



Photochemistry within a Water-Soluble Organic Capsule

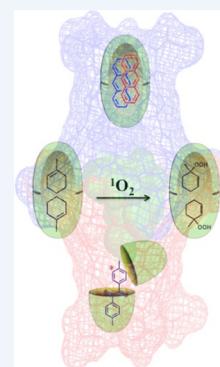
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CONSPECTUS: Photochemistry along with life as we know it originated on earth billions of years ago. Supramolecular Photochemistry had its beginning when plants that sustain life began transforming water into oxygen by carrying out light initiated reactions within highly organized assemblies. Prompted by the efforts of J. Priestly (photosynthesis), F. Sestini, S. Cannizaro, and C. Liebermann (solid-state photochemistry of santonin, quinones, and cinnamic acid), orderly scientific investigations of the link between light absorption by matter and molecules and the chemical and physical consequences began in the mid-1700s. By 1970 when Molecular Photochemistry had matured, it was clear that controlling photochemical reactions by conventional methods of varying reaction parameters like temperature and pressure would be futile due to the photoreactions' very low activation energies and enthalpies.

During the last 50 years, the excited state behavior of molecules has been successfully manipulated with the use of confining media and weak interactions between the medium and the reactant molecule. In this context, with our knowledge from experimentation with micelles, cyclodextrins (CD), cucurbiturils (CB), calixarenes (CA), Pd nanocage, crystals, and zeolites as media, we began about a decade ago to explore the use of a new water-soluble synthetic organic cavitand, octa acid (OA) as a reaction container. The uniqueness of OA as an organic cavitand lies in that two OA molecules form a closed hydrophobic capsule to encapsulate water-insoluble guest molecule(s). The ability to include a large number of guest molecules in OA has provided an opportunity to examine the excited state chemistry of organic molecules in a hydrophobic, confined environment. OA distinguishes itself from the well-known cavitands CD and CB by its active reaction cavity absorbing UV-radiation between 200 and 300 nm and serving as energy, electron, and hydrogen donor. The freedom of guest molecules in OA, between that in crystals and isotropic solution can be transformed into photoproducts selectivity. The results of our photochemical investigations elaborated in this Account demonstrate that OA with a medium sized cavity exerts better control on excited state processes than the more common and familiar organic hosts such as CD, CB, CA, and micelles. By examining the photochemistry of a number of molecules (olefins, carbonyls, aromatics and singlet oxygen) that undergo varied reactions (cleavage, cycloaddition, *cis-trans* isomerization, oxidation and cyclization) within OA capsule, we have demonstrated that the free space within the container, the capsule influenced conformation and preorientation of guest molecules, supramolecular steric control, and capsular dynamics contribute to the altered excited state behavior.

In this Account, we have shown that photochemistry based on concepts of physical organic and supramolecular chemistry continues to be a discipline with unlimited potential. The future of supramolecular photochemistry lies in synthetic, materials, medicinal, and biological chemistries. Success in these areas depends on synthesizing well-designed water-soluble hosts that can emulate complex biological assemblies, organizing and examining the behavior of supramolecular assemblies on solid surfaces, rendering the photoreactions catalytic, and delivering encapsulated drugs in a targeted fashion.



1. INTRODUCTION

Pioneering work by several researchers that led to an understanding of "Molecular Photochemistry" shifted the focus of photochemical research in late 1970s to controlling and manipulating photochemical reactions.^{1–4} Due to the fact that photoreactions have very low activation energies temperature was not an option. This led to exploring the "medium", especially the ones that offer a highly organized and confining environment, as a tool. In this context, diverse types of organized media in liquid, semisolid and solid forms have been explored to manipulate excited state processes.^{3,4} With interest in photoreactions in organized assemblies,^{5–10} we came across a new water-soluble organic cavitand known as octa acid (OA) whose synthesis and binding properties were reported by Gibb and Gibb.¹¹ Our studies reported below demonstrate that OA exerts better control on excited state processes than hitherto known organic hosts. Photochemical studies in water-soluble cavitands

such as cyclodextrins,⁷ cucurbiturils,¹² and Fujita's Pd host,¹³ and micelles¹⁴ are directly relevant to the results reported here. All the above media provide an interface between external water and internal organic-like environment. In addition to preorganizing reactant molecules, the interface also allows the reactants and the reactive intermediates to escape the confined environment leading to poor product selectivity. One of the rare and appealing features of OA is the closed capsule it forms in the presence of a guest molecule. Most common hosts mentioned above neither are easily water-soluble nor form capsules. OA forms water-soluble capsular complexes ($\sim 10^{-2}$ M) with a variety of organic molecules. Most of the recently reported covalently linked, hydrogen bonded and metal coordinated cages/capsules that can act as hosts are either soluble in organic solvents only or absorb

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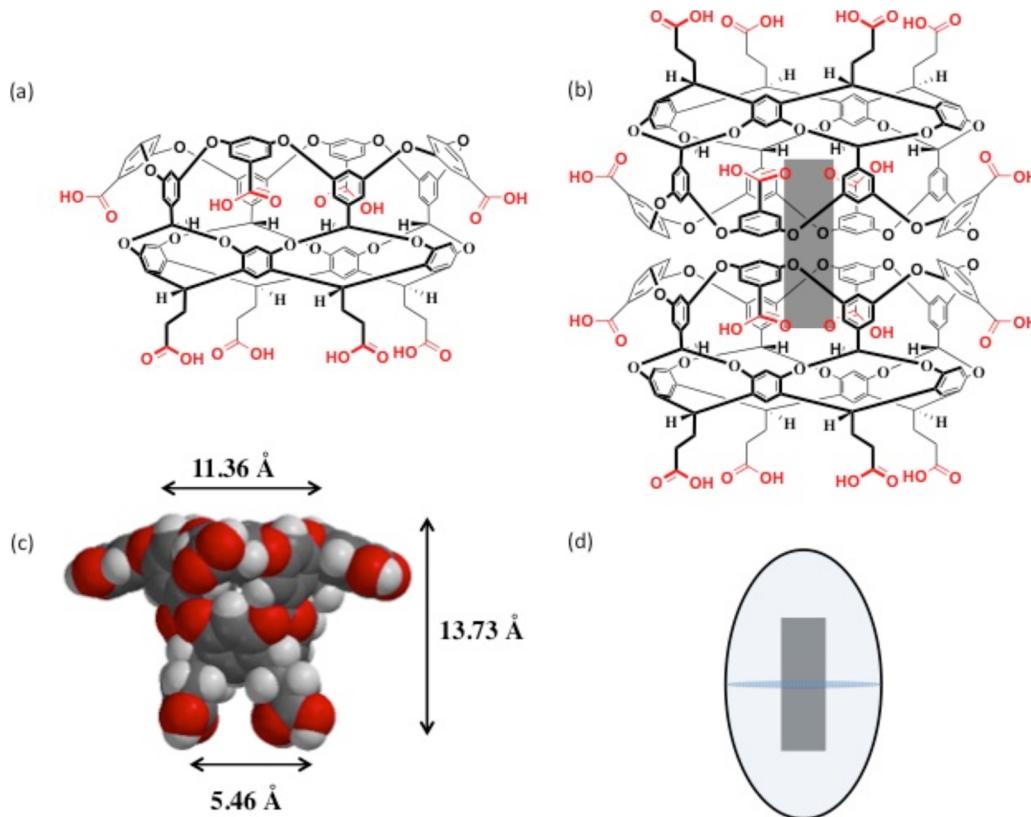


Figure 1. (a) Molecular structure of OA. (b) Molecular structure of OA capsule; the gray rectangle represents guest. (c) CPK model of OA and with dimensions marked. (d) Cartoon representation of OA capsule.

light in the region where guest molecules do or the guest has to be introduced during the synthesis or too small to accommodate large molecules of photochemical interest.^{13,15,16}

The results of our studies related to photoreactions within an OA capsule are highlighted in this Account. Aspects like the dynamics of OA and host–guest complexes, communication of molecules (spin-energy and electron transfer) across OA walls in solution, and photochemistry of OA–guest complexes aligned on surfaces have been reviewed by us recently.^{17,18} Our results in a broader context have been summarized in a recent review.¹⁹ For contributions by other groups on supramolecular photochemistry, recent reviews and monographs should be consulted.^{2–4,19–22}

