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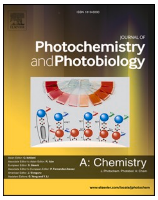

Confinement directed Photoreactivity of β-Enaminones

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ABSTRACT

Photolysis of β-enaminones within the supramolecular cavity of octa acid leads to dihydropyran products. The supramolecular cavity can be recycled in a sustainable fashion through multiple cycles with sequential addtion of β- enaminones leading to the products with moderate to good yields. The overall process involves the use of 20 mol% of supramolecularr host over 10 cycles.

1. Introduction

Nature has engineered enzymatic reactions by manipulating the environment around reactant molecules leading to enhanced chemical reactivity and selectivity.[1–3] Chemists have been attempting to mimic this feature to gain control over reactivity and selectivity with molecular systems by employing synthetic nanocontainers [4] with the ability to confine and orient reactive substrate(s).[5–7] Over the last four decades, while manipulation of molecules through confinement has made progress, solution to the problem of supramolecular photocatalysis is yet to be found. Surprisingly, there are only very limited examples in literature.[8–12] The challenges involved in developing a versatile organic/inorganic supramolecular photocatalytic system include cavity size, built-in weak-interactions to hold the guest reactant relative to the product, and recyclability.[10–12] In this report we disclose the results of influence of a supramolecular capsule made up of two molecules of octa acid (OA) cavitand [13–16] on the photoreaction of β-enaminones (Fig. 1).[17] Interestingly, while the capsule meets the criteria required for recycling, at this stage supramolecular photocatalysis has to be carried out manually. To our knowledge this is one of the few examples where a synthetic reaction cavity has shown a tendency to function as a photocatalyst. In this context, the results presented here are valuable to design in future host molecules that can act as a supramolecular photocatalyst.[18,19].

Octa acid (OA), (Fig. 1) with its hydrophobic cavity has the ability to include organic molecules in water at pH ~ 8.5. Unlike well-known hosts such as cyclodextrins [20,21] and cucurbiturils,[22–24] OA forms a capsular assembly within which the reactant guest molecules are well protected from water.[14–16] This prompted us to examine the photochemistry of β-enaminones **1a-c** (Fig. 1) which was recently established to undergo a novel type of excited-state transformation to yield the cyclic product **2**.[17] The goal was to probe whether the confined space would permit the transformation, and if it does would the reaction be catalytic with respect to the host.

2. Results and discussion

We initiated the investigation by evaluating the feasibility of encapsulation of β-enaminones **1a-c** within OA. β-Enaminones **1a-c** were insoluble in water/borate buffer as evidenced by a turbid solution, which upon addition of OA, led to complexation with the solution becoming transparent. ^{1}H NMR titration experiments revealed the formation of a 2:1 (host:guest) complex (capsuleplex; Fig. 1).[25] Irradiation of β-enaminones **1a-c** encapsulated within OA with ~ 350 nm lamps in a Rayonet reactor gave the corresponding dihydropyran photoproduct **2a-c** (Scheme 1) as confirmed from their ^{1}H NMR spectra and by comparison with authentic samples.[25] In cases where **2** was included within OA, the bridge methyl resonances were broad suggesting that it experiences multiple environments during the lifetime of the NMR signals collection (Figures S1-S11).[25] This is likely when the capsule is not tightly closed and opens and closes within the lifetime of NMR. To support this possibility, MD simulations of the host–guest complexes of OA and **2a-c** were performed (Fig. 2).[25] The simulation revealed partial opening of the OA capsule in the case of **2a** and **2c** and not in the

