedure to release hydrophobic acid molecules in water at will in a timely manner with light. In addition, the system offers an unanticipated opportunity to probe the mechanistic dichotomy of a diradicaloid intermediate expressing both radical and ionic behavior when generated by coumarylmethyl ester photolysis in a hydrophobic environment.



By combining two fundamental photochemical concepts, namely "supramolecular encapsulation"[1,2] and "photo-triggering",[3,4] we show in this report that it is possible to solubilize and isolate hydrophobic molecules in water and release their cargo with light as the reagent. Such an encapsulation has also enabled us to reveal the existence of a latent radical pathway during phototriggering using a coumaryl photoprotecting group. One aspect of supramolecular photochemistry involves a study of the excited-state behavior of an isolated molecule within a water-soluble host. We have recently established that excited-state behavior of molecules can be altered by fully encapsulating them within a closed molecular capsule formed by octaacid (OA).[5] Because most excited-state processes are much more rapid than the disassembly of the capsule,[6,7] photophysical and the initial photochemical excited-state processes are frequently completed before substrate is exposed to or interacts with the solvent. This prompted us to explore whether we could vary the phototrigger process within the capsule in order to expose the photolysis intermediates to an aqueous environment during the release process. Such a possibility would be of extreme interest in delivering drugs, releasing fragrances and pheromones, examining dynamics of biological systems, and initiating polymerization in lithographic and electronic applications.[8−12] Varying the photorelease mechanics and rates would enable us to probe the dynamics of disassembly ↔ assembly of the OA capsule.

In this study, we have exploited the well-known caging analogues as esters of the 7-(methoxycoumaryl)-4-methyl chromophore.[13−18] The photolyses were carried out in water at pH 8.7 with OA[19] as the solubilizing host for the caged esters **1**−**7** (Scheme 1). Our results establish that acids **10**−**16** are released from esters **1**−**7** by exposure to UV light. Interestingly,

Scheme 1. Structures of Water-Soluble OA Cavitand, 7-(Methoxycoumaryl)-4-methyl Esters 1−7, and the Released Carboxylic Acids and Photoproducts



these and the byproducts formed could be rationalized on the basis of formation of a diradicaloid intermediate,[20,21] providing a pathway to radical-derived products within the OA capsule and ion-derived products outside of the capsule.

The 7-(methoxycoumaryl)-4-methyl esters **1**−**7** were synthesized by methods reported[22] in the Supporting Information and were characterized by their ^{1}H and ^{13}C NMR, UV−vis, fluorescence, and mass spectral analyses (Figures S1−S28 and S32−S41). Inclusion of esters **1**−**7**

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within OA was achieved by incrementally adding a DMSO stock solution of the esters to aqueous solutions of OA at pH 8.7 in $Na_2B_4O_7$ buffer. Encapsulation of the esters by OA was confirmed from the characteristic ^{1}H NMR shifts of the ester's aliphatic protons (notice the signals below δ 0.5 in Figures 1, 3, and 4). The NMR signals of the guest within OA were assigned with the help of COSY spectra of the complexes (Figures S42–S55). On the basis of ^{1}H NMR titration experiments and integration of the host and guest ^{1}H NMR signals (Figures S56 and S57), the molar ratio of ester to OA was established to be 1:2 guest/host, e.g., **1**@$(OA)_2$. A decrease in the fluorescence intensity of the esters was noted upon addition of OA to the ester solution (Figures S34 and S36–41).[23] This is consistent with reports that 7-methoxycoumarin derivatives have higher emission yield in polar relative to nonpolar media.[24,25]

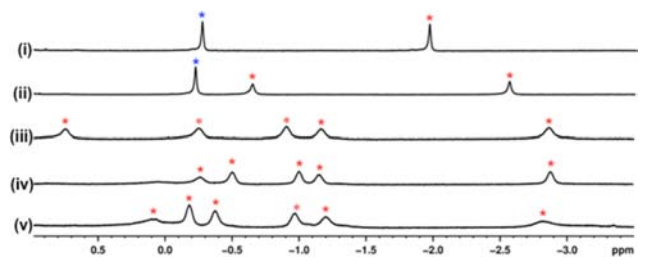

Figure 1. Selected guest region of the ^{1}H NMR spectra of the complexes [guest@$(OA)_2$ (2:1)]: (i) **1**, (ii) **3**, (iii) **5**, (iv) **6**, (v) **7**. The blue asterisk indicates the −OMe proton peak of OA-bound guest, and the red asterisk indicates the OA-bound guest aliphatic proton peaks.