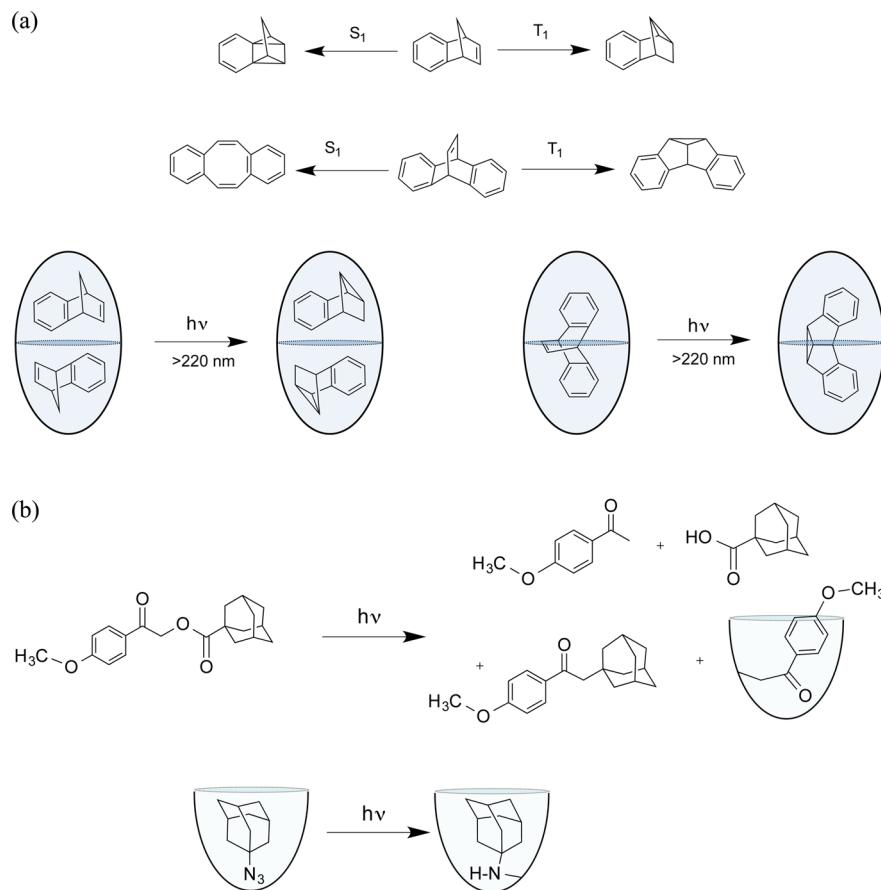
2. PROPERTIES OF OA AND ITS COMPLEXES

The water-soluble cavitand with four carboxylic acid groups at the top and four at the bottom is generally known by the trivial name octa acid (OA) (Figure 1). OA has two openings: one at the top (11.4 Å) and one at the bottom (5.5 Å) (Figure 1). Constructed from methylenedioxy substituted phenyl bridges and benzoic acid units, it absorbs light up to 300 nm and emits weak fluorescence (310–420 nm). The S_1 and T_1 energies of OA were estimated to be ~95 and ~70 kcal/mol. Scheme 1a presents two examples where OA acts as the triplet sensitizer.²³ From fluorescence quenching of a series of electron acceptors, OA is found to be a good electron donor with an estimated oxidation potential of ~1.5 eV.²³ The several benzylic hydrogens in the interior wall of OA can be abstracted by the reactive species generated upon excitation of guests. Two such examples are included in Scheme 1b.^{24,25}

OA is sparingly soluble ($\sim 10^{-5}$ M) in neutral water. However, under basic conditions (borate buffer, pH > 8.5), it is soluble to

the extent of 10^{-2} M. At concentrations above 10^{-3} M, OA molecules aggregate in solution as is evident from broad ^1H NMR signals. In the presence of a guest molecule, formation of a 1:1 cavitandplex or 2:1 or 2:2 capsuleplex (ratio is expressed as host/guest and represented as guest@OA) results in sharpening of all host signals suggesting that the host–guest complexes are no longer aggregated.²⁶ Generally amphiphilic molecules with an ionic (hydrophilic) head group and hydrophobic body (e.g., 1-adamantane carboxylic acid) form 1:1 cavitandplex and neutral hydrophobic molecules (e.g., adamantyl ester and adamantane) depending on their size, shape, and concentration form either a 2:1 or a 2:2 capsuleplex. A comparison of the complexing abilities of naphthalene, anthracene, tetracene, and pentacene reveals the role of the dimensions of the guest in controlling the ratio of the host–guest complex. Naphthalene and anthracene form 2:2 capsuleplex while tetracene and pyrene form a 2:1 capsuleplex; long aromatic molecules like pentacene and bulkier benzpyrene do not complex with OA. Hydrocarbons with flexible methylene chain even up to 22 Å form 2:1 capsuleplexes (Figure 2).

Photophysical data of probes such as of pyrene, pyrene aldehyde, 2-acetyl anthracene and coumarin-1 and measured EPR coupling constants of nitroxides reveal OA capsule to have internal polarity close to that of benzene with no water inside.²⁷ Variable temperature ^1H NMR experiments and molecular dynamics simulations point out that the confined guest molecules undergo tumbling and rotational motion along the X, Y, and Z axes in 2:1 complexes and sliding motion in 2:2 complexes (Figure 3b–d). The capsular complex also partially opens and closes as illustrated in Figure 3f.^{28–30} Confinement in OA capsule and placement of molecules in conformations/orientations different from those in solution provide opportunities to explore

Scheme 1. Reactions Where OA Is (a) Triplet Sensitizer and (b) Hydrogen Donor^a

^aTwo reactions at the top are the probes used to test the sensitizing ability of OA.

photochemistry under confined environment. This translates into selectivity in photoreactions as highlighted with examples in the following sections.

3. OA AS A PHOTOCHEMICAL REACTION CONTAINER

Within the OA capsule the guest molecule(s) are held through weak interactions such as $\text{CH}-\pi$, van der Waals, and hydrophobic interactions.⁹ We highlight below with select examples from our studies OA capsule's influence on the excited state behavior of included guest molecules. In each case the features that are likely responsible for the unique behavior within OA is highlighted.

3.1. Norrish Type I Reaction of Carbonyl Compounds: Cage Effect and Role of Capsular Free Space

Norrish type I (α -cleavage) reaction of dibenzylketones serves as a benchmark reaction to ascertain the confining ability of a medium during a photoreaction.¹ The reaction sequence the excited dibenzylketone undergoes as sketched in Scheme 2 starts from the α -cleavage to yield the primary radical pair (RP-1), which loses CO to form a secondary radical pair (RP-2). In solution the products resulted from RP-2, for example, dibenzylketone, yielded 1,2-diphenylethane exclusively. Within OA capsule dibenzylketone gave the rearranged starting ketone p-RP from RP-1 in 56% yield.³¹ This unprecedented behavior suggested tumbling of the confined RP-1 (Figure 4) before recombining. The fact that *para*-methyl dibenzylketone gave 1-phenyl 2-tolylethane (AB) as the sole product within OA while yielding 1:2:1 mixture of AA (diphenylethane), AB, and

BB (1,2-ditolytylethane) in solution in organic solvents suggested that OA is able to provide 100% cage effect. Such high cage effect is rarely achievable in any media except crystals.

Based on the observed 100% cage effect we speculated that we could control the capsular free space and thereby the mobility of the intermediates and finally the products by varying the *para*-alkyl chain length in *para*-alkyl dibenzylketones. The structures of OA-guest complexes derived from ¹H NMR and the products of photolysis of a few selected *para*-alkyl dibenzylketones of varying alkyl chain lengths are included in Figure 5.^{32,33} Based on these results, we believe that the longer alkyl chains of these guests are folded resulting in pushing the unsubstituted benzyl ring deeper into the narrower end of the capsule. This action reduces the cavity's free space and restricts the rotation of the ketone (Figure 4). To our knowledge, this is the first example of "product distribution control" aided by a remote group within a restricted space in solution.

3.2. Norrish Type I and Type II Reactions of Carbonyl Compounds: Conformational Control

α-Alkyl dibenzylketones undergo both conformation-independent (Norrish type I) and dependent (Norrish type II) reactions in solution (Scheme 3).¹ Photoproduct distributions of OA confined and free *α*-alkyl dibenzylketones presented in Scheme 4 reveal:³⁴ (a) In solution, in the absence of OA, propyl- through octyl-alkyl substitutions resulted in the same product distribution with major products from type I (>80%) and minor ones from type II reactions. (b) While in solution, the type I reaction gave AA, AB, and BB products (Scheme 3) from RP-2 only, within OA

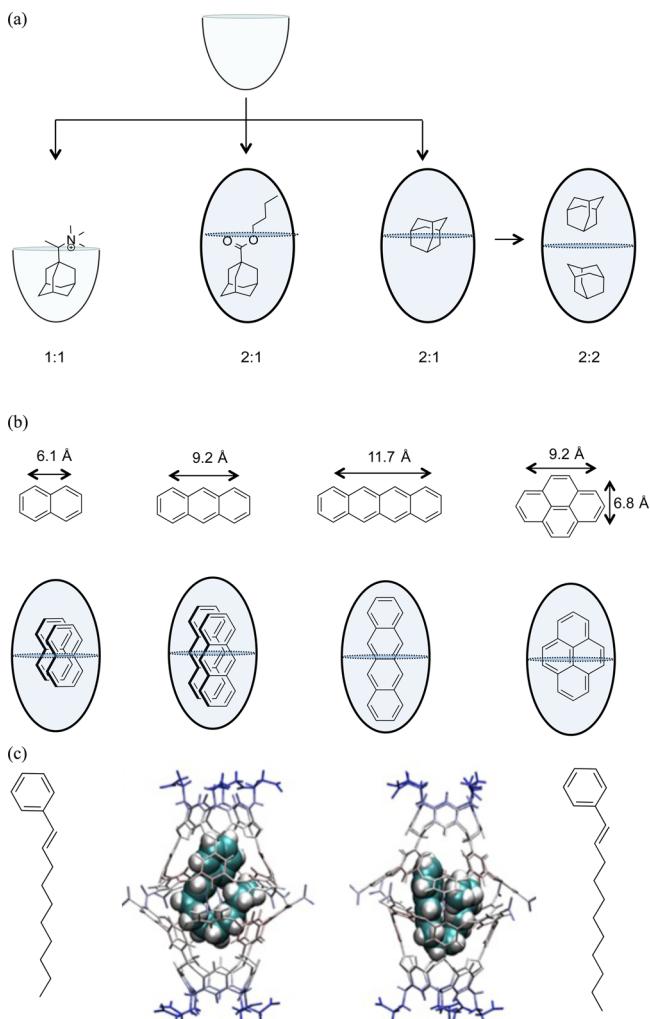


Figure 2. Illustrations of types of complexes OA forms with organic molecules. Structures in (c) were generated by MD simulations.

products from both intermediates RP-1 (**1** and **2**; Scheme 3) and RP-2 (only AB and rearranged AB) were obtained; (c) Of the

examined α -alkyl substituted dibenzylketones only the methyl to pentyl compounds gave rearranged starting ketones **1** and **2**. (d) While smaller alkyl chains gave mostly ketone **2**, the medium alkyl chains gave almost equal amounts of both ketones **1** and **2**. (e) The ratio of type I to II products was very much dependent on the chain length of the α -propyl- through octyl-dibenzylketones varying from 89:11 (α -propyl) to 10:90 (α -octyl).

