ChemComm

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Journal:	*ChemComm*
Manuscript ID	CC-FEA-03-2022-001758.R1
Article Type:	Feature Article

Photochemistry in a capsule: Controlling excited state dynamics *via* confinement

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Abstract

Exerting control on excited state processes has been a long-held goal in photochemistry. One approach to achieve control has been to mimic the biological systems in Nature (e,g., photosynthesis) that has perfected it over millions of years by performing the reactions in highly organized assemblies such as membranes, proteins etc., by restricting the freedom of reactants and directing them to pursue a select pathway. Duplication of this concept in a smaller scale in a laboratory involves the use of highly confined and organized assemblies as reaction containers. This article summarizes the studies in the author's laboratory using a synthetic, well-defined reaction container known as octa acid (OA). OA, unlike most commonly known cavitands forms a capsule in water and remains closed during the lifetime of the excited states of included molecules. Thus the described excited state chemistry occurs in a small space with hydrophobic characteristics. Examples where the photophysical and photochemical properties are dramatically altered, compared to that in organic solvents wherein the molecules are freely soluble, are presented to illustrate the value of restricted environment in controlling the dynamics of molecules on an excited state surface. While ground state complexation of the guest and host is controlled by well-known concepts of tight-fit, lock and key, complementarity etc., free space around the guest is necessary for it to be able to undergo structural transformations in the excited state where the time is short. This article highlights the role of free space during dynamics of molecules within a confined, inflexible reaction cavity.

Introduction

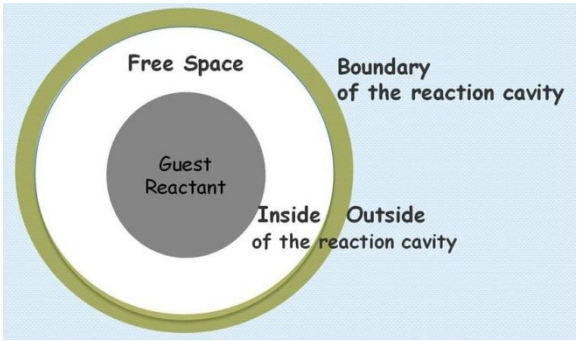
This review highlights a few of the activities of the author's group on excited state chemistry of organic molecules included in a nano reaction container commonly known as octa acid (OA) capsule.[1] Photochemistry in confined space has a long history with continual search for reaction containers that can offer needed selectivity, easy to access and use, and more versatile with respect to guests.[2-10] The reaction containers in general are characterized in terms of their ability to interact with the guests through weak interactions (active and passive),[11, 12] presence of free space/volume (ability to accommodate shape changes during a reaction) and ability to adjust to overall shape changes (soft/flexible and hard/stiff).[13, 14] Excellent text-book introduction to such topics and exhaustive reviews comparing various reaction containers identifying commonalities are available.[13-16] Control is also achieved without total encapsulation but through weak interactions between two molecules. A number of reviews and books are available on this topic under the title 'Supramolecular Chemistry', a subject pioneered by Pederson, Lehn, Cram, Balzani and Stoddart.[9, 10, 17, 18] Several recent reviews are available on the use of principles of supramolecular chemistry to control excited state properties .[19-25] The current article focusses mostly on 'confinement' through spatial control.

History of photochemistry in organized assemblies and nano-containers: Photochemistry and photophysics of organic molecules are generally conducted in isotropic organic solvents where excited state properties are controlled by inherent electronic and steric features, weak interactions between solvent molecules and the excited reactant molecule and by the bulk properties of the medium.[26] In the 60's it was realized that better control on photoreactions can be achieved if the medium is better organized than isotropic solvents and rigid. This led to the recognition of an area of research now known as the photochemistry of organic crystals,[27, 28] pioneered by Schmidt's group at Weizmann Institute and possibly initiated in the 19th century by German and Italian chemists.[29-32] The rigid crystalline state that helped achieve selectivity also curtailed many reactions that normally occur in solution leading to the search for an organized medium less rigid and more flexible than crystals, while at the same time able to organize/confine molecules. Although several media such as liquid crystals, gels, membranes, vesicles, monolayers, LB-films fit this requirement, their usefulness as reaction media was limited.[3, 4, 7] Porous solids such as organic clathrates, zeolites and metal organic framework

(MOF) providing the reactant molecules more freedom than crystals still being explored show promise.[33-38]

