Role of Supramolecular Steric Compression During Photoinduced Intramolecular Hydrogen Abstraction Reactions of Ketones and Thioketones

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Abstract

Excited state behavior of molecules is influenced by the environment in which they are present. The influence of solvents on reactions is understood in terms of the bulk properties of the solvent such as polarity, polarizability, hydrogen bonding, solvophobic interactions etc. Under these conditions, the 'space' surrounding the guest does not play any role in influencing the fate of an excited molecule. The current study focusses on understanding the factors that control the excited state reactivity of molecules within a confined space. In this context organic capsules assembled from two molecules of octa acid serves as the host and aryl alkyl ketones and aryl alkyl thioketones as reactive guests. One obvious prediction has been when the product is larger in size than the host capsule it would not be formed within the confined space although this may be the predominant product in solution. The authors demonstrate below that even if the product fits well within the capsule it may not be formed if the intermediate structures that connects the reactant to product does not fit within the capsule. The above hidden factor that controls photoproduct distribution has been investigated employing several aryl alkyl ketones that undergo γ-hydrogen abstraction as guests. In some of the examples investigated here, the Yang cyclization product, cyclobutanol, is suppressed within OA capsule even though it fits well within the capsule. Another factor that has come to light is 'time'. Aryl alkyl thioketones that react from short lived second excited state (S_2) fail to undergo δ-hydrogen abstraction within OA capsule although this is the only photoreaction in solution. MD simulations of the thioketones suggest that within the capsule the relevant hydrogens are not within the ideal geometry required for abstraction. Lack of reactivity is attributed to the insufficient time for the excited molecule to achieve the required conformation within the narrow space. Longer lived aryl alkyl ketones had no such problems in adopting a conformation required for hydrogen abstraction. Obviously,

time becomes critical when the space is narrow. The results reported here brings out that one could consider 'free space' and 'time' as valuable tools to control product distribution while performing photochemistry in supramolecular assemblies.

Key words: Host-guest complex, Supramolecular photochemistry, Norrish Type I and Type II reactions, photocyclization of thioketones, octa acid capsule

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Introduction

Molecular photochemistry is generally understood in terms of the inherent features of the reacting molecule and the fluctuating medium in which it is present.[1-3] In an isotropic solvent medium, all reacting molecules would experience an average microenvironment by virtue of fast relaxation time of the solvent and high mobility of the reacting molecules. Also, because the solvent medium is flexible (soft) and has inherent invisible mobile free space, steric interactions between the reacting and the solvent molecules would play no role in product selectivity. Free space, the space needed for molecular transformation is not of concern. However, when the medium is 'stiff' (hard or inflexible) with limited fixed free space (*e.g.*, crystals, glass etc.) the steric interactions between the reacting molecule as well as reactive intermediate(s) and the medium is expected to influence the reactivity of molecules both in the ground and excited states.[4] Below we provide examples that brings out the importance of supramolecular[5] steric features during a photoreaction within a well-defined reaction cavity of size slightly larger than the reactant molecules.[6]

During the last three decades, driven by the desire to control excited state processes supramolecular organized structures have been explored as reaction media.[7-12] These include rigid solids (crystals, zeolites, clays, silica etc.), soft flexible organized assemblies such as micelles, vesicles, liquid crystals, mono and multilayers and well-designed water-soluble hosts.[13-15] Our recent interest has been on the last class of molecules that include cyclodextrins (CD), cucurbiturils (CB), calixarenes (CA), Pd nanohost (PdNH) and octa acid (OA).[7, 16-21] Desire to perform excited state reactions in a closed environment and in water prompted us to explore OA as a reaction container.[22] Importantly, CD, CB, CA and PdNH form open complexes (cavitandplex) wherein the guest molecules are not fully confined.[23] Interestingly, OA in presence of an organic guest molecule forms a water-soluble closed capsule (capsuleplex) (Figure 1).[24-28] Under such conditions, the excited reactant molecule remains confined within the nanocapsule. Thus far, selectivity in organized structures has been rationalized on the basis of the size of products formed. We show below that the size of the transient structures that connect the reactant to products do matter when the space is restricted and time is short.

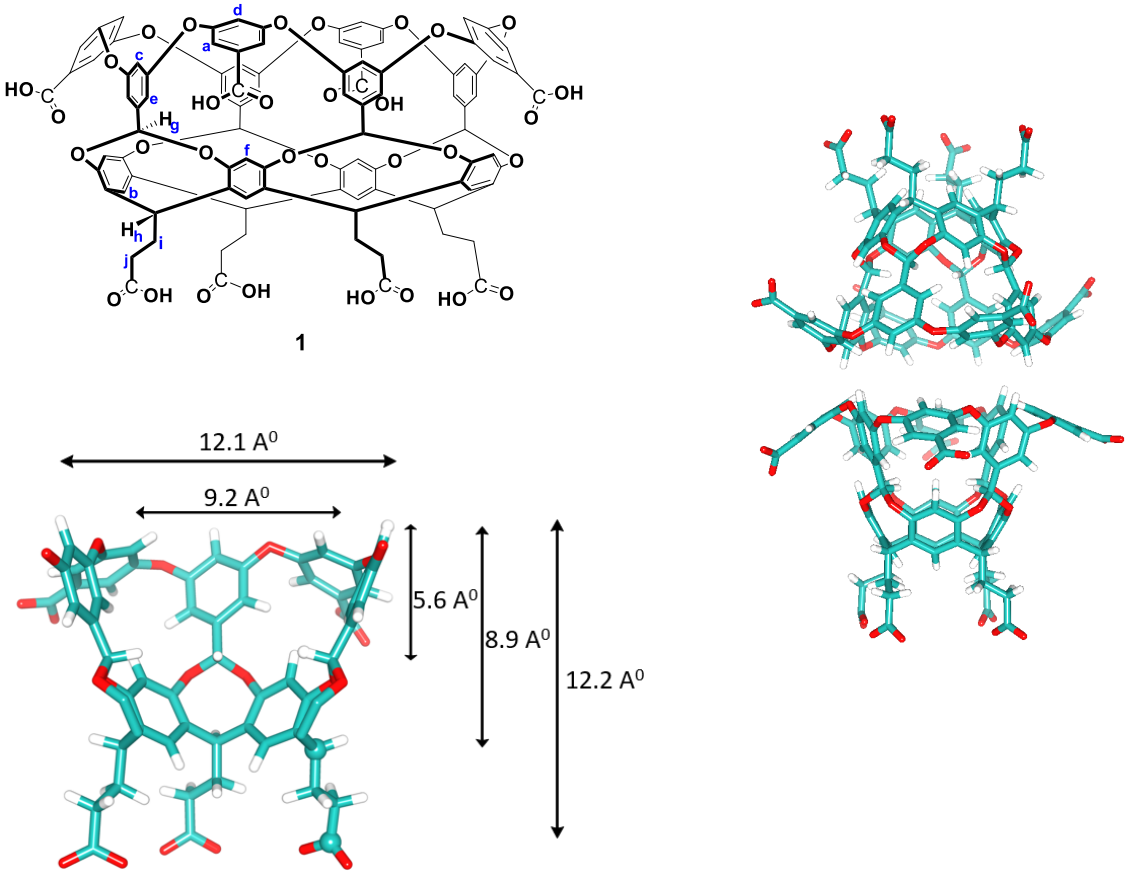
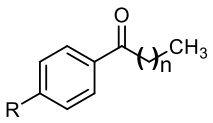


Figure 1. Structure and dimensions of octa acid (host) and the structure of a dimeric capsule shown without guest. Capsules are formed in buffer solution only in presence of a guest.

The host OA with a rigid inflexible wall is expected to forbid formation of products that are larger in size than the interior of the capsule. Thus, when there are multiple products formed in an isotropic solution, the OA reaction cavity would favor a product that is smaller and exclude the ones that are larger than interior of the cavity.[29-31] The one question that needs an answer is whether the capsule would influence product distribution even when all products fit equally well within. We illustrate below using the well-known Norrish-Yang reaction of aryl alkyl ketones (Scheme 1)[23] that the product selectivity can result within a confined space even when products of similar sizes are formed. It is quite likely that as the reactant transforms itself to products it may go through structures that are larger in size than the interior of the reaction container. Such a set-up would lead to unanticipated product selectivity. The examples

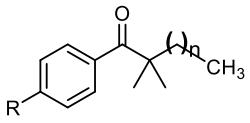
presented here illustrate this likely scenario and underscore the importance of supramolecular steric hindrance between the intermediary structures and the walls of the reaction container. Results are rationalized on the basis of the reaction cavity model earlier proposed by Weiss, Ramamurthy and Hammond (WRH model).[4, 32]



2, n=6, R=H; **5**, n=6, R=CH_3;

