Organic LETTERS

Letter

pubs.acs.org/OrgLett

Photorelease of Incarcerated Guests in Aqueous Solution with Phenacyl Esters as the Trigger

Pradeepkumar Jagadesan,[†] José P. Da Silva,[‡] Richard S. Givens,*[,§] and V. Ramamurthy*[,†]

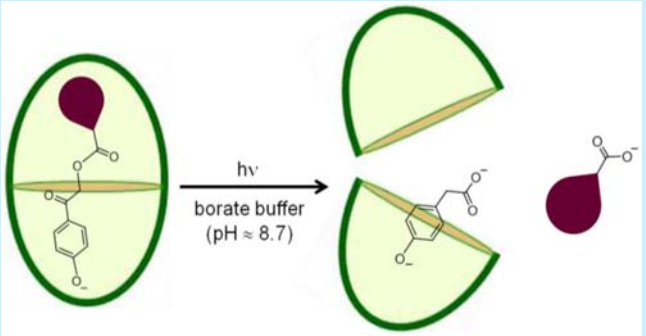
[†]Department of Chemistry, University of Miami, Coral Gables, Florida 33124, United States

[‡]Meditbio, FCT, Universidade do Algarve, Campus de Gambelas, 8005-139 Faro, Portugal

[§]Department of Chemistry, University of Kansas, Lawrence, Kansas 66045, United States

Supporting Information

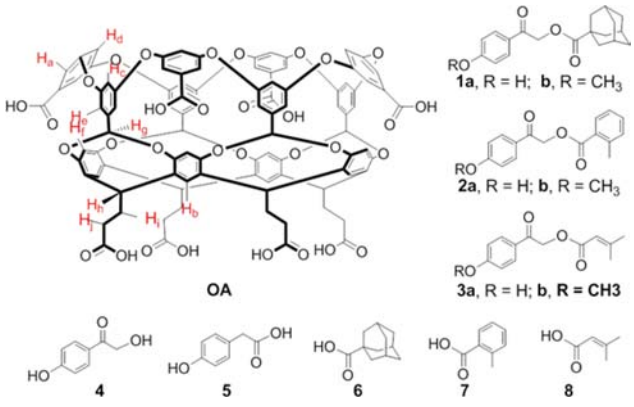
ABSTRACT: We report the clean, efficient photorelease of a series of carboxylic acids embedded in octa acid (OA) host and protected by a *p*-hydroxyphenacyl cage. A key role is played by the cage by providing hydrophobicity for entry into the OA enclosure and yet readily removable as a photoactivated protecting group for release from the host. The rapid photo-Favorskii rearrangement of the departing chromophore does not react with the host OA but diminishes hydrophobicity of the OA contents, leading to their facile release into the solvent.



Supramolecular chemistry has caught the interest of scientists in fields as diverse as fluorescence spectroscopy, chemical dynamics, biochemistry, drug delivery, and "catch and release" sequestration methodology.[1,2] Likewise, the photochemistry of host−guest (H−G) assemblies has attracted considerable interest for three decades with recent studies focused on the effects of confinement on dynamical behavior of the guest in organized H−G assemblies. Molecules irradiated in an enclosed assembly have displayed varied, sometimes unanticipated, behavior. Some hosts, such as micelles, cyclodextrins, cucurbiturils, or organometallic nanoclusters, partially expose the guest to the aqueous exterior[2b] complicating the environmental effects on the photochemistry. In contrast, we have focused our interests on the behavior of the water-soluble cavitand octa acid (OA, Scheme 1), which forms an enclosed capsule of either a 2:1 or 2:2 H−G complex,[2c,3,4] fully protecting the encapsulated guest from the aqueous media. In principle, encapsulated guests can be transported from site to site in aqueous media and then deposited at a selected location, provided there is a mechanism for opening the capsule, e.g., by a spatially or temporally controlled photorelease processes. This Letter addresses the release by photolysis of encapsulated carboxylic acids that have been coupled to photoremovable protecting groups (PPGs). The photoproducts are incompatible with the host, freeing them into the solvent.