One- and two-dimensional ^1H NMR derived structures of the guests within the OA capsule (Scheme 4) help understand these spectacular product distribution dependence on the alkyl substituent's length. The results and the guest structures within OA of three representative examples (α -methyl, α -pentyl, and α -octyl dibenzylketones) discussed below help grasp the role of confinement, free space and conformational control on photoreactions: (a) Low yield of type II products from α -pentyl dibenzylketone and their larger yield in α -octyl dibenzylketone are consistent with the conformation of the reactants within OA (Scheme 4). (b) The different amounts of the rearranged products from RP-1 in all three ketones are in accordance with the available free space required for rotation of benzyl radical intermediates within the OA capsule. The dearth of free space in α -octyl dibenzylketone around both the phenyl groups limits the rotation of the benzyl radicals resulting from α -C–C cleavage. In contrast, availability of free space in α -methyl and α -pentyl dibenzylketones permits rotation of the two benzyl radical intermediates resulting in rearranged ketones. (c) Finally, the conformation and the free space within the OA capsule in α -methyl and α -pentyl dibenzylketones rationalize the varied yield of **1** and **2** (Scheme 3). Of the available two α -C–C bonds in α -methyl dibenzylketone, the more readily cleavable alkyl substituted one leads to a major amount of **2**. However, in the case of α -pentyl dibenzylketone, due to lack of free space, the 1-phenyl hexyl radical resulting from such a cleavage recombines without rearrangement of the RP-1 radical pair. Under such conditions, the less favored cleavage of the unsubstituted side competes to lead to the product **1**. Regeneration of the reactant ketone from the return of RP-1 though not established in α -alkyl dibenzylketones it has been demonstrated in analogous α -alkyl-deoxybenzoins by monitoring the optical purity of the reactant α -alkyldeoxybenzoins with irradiation time.³⁵ The above results

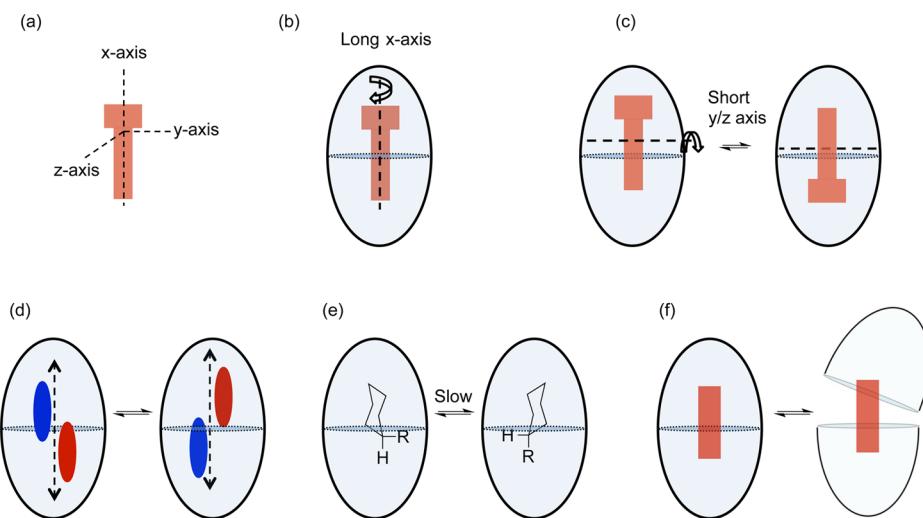
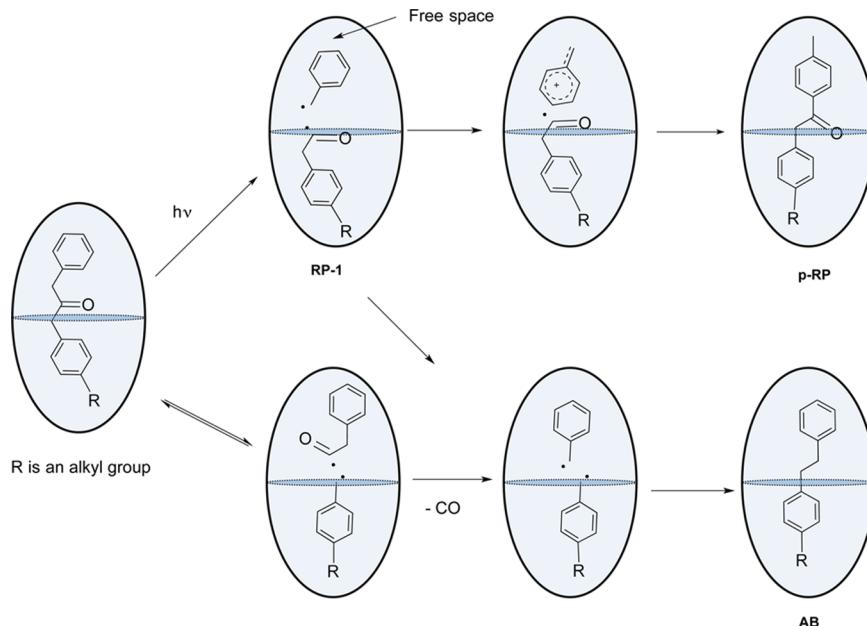
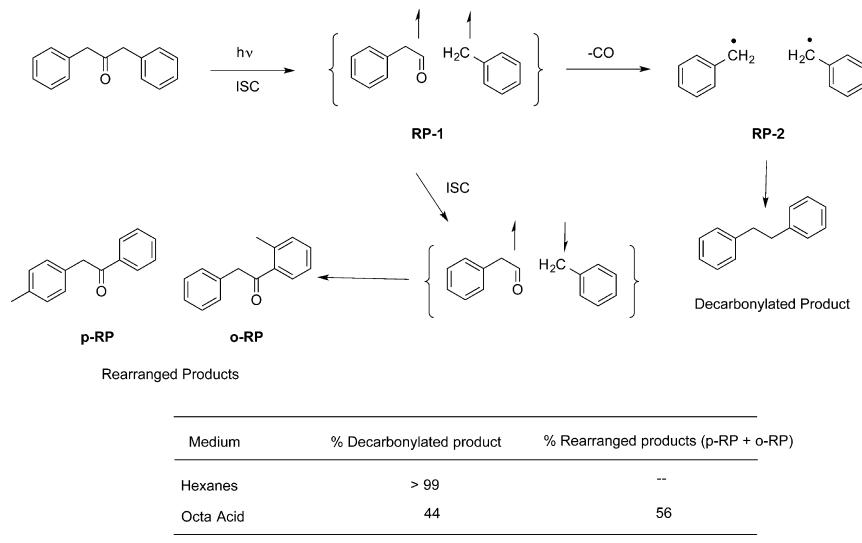


Figure 3. Cartoon illustration of various motions of included guest molecule(s) and OA complexes as a whole: (a) axes representation; (b) rotation along the long axis; (c) tumbling along the short axis; (d) sliding motion in 2:2 complexes; (e) conformational equilibrium in cyclohexyl systems; and (f) capsule's partial opening-closing.

Scheme 2. Products and Intermediates during the Norrish Type I Reaction of Dibenzylketone**Figure 4.** Importance of capsular free space during the formation of the rearranged ketone, p-RP.

highlight the determining role of a remote tether on the excited state chemistry of reactants in a confined space.

3.3. Geometric Isomerization of Olefins: Supramolecular Steric Effect

Geometric isomerization of olefins is one among the many crucial primary photoreactions in several biological events. In the protein environment, the isomerization is frequently site-selective and more efficient than that in an isotropic solvent. These features are attributed to intermolecular steric interaction (supramolecular steric effect) between the reactant and the surrounding protein during the volume demanding geometric isomerization. We show below that a similar effect operates within OA capsules leading to selectivity during isomerization of olefins.

trans-4,4'-Dimethylstilbene which aggregated and exhibited a broad emission in water formed stable 4,4'-dimethylstilbene@OA₂ capsular assemblies with OA. This complex emitted structured fluorescence with a lifetime of 1.5 ns (τ in hexane <0.5 ns)

(Figure 6a). Prolonged irradiation of either *trans* or *cis* isomer included in OA established a photostationary state consisting of 80% *trans* and 20% *cis*, distinctly different from the 17% *trans* and 79% *cis* in hexane.^{36,37} Importantly, the position and the number of methyl substituent affected the excited state behavior of methylated stilbenes within OA (Figure 6b). For example, in the series of 4,4', 3,3', and 2,2'-dimethylstilbenes, *trans*-4,4'-isomer was unique while the latter two behaved alike in OA and hexane. Monomethyl stilbenes, independent of the methyl group's location, showed no difference in behavior between OA and hexane. Location of the methyl groups within OA of *trans*-4,4'-dimethylstilbene explains its unique behavior (Figure 7a); its two methyl groups are anchored through C–H–π and van der Waals interaction at the two narrower ends of the OA capsule where the free space is small for the volume demanding *trans*–*cis* isomerization. The methyl groups at 3,3' and 2,2' positions localized at broader regions of the capsule experiencing lesser steric hindrance behaved like in an isotropic solution. The OA