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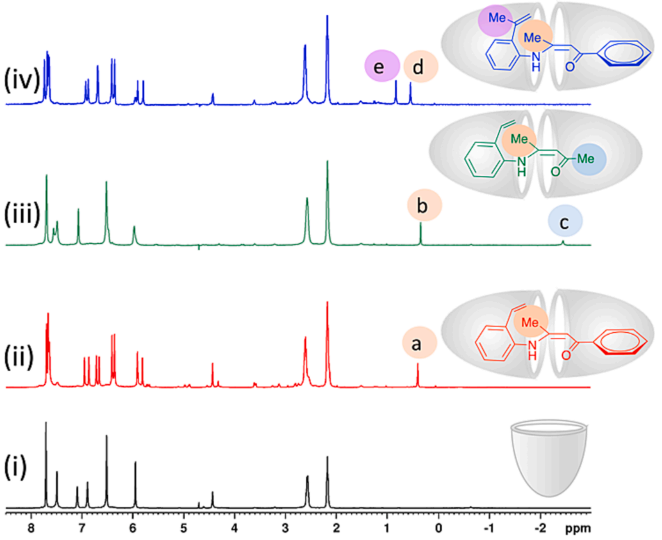
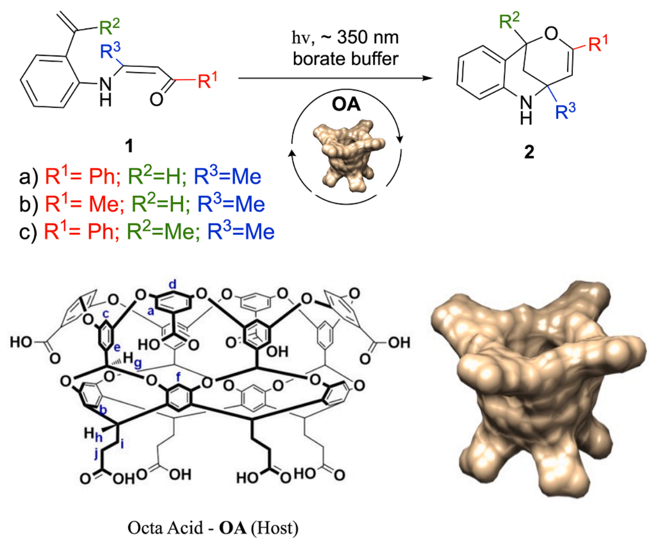


Fig. 1. ^{1}H NMR spectroscopy of i) 1 mM OA in 10 mM borate buffer, ii) **1a** @OA$_2$, iii) **1b** @OA$_2$, and iv) **1c** @OA$_2$. "a-e" represents the methyl resonances of encapsulated guests.



Scheme 1. Photoreactivity of β-enaminone **1a-c** leading to the corresponding dihydropyran type photoproduct **2a-c** in the presence of octa acid (OA).

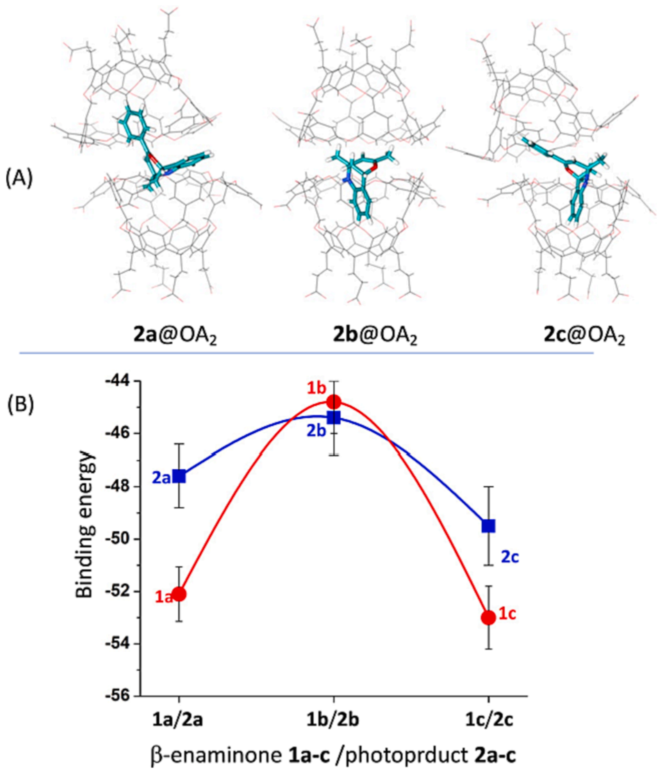


Fig. 2. TOP Molecular dynamics (MD) simulated in water representative structures of **2a**, **2b**, and **2c** in OA. Bottom: Binding affinity trends in β-enaminones **1a-c** and the corresponding photoproducts **2a-c** determined by MD simulations.