While there are a plethora of known PPGs or cages available as candidates that could assist in opening the OA host, we have selected *p*-hydroxyphenacyl (pHP)[5,6] as the chromophore to cage the guest. We anticipate that the release of caged carboxylic acids will occur upon irradiation of OA encapsulated pHP esters. The well-established mechanism of pHP photochemistry includes a concomitant photo-Favorskii rearrangement of the chromophore,[7] a process that should test the robustness of the photochemistry, the relative rates of OA opening,[8] and the vulnerability of the host and guest to environmental changes within and outside the H−G complex. Scheme 1 gives the structures of OA, the three pHP esters (**1a−3a**) of acids **6−8**, and two anticipated photochemical byproducts. This study contrasts with earlier results employing

Scheme 1. Structures of Water-Soluble Octa Acid (OA) Cavitand, *p*-Hydroxyphenacyl (pHP) Esters (1a, 2a, and 3a), *p*-Methoxyphenacyl (pMP) Esters (1b, 2b, and 3b), and Photoproducts



Received: January 26, 2015
Published: February 23, 2015

DOI: 10.1021/acs.orglett.5b00252
Org. Lett. 2015, 17, 1276−1279

p-methoxyphenacyl (pMP)[4] as protected esters **1b**–**3b** (see Scheme 1).

The pHP esters were synthesized by methods reported earlier[4,9] (Supporting Information (SI)). For H–G titration experiments, DMSO-d_6 solutions of the esters were incrementally added to D_2O solutions of OA at pH 8.7 with $Na_2B_4O_7$ buffer and monitored by ^{1}H NMR (Figure 1). The upfield shifts of the ester aliphatic protons were used to measure the extent of the OA:pHP ester H–G complex.[3,4]

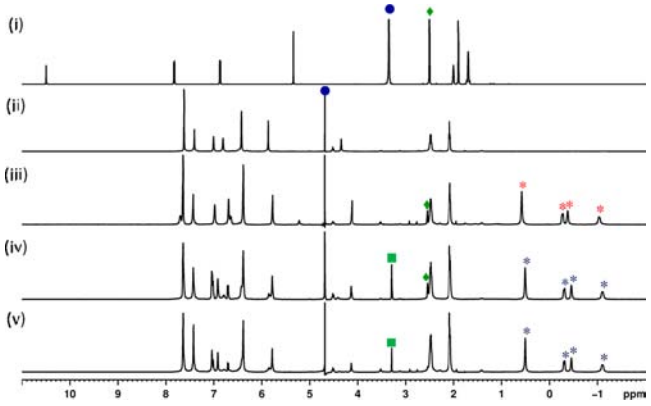


Figure 1. ^{1}H NMR (500 MHz) spectra of (i) **1a** in DMSO-d_6; (ii) OA ([OA] = 1 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O, pH = 8.7); (iii) **1a**@$(OA)_2$ ([OA] = 1 mM and [**1a**] = 0.5 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O); (iv) after 40 min irradiation of (iii) at $\lambda \geq 300$ nm; and (v) a mixture of **5** (0.5 mM), **6** (0.5 mM), and OA (1 mM) in 10 mM $Na_2B_4O_7$ buffer/D_2O. Symbols (red *) and (blue *) indicate aliphatic protons of OA incarcerated **1a** and **6**, respectively, (green ■) the $-CH_2-$ of **5**, and (blue ●) and (green ◆) the residual solvent peak of H_2O and DMSO-d_6, respectively.

Addition was continued until there was no further spectral change or the solution became turbid. For pHP ester **1a** (shown in Figure 1 (iii)) as well as esters **2a** and **3a** (Figures S19(ii) and S20(ii)), the molar ratios of OA to pHP esters were 2:1 H–G complexes, i.e., **1a**@$(OA)_2$. The esters **1a**–**3a**, which slowly hydrolyze in aqueous base, are very stable as their conjugate bases when encapsulated in the OA devoid of water, consistent with our observations that the OA cavity interior is hydrophobic.

UV–vis spectra of **1a** at pH <2, 7, and 8.7 (Figure 2a–c) demonstrate the pH dependence of the pHP chromophore indicating that the conjugate base of the pHP ester is

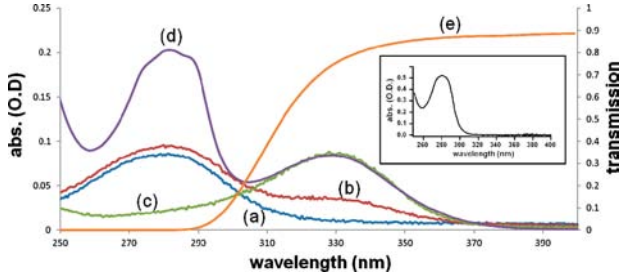
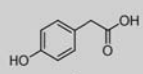
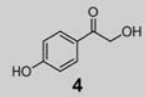