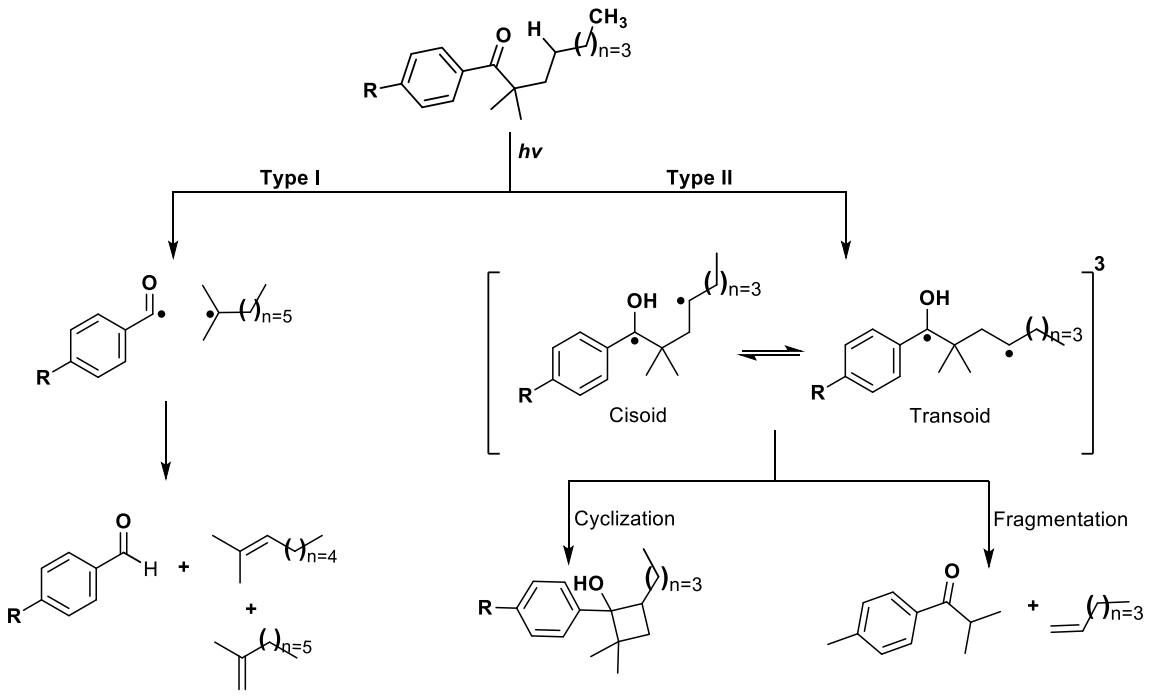
3, n=8, R=H; **6**, n=9, R=CH_3;

4, n=9, R=H;



7, n=5, R=H;

8, n=5, R=CH_3;



Scheme 1. Type I and II reactions of aryl alkyl ketones and photoproducts.

The goal of this investigation is to further substantiate the utility of the WRH model for understanding and making predictions about photoreactions in confined media. As per this model, the photoreactions within a supramolecular assembly can be visualized to occur in a confined space represented as a circle/sphere (Figure 2).[4, 32] The circle symbolizes a closed

reaction cavity in three dimensions. In the current case it represents interior of the OA capsule (Figure 1). The features that distinguish the supramolecular reaction cavities from isotropic solution media are their ability to: (a) pre-orient the reactants through weak interactions, (b) enforce supramolecular steric hindrance through their inflexible wall, (c) ability to control the freedom of reactants through reduced free space within the cavity and (d) discriminate products and intermediates of different sizes and thus favor products that fit within the cavity. Based on the features outlined in WRH model, OA capsule[24, 27] can be considered to possess a hard active reaction cavity with inflexible wall and fixed free space. The cavity is defined active because with weak interactions such as van der Waals, π–π and CH---π, it can pre-organize a guest molecule along a particular reaction co-ordinate. It is also considered hard (inflexible) because the walls are rigid and don't accommodate changes like a solvent medium would. In general, photoreactions can be considered to follow two pathways, one involving intermediate (R, R*, I, P) and the other without intermediate (R* to P). In the examples discussed here the photoreaction proceeds *via* an intermediate (Figure 2).

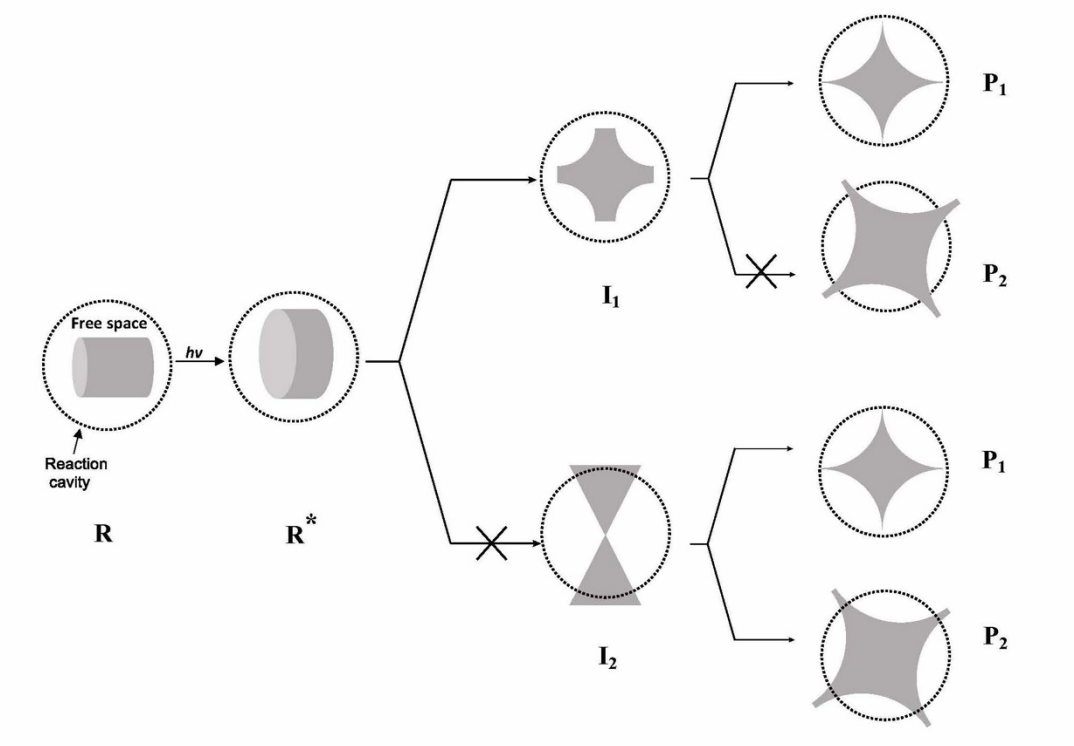


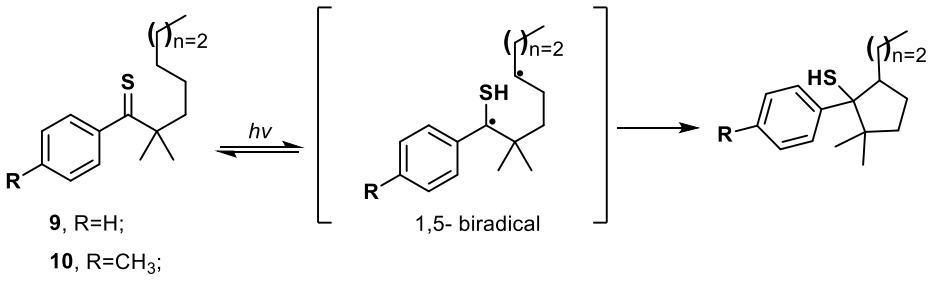
Figure 2. Changes in the structure of the reactant as it proceeds to the product in a reaction cavity illustrated in a cartoon fashion. In one case selectivity comes from the product being too large and in the other the intermediate structure being too large to fit in the reaction cavity.

For some time, our group has been exploring the value of OA capsule in controlling photoreactions.[24, 27] Select examples of these include: (a) Norrish Type I and Type II reactions of 1-methylcyclohexylphenyl ketone.[33] In this case, the γ-hydrogen abstraction that occurs in solution does not take place within OA capsule, instead Type I cleavage predominates. This is attributed to pre-orientation of the reactive –(C=O)Ph group away from the γ-hydrogen. Inability of the –(C=O)*Ph group to adopt the required conformation for hydrogen abstraction allows the less facile Type I process to take over. Thus, in this example the capsule pre-orients the R* towards a reaction co-ordinate that is not favored in solution. (b) Photodimerization of anthracene that proceeds with high quantum yield in solution does not occur within OA.[29, 34] Interestingly this gives rise to never-before observed excimer emission from anthracene. This is a consequence of the OA reaction cavity's inability to accommodate the structural changes from two monomers to a dimer in the restricted space. Similar selectivity is noted during the

dimerization of indene and acenaphthylene within OA capsule.[30, 31] In these reactions the excited guest although has freedom to pursue the reaction that occurs in solution, it is prevented to do so by the higher barrier due to the product being too large to stay within the capsule. (c) The third group of molecules that undergo both Norrish Type I and Type II reactions are α-alkyldibenzylketones and α-alkyldeoxybenzoins.[27, 35-37] Variations in product distribution between solution and within OA capsule are understood in terms of free space within the OA capsule. In these examples the pathway that requires more space is curtailed when the long alkyl chain (of α-alkyldibenzylketones and alkyldeoxybenzoins) itself occupies the space. (d) The geometric isomerization of 4,4'-dimethyl stilbene and 4,4'-azobenzene within OA capsule brings out the importance of yet another hidden feature of a photoreaction that could be used to control reactions by reducing the size of a reaction cavity.[38-43] While, within OA capsule 4,4'-dimethyl substituents prevented the isomerization of stilbene from *trans* to *cis* isomer they had no effect in the case of azobenzene. This was attributed to the differences in the mechanism of geometric isomerization. Stilbene proceeds via volume demanding torsional motion while azobenzene proceeds via volume conserving pyramidalization. Apparently when the space becomes premium the azo molecules chooses a less volume demanding pathway to reach the *cis* isomer. Such an option does not exist in the case of stilbenes. These two examples elegantly illustrate the importance of closely monitoring the role of confinement along the reaction co-ordinate from reactant to product. Even if the final product could fit within the confined space, inability of the structures along the pathway to fit will have consequence on the final outcome of a photoreaction.