Table 1
The yield of photoproducts from photolysis of β-enaminone@OA$_2$ complex.

Entry	Photolyzed Complex[a]	Total cycles	% Yield of 2 [b]
1	**1a** @OA$_2$	1	51
2	**1a** @OA$_2$	10	46
3	**1b** @OA$_2$	1	75
4	**1c** @OA$_2$	1	51

[a] [β-enaminone] = 2 mM.
[b] Yield based on ^{1}H NMR spectroscopy with triphenylmethane internal standard.

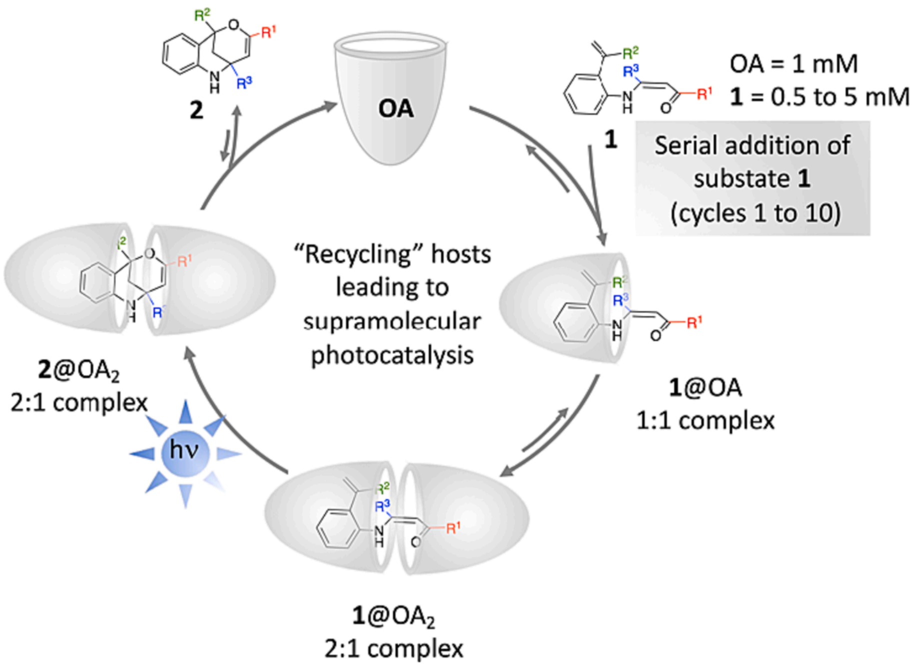
Table 2
The irradiation of **1a** with various mole % of OA.

Entry	[1a]	mole% OA	% 2a	[1a: 2a] [a]
1	2 mM	10 (0.2 mM)	7	92:08
2	2 mM	20 (0.4 mM)	10	88:12
3	2 mM	30 (0.6 mM)	16	72:28
4	2 mM	50 (1 mM)	22	71:29
5	2 mM	100 (2 mM)	24	71:29
6	2 mM	150 (3 mM)	39	51:49
7	2 mM	200 (4 mM)	50	40:60

[a] Ratio by ^{1}H NMR spectroscopy based on unreacted β-enaminone. [b]Due to solubility issues higher concentration was not employed in the absence of OA.

case of photoproduct **2b** (Fig. 2). This is likely due to the size of photoproduct **2b** that features a R^1 alkyl substituent when compared to photoproducts **2a** and **2c** both of which feature R^1 aryl substitution. MD simulations suggested that photoproducts **2a** and **2c** form a weaker complex than the corresponding reactants **1a** and **1c**. A point to note from the estimated MD simulation binding energies is that in the case of substrate **1b** the corresponding photoproduct **2b**, forms a stable complex with OA capsule than the reactant (Fig. 2b). One should be aware that the binding affinities of **1a-c** and **2a-c** derived from MD simulation are not absolute but rather present the trend in the system. This created an ideal condition for exploring supramolecular catalysis in the case of **1a** and **1c** but not in the case of **1b**. To test the supramolecular photocatalytic ability of OA in the case of **1a** and **1c**, expecting the product could be displaced by the reactant, we added aliquots of the reactants upon completion of the irradiation. This expectation was indeed realized. Irradiation of the newly formed complex gave additional products. Since the reactants when present outside OA is insoluble in buffer solution, we were unable to have excess of the reactant in solution. Therefore, the feasibility of catalysis can only be established manually. The sequence of experiments is detailed below as steps a-g employing the reactant **1a** as an example.