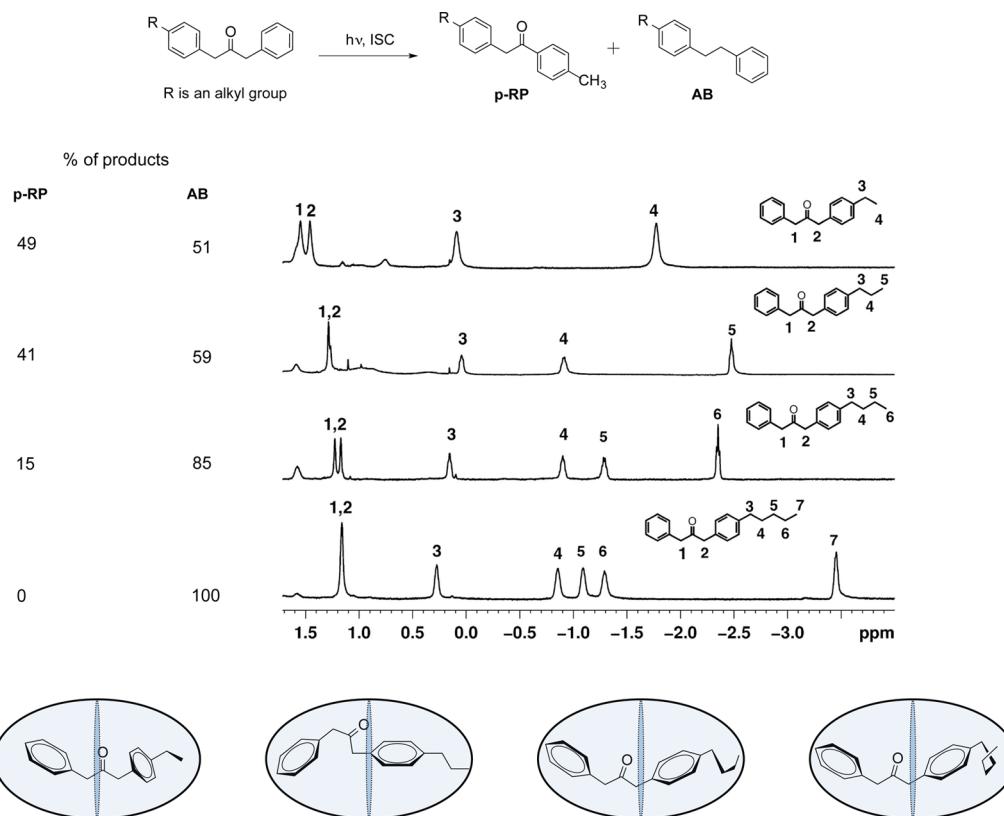
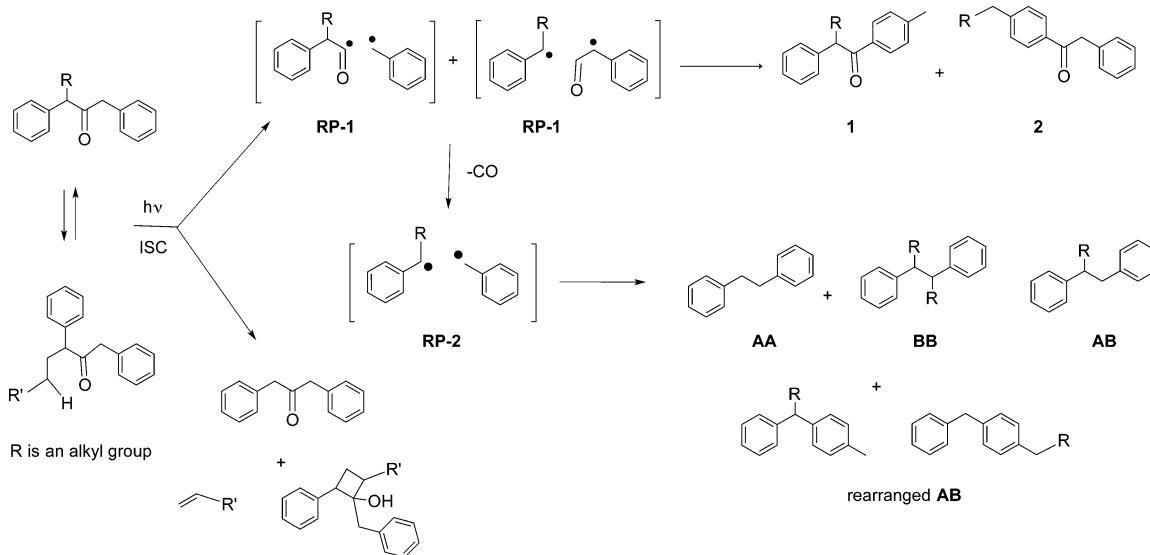


Figure 5. 4-Alkyl chain-length dependent structure of host–guest complexes and their photoproducts. Note the upfield shift of the alkyl signals in the ¹H NMR spectra.

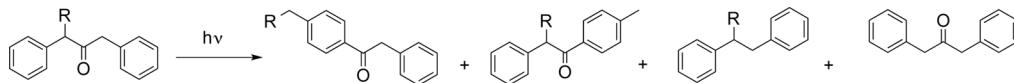
Scheme 3. Intermediates and Products during the Norrish Type I and Type II Reactions of α -Alkyl Dibenzylketones; R Is an Alkyl Group



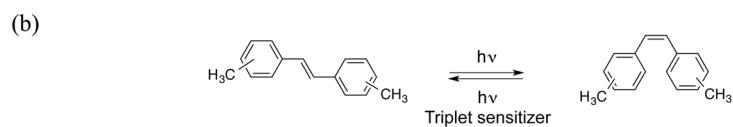
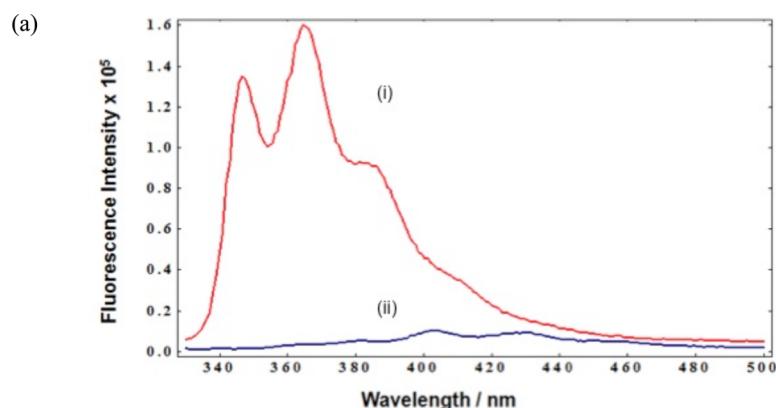
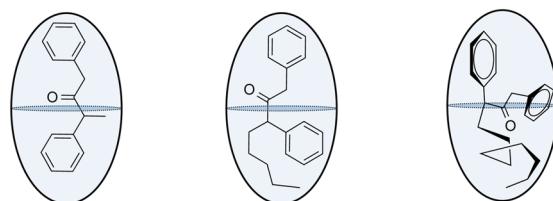
capsule is not expected to have any effect in monomethyl stilbenes as noted in this study due to the possibility of rotation of the unsubstituted phenyl group that are not restricted by the capsule (Figure 7b).

The second example in this context comes from the benzylidene-3-methylimidazolidinone (BMI) chromophore (Scheme 5), a molecule highly fluorescent when present in fluorescent proteins. Examination of a large number of model fluorescent protein chromophores with alkyl groups on both the

phenyl and imidazolidinone rings (Scheme 5, R₁ and R₂) revealed many to be highly fluorescent when included within OA while only weakly so in acetonitrile.^{38,39} One such example is illustrated in Figure 8a. The extent of OA's influence on these molecules, like the stilbenes discussed above, depends on the nature and position of the substituents. For example, while *ortho*-methyl enhanced the fluorescence, *meta* and *para* methyl substitution did not (Figure 8b). This could be understood on the basis of the structures, derived from 1D and 2D ¹H NMR,

Scheme 4. α -Alkyl Chain Length Dependent Structure of Host–Guest Complexes and Their Photoproducts; R Is an Alkyl Group

R =	% of products			
-CH ₃	21	4	75	-
-C ₅ H ₁₁	32	34	28	6
-C ₈ H ₁₇	-	-	10	90



¹ H-NMR chemical shift of CH ₃ within OA (ppm)	-2.3	-1.6	-0.8
Photostationary state (cis:trans) upon direct irradiation	20:80	85:15	85:15
Photostationary state (cis:trans) upon direct irradiation	0:100	85:15	85:15
Lifetime of S ₁ (ns)	1.51	0.85	1.16

Figure 6. (a) (i) Fluorescence emission spectra of 4,4'-dimethylstilbene@OA₂ ([stilbene] = 2 × 10⁻⁵ M; [OA] = 4 × 10⁻⁵ M) and (ii) 4,4'-dimethylstilbene (~2 × 10⁻⁵ M) in borate buffer (1 × 10⁻² M; λ_{ex} = 320 nm). (b) Comparison of the data from NMR, photochemical, and photophysical studies of three dimethylstilbenes.

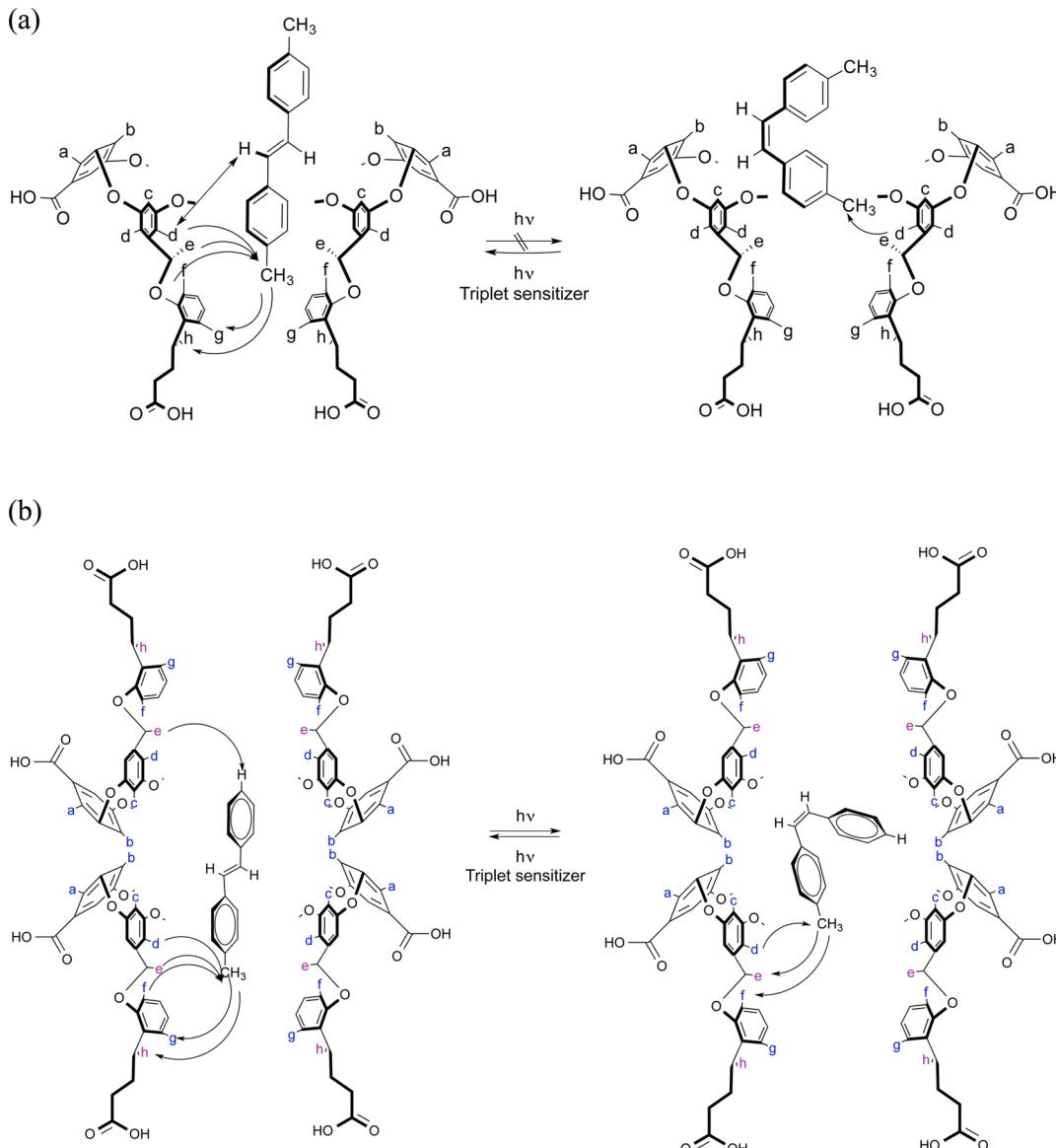
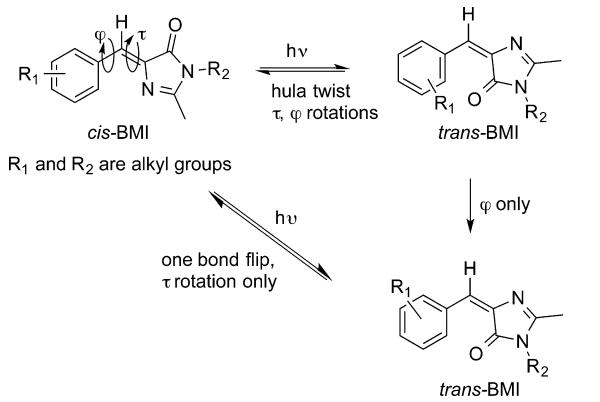