In this study we have expanded the feature brought out by azobenzenes with the classic intramolecular hydrogen abstraction reactions of ketones and thioketones (Schemes 1 and 2).[44-52] In solution the Norrish Type I and Type II and Yang cyclization of arylalkyl ketones have been established to occur from excited nπ* triplet state (Scheme 1).[23] Although one might expect the hydrogen abstraction reaction to be curtailed or slowed due to reduced mobility of the alkyl chain in a confined reaction cavity, the arylalkyl ketones **2**-**8** investigated here reacted facilely within OA. This gave us an opportunity to examine the role of reduced space on product distribution from these ketones. Results presented here bring to light yet another feature namely 'space' that could be used as a tool to control phototransformations in organized assemblies. Having identified space as a tool, we were curious of the role of 'time' in a restricted space. This

led us to investigate the photochemistry of thiocarbonyl compounds which are known to react from short lived ($\tau \sim 10^{-10}$ sec) upper excited singlet state (S_2). The lifetime difference between the reactive state of C=O and C=S chromophores is close to four orders of magnitude. Arylalkyl thioketones react from S_2 and yield cyclopentyl system instead of cyclobutyl system which is common in the case of arylalkyl ketones (Scheme 2).[49, 51] In this study we have examined the photochemical behavior of two arylalkyl thioketones (**9** and **10**, Scheme 2) within OA capsule and in hexane. As expected, δ-hydrogen abstraction occurred in hexane while within OA capsule there was no product. One interpretation of this observation is that the excited state lifetime is too short (10^{-10} sec) for the alkyl chain to explore multiple conformations within the narrow capsule to find one that would favor hydrogen abstraction. Probably, the confined molecule requires much longer time to perform the same function as in isotropic solution. A comparative analysis of the photobehavior of C=O and C=S chromophores within OA capsule presented here reveals the importance of space and time in controlling photoreactions of confined molecules.



Scheme 2. Intramolecular hydrogen abstraction reaction of excited aryl alkyl thioketones.

Experimental

Materials and Methods: Guests 1-phenyloctan-1-one (**2**), 1-phenyldecan-1-one (**3**), 1-phenylundecan-1-one (**4**) were used as received from Sigma-Aldrich. The host octaacid (OA, **1**), [22] guests **5--10** were synthesized by following literature procedures (details provided as Supplementary Material, SM). [33, 52, 53] The final products were characterized by 1D and 2D ^{1}H NMR and mass spectra.

Instrumentation: All ^{1}H NMR spectra were recorded on a 500 MHz or 400 MHz NMR spectrometer. Agilent 6890 GC instrument equipped with MS detector was used for GC-MS analysis to identify photoproducts. UV-Vis absorption spectra were recorded on Shimadzu UV-3150 spectrometer. Photoluminescence studies were carried out using Edinburgh FL900 fluorimeter.

General procedure for complexation and characterization: All host-guest complexation were monitored by ^{1}H NMR at 25 °C. For host-guest titration experiments D_2O solution (0.6 mL) of host OA (1mM OA in 10 mM $Na_2B_4O_7$) was taken in NMR tube to which aliquots of 0.25 equivalents of guest (2.5 μL of a 60 mM solution in DMSO- d_6) were added. The ^{1}H NMR spectra were recorded after shaking the NMR tube for 5 min after each addition. Completion of complexation was deduced by disappearance of the free host OA signals and appearance of signals due to free guest in water. The ^{1}H NMR spectra of the complexes provided in Figures S1-S9 (see SM) confirmed the inclusion of guests within OA. COSY and NOESY spectra were recorded to assign the signals of the guest and to ascertain the location of the guest within OA (Figures S10-S25 in SM).

General procedure for irradiation, extraction, and analysis: All ketones were irradiated in n-hexane and resulting photoproducts were analyzed and characterized by GC and GC-MS respectively. For photolysis of host-guest complexes, stock solutions of guest **2-10** in DMSO-d_6 and OA solution (5mM) in sodium tetraborate-D_2O buffer were prepared. A solution of host and guest prepared in 2:1 mole ratio in D_2O was irradiated using a medium pressure Hg lamp for required duration to achieve ~20-25% conversion. Prior to irradiation the solution was bubbled with nitrogen for 20 mts and upon completion of irradiation the photoproducts were extracted with chloroform, and the organic layer was analyzed by GC and GC-MS.

General procedure for recording emission spectra: Fluorescence and phosphorescence of OA included **9** and **10** in borate buffer solution **(**10^{-5} M) were recorded at room temperature following bubbling with nitrogen for 30 mts. Emissions were recorded by exciting the solution at 320 nm. To record phosphorescence 490 nm cut-off filter was placed on the emission arm of the spectrometer.

*Computational methods***:** Simulation of guest molecule within OA was performed by following the procedure outlined below: The guest molecules **2**, **3**, **4** and **5** were modeled using the Gauss View program, and the 3D structure of OA was taken from our previous **s**tudy**.**[33]

These structures were optimized without any geometrical constrains at the B3LYP/D3BJ level[54-57] utilizing the Gaussian 09 software package.[57] In these calculations, the O and S atoms were treated with 6-31+g(d) and C and H with the 6-31g(d) basis set, respectively.[58, 59] The RESP charges for OA and guest molecules were calculated using antechamber, an inbuilt tool in the Amber program.[60, 61] These charges were utilized to create topology files that define molecular parameters. To derive the initial structures of the host-guest complexes, molecular docking procedure was performed using the AutoDock Vina 1.5.6. program package.[62] The most promising poses provided by these docking procedures were subsequently used for MD simulations utilizing the GROMACS program package[63, 64] and AMBER03 force field.[65] In all simulations, the starting structure (host-guest complex) was placed in a cubic box with dimensions of 60 × 60 × 60 $Å^3$, and the remaining space of the box was filled with the TIP3P water molecules.[66] Then, the system was neutralized by replacing some water molecules by sodium and chloride ions. These models were subsequently energy-minimized with a steepest descent method for 3000 steps. All MD simulations were performed on the energy minimized structures for 100 ns using a constant number of particles (N), pressure (P), and temperature (T) (NPT ensemble). The bond lengths of the OA were constrained by the LINCS algorithm[67] whereas the SETTLE algorithm[68] was used to constrain the bond lengths and angles of the water molecules. The long-range electrostatic interactions were calculated by the Particle-Mesh Ewald method.[69] The MD trajectories for each model were calculated with a time step of 2 fs. Next, the most representative structures for OA-guest complexes were derived from a cluster analysis. For visualization and preparation of the structural diagrams, Yasara,[70] Chimera[71] and VMD[72] programs were utilized.

Results

To probe the effect of confined space on the photobehavior of carbonyl and thiocarbonyl chromophores, arylalkyl ketones **2**-**8** and arylalkyl thioketones **9** and **10** (Schemes 1 and 2) were chosen. ^{1}H NMR spectroscopy was employed to ascertain the formation of OA complexes of **2**-**10**. ^{1}H NMR spectra of OA complexes of **7**-**10** are shown in Figure 3. Similar spectra for the OA complexes of **2**-**6** are included as Supplementary material (Figures S1-S9). In all spectra the guest signals were upfield shifted. This is characteristic indication of the guest inclusion within OA capsule.[73-75] To determine the host:guest ratio ^{1}H NMR titration experiments by the

gradual addition of small amounts of the guest to a given concentration of OA in borate buffer were performed. As an example of titration experiments the spectra obtained with **8** are shown in Figure 4. The important point to note in the figure is that upon addition of more than 0.5 eq. of guest ketone to 1 eq. of OA the solution turned turbid and signals due to free ketones were seen in water (see the signals marked as filled triangle in Figure 4). Similar titration in all cases confirmed the OA complexes to be 2:1 (H:G). To complement the structural characterization by NMR, MD simulation of guests **7**-**10** within OA capsule was performed. The MD simulated structures are shown in Figure 5. From these we infer the capsule is fully closed and the γ-hydrogens in **7** and **8** are within 3 Å to the C=O chromophore. Similarly, δ-hydrogens in **9** and **10** are at ~ 5 Å to the C=S chromophore. ^{1}H NMR chemical shifts of the guest@OA_2 indicate that the alkyl chains in these molecules are linear (not coiled as in solution) and the molecules are anchored at the two ends through alkyl and *para*-methyl groups. A point worthy of note is that an unsymmetrical molecule (interms of overall structure) when included within OA capsule tend to provide different amounts of shielding/deshielding for the chemically equivalent hydrogens present on the top and bottom part of the capsule. This is more so when the guest molecule can't tumble within the capsule in the NMR time scale. Under such conditions the host signals are split. This is evident in Figure 3. However, it is important to note that all hydrogens are split by the included guest. Therefore, some signals appearing as single peak is not of concern.