Experimental sequence that revealed the occurrence of photocatalysis is described in detail below: (a) A 2:1 capsular complex of OA and **1a** was formed by stirring 1 mM OA and 0.5 mM **1a** in aqueous borate buffer and characterized by ^{1}H NMR spectroscopy. (b) The



Scheme 2. Supramolecular photocatalysis mediated by octa acid.

sample was irradiated at $\sim$ 350 nm and the progress was monitored by ^{1}H NMR spectroscopy. (c) Complete consumption of **1a** was noted after 25 min of irradiation. At this stage a fresh batch of 0.5 mM of **1a** was added. ^{1}H NMR spectrum revealed the formation of fresh complex resulting from expulsion of the product **2a** from the capsule. Presence of **2a** in water resulted in the solution becoming turbid. To avoid scattering during irradiation, **2a** was precipitated out by centrifuging the solution. (e) The transparent solution containing the second batch of **1a**@OA$_2$ complex was irradiated, and the corresponding photoproduct was centrifuged as before. (f) The sequential addition of β-enaminone reactant followed by irradiation and photoproduct removal by centrifugation was repeated for up to 10 cycles. (g) After 10 cycles, all the centrifuged photoproduct **2a** were combined and analysed by recording ^{1}H NMR spectra and the combined yield is provided in Table 1. The same sequence was also employed for the β-enaminone **1c** with OA. A point we want to note is that despite full conversion of reactant β-enaminone the yield of the photoproduct was 46% for **1a** (after 10 cycles), 75% for **1b** (after 1 cycle), and 51% for **1c** (after 1 cycle). We currently do not have a clear explanation of why the yields are moderate in spite of near quantitative conversion under our experimental conditions and only speculate about the likely reason for the observed yield. The reduced total yield could be attributed to lack of total complexation of the reactants under the conditions employed for irradiation. The experiments carried out with different ratios of OA and **1a** supported this rationale. As shown in Table 2 the yield of the final product increased with increasing amounts of OA. A point to note is that under our condition only the **1**@OA$_2$ complex reacts as the uncomplexed form is insoluble at the concentration employed i.e., the observed photoproduct is from within the OA cavity and not from outside. As a control study heating **1a** in borate buffer at 85° C for 100 min did not give **2a** suggesting that light is required for the transformation.

Based on the observed reactivity of β-enaminone we propose a supramolecular process (Scheme 2) in which OA enhances the photochemical reactivity in water/buffer. In the presence of OA, β-enaminone **1** forms a 2:1 host–guest complex **1**@OA$_2$. Irradiation of this **1**@OA$_2$ complex at $\sim$350 nm, results in the formation of photoproduct **2** that remains encapsulated within the OA i.e., **2**@OA$_2$. Addition of β-enaminone **1** to this irradiated mixture, results in the expulsion of the photoproduct **2** from OA with concurrent formation of **1**@OA$_2$ complex due to the weak binding of the photoproduct **2** when compared toβ-enaminone **1**.

3. Conclusions

Thus, our study has shown that one can carry out the photochemical reaction within a supramolecular capsule. The supramolecular capsule can be recycled effectively in which the overall transformation is carried out in sub-stochiometric amounts with respect to the reactant. The results presented here are for a model system based on β-enaminone and OA that will aid in the conceptual design and development of host–guest systems for supramolecular photocatalysis.

CRediT authorship contribution statement

Dipendra Khadka: Formal analysis, Data curation. **Lakshmy Kannadi Valloli:** Formal analysis, Data curation, Methodology. **V. Ramamurthy:** Funding acquisition, Conceptualization. **J. Sivaguru:** Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data. Electronic Supplementary information (ESI) available: Host-guest complexation by NMR spectroscopy of both the reactants and the photoproducts. Experimental procedures for irradiation and photoproduct characterization.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jphotochem.2023.115175.

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