Figure 7. Structures of *cis*- and *trans*-4,4'-dimethylstilbenes and 4-methylstilbenes included within OA capsule based on NOESY data and computer modeling. Since 4,4'-dimethylstilbene is symmetric, only half the capsule is shown.

Scheme 5. Possible C–C and C=C Rotational Motions of Benzylidene-3-methylimidazolidinone



single bond (free-rotor) (Scheme 5). Among the methylated BMIs, the *ortho* methylated phenyl group would exert larger sweeping motion than the *meta* and *para* isomers. This rotational motion is likely to be prohibited within OA due to supramolecular steric effect leading to enhanced fluorescence. Another type of rotation, namely around C=C would result in *cis*–*trans* isomerization. Again, similar to stilbenes, the photostationary state composition of some BMIs differed between acetonitrile solution and the OA capsule. For example, in the case of the *ortho*-methyl-*N*-propyl system, the *cis*:*trans* ratio was 39:61 in acetonitrile and 6:94 in OA (Figure 8b). Since the large differences in photostationary state composition were noticed even in systems that showed no enhancement of fluorescence, the processes of rotation of the C–C and the C=C bonds are not subjected to the same type of steric encumbrance. Examination of the geometric isomerization of stilbenes and benzylidene-3-methylimidazolidinones has revealed that OA capsule can influence the excited state processes that involve large volume demanding rotations.

shown in Figure 8b. In methyl substituted BMIs one of the radiationless decay paths involves free rotation around the C–C

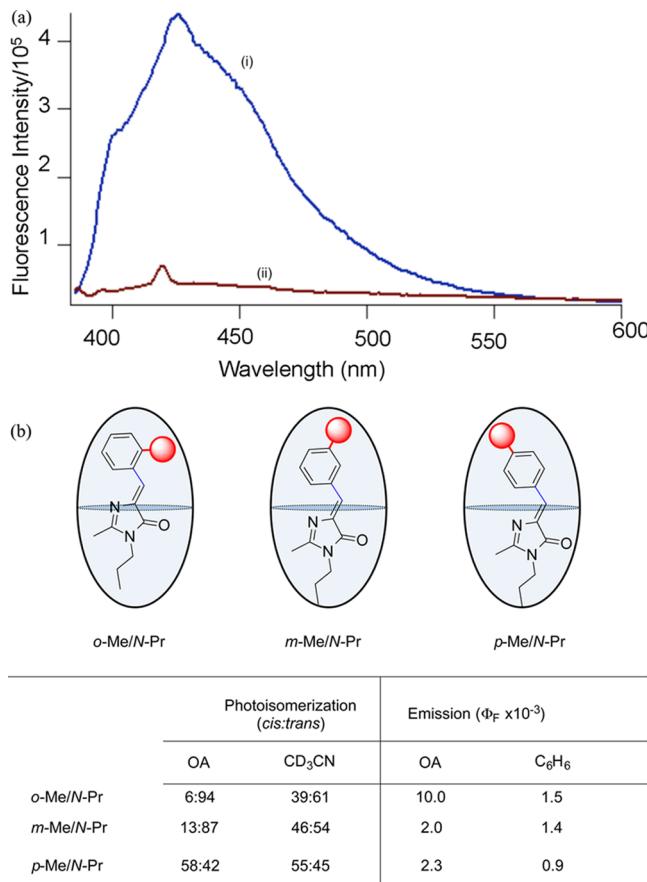


Figure 8. (a) (i) Fluorescence spectra of *cis*-3-methyl-N-propyl imidazolidinone@OA₂ ([*cis*-3-methyl-N-propyl imidazolidinone] = 1×10^{-5} M; [OA] = 2×10^{-5} M) in borate buffer and (ii) *cis*-3-methyl-N-propyl imidazolidinone (1×10^{-5} M) in benzene ($\lambda_{ex} = 370$ nm). (b) Dependence of fluorescence enhancement and photo-stationary state composition on the location of methyl group in BMIs@OA₂.

3.4. Cycloaddition Reactions of Olefins and Aromatics: Localization and Orientational Effects

Regioselective photocycloaddition reactions in micelles brought out how preorientation of molecules at hydrophobic–hydrophilic interfaces could be transformed into stereo- and region-selective cyclobutanes overcoming the inherent steric and electronic features that control the chemistry in isotropic solution.⁴⁰ The closed OA container despite lacking a hydrophobic–hydrophilic interface is better able to bind and localize more than one molecule. The localization effect allows for efficient dimerization even when the bulk concentration is extremely low or the reactants are not water-soluble. Further, due to the confining nature of the capsule, the reactant molecules are forced into a specific orientation with very little freedom. Thus, similar to crystals and micelles, the OA capsule offers a platform to carryout selective photodimerizations. A few examples presented below bring out the power of the OA capsule in defeating the forces controlling photocycloaddition in a solution.

Direct excitation, triplet sensitization and electron transfer sensitization of indene and *para*-methylstyrene in organic solvents lead to *head–head* (*syn* and *anti*) dimers as major products (Scheme 6a and b).^{36,41} As per ¹H NMR experiments, indene formed a 2:2 complex with OA (Figure 9a) while *para*-methylstyrene formed two noninterconverting 2:2

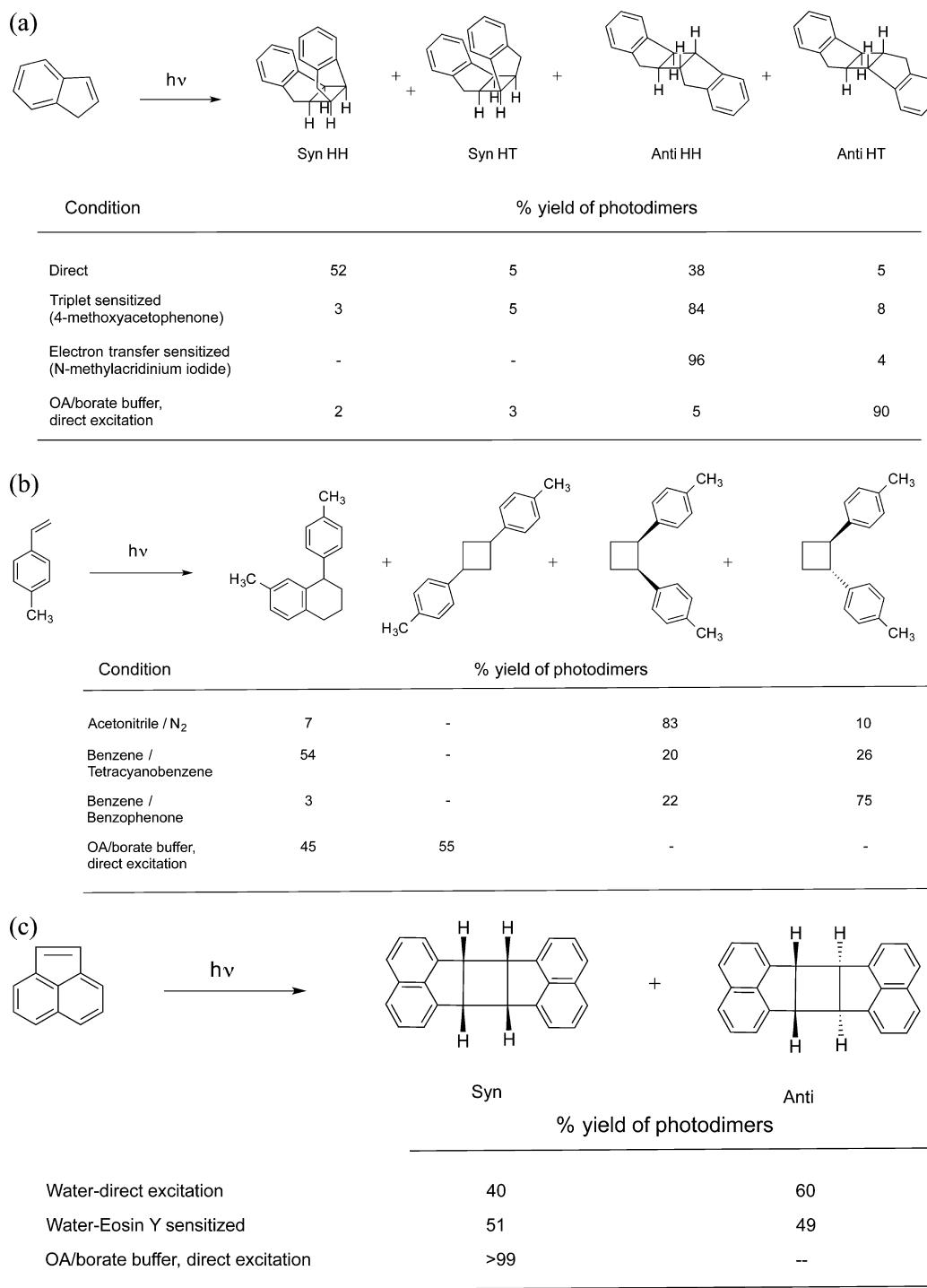
complexes of different relative olefin orientations (Figure 9b). Irradiation of indene₂@OA₂ gave *anti-head–tail* dimer that was not formed in solution under any conditions (Scheme 6a). The need to maximize van der Waals interaction with the host interior probably directed indene to prefer the *head–tail* arrangement that fills the entire cavity, which upon excitation transformed into *head–tail* dimer. Excitation of a mixture of two host–guest complexes of *para*-methylstyrene resulted in two products, both from *head–tail* arrangement of the olefins, in the same ratio as the two complexes (Scheme 6b).^{36,41} A rationale similar to the one for indene holds good in this case also. In solution, the nature of the dimer product was controlled by the relative stability of the diradical intermediate (*head–head* 1,4-diradical) formed. Within the OA capsule, its determining role seems lost. The third example deals with photodimerization of acenaphthylene that yielded *syn* and *anti* dimers upon excitation in solution (Scheme 6c).⁴² Acenaphthylene resulting in *syn* dimer exclusively (30% yield in 2 h) on irradiation as OA complex gave <1% yield of a mixture of *syn* and *anti* dimers (2.5:1 ratio) in either methanol or benzene under equivalent conditions. The tremendous increase in the efficiency of dimerization and selectivity of the dimer in OA resulted from the local concentration and orientation effects. Additionally, the inability of the *anti* dimer to fit within the OA cage probably precluded its formation.