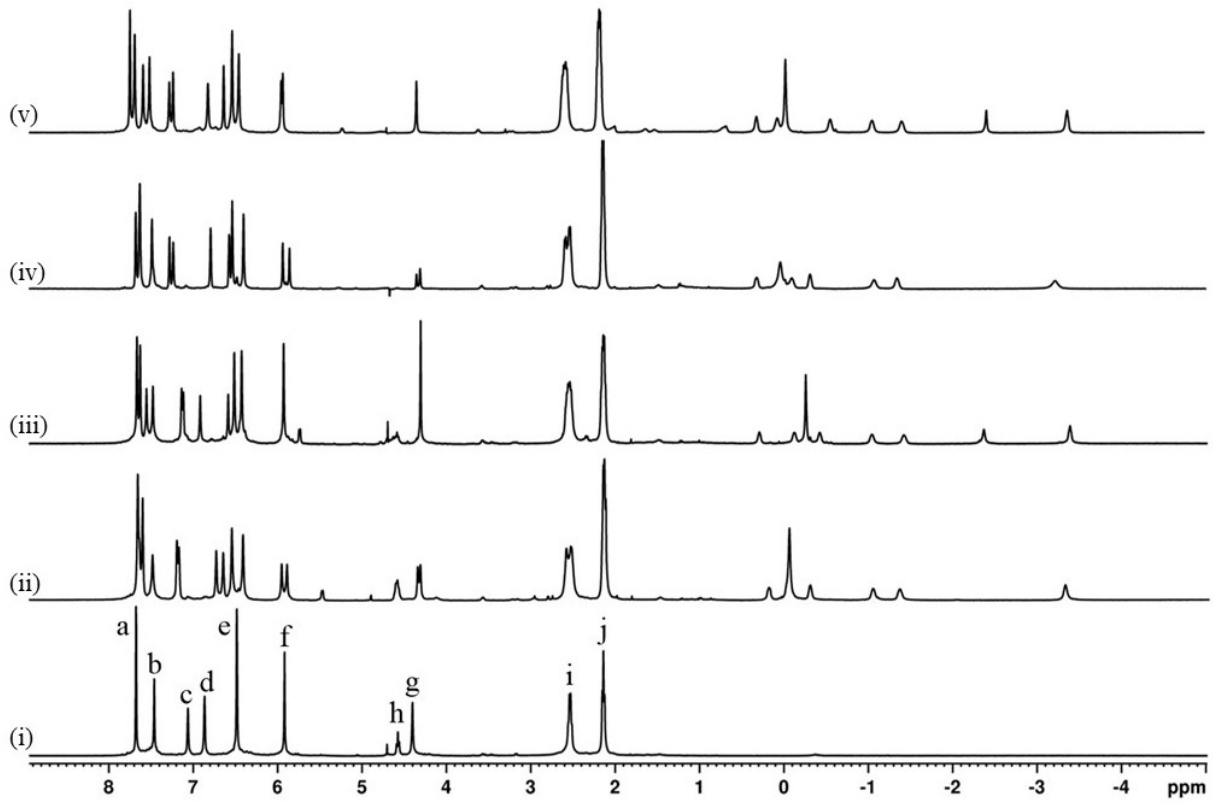


Figure 3. ^{1}H-NMR spectra of i) 1mM octa acid (free host: OA) in 10mM sodium borate buffer, ii) 2:1 host-guest complex of **7** with OA, iii) 2:1 host-guest complex of **8** with OA, iv) 2:1 host-guest complex of **9** with OA, and v) 2:1 host-guest complex of **10** with OA.

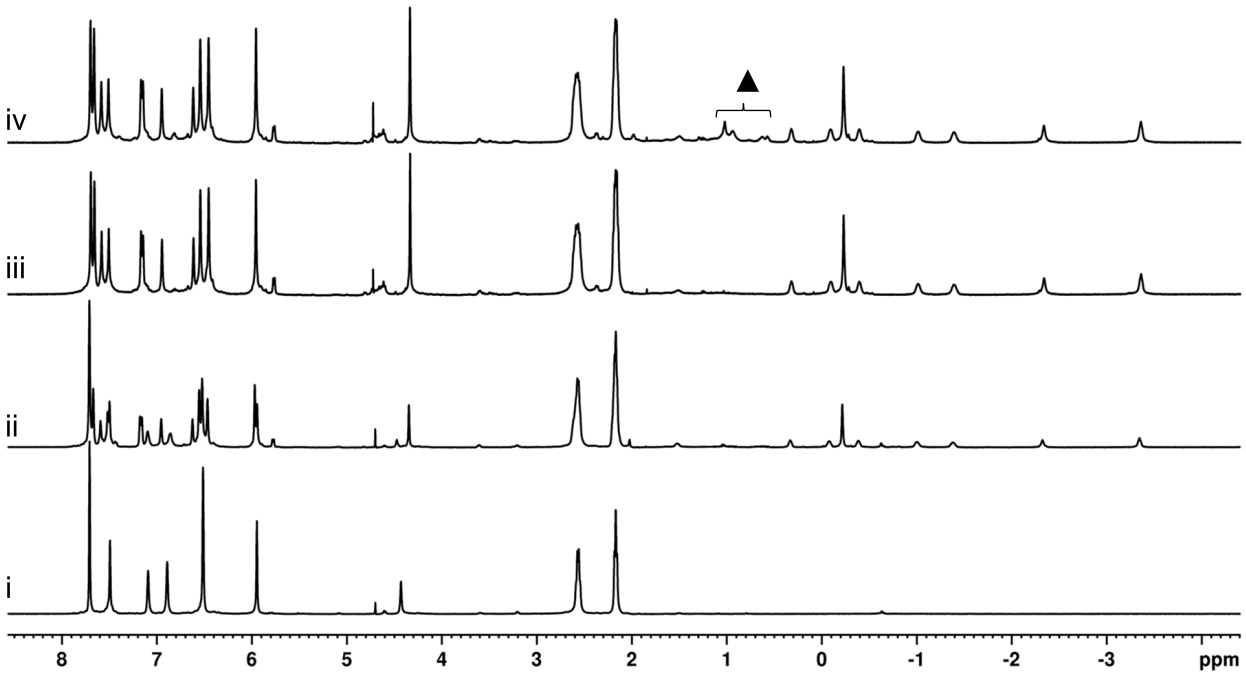


Figure 4. ^{1}H NMR titration spectra of **8** with OA. i) 1mM octa acid, ii) addition of 0.25 eq of **8**, iii) addition of 0.5 eq of **8**, and iv) addition of 0.75 eq of **8**. Addition of **8** beyond 0.5 eq results in slight turbidity and at this stage signals corresponding to uncomplexed guest molecules are seen; these signals are marked in the spectra (▲).