Figure 2. Absorption spectra of **1a** ([**1a**] = 10 μM) (a) in 70% aqueous $HClO_4$ (pH <2); (b) in water (pH ≈ 7); (c) in 10 mM $Na_2B_4O_7$ buffer/H_2O (pH = 8.7); (d) **1a**@$(OA)_2$ in 10 mM $Na_2B_4O_7$ buffer/H_2O ([**1a**] = 10 μM and [OA] = 20 μM (pH = 8.7)); and (e) transmission spectrum of Pyrex filter. Inset: absorption spectrum of OA ([OA] = 50 μM) in 10 mM $Na_2B_4O_7$ buffer/H_2O (pH = 8.7).

sequestered (Figure 2d; see Figures S24(v),(vi)). The π,π^* transitions of the conjugate bases absorb at 330 nm, so Pyrex filters employed for the photolysis reactions ensure that the absorbing chromophores are the pHP conjugate bases and not OA (Figure 2**e**, for comparison, see Figures S37 and S38 for the corresponding pMP ester **1b**). A difference spectrum of **1a** at pH <2 subtracted from one at pH 8.7 shows that excitation dominates at >300 nm, the Pyrex filter cutoff (Figure S36). It should be noted that all three esters, **1a**–**3a**, were stable to hydrolysis as their encapsulated OA complexes.

Photolysis of **1a**@$(OA)_2$ in aqueous borate buffer for 30 min at >300 nm with a 450 W medium pressure lamp through a Pyrex filter was tracked by the appearance of ^{1}H NMR singlets at 0.5, −0.3, −0.45, and −1.1 ppm that are assigned to the conjugate base of 1-adamantane carboxylic acid (**6**) in OA (**6**@OA, 67% yield) and a singlet at 3.3 ppm assigned to the chromophore's rearrangement product, *p*-hydroxyphenyl acetate (**5**) in OA (**5**@OA), both as 1:1 OA cavitand complexes (see Figure 1(iv),(v)). The conversion to products increased to 100% by irradiating the sample an additional 20 min (Table 1).

Table 1. Percent Comparisons of Photolysis Conversions and Yields Based on Consumed pHP ester for 1a, 2a, and 3a with or without OA Encapsulation in Aqueous Borate Buffer at pH 8.7; Error Limits Are ±10%

ester, with and without OA	conversion	released acid[a]	 **5**	 **4**
1a, OA, aq[b]	67	92	82	6
OA, aq[c]	100	90	92	8
w/o OA, aq[c]	91	94	90	6
2a, OA, aq[b]	77	75	81	7
OA, aq[c]	94	84	90	8
w/o OA, aq[c]	91	85	83	7
3a, OA, aq[b]	62	78	79	8
OA, aq[c]	84	80	92	8
w/o OA, aq[c]	79	73	83	7

[a]1-Adamantanecarboxylic acid, *o*-toluic acid, and 3,3-dimethylacrylic acid from pHP esters **1a**, **2a**, and **3a**, respectively. [b]After a 30 min irradiation of the OA. [c]After 50 min irradiation.

Product identifications were confirmed by liquid chromatography coupled to a diode array detector and to a mass spectrometer (LC-DAD-MS) or by gas chromatography (GC)-MS. Progress of the reaction was followed at 275 nm (DAD) and under single ion monitoring (SIM) in the negative polarity (MS). Product **8** was analyzed by GC-MS in the SIM mode (see SI). A minor photoproduct, 2,4′-dihydroxyacetophenone (**4**), was also detected (<10%). The time-dependent product yields of the released acid approached 100% (Figure 3). Irradiations of the OA encapsulated conjugate bases of the pHP esters **2a** and **3a** (Figures S17 and S20) in aqueous borate buffer gave the expected carboxylic acids **7** and **8**, the rearranged chromophore 4-hydroxyphenylacetic acid (~90%, **5**) (see Figure S14), and the minor photosolvolysis product 2,4′-dihydroxyacetophenone (**4**, ~7%) detected by LC.