The most exciting result relates to anthracene within OA capsule.⁴³ Anthracene, well-known to dimerize with a limiting quantum yield of 1.0, does not show any excimer emission in solution. Its excimer emission has only been recorded by photofragmenting the synthetic dimer either in the crystalline state or in an organic glass at 77 K.⁴⁴ Within the OA capsule, two molecules of the sparingly water-soluble anthracene could be included in a slipped geometry (Figure 2b). This upon irradiation showed intense excimer emission but did not dimerize (Figure 10). The long lifetime of this emission ($\tau = 263$ ns) is consistent with the sandwich excimer ($\tau > 200$ ns) formed upon photofragmentation of the anthracene dimer in the crystalline state.⁴⁴ The absence of dimerization could be attributed to the slipped arrangement and to the tight space that prevented the anthracene molecules from realigning to form bonds across 9,9' and 10 and 10' positions.

3.5. Oxidation of Olefins by Singlet Oxygen: Supramolecular Steric Effect and Importance of Capsular Dynamics

Singlet oxygen oxidation of olefins described below brings out how the different extents of steric hindrance in OA capsule to various potentially reactive sites can result in product selectivity. Addition of singlet oxygen to an olefin with several allylic hydrogens results in multiple allylic hydroperoxides via “ene” reaction.⁴⁵ For example, 1-alkyl cycloalkenes react with singlet oxygen in solution to yield three allylic hydroperoxides in unequal amounts (Scheme 7).⁴⁶ Four of the 20 closely similar structured olefins studied showed dramatically altered product distribution with the minor (<20%) product in solution being the major (>90% yield) one within the OA capsule (Scheme 7).⁴⁶ With only a fifth of tested olefins showing a change in behavior, the OA-capsule-like enzyme is substrate specific. The obtained selectivity could be understood only on the basis of supramolecular structure of the host–guest complex as illustrated below with 1-methylcyclohexene. ¹H NMR data suggested 1-methylcyclohexene₂@OA₂ complex to adopt the structure shown in Figure 11. Of the three allylic hydrogens, H_c (closer to the middle of the OA capsule) would be most accessible,

Scheme 6. Product Distribution of Photodimerization under Various Conditions of (a) Indene, (b) *para*-Methylstyrene, and (c) Acenaphthylene



and H_a (methyl) (anchored at the tapered end of the capsule) the least accessible to singlet oxygen that is likely to enter the capsule from the median. This is consistent with the observed products distribution (*Scheme 7*); of the three potentially reactive allylic hydrogens, only H_c was targeted within OA by singlet oxygen.

In this study, singlet oxygen was generated by two methods: In one, water-soluble Rose Bengal and in the other water insoluble 4,4'-dimethylbenzil (DMB) encapsulated within OA were used as sensitizers. We hypothesized partial opening-closing of the

capsule in the time scale of 5 μ s²⁹ would allow singlet oxygen generated by Rose Bengal to enter the capsule and oxidize the olefin. In the case of DMB@OA₂ even singlet oxygen generation required capsule opening. Our earlier inference of the capsule's *partial* opening-closing in the time scale of 5 μ s predicted numerous such action during the 596 μ s lifetime of encapsulated DMB triplet when oxygen could enter the capsule and get excited to singlet oxygen.²⁹ The differing singlet oxygen lifetimes in these complexes with solvents H₂O and D₂O (5 and 41 μ s respectively) pointed to the oxygen spending most of its lifetime

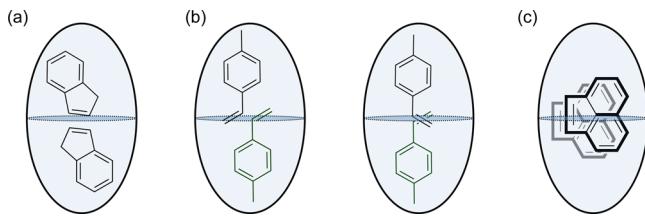


Figure 9. Orientation of two molecules of (a) indene, (b) para-methylstyrene, and (c) acenaphthylene within OA capsule.

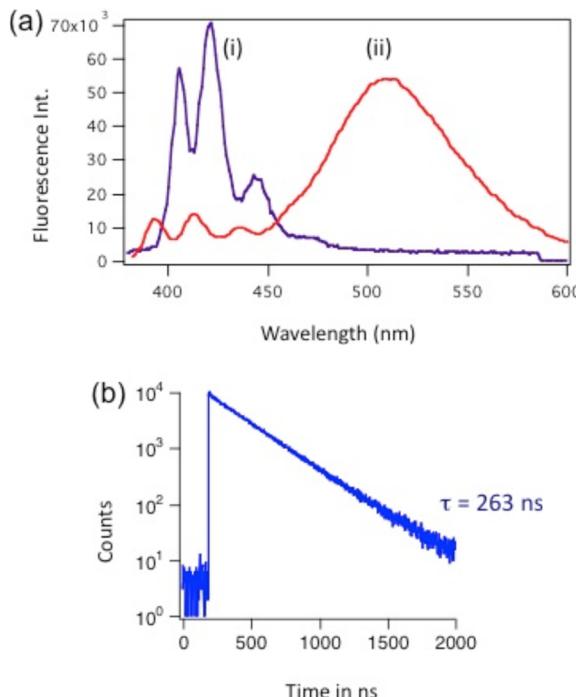
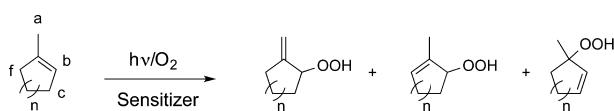


Figure 10. (a) Emission spectra of anthracene in borate buffer in presence and absence of OA. (i) Monomer emission from anthracene in borate buffer and (ii) anthracene₂@OA₂ “excimer” emission in borate buffer. (b) Decay of anthracene₂@OA₂ excimer emission.

Scheme 7. Product Distribution upon Photooxidation of 1-Methylcycloalkenes within OA and in Acetonitrile



Molecule	Condition	% yield of oxidation products		
n=1	CH ₃ CN / Rose bengal	4	43%	53%
	Octa acid / Rose bengal	-	5%	95%
n=2	CH ₃ CN / Rose bengal	44	20%	36%
	Octa acid / Rose bengal	10	-	90%
n=3	CH ₃ CN / Rose bengal	4	48%	48%
	Octa acid / Rose bengal	4	6%	90%

in the aqueous medium rather than within the capsule.²⁹ The capsule generated singlet oxygen is thus presumably detained in the aqueous exterior to enter the capsule when it opens to oxidize the olefin (Figure 12). These coordinated, cascading events leading to selective oxidation of olefins highlight the opportunities OA capsule offers for bimolecular reactions in water.

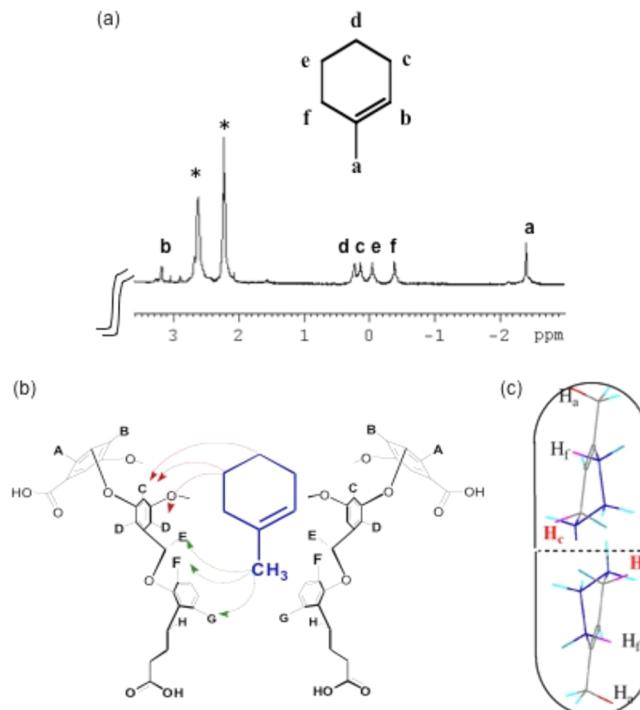


Figure 11. (a) ¹H NMR spectrum of 1-methylcyclohexene₂@OA₂. (b) NOE correlations between guest olefin and host OA protons. (c) Cartoon representation of the orientation of 1-methylcyclohexene within OA.