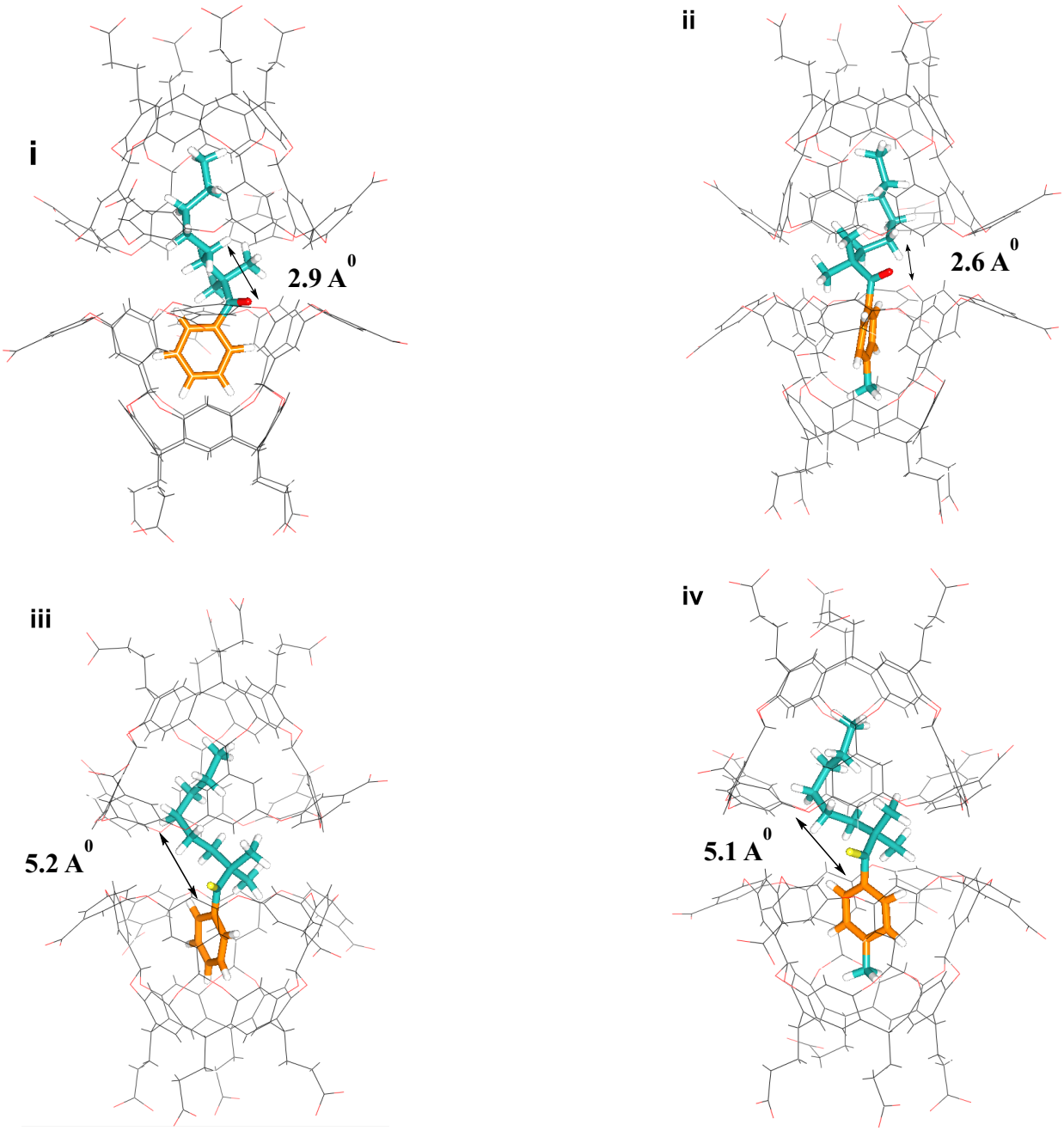


Figure 5. MD simulated structures of 2:1 host-guest complexes of i) **7@**OA_2; ii) **8@**OA_2; iii) **9@**OA_2 and iv) **10@**OA_2. All molecules fit well within the capsule and the alkyl chain is not coiled (see experimental for details of the procedure).

Following the characterization of the OA complexes, irradiations were performed employing 450W medium pressure mercury lamp and Pyrex NMR tubes. Progress of the

reaction was monitored by recording ^{1}H NMR spectra at regular intervals. Upon completion of the reaction products extracted with $CHCl_3$ were analyzed by GC and GC-MS. Upon irradiation **2**-**6** undergoes only Norrish Type II reaction while **7** and **8** yield products of both Type 1 and Type II reactions (Scheme 1). To assess the influence of confined space, variation in product distributions within OA in borate buffer solution was compared with that in isotropic hexane solution (Tables 1 and 2). Similarly, thioketones **9** and **10** (Scheme 2) were irradiated in hexane and as OA complexes in borate buffer. Results are presented in Table 3.

Table 1. Distribution of products upon excitation of ketones **2-6** in hexane and within OA in borate buffer.

Medium	Fragmentation (F)	Cyclobutanol (C)	F/C	*trans*-CB / *cis*-CB[a]
2/Hexane	66	34	1.9	3
2@OA_2/Buffer	71	29	2.3	1.7
3/Hexane	63	37	1.7	2.2
3@OA_2/Buffer	76	24	3.1	0.6
4/Hexane	59	41	1.4	2.6
4@OA_2/Buffer	75	25	3.0	0.3
5/Hexane	66	34	2.0	3.5
5@OA_2/Buffer	70	30	2.3	1.8
6/Hexane	61	39	1.5	3
6@OA_2/Buffer	78	22	3.4	0.4

(a) *trans*-CB= *trans*-cyclobutanol; *cis*-CB= *cis*-cyclobutanol

Table 2. Distribution of products upon excitation of ketones **7** and **8** in hexane and within OA in borate buffer.

Entry	Type I %	Type II		Type I / Type II	F/C	Distance [c] (γ - H)
		Fragmentation (F) %	Cyclobutanol (C) %			
7/Hexane [a]	9	8	83	0.09	0.96	
7@OA_2/Buffer [b]	18	74	8	0.22	9.25	2.9 Å(γ)
8/Hexane [a]	12	1	87	0.14	0.01	
8@OA_2/Buffer [b]	36	57	7	0.56	8.14	2.6 Å (γ)

(a): n-hexane (solvent); (b): water (solvent); (c) Distance estimated from MD simulation

Table 3. Distribution of products upon excitation of thioketones **9** and **10** in hexane and within OA in borate buffer.

Entry	Cyclopentane thiol (C) %	Distance[d] (δ -H)
9 /Hexane [a]	100 (4h)[c]	
9@OA_2/Buffer [b]	3 (4h)[c]	5.2 Å
10 /Hexane [a]	100 (4h)[c]	
10@OA_2/Buffer [b]	8.5 (4h)[c]	5.1 Å

(a): n-hexane; (b): water (c): Irradiation time. (d): Distance estimated from MD simulation.

Discussion

Results presented above lead to the following conclusions: (a) The ketones and thioketones used as guests form stable 2:1 capsular complex in aqueous borate buffer solution.

(b) Ketones **2**-**8** undergo the same reaction (Norrish Type I, Type II and Norrish-Yang cyclization) both in hexane solution and within OA capsule in borate buffer. However, the product distribution under the two conditions is different. (c) Thioketones **9** and **10** examined here undergo de Mayo photocyclization (1,5-hydrogen abstraction followed by cyclization) in hexane. However, upon irradiation within OA capsule no products were isolated. (d) Based on the published literature we assume that the ketones react from long-lived triplet T_1 state ($\tau = 3.5 \times 10^{-6}$ sec)[44, 76] and the thioketones from the short lived S_2 state ($\tau \sim 1 \times 10^{-10}$ sec).[47, 51]

Influence of OA capsule on ^{1}H NMR chemical shifts of the guests is well-established.[73, 75] Linear conformation of the methylene chain and the anchoring of the guest by the methyl group(s) of the guest ketones and thioketones are clear from the up-field chemical shifts of the included guests with respect to $CDCl_3$ solution (Figure S1-S9 in Supplementary Material and Figure 4). Analysis of the spectra reveals that the methyl group of the alkyl chain in all cases appear closer to δ -3 ppm suggesting that the methyl group is anchored at one of the two terminals of the capsule.[75] Further, the CH_2 groups of the alkyl chain appear as independent signals with decreasing upfield shift suggesting that the chain remains in an extended conformation within the OA capsule. In $CDCl_3$ solution these signals are crowded together and appear as broad multiplets. The clear separation of CH_2 signals within OA reminds one of the 'lanthanide shift reagents' that is used to simplify the NMR spectra of complex organic molecules.[77] Yet another interesting observation is that while the host signals for the two halves of the capsule in the case of **2**-**4** appear as single signals, in the case of **5**-**10** two independent signals for identical hydrogens for the top and bottom OA molecules are readily identified. This implies that the top and bottom halves of the **5**-**10** encapsulated capsules remain magnetically non-equivalent.[73-75, 78] The fact that there is only one signal for chemically equivalent hydrogens of the two halves of the capsule for OA complexes of **2**-**4** suggest that in these cases the guest freely tumbles within the capsule making the two halves magnetically equivalent in the NMR time scale. Presence of *para* methyl or α,α'-dimethyl in **5**-**10** apparently restricts the tumbling of the guest within the capsule making the top and bottom halves of the capsule magnetically non-equivalent.[73] Since the excited state reactions occur at much shorter time scale (10^{-6} - 10^{-10} sec) than the time required for NMR detection, we assume that all molecules investigated here remain in the extended conformation with the terminal methyl

anchored at one end of the capsule. MD simulated structures shown in Figure 5 support the conclusions drawn from NMR spectra.