DOI: 10.1021/acs.orglett.5b00252
Org. Lett. 2015, 17, 1276–1279

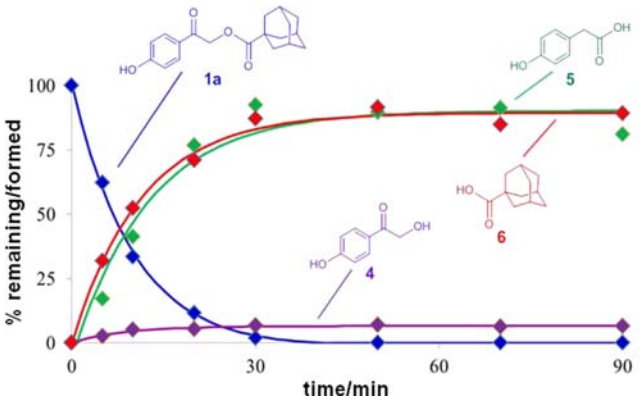


Figure 3. Product distribution for the time-dependent photolysis of pHP ester **1a** at $\lambda > 300$ nm (xenon lamp, Pyrex filter) as a 2:1 octa acid complex (**1a**@$(OA)_2$, [**1a**] = 25 μM) in aqueous borate buffer (10 mM; pH = 8.7) to 1-adamantanecarboxylic acid (**6**), *p*-hydroxyphenylacetic acid (**5**), and 2,4′-dihydroxyacetophenone (**4**).

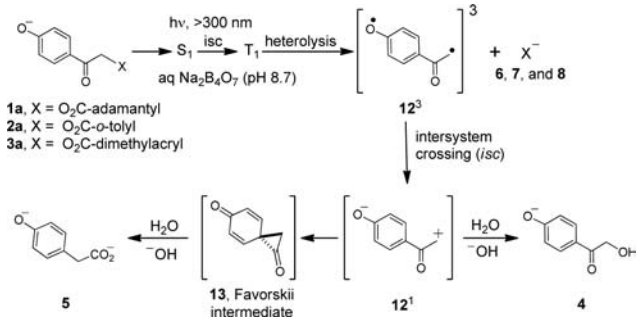
The time-dependent photolyses of the three pHP esters yielded nearly identical product distributions and rates of conversion, independent of the ester's encapsulation by OA host or not (Table 1). While the reaction appears to be slightly more efficient when encapsulated within OA, the photorelease reactivities of the three esters appear to be essentially independent of both the nature of the leaving carboxylate moiety and the presence of OA as shown by the reaction profiles (Figures 3, S18, and S21).

The minor photosolvolysis product **4** has been observed in prior studies of pHP esters when neutral aqueous media were employed, but the effect of pH had not been examined. For **1a**−**3a**, the photolyses were carried out in aqueous borate buffer (pH 8.7) and at neutral pH in aqueous MeCN in the absence of OA host. LC−MS analyses confirmed the release of the carboxylic acids **6**−**8** in all cases as well as the chromophore rearrangement product **5** and the solvolysis product **4** (Table 1 and Figure S15).

A comparison of the time-dependent ^{1}H NMR spectra of the photolysis mixtures in the OA encapsulated and free, unencapsulated caged esters indicates that decaged acids **7** and **8** are released into the aqueous base, whereas, in the case of **1a**, the released acid **6** remains within an OA hemisphere. We attribute this difference between **6** and **7**/**8** to the increased hydrophobicity of **6**.

Furthermore, the photoproduct mixtures from pHP esters **1a**, **2a**, and **3a** show no evidence of reaction between the ester and the host OA contrasting with earlier results with OA enclosed *p*-methoxyphenacyl esters **1b**, **2b**, and **3b**. The *p*-methoxyphenacyl esters react by a homolytic release mechanism for the leaving group leading to reactive radical intermediates.[4,6b,7c] Thus, the absence of radical attack on the OA by pHP ester photolysis as evidenced by the lack of OA adducts and the high yield of *p*-hydroxyphenyl acetic acid **5** (>90%) suggests that the photorelease mechanism for OA encapsulated pHP esters differs from that of the *p*-methoxyphenacyl esters.[6,7,10] In isotropic solutions, the conjugate base of *p*-hydroxyphenacyl esters proceeds through the photo-Favorskii rearrangement from their pHP triplet state forming a short-lived (0.5 ns) triplet biradical (Scheme 2). While we lack sufficient evidence to unequivocally assign a mechanistic pathway, the facts that release of acids from pHP esters **1a**−**3a** show no evidence of radical attack on OA,

Scheme 2. Suggested Mechanism for the Photorelease of Carboxylic Acids from Their pHP Esters 1a, 2a, and 3a within OA Capsules



produce no decarboxylation byproducts from the carboxylic acids released, and give no radical coupling byproducts, three reactions that are observed for methoxyphenacyl cage reactions, strongly indicate that the encapsulated conjugate bases of the pHP esters proceed exclusively via heterolytic cleavage. A short-lived, neutral triplet biradical $\mathbf{12}^3$ is initially formed, which intersystem crosses[10] then closes to **13** following the established photo-Favorskii pathway for the protonated pHP chromophore. Currently, we are pursuing additional studies to extend the variety of substrates released and to examine the mechanism for release from pHP substrates confined within an OA host.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H and ^{13}C NMR, and ESI-MS spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: murthy1@miami.edu.
*E-mail: givensr@ku.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

V.R. thanks the National Science Foundation (CHE-1411458 and CHE-1111392) for financial support. R.S.G. thanks the Kansas University Endowment Association for partial financial support.