Of the seven esters examined, **1**, **3**, and **4** were soluble, **5** was sparingly soluble, and **2**, **6**, and **7** were insoluble in water (Figure 2 and Figure S32). Despite their differences in inherent solubility, esters **1**–**7** were soluble in water in the presence of OA according to ^{1}H NMR, absorption, and emission spectra (Figure 2 and Figure S32). Separate UV–vis spectra of **2**, **4**, and OA in aqueous $Na_2B_4O_7$ buffer media at pH 8.7 are compared with their corresponding OA complexes in Figure 2. The coumaryl chromophore is sufficiently red-shifted to ensure that, upon irradiation of the complex above 300 nm (Pyrex filter), only the guest 7-(methoxycoumaryl)-4-methyl esters absorb incident light.

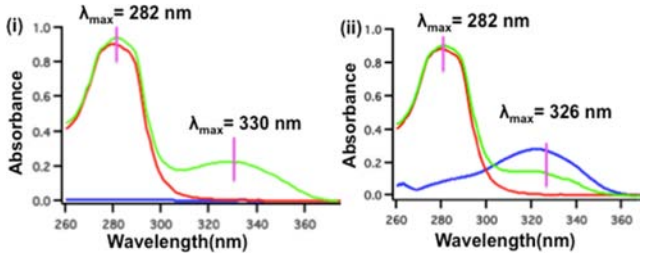

Figure 2. (i) UV–vis spectra of OA (red), **2** (blue), and **2**@$(OA)_2$ (green); (ii) UV–vis spectra of OA (red), **4** (blue), and **4**@$(OA)_2$ (green) at [guest] = 50 μM, [OA] = 100 μM in $Na_2B_4O_7$ buffer/H_2O.

Photorelease of the acids **10**–**16** from coumarylmethyl esters **1**–**7** was accomplished by irradiating the OA complex at $\lambda >$ 300 nm employing a 450 W medium-pressure mercury/xenon lamp and a Pyrex filter in aqueous borate buffer. Release of the acid was monitored by recording ^{1}H NMR (Figures S64–S70) and emission spectra (Figures S60–S63) and by analyzing the irradiated samples by LC–MS (Figures S72 and S73). The coumarylmethyl photoprotecting group (PPG) is known to react through its singlet state and is much less efficient (Φ = 10^{-3}) than other well-known PPGs such as the *o*-nitrobenzyl (oNB) and *p*-hydroxyphenacyl (pHP) chromophores.[3,4,13] This apparently remains the case when **1**–**7** are encapsulated in OA since these release reactions required longer irradiation times; in some cases, several hours of exposure were required.

The environment surrounding the released acid was identified through ^{1}H NMR spectra of the irradiated solution. In Figures 3 and 4, partial ^{1}H NMR spectra of the phototrigger, the OA complex, irradiated sample, and the acid are shown. Clearly, in the case of **2**, the spectrum of the irradiated sample was identical to that of the 1:1 complex of 1-adamantyl carboxylic acid and OA (Figure 3). On the other hand, in the case of **4**, the spectrum of the irradiated sample was identical with that of butyric acid in borate buffer solution (Figure 4). On the basis of ^{1}H NMR spectra of the irradiated solutions (Figures 3 and 4 and Figures S64–S70), we conclude that when acids **10**–**16** are released upon irradiation of the OA complexes of **1**–**7** the released acids prefer either the interior of