First, we address the question of the photointernes of the two thioketones **9** and **10** within OA capsule. The ^{1}H NMR spectra displayed in Figure 3 (traces iv and v) confirm that these two molecules form a stable 2:1 (host to guest) complex with OA. From the spectra we infer that the molecules do not tumble inside the capsule and are stationary in the NMR time scale. As reported in the literature both molecules show fluorescence from S_2 (violation of Kasha rule) in hexane at room temperature (Figure S30 in Supplementary Material). The S_2 lifetime of thioketones similar to **9** and **10** were measured to be in the range 418 to 260 ps in hexane.[49, 51] S_2 emission was also observed from OA encapsulated **9** and **10** in borate buffer (Figure S31 in Supplementary Material). The fact that the emission and excitation spectra are identical both in hexane and within capsule suggested that the excited state photophysics of C=S chromophore did not change with the medium. Consistent with the established room temperature phosphorescence from OA encapsulated guests,[79, 80] these molecules as OA complexes emit phosphorescence at room temperature in aqueous solution (Figure S32 in Supplementary Material). In hexane there was no phosphorescence. This is consistent with the earlier observation of room temperature phosphorescence from molecules included in OA.[79, 80]

Although the photophysics of encapsulated **9** and **10** did not show any surprises, their photochemistry was quite different from that in hexane. de Mayo's group has established that arylalkyl thioketones of the type we have explored, upon excitation undergo δ-hydrogen abstraction and cyclizes to a five membered cyclopentyl thiol (Scheme 2).[47, 48, 51] This reaction is distinctly different from that of the corresponding ketones which undergo γ-hydrogen abstraction to yield cyclobutanol (Norrish-Yang reaction).[81] Thioketones **9** and **10**, as expected, cyclized to cyclopentyl thiol (Scheme 2) upon irradiation in Pyrex NMR tubes with medium pressure mercury lamp. Surprisingly under the same condition these two molecules did not undergo any reaction even after 4 h of irradiation. After irradiation thioketones were recovered quantitatively (Table 3). Thus, the molecule that is reactive in an isotropic solution becomes inert within OA capsule. This can't be attributed to lack of absorption by the thioketones or quenching of the excited state by OA or other impurities. The fact that OA encapsulated 9 and 10 show S_2 emission confirms the generation of photophysically active S_2 state of 9 and 10 although they are photochemically inactive within OA capsule.

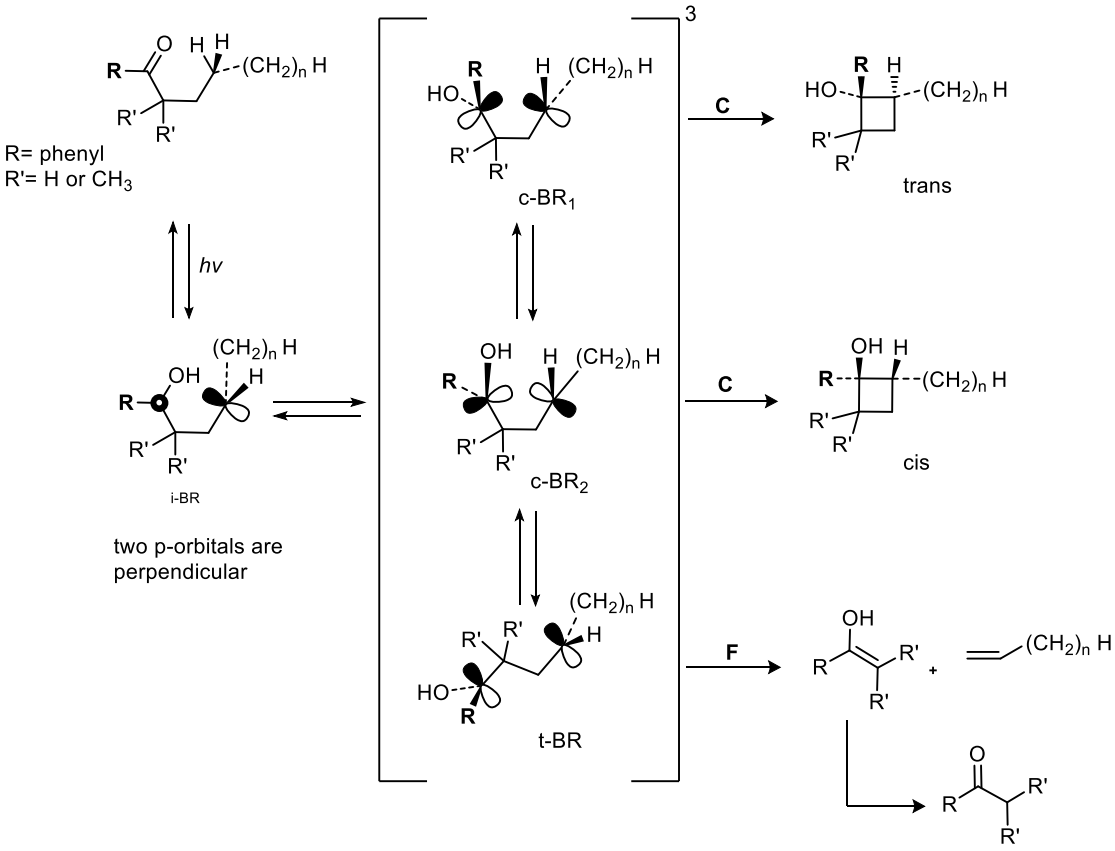
MD simulated structures of **9** and **10** within OA are shown in Figure 5. Since the hydrogen abstraction in these cases occurs from ππ* state, the geometry required for δ-H abstraction by C=S is expected to be different from those for carbonyl chromophore where the abstraction occurs from nπ* triplet. Scheffer's group has performed intramolecular hydrogen abstraction reactions of molecules containing C=S chromophore in the solid state.[82] They find that for the hydrogen abstraction to occur the S---H distance should be within 3.8 Å. Supporting this is the observation that thioamides with hydrogens 5Å away do not react in the crystalline state. As per the MD simulated structures (Figure 5) in our case the S--- δ-H is estimated to be 5.1 and 5.2 Å which according to the above report is too far to react. While in solution, since the molecule is flexible it would achieve the required conformation within the short lifetime S_2 state, within the capsule thioketones may not be able to adopt the required conformation in sub-nanosecond time scale Therefore, the lack of reactivity of **9** and **10** could be attributed to them remaining in a frozen conformation during the excited state lifetime as shown in Figure 5. The photochemical behavior of OA encapsulated **9** and **10** highlights the importance of considering the role of 'time' while understanding the chemical behavior of a molecule entrapped in a small space.

The second set of molecules we wish to consider are the ketones **7** and **8** (Scheme 1) that undergo both Norrish Type I and Type II reactions from the excited nπ* triplet state.[1, 44, 52] From Table 2 it is clear the reactions these two molecules undergo in hexane and within OA capsule are similar. This behavior is different from the thioketones discussed above. In addition to the reactive state difference, MD simulated structures presented in Figure 5 have an answer for this variance. In these two structures the γ-hydrogens are within 3Å from the carbonyl oxygen, much closer than in thioketones (~5Å). Through extensive x-ray structural correlations Scheffer has shown that for γ-hydrogen abstraction to occur in crystals the C=O ----H_γ distance should be less than the sum of the van der Walls radii (< 2.72 Å).[83] The distance estimated from MD simulated structures are 2.9 Å and 2.6 Å. The long triplet lifetime (~ μs) would be sufficient for the alkyl chain to explore conformations in which the γ-hydrogen is within the van der Walls radius of the O atom of the C=O group (2.72 Å). The change required unlike in thioketones is not much. Since the Type I cleavage does not require any special conformation, occurrence of this both in hexane and within OA capsule is expected. Thus, the dramatic difference in photobehavior of ketones and thioketones within OA capsule can be attributed to the distance

between the excited chromophore and the hydrogen to be abstracted and the difference in lifetime of the reactive state.

Perusal of Table 2 reveals that in the case of **7** and **8** the 1,4-diradical resulting from γ-hydrogen abstraction prefers to fragment than cyclize within OA capsule while in hexane it is the opposite. Mechanism of γ-hydrogen abstraction and conversion of the resulting 1,4-diradical to olefin and cyclobutanol have been extensively investigated.[1, 44-46, 52, 76] As illustrated in Scheme 3, the triplet nπ* excited carbonyl upon abstraction of the γ-hydrogen generates a *cisoid* 1,4-diradical where the two p-orbitals with an odd electron on each with the same spin are perpendicular to each other. This conformation is suitable for neither cyclization nor fragmentation. Only reaction that can occur is the reverse hydrogen transfer. Even this would be slowed because the generated diradical would be triplet. Because of this since the triplet 1,4-diradical would have a long lifetime,[45, 76] it could establish an equilibrium with the corresponding more stable *transoid* conformer before a stable product could be formed. This process requiring large rotational motion would expected to be slow within the confined capsule. Therefore, we expect both cyclization and fragmentation to occur mainly from the *cisoid* 1,4-diradical within OA capsule. Cyclobutanol formation requires the two perpendicular orbitals in *cisoid* 1,4-diradical to become parallel and directly face each. Fragmentation requires the two p-orbitals to become parallel to the central C-C bond but this is easier to attain than the rotational motions required to form cyclobutanol. Outcome of these motions are illustrated in a cartoon fashion in Figure 6. Although such rotation would not face any hindrance in solution, within the OA capsule steric interaction between the rotating phenyl or the alkyl group (depending on which p-orbital executes the rotation) and the walls of OA is likely to increase the barrier for rotation. This will translate into the decreased yield of cyclobutanol. Under such conditions, most likely the fragmentation would take over. MD simulation of the conversion of 1,4-diradical to cyclobutanol nicely brings out this hidden feature which is hard to visualize (Figure 7). According to MD simulated structures although both the initial ketone and the final cyclobutanol fit well within the OA cavity, the rotation results in hindrance between some parts of the diradical and the walls. To make sure this is indeed true, the cyclobutanols from ketone **7** were independently synthesized and complexed with OA. The NMR spectra shown in Figure 8 confirm that the two isomers of cyclobutanols fit within OA capsule (note the two methyl signals at δ -2.45 and -3.2 ppm in Figure 8, trace iii corresponding to two isomeric cyclobutanols).