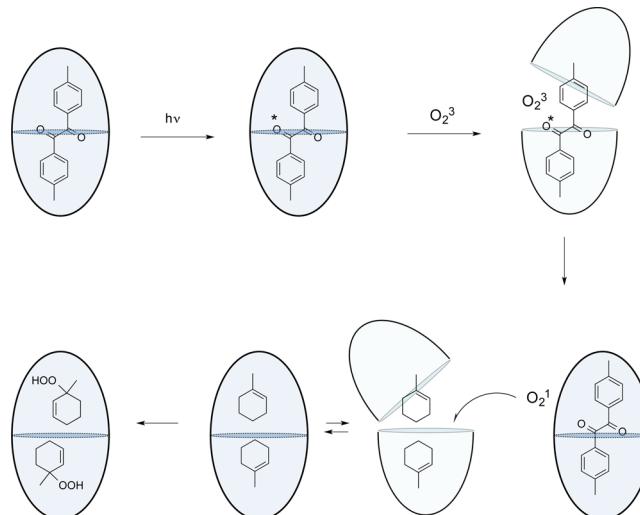


Figure 12. Sequence of events leading to the oxidation of 1-methylcyclohexene₂@OA₂ by singlet oxygen generated by 4,4'-dimethylbenzil@OA₂.

3.6. Chiral Induction in Electrocyclic Reactions: Role of Restricted Mobility

The final example relates to chiral induction in photoreactions, a challenge that has attracted considerable attention during the last two decades.⁴⁷ Chiral induction in the nonchiral OA would require coclusion of a chiral inductor or a chiral auxiliary covalently linked to the reactant molecule. Inability to include two different molecules (a reactant and a chiral inductor) within OA capsule left the latter method as the sole option. The three examples provided below establish that OA has the ability to confine the guest and enhance the interaction between the sites of reaction and chiral induction.^{48,49}

Scheme 8. Chiral Products and de Obtained upon Photocyclization of Tropolone Ether, Cyclohexadienone, and Pyridone

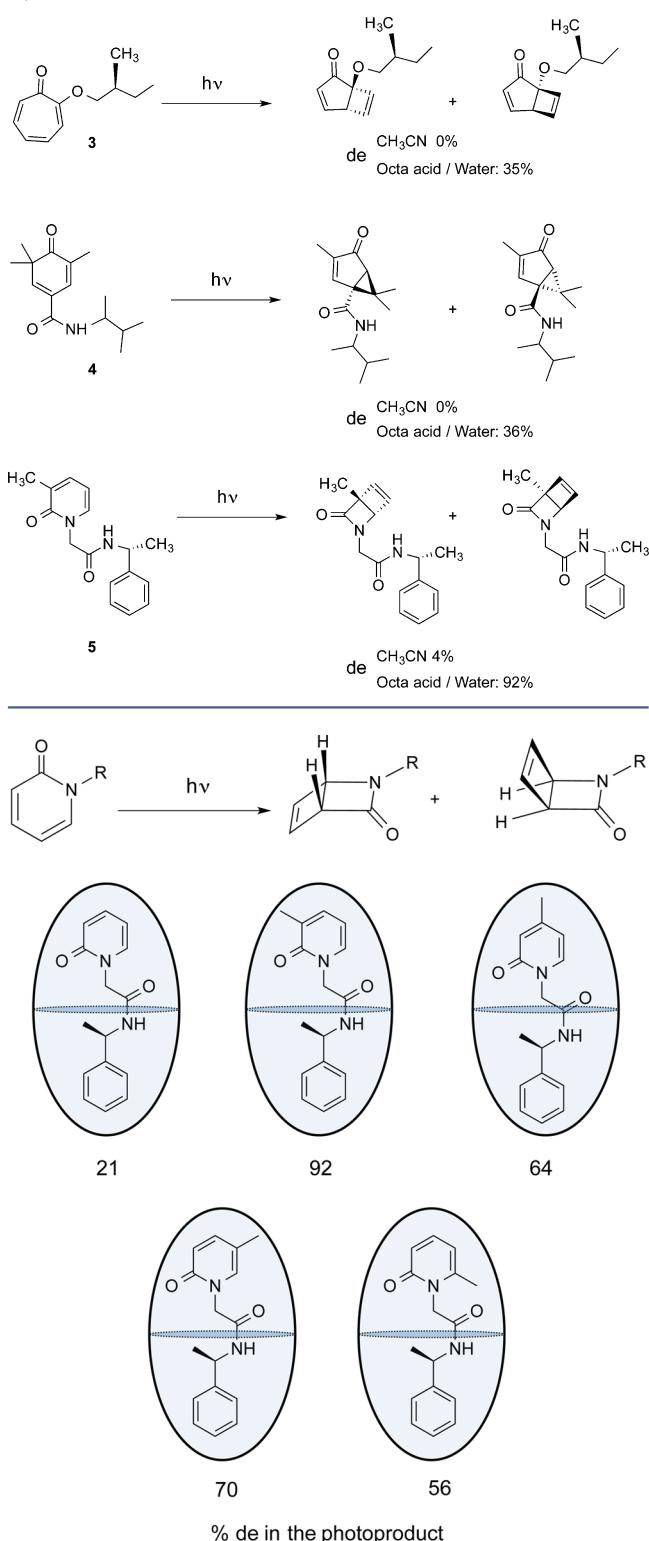


Figure 13. Dependence of chiral induction (% de) on the location of the methyl group during photocyclization of methypyridones within OA.

The three systems, tropolone ether **3**, cyclohexadienone **4**, and pyridone **5**, we have examined within OA capsule are shown in Scheme 8 along with their chiral products. When **3–5** were irradiated in acetonitrile, the diastereomeric excess (de) on the

photoproducts was less than 3%, showing that the presence of the chiral auxiliary at a remote location had very little effect on the reaction. On the other hand, **3@OA₂** and **4@OA₂** yielded photoproducts with de's of 35% and 36% respectively establishing the ability of OA to confine and restrict a guest and thus bias the photoreaction toward one diastereoisomer. We then investigated the photocyclization of five pyridones with remotely attached chiral auxiliary. The obtained de and the structures of the complexes inferred from ¹H NMR are provided in Figure 13. The negligible de in acetonitrile (<5%) was enhanced up to 92% within OA. A chiral induction of 92% is unprecedented within an organic capsule in solution. As would be expected small changes in the structure (focus on the location of the methyl group in Figure 13) resulted in large changes in de. The examples provided are suggestive of the future promise for OA as a reaction container in chiral photochemistry.

4. SUMMARY

In this Account, we have highlighted the value of OA as a reaction container to modify the excited state chemistry of organic guest molecules in water. The active cavity of OA absorbs light up to 300 nm and is capable of donating triplet energy, electron, and hydrogen.^{23,24} Expectedly, depending on the structure of the guest, OA forms 1:1, 2:1, or 2:2 hydrophobic host–guest complexes.²⁶ The guest molecules within the capsule depending on their size, shape and structure undergo different types of motions, with freedom intermediary between that in crystals and in isotropic solution.^{29,30} Select examples discussed here highlight how restricted mobility can be translated into unprecedented product selectivity. The unique feature of OA, namely, the ability to form a closed capsular assembly with guests, permits photoreactions to be carried out in water in a hydrophobic environment.

The future of container/capsular photochemistry will depend on its value in synthetic, materials, and biological chemistry. Only when the photoreactions conducted in capsules become catalytic and highly regio- and stereoselective are they likely to appeal to synthetic chemists. The ability to organize and investigate supramolecular assemblies on ordered surfaces (supramolecular surface photochemistry) will facilitate entry into materials and energy applications.¹⁷ The capsule's value in medicinal chemistry as drug delivery vehicles and as probes of cell interior depend on our ability to transport the capsule to the desired venue and release the guest at will through phototriggering processes.^{25,50} In my opinion, the capsular assemblies hold considerable potential waiting to be fully exploited.

■ AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

Biography

Vaidhyanathan Ramamurthy (Professor at University of Miami) had his scientific training in the laboratories of R. S. H. Liu (University of Hawaii, Honolulu), P. de Mayo (The University of Western Ontario, London, Canada), and N. J. Turro (Columbia University, New York). His current research interests are in the area of photochemistry in crystals, zeolites, cavitands, and capsules.