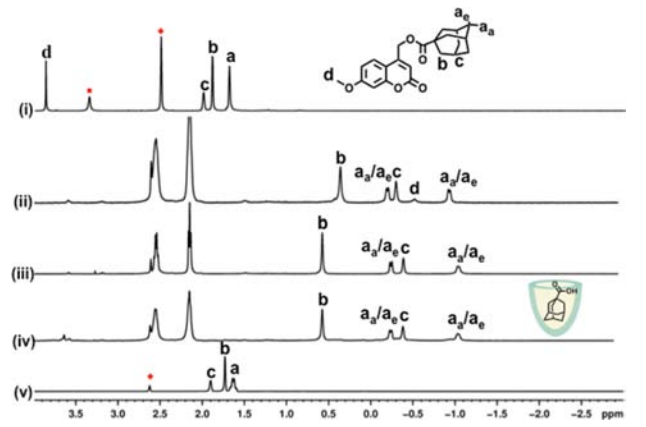

Figure 3. ^{1}H NMR spectra (500 MHz, 10 mM $Na_2B_4O_7$ buffer/D_2O, pH = 8.7) of (i) **2** in DMSO-d_6 (ii) **2**@$(OA)_2$ ([OA] = 1 mM and [**2**] = 0.5 mM); (iii) 30 min irradiation of (ii) at ($\lambda \geq$ 300 nm); (iv) 1-adamantanecarboxylic acid@OA ([OA] = 1 mM, [1-adamantanecarboxylic acid] = 1.0 mM); (v) 1-adamantanecarboxylic acid in $Na_2B_4O_7$ buffer/D_2O. Symbols ◆ and ■ indicate the residual solvent peaks of DMSO-d_6 and water, respectively. For full spectra, see Figure S65.

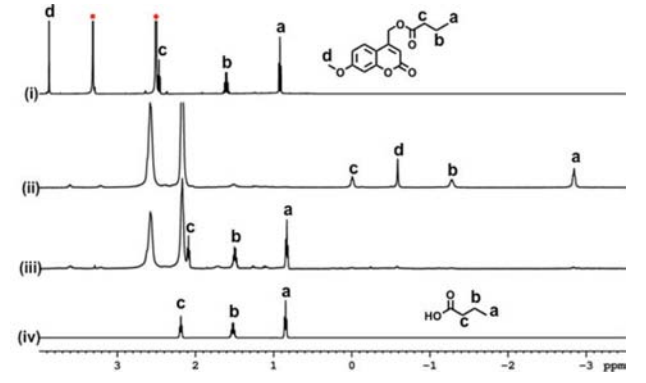

Figure 4. ^{1}H NMR spectra (500 MHz, 10 mM $Na_2B_4O_7$ buffer/D_2O, pH = 8.7) of (i) **4** in DMSO-d_6, (ii) **4**@$(OA)_2$ ([OA] = 1 mM and [**4**] = 0.5 mM), (iii) 5 h irradiation of (ii) at ($\lambda \geq$ 300 nm), (iv) butanoic acid in $Na_2B_4O_7$ buffer/D_2O. Symbols ◆ and ■ indicate the residual solvent peaks of DMSO-d_6 and water. For full spectra, see Figure S67.

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Table 1. Yields of Photoproducts (%) Based on Consumed Ester upon Photolysis of OA Complexes of Coumarylmethyl Esters 1−7 in Aqueous Borate Buffer at pH 8.7[a]

	yields of photoproducts (%)				
reactant molecules	**8**[b]	**9**[b]	**17−23**[c,d]	OA-Cou[c]	X-COOH (**10−16**)
1	74 ± 7	<0.5	<0.5 (**17**)	14 ± 4	98 ± 1 (**10**)[e]
2	81 ± 6	1 ± 0.3	7.8 ± 2 (**18**)	6 ± 2	90 ± 5 (**11**)[f]
3	70 ± 5	<0.5	<1 (**19**)	7 ± 2	94 ± 1 (**12**)[e]
4	69 ± 7	1.2 ± 0.4	3 ± 0.5 (**20**)	7 ± 2	86 ± 5 (**13**)[e]
5	68 ± 6	1.5 ± 0.3	3 ± 0.5 (**21**)	10 ± 2	82 ± 5 (**14**)[e]
6	57 ± 6	0.9 ± 0.3	<1 (**22**)	8 ± 3	72 ± 8 (**15**)[f]
7	48 ± 8	0.7 ± 0.4	<1 (**23**)	12 ± 3	69 ± 6 (**16**)[f]