NMR spectrum of irradiated **7**@OA_2 did not show any cyclobutanols in the product mixture (Figure 8, trace ii). Thus, the selectivity is not the result of product being too larger to fit in the capsule.



Scheme 3. Mechanism of products formations involving 1,4-diradical upon irradiation of aryl alkyl ketone.

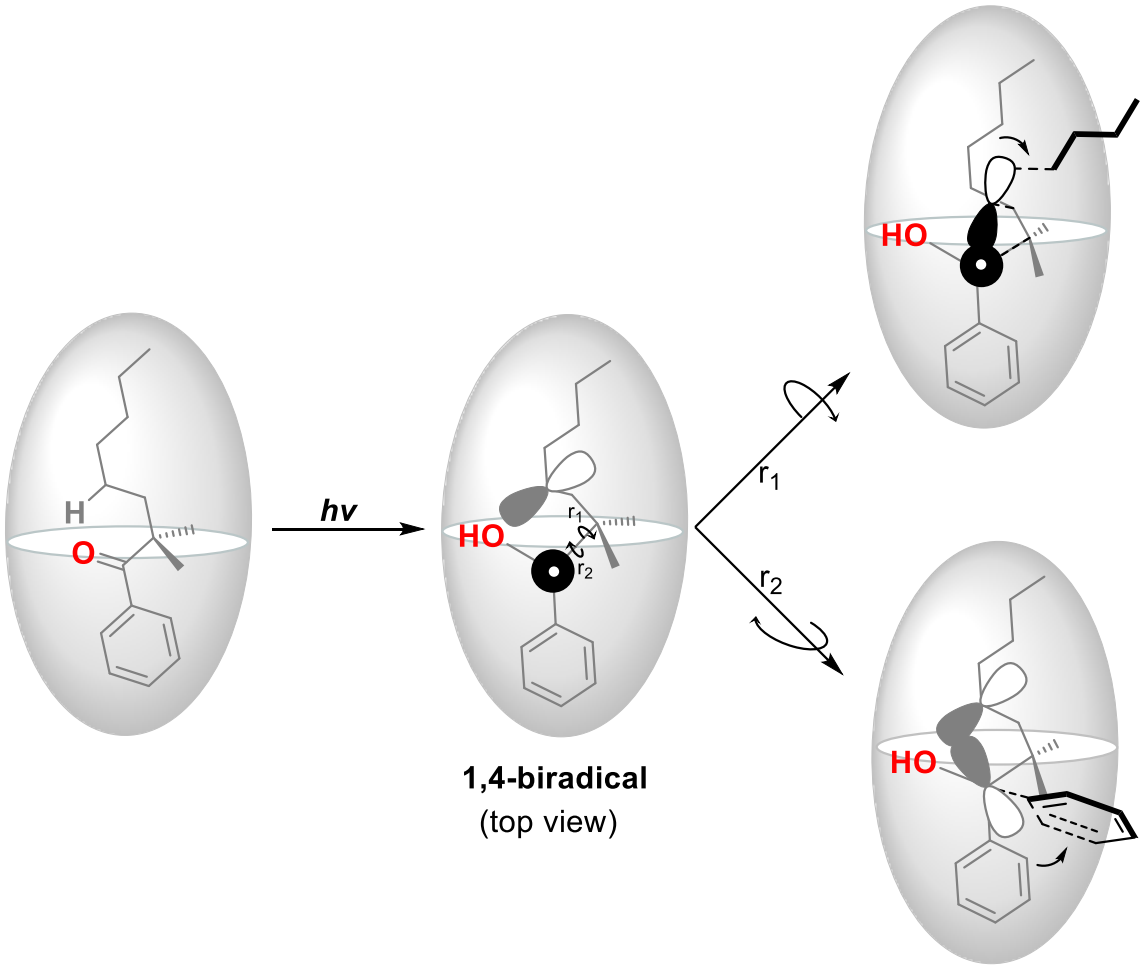


Figure 6. A graphical visualization of cyclobutanol formation from ketone **7** within OA capsule. The process of cyclization results in steric hindrance between the reactive intermediate 1,4-diradical and the walls of the capsule. Note during the cyclization either the alkyl or aryl group comes out of the capsule. The intermediate is too large to fit in.

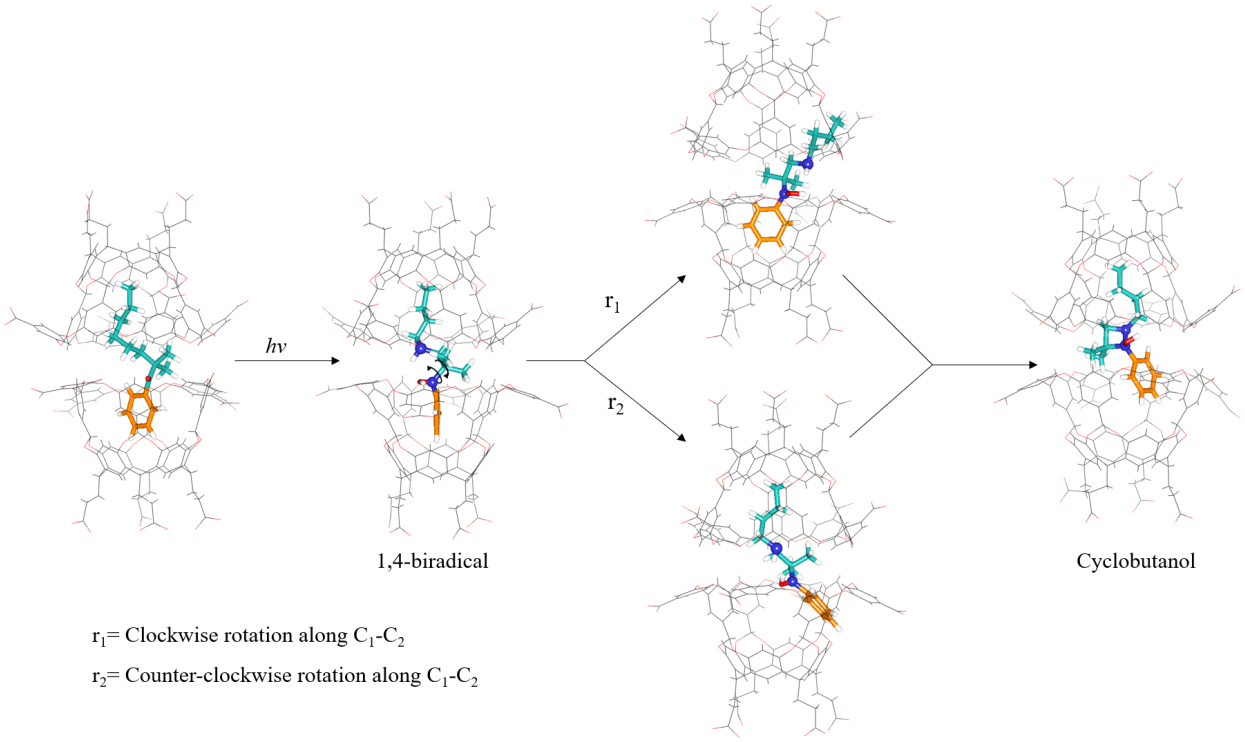


Figure 7. MD simulation of cyclobutanol formation from ketone **7** within OA capsule. The process of cyclization results in steric hindrance between the reactive intermediate 1,4-diradical and the walls of the capsule. Resemblance between Figures 6 and 7 is obvious.