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■ REFERENCES

- (1) Turro, N. J.; Ramamurthy, V.; Sciaiano, J. C. *Modern Molecular Photochemistry of Organic Molecules*; University Science Books: Sausalito, CA, 2010.
- (2) Balzani, V.; Scandola, F. *Supramolecular Photochemistry*; Ellis Horwood: Herts, U.K., 1991.
- (3) *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; Wiley-VCH: New York, 1991.
- (4) *Supramolecular Photochemistry*; Ramamurthy, V., Inoue, Y., Eds.; John Wiley: Hoboken, NJ, 2011.
- (5) Devanathan, S.; Syamala, M. S.; Ramamurthy, V. Photoreactions in hydrophobic pockets. *Proc. Indian Acad.* **1987**, *98*, 391–407.
- (6) Ramamurthy, V.; Venkatesan, K. Photochemical reactions of organic crystals. *Chem. Rev.* **1987**, *87*, 433–481.
- (7) Ramamurthy, V.; Eaton, D. F. Photochemistry and photophysics within cyclodextrin cavities. *Acc. Chem. Res.* **1988**, *21*, 300–306.
- (8) Ramamurthy, V.; Eaton, D. F.; Caspar, J. V. Photochemical and photophysical studies of organic molecules included within zeolites. *Acc. Chem. Res.* **1992**, *25*, 299–307.
- (9) Weiss, R. G.; Ramamurthy, V.; Hammond, G. S. Photochemistry in Organized and Confining Media: A Model. *Acc. Chem. Res.* **1993**, *26*, 530–536.
- (10) Sivaguru, J.; Natarajan, A.; Kaanumalle, L. S.; Shailaja, J.; Uppili, S.; Joy, A.; Ramamurthy, V. Asymmetric Photoreactions Within Zeolites: Role of Confinement and Alkali Metal Ions. *Acc. Chem. Res.* **2003**, *36*, 509–521.
- (11) Gibb, C. L. D.; Gibb, B. C. Well-Defined, Organic Nanoenvironments in Water: The Hydrophobic Effect Drives a Capsular Assembly. *J. Am. Chem. Soc.* **2004**, *126*, 11408–11409.
- (12) Vallavouj, N.; Sivaguru, J. Supramolecular Photocatalysis: combining confinement and non-covalent interactions to control light initiated reactions. *Chem. Soc. Rev.* **2014**, *43*, 4084–4101.
- (13) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. Functional Molecular Flasks: New Properties and Reactions within Discrete, Self-assembled Hosts. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418–3438.
- (14) Turro, N. J.; Gratzel, M.; Braun, A. M. Photophysical and photochemical processes in micellar systems. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 675–696.
- (15) Ajami, D.; Liu, L.; Rebek, J. Soft templates in encapsulation complexes. *Chem. Soc. Rev.* **2015**, *44*, 490–499.
- (16) Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. Supramolecular Catalysis in Metal-Ligand Cluster Hosts. *Chem. Rev.* **2015**, *115*, 3012–3035.
- (17) Ramamurthy, V.; Jockusch, S.; Porel, M. Supramolecular Photochemistry in Solution and on Surfaces: Encapsulation and Dynamics of Guest Molecules and Communication between Encapsulated and Free Molecules. *Langmuir* **2015**, *31*, 5554–5570.
- (18) Ramamurthy, V.; Gupta, S. Supramolecular photochemistry: from molecular crystals to water-soluble capsules. *Chem. Soc. Rev.* **2015**, *44*, 119–135.
- (19) Ramamurthy, V.; Mondal, B. Supramolecular photochemistry concepts highlighted with select examples. *J. Photochem. Photobiol. C* **2015**, *23*, 68–102.
- (20) Shimizu, L. S.; Salpage, S. R.; Korous, A. A. Functional Materials from Self-Assembled Bis-Urea Macrocycles. *Acc. Chem. Res.* **2014**, *47*, 2116–2127.
- (21) Bohne, C. Supramolecular dynamics. *Chem. Soc. Rev.* **2014**, *43*, 4037–4050.
- (22) Bibal, B.; Mongin, C.; Bassani, D. M. Template effects and supramolecular control of photoreactions in solution. *Chem. Soc. Rev.* **2014**, *43*, 4179.
- (23) Jagadesan, P.; Mondal, B.; Parthasarathy, A.; Rao, V. J.; Ramamurthy, V. Photochemical reaction containers as energy and electron-transfer agents. *Org. Lett.* **2013**, *15*, 1326–1329.
- (24) Gupta, S.; Choudhury, R.; Krois, D.; Wagner, G.; Brinker, U. H.; Ramamurthy, V. Photochemical Generation and Reactivity of Carbenes Within an Organic Cavitand and Capsule: Photochemistry of Adamantanediazirines. *Org. Lett.* **2011**, *13*, 6074–6077.
- (25) Jayaraj, N.; Jagadesan, P.; Samanta, S. R.; Da Silva, J. P.; Ramamurthy, V. Release of Guests from Encapsulated Masked Hydrophobic Precursors by a Phototrigger. *Org. Lett.* **2013**, *15*, 4374–4377.
- (26) Jayaraj, N.; Zhao, Y.; Parthasarathy, A.; Porel, M.; Liu, R. S. H.; Ramamurthy, V. Nature of Supramolecular Complexes Controlled by the Structure of the Guest Molecules: Formation of Octa Acid Based Capsuleplex and Cavitandplex. *Langmuir* **2009**, *25*, 10575–10586.
- (27) Porel, M.; Jayaraj, N.; Kaanumalle, L. S.; Maddipatla, M. V. S. N.; Parthasarathy, A.; Ramamurthy, V. Cavitand Octa Acid Forms a Nonpolar Capsuleplex Dependent on the Molecular Size and Hydrophobicity of the Guest. *Langmuir* **2009**, *25*, 3473–3481.
- (28) Choudhury, R.; Barman, A.; Prabhakar, R.; Ramamurthy, V. Hydrocarbons Depending on the Chain Length and Head Group Adopt Different Conformations within a Water-Soluble Nanocapsule: ¹H NMR and Molecular Dynamics Studies. *J. Phys. Chem. B* **2013**, *117*, 398–407.
- (29) Jayaraj, N.; Jockusch, S.; Kaanumalle, L. S.; Turro, N. J.; Ramamurthy, V. Dynamics of Capsuleplex Formed between Octacaid and Organic Guest Molecules- Photophysical Techniques Reveal the Opening and Closing of Capsuleplex. *Can. J. Chem.* **2011**, *89*, 203–213.
- (30) Kulasekharan, R.; Jayaraj, N.; Porel, M.; Choudhury, R.; Sundaresan, A. K.; Parthasarathy, A.; Ottaviani, M. F.; Jockusch, S.; Turro, N. J.; Ramamurthy, V. Guest Rotations within a Capsuleplex Probed by NMR and EPR Techniques. *Langmuir* **2010**, *26*, 6943–6953.
- (31) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. Controlling Photochemistry with Distinct Hydrophobic Nanoenvironments. *J. Am. Chem. Soc.* **2004**, *126*, 14366–14367.
- (32) Sundaresan, A. K.; Ramamurthy, V. Making a Difference on Excited-State Chemistry by Controlling Free Space within a Nanocapsule: Photochemistry of 1-(4-Alkylphenyl)-3-phenylpropan-2-ones. *Org. Lett.* **2007**, *9*, 3575–3578.
- (33) Sundaresan, A. K.; Ramamurthy, V. Consequences of controlling free space within a reaction cavity with a remote alkyl group: photochemistry of para-alkyl dibenzyl ketones within an organic capsule. *Photochem. Photobiol. Sci.* **2008**, *7*, 1555–1564.
- (34) Gibb, C. L. D.; Sundaresan, A. K.; Ramamurthy, V.; Gibb, B. C. Temptation of the Excited-State Chemistry of alpha-(n-Alkyl) Dibenzyl Ketones: How Guest Packing within a Nanoscale Supramolecular Capsule Influences Photochemistry. *J. Am. Chem. Soc.* **2008**, *130*, 4069–4080.
- (35) Kulasekharan, R.; Maddipatla, M. V. S. N.; Parthasarathy, A.; Ramamurthy, V. Role of Free Space and Conformational Control on Photoproduct Selectivity of Optically Pure a-Alkyldeoxybenzoins within a Water-soluble Organic Capsule. *J. Org. Chem.* **2013**, *78*, 942–949.
- (36) Parthasarathy, A.; Kaanumalle, L. S.; Ramamurthy, V. Controlling Photochemical Geometric Isomerization of a Stilbene and Dimerization of a Styrene Using a Confined Reaction Cavity in Water. *Org. Lett.* **2007**, *9*, 5059–5062.
- (37) Parthasarathy, A.; Ramamurthy, V. Role of Free Space and Weak Interactions on Geometric Isomerization of Stilbenes held in a Molecular Container. *Photochem. Photobiol. Sci.* **2011**, *10*, 1455–1462.
- (38) Baldridge, A.; Samanta, S. R.; Jayaraj, N.; Ramamurthy, V.; Tolbert, L. M. Activation of fluorescent protein chromophores by encapsulation. *J. Am. Chem. Soc.* **2010**, *132*, 1498–1499.
- (39) Baldridge, A.; Samanta, S. R.; Jayaraj, N.; Ramamurthy, V.; Tolbert, L. M. Steric and Electronic Effects in Capsule-Confined Green

Fluorescent Protein Chromophores. *J. Am. Chem. Soc.* **2011**, *133*, 712–715.

(40) Lee, K. H.; de Mayo, P. Biphasic photochemistry: Photochemical regiospecificity and critical micelle concentration determination. *Photochem. Photobiol.* **1980**, *31*, 311–314.

(41) Parthasarathy, A.; Samanta, S. R.; Ramamurthy, V. Photodimerization of hydrophobic guests within a water-soluble nanocapsule. *Res. Chem. Intermed.* **2013**, *39*, 73–87.

(42) Kaanumalle, L. S.; Ramamurthy, V. Photodimerization of acenaphthylene within a nanocapsule: excited state lifetime dependent dimer selectivity. *Chem. Commun.* **2007**, 1062–1064.

(43) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. A Hydrophobic Nanocapsule Controls the Photophysics of Aromatic Molecules by Suppressing Their Favored Solution Pathways. *J. Am. Chem. Soc.* **2005**, *127*, 3674–3675.

(44) Chandross, E. A.; Ferguson, J.; McRae, E. G. Absorption and Emission Spectra of Anthracene Dimers. *J. Chem. Phys.* **1966**, *45*, 3546–3553.

(45) *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1978.

(46) Natarajan, A.; Kaanumalle, L. S.; Jockusch, S.; Gibb, C. L. D.; Gibb, B. C.; Turro, N. J.; Ramamurthy, V. Controlling Photoreactions with Restricted Spaces and Weak Intermolecular Forces: Exquisite Selectivity during Oxidation of Olefins by Singlet Oxygen. *J. Am. Chem. Soc.* **2007**, *129*, 4132–4133.

(47) *Chiral Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Marcel Dekker: New York, 2004; Vol. 11.

(48) Sundaresan, A. K.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. Chiral photochemistry in a confined space: torque-selective photoelectrocyclization of pyridones within an achiral hydrophobic capsule. *Tetrahedron* **2009**, *65*, 7277–7288.

(49) Sundaresan, A. K.; Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. Chiral Photochemistry within a confined space: diastereoselective photorearrangements of a tropolone and cyclohexadienone included in a synthetic cavitand. *J. Chem. Soc., Dalton Trans.* **2009**, 4003–4011.

(50) Jagadesan, P.; Da Silva, J. P.; Givens, R. S.; Ramamurthy, V. Photorelease of Incarcerated Guests in Aqueous Solution with Phenacyl Esters as the Trigger. *Org. Lett.* **2015**, *17*, 1276–1279.