[a]Error limits are ±10%. [b]Determined using authentic standards by liquid chromatography coupled to a diode array detector (LC−DAD) at 320 nm. [c]Determined assuming ε of 7-methoxy-4-methylcoumarin at 350 nm. [d]X = methyl, adamantyl, 2-methylpropenyl, hexyl, pentyl, heptyl, and nonyl. [e]Determined by NMR. [f]Determined using authentic standards employing LC−MS with negative polarity.

OA or the aqueous base exterior, depending on their hydrophobicity. Further work is needed to understand the differences in time required to achieve the same conversion from different triggers (**1**−**7**).

As expected, the 7-(methoxycoumaryl)-4-methyl chromophore is hydrolyzed primarily to the corresponding alcohol **8** (50−82%; Table 1). LC−MS (Figure 5) and fluorescence

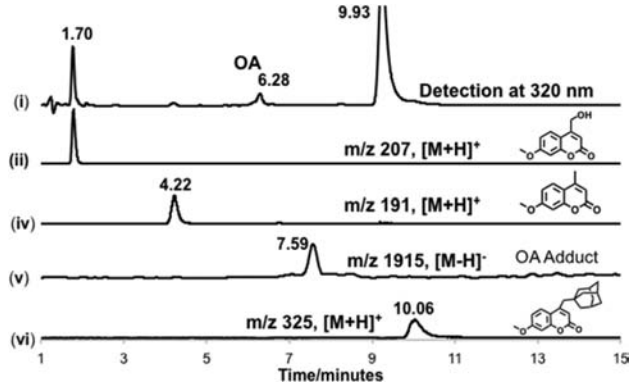
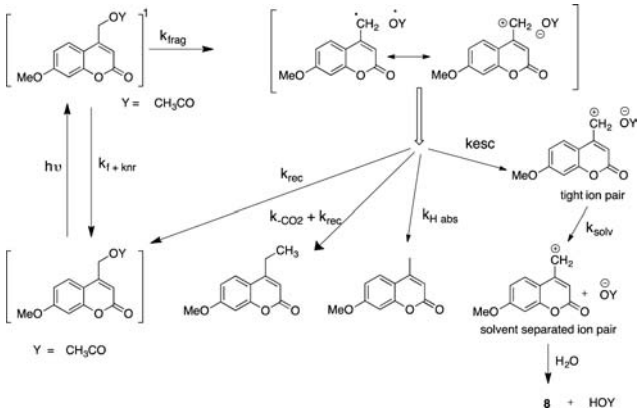


Figure 5. LC−DAD and LC−MS traces of **2**@$(OA)_2$ after 30 min irradiation (λ > 300 nm). (i) LC−DAD trace at 320 nm, (ii) single ion trace at m/z 207, corresponding to $[M + H]^+$ of 7-(methoxycoumaryl)-4-methanol, (iii) single ion trace at m/z 191, corresponding to $[M + H]^+$ of 7-methoxy-4-methylcoumarin, (iv) single ion trace at m/z 1915, assigned to $[M - H]^-$ of a 7-(methoxycoumaryl)-4-methanyl OA adduct, (v) single ion trace at m/z 325, assigned to $[M + H]^+$ of 1-(7-(methoxycoumaryl)-4-methanyl)adamantane, the decarboxylated **2**.

(Figures S60−63) confirmed the formation of **8** as the major product. Formation of minor amounts (∼15%) of radical-derived products was identified by LC−MS. These include 7-methoxy-4-methylcoumarin (**9**) (<2%) formed by H-abstraction from OA by the 7-(methoxycoumaryl)-4-methyl radical and coupling products from homolytic decarboxylation of the esters (∼15%) (see Figure 5, spectra b) in Figures S4, S8, S12, S16, S20, S24, S28, and S73 in the SI). Evidence for the above OA-coupling products was obtained from the m/z values and fragmentation patterns acquired by liquid chromatography (LC) coupled to mass spectrometry (LC−MS, Figure 5) and by electrospray ionization mass spectrometry (ESI-MS) by infusion of the photolyzed ester@OA samples. The coupling products gave m/z isotopic distributions that were in good agreement with the simulated spectra based on the predicted molecular formula (Figure S72). On the basis of these identified products, it is clear that the photorelease is occurring via both ionic (major) and radical (minor) pathways.