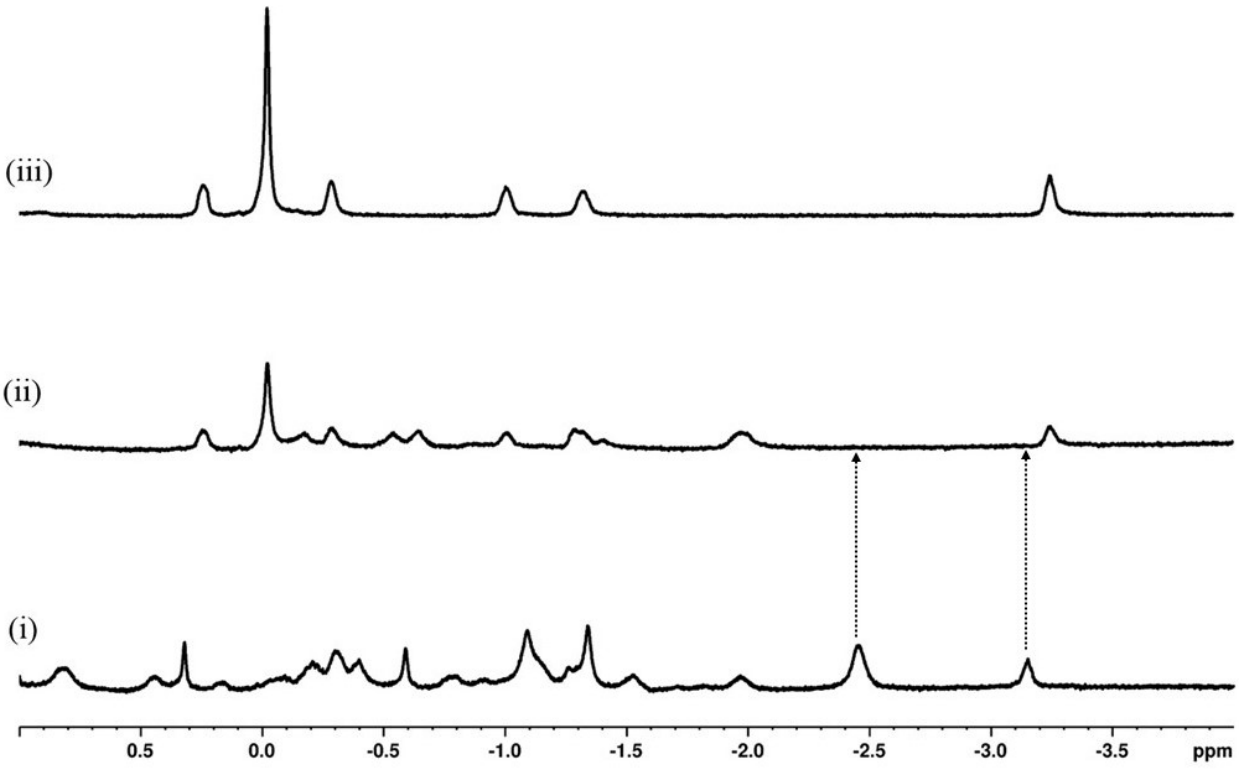


Figure 8. ^{1}H NMR spectra of (i) *cis* and *trans*-cyclobutanol@OA_2 from ketone **7** (- 0.15 mM *cis*+ 0.35 mM *trans* CB in 1 mm OA); (ii) **7**@OA_2 after irradiation and (iii) **7**@OA_2 before irradiation; all spectra in borate buffer-D_2O. *cis* and *trans*-Cyclobutanols were independently synthesized by solution irradiation and complexed with OA for (i). The NMR spectrum of OA irradiated sample was compared with (i). The signals due to the methyl group in alkyl substituent are shown; the dotted lines indicate the absence of the cyclobutanols upon irradiation of **7**@OA_2 in borate buffer.

To corroborate the above observation we examined the photobehavior of similar ketones of smaller size (ketones **2**-**6**; Scheme 1). The ^{1}HNMR spectra displayed in Figures S1-S5 (Supplementary Material) clearly show that the ketones are included within OA capsule. Once again, the signal for the terminal methyl is shifted most (δ -3 ppm) indicating this group anchors the molecule at one terminal of the capsule. The fact that every CH_2 group has an independent signal (exception **6**) suggests that the alkyl chain remains stretched within the capsule. Interestingly, in the case of **2, 3** and **4** the signals for chemically equivalent hydrogens in both OA molecules that form the capsule appear as single peaks. However this is not the case in the

case of **5** and **6**. Apparently *para*-methyl substituent on the phenyl group and the methyl on the alkyl end by anchoring the molecule at the two poles of the capsule prevent its tumbling within OA capsule. We believe appearance of independent signals for the two halves of the capsule in one case and only one set of signals in the other is an indication of ketones **2, 3** and **4** tumbling freely in the NMR time scale while **5** and **6** are slow to do so.

Examination of Table 1 reveals that in the case of ketones **2-6** fragmentation is favored within OA capsule but products from this process is not exclusive. This behavior is different from that of α,α-dimethyl substituted ketones **7** and **8**. Fragmentation/cyclization (F/C) ratio within OA *vs* hexane for **7** is 9.6 while for **2** it is 1.2 (Tables 1 and 2). Apparently, cyclobutanol is favored more in the case of **2**-**6** than with **7** and **8**. Most likely, replacement of the α, α-dimethyl groups by hydrogens in **2**-**6** decreased the steric repulsion between the walls of the capsule and the intermediate 1,4-diradical. The observations made in this study reveal that the confined media can not only alter the product distribution through steric exclusion of larger products (*e,g*, anthracene dimer) but also smaller products that fit in. The latter could occur when the motions required for formation of final products sweep more volume than the capsule can accommodate. In the examples examined here, the 1,4-diradical to cyclobutanol pathway sweeps a larger volume than the OA capsule can tolerate. This restriction would not be that important if the supramolecular medium is more flexible as in micelles. Type II reactions of ketones have been extensively investigated in several organized/confined media. Interestingly, in most organized media (liquid crystals, cyclodextrins, solid inclusion complexes of urea and Dianin's compound) fragmentation is favored.[84-91] The best examples come from photoreactions of ketones in zeolites, especially ZSM-5 that has channel structure.[92-94] In these examples only fragmentation occurs. Results bear similarity to the behavior observed within OA capsule.

Conclusions

During the last five decades there have been sustained efforts to understand the reactivity of molecules in organized and confined assemblies. This probably resulted from the desire to decipher the behavior of small molecules that trigger functions in biological systems. Also, much of materials we use in everyday life are solids. Thus, restricting our understanding of molecules to solution is not sufficient to comprehend the world around us and to make the full

use of our knowledge to everyday living. With this rationale supramolecular photochemists focus on exploring the excited state behavior of molecules in organized assemblies. The organized assemblies include micelles, gels, vesicles, polymers, liquid crystals, crystals, solid internal and external surfaces (zeolite, silica and clay) and water-soluble host-guest systems. Each of these media is unique and distinctly different. The behavior of molecules in these systems cannot be fully understood based on their electronic and steric features that form the basis of physical organic chemistry.

In spite of significant differences between these systems, photoreactions in these can be understood on the basis of 'reaction cavity' model originally proposed by Cohen for reactions in crystals.[95] A modified version of the above model was proposed by one of the authors in collaboration with Weiss and Hammond.[4, 32] This model emphasizes the importance of free space within the reaction cavity, flexibility of the cavity, steric hindrance between the reactant guest and the cavity and the weak interaction between the cavity and the guest. Adopting this model, we have rationalized our observations of product selectivity during photoreactions of ketones and thioketones within OA capsule. The main learning resulting from this study is that a rigid (inflexible) organized assembly such as OA capsule enforces selectivity by intimately interacting with the reactant molecule from the beginning to the end along the reaction co-ordinate. The medium will not tolerate any structural reorganization along the reaction co-ordinate that is larger than the interior of the cavity. Thus, to decide the outcome of a reaction it is not enough to examine whether the final product would fit within the reaction cavity. Even if the ultimate product is smaller than the cavity, whether it would be formed would depend on the structures that connect the reactant to the product. The photoisomerization of azobenzenes studied previously[40-42] and γ-hydrogen abstraction reaction of aryl alkyl ketones investigated here provide insight into the 'stress' a reacting molecule must withstand when the space is restricted. In both examples the final product is smaller in size than the cavity, but the pathway that leads to the final product requires more room than the cavity can provide. Under this condition *trans*-azobenzene reaches the final product *cis* isomer by changing the pathway (pyramidalization rather than torsional motion). On the other hand, the 1,4-diradical resulting from arylalkyl ketone has only one pathway to reach the cyclobutanol and when that is blocked the final product is not formed. Results presented here on the excited state behavior of aryl alkyl ketones reveals that there is much to be understood on the nature of control one can achieve

by making use of confined and organizes reaction cavities. The concept that reactant molecules would be able to yield only the product whose pathway from reactant to product involve structures that are small enough to fit within the reaction cavity has some resemblance to the 'principle of least motion'.[96] The principle of least motion states that 'those elementary reactions will be favored that involve the least change in atomic position and electronic configuration.' In terms of structures (rather than energy) this may be more true when the medium is rigid and the available space is small. From the results presented here it is clear that further probing is required to fully understand the influence of space and time on photoreactions.

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.

Acknowledgements

The authors thank the National Science Foundation (CHE- 2204046) for financial support. The authors thank Prof. Rajeev Prabhakar and Dr. Vindi M. Jayasinghe-Arachchige for help with MD simulations.

Appendix A. Supplementary material

Supplementary data to this article can be found online at ------.

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