■ REFERENCES

(1) For comprehensive reviews, see: (a) Ramamurthy, V.; Gupta, S. *Chem. Soc. Rev.* **2015**, *44*, 110−135. (b) Ramamurthy, V., Inoue, Y., Eds. *Supramolecular Photochemistry*; John Wiley: Hoboken, NJ, 2011. (c) Brinker, U. H., Mieusset, J.-L., Eds. *Molecular Encapsulation*; John Wiley: Chichester, U.K., 2010.

(2) (a) Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2004**, *126*, 11408−11409. (b) Jordan, J. H.; Gibb, B. C. *Chem. Soc. Rev.* **2015**, *44*, 547−585. (c) Gupta, S.; Choudhury, R.; Krois, D.; Wagner, D.; Brinker, U. H.; Ramamurthy, V. *Org. Lett.* **2011**, *13*, 6074−6077.

(3) (a) Jayaraj, N.; Zhao, Y.; Parthasarathy, A.; Porel, M.; Liu, R. S. H.; Ramamurthy, V. *Langmuir* **2009**, *25*, 10575−10586. (b) Porel, M.; Jayaraj, N.; Kaanumalle, L. S.; Maddipatla, M. V. S. N.; Parthasarathy, A.; Ramamurthy, V. *Langmuir* **2009**, *25*, 3473−3481.

DOI: 10.1021/acs.orglett.5b00252
Org. Lett. 2015, 17, 1276−1279

(4) Jayaraj, N.; Jagadesan, P.; Samanta, S. R.; Da Silva, J. P.; Ramamurthy, V. *Org. Lett.* **2013**, *15*, 4374−4377.
(5) (a) Klán, P.; Šolomek, T.; Bochet, C.; Blanc, A.; Givens, R. S.; Rubina, M.; Popik, V.; Kostikov, V.; Wirz, J. *Chem. Rev.* **2013**, *113*, 119−191. (b) Goeldner, M.; Givens, R. S. *Dynamic Studies in Biology*; Wiley-VCH: Weinheim, Germany, 2005. (c) Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4900−4921.
(6) (a) Givens, R. S.; Rubina, M.; Wirz. *J. Photochem. Photobiol. Sci.* **2012**, *11*, 472−488. (b) Park, C.-H.; Givens, R. S. *J. Am. Chem. Soc.* **1997**, *120*, 2453−2463.
(7) (a) Givens, R. S.; Heger, D.; Hellrung, B.; Kamdzhilov, Y.; Mac, M.; Conrad, P. G.; Cope, E.; Lee, J. I.; Mata-Segreda, J. F.; Schowen, R. L.; Wirz, J. *J. Am. Chem. Soc.* **2008**, *130*, 3307−3309. (b) Ma, C.; Kwok, W. M.; Chan, W. S.; Zuo, P.; Kan, J. T. W.; Toy, P. H.; Phillips, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 1463−1472. (c) Solomek, T.; Heger, D.; Ngoy, B.; Givens, R. S.; Klán, P. *J. Am. Chem. Soc.* **2013**, *135*, 15209−15215. (d) Senadheera, S. N.; Yousef, A. I.; Givens, R. S. *Beilstein J. Org. Chem.* **2014**, *10*, 2038−2054.
(8) Jayaraj, N.; Jockusch, S.; Kaanumalle, L. S.; Turro, N. J.; Ramamurthy, V. *Can. J. Chem.* **2011**, *89*, 203−213.
(9) (a) Givens, R. S.; Weber, J. F. W.; Conrad, P. G., II; Orosz, G.; Donahue, S. L.; Thayer, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 2687−2697. (b) Givens, R. S.; Weber, J. F. W.; Jung, A. H.; Park, C.-H. In *Methods in Enzymology*, Marriott, G., Ed.; Academic Press: New York, 1998; Vol. *291*, pp 1−29.
(10) Buck, A. T.; Beck, C. L.; Winter, A. *J. Am. Chem. Soc.* **2014**, *136*, 8933−8940.

DOI: 10.1021/acs.orglett.5b00252
Org. Lett. 2015, 17, 1276−1279