Prior studies have established the nature of the lowest excited singlet state of coumarylmethyl esters to depend on the environment, nπ^* in nonpolar and $\pi\pi^*$ in polar medium.[26] Since the internal polarity of the OA capsule is benzene-like, the photoreaction of OA-encapsulated coumarylmethyl esters are expected to originate from the nπ^* singlet state. Consequently, a reasonable mechanistic sequence for coumaryl methyl esters in OA capsules accommodates formation of both radical and ionic derived products and includes the following: (a) excitation of 7-methoxycoumaryl ester to its nπ^* excited state; (b) decay of the excited state via fluorescence and homolysis of the CH_2−OCO bond to a diradicaloid species that has both radical and ionic character (radical pair−ion pair); (c) partition of the diradicaloid intermediate among processes including recombination (k_{rec}), decarboxylation (k_{-CO2}), and H-abstraction ($k_{H\text{-}abs}$) via the radical pathway and solvolysis (k_{solv}) through the ion pair component, as depicted in Scheme 2.

Scheme 2. Suggested Mechanism for the Photorelease of Carboxylic Acids from Their 7-(Methoxycoumaryl)-1-methyl Esters within OA Capsules



The solvolytic route would be favored in highly polar media, whereas the radical pathway is favored in nonpolar environments. Since the ester is initially contained within the internal hydrophobic cavity of OA, its initial excitation leads to diradical fragmentation (a diradicaloid) that favors hydrogen abstraction from the readily available OA backbone along with decarboxylation. Subsequent exposure of the intermediate diradicaloid to

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increasingly aqueous environments prompts greater bifurcation toward an ionic pathway. This, we postulate, becomes the major pathway producing the acid products **10**−**16** and 4-coumarylmethanol **8**. Solvent imposes a delicate balance between radical and ionic pathways in the photochemistry of esters as has been demonstrated by the solvent effects on photosolvolysis[27] and photodecarboxylation reactions.[28] Similarly, benzyl esters and aryl γ-butyrolactones undergo photodecarboxylation in non-nucleophilic solvents by a stepwise, reversible radical-pair mechanism or solvent addition in aqueous methanol.

It is noteworthy that *p*-methoxyphenacyl (pMeOP) esters display parallel behavior and complexity with coumarylmethyl esters, yielding both radical and nucleophilic addition products when encapsulated in OA.[29] The principal difference between coumarylmethyl and pMeOP is that they proceed from different spin states.[29] For coumarylmethyl, recombination of the singlet-derived biracials often dominates. On the other hand, these reactions contrast with pHP esters,[30] wherein release of the acid occurs from a very short-lived triplet state that generates only ionic intermediates in less than a nanosecond.[31]

In conclusion, we have established that OA encapsulation permits the dissolution of hydrophobic esters in water from which the release of the corresponding acids is accomplished "at will" in a timely manner. 7-(Methoxycoumaryl)-4-methyl esters serve as the trigger. The OA capsule has also provided us an unanticipated opportunity to probe the mechanistic dichotomy of a diradicaloid intermediate expressing both radical and ionic behavior when generated by coumarmylmethyl ester photolysis.[20] The relevant bifurcation between these two pathways, according to a recent report, is strongly influenced by the 7-substituent on the coumarylmethyl ring. Because substituted coumaryl absorption extended well into the visible region, we will use this to further test our mechanistic hypothesis for triggering the capsule opening with visible light by investigating dialkylamino-substituted coumaryl-4-methyl esters. This concept of combined supramolecular photochemistry and organic photochemistry could be explored for the release of small biologically active molecules in aqueous surroundings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02655.

Experimental procedures; ^{1}H and ^{13}C NMR, UV, fluorescence, excitation, and ESI-MS spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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