Ready availability and ease of use have made micelles the most successful reaction medium of the various organized assemblies to photochemists. Pioneering contributions in 70s and 80s by Turro, de Mayo, Thomas, Fendler and others established the value of micelles as a unique reaction medium for excited state reactions.[39-42] Contrast to crystals, micelles are less well ordered, not too rigid and afford limited freedom for the guest molecule. However, owing to their flexibility and dynamic character the selectivity achieved was lesser than in crystals, zeolites etc. leading to a search for water-soluble organic hosts fulfilling these deficiencies. Cyclodextrins (CD),[43, 44] already popular as artificial enzymes fit the need and was followed in the two or three decades by a multitude of synthetic cavitands such as cucurbiturils (CB),[45] calixarenes (CA),[46] Fujita's Pd nanohost[47] and several other related synthetic hosts.[6] These hosts with multiple openings were unable to contain the guest reactants within them. Cram then synthesized hemicarcerands, a fully closed organic capsule.[48] He was also the first one to report the synthesis of a water soluble hemicarcerand known by the name octa acid.[49] The ground-breaking publication of trapping highly reactive and long sought cyclobutadiene within a synthetic hemicarcerand provided confidence in discovering elegant chemistry with the 'right' choice of a reaction container.[50] Steady availability of new cavitands and capsules from the laboratories of Rebek,[51] Raymond,[52] and others[6, 53-55] while providing new avenues for supramolecular chemists were not as attractive to photochemists due to being highly specialized, challenging to synthesize in large quantities and having absorption problems. Thus, the reaction container the author is interested in could come from crystals, zeolites, organic cavitands, micelles. His pursuit for a better reaction container than the currently available ones has led to the octa acid cavitand reported by Gibb and Gibb. The reaction container in principle could be thought of as a closed circle or sphere with the features shown in Figure 1. The size and location of free space within the circle and the ability of the circle to adjust its shape as per need have an important consequence on the selectivity.[13, 14]

(a)



(b)

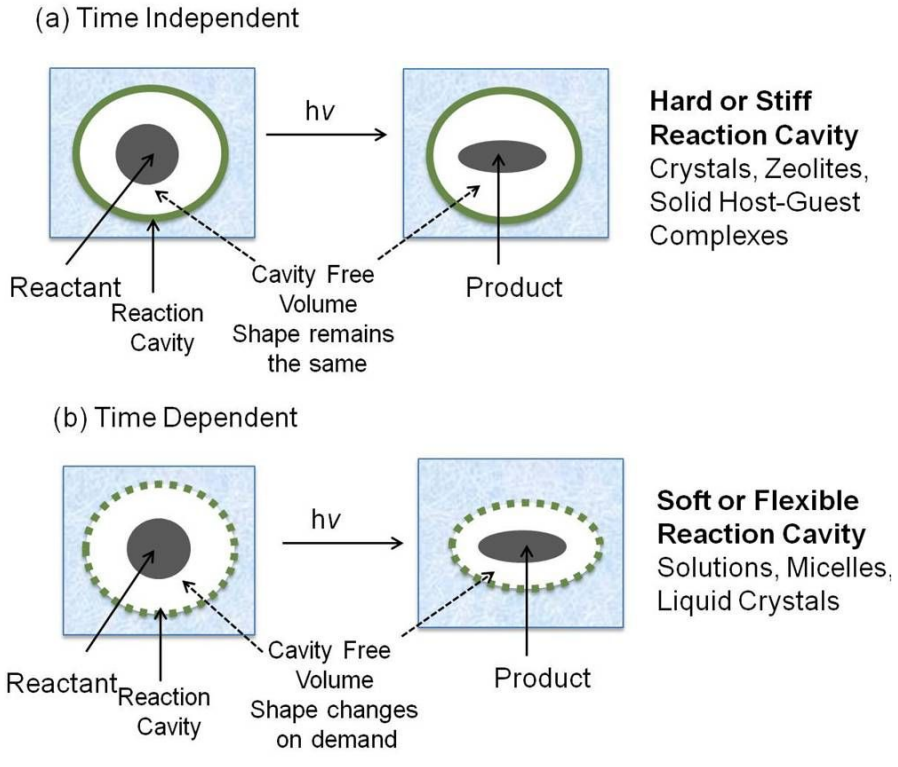


Figure 1. (a) Cartoon representation of reaction cavity showing reactant, inside and outside of the cavity and cavity free space. (b) Cartoon representation of importance of free space around a reactant in a reaction cavity. Two types of reaction cavities (stiff and flexible; also known as

hard and soft) are shown. Note: in the latter the extent of free volume changes with the demand (Adopted from V. Ramamurthy and S. Gupta, *Chem. Soc. Rev.,*2015, **44**, 119-135)

Identification of octa acid as a nano reaction container:

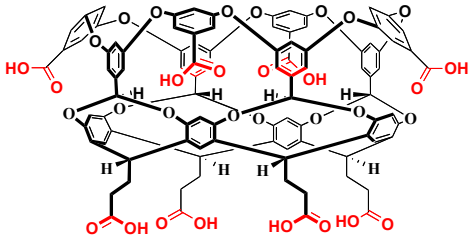
Inspired by the above history the author collaborated with Gibb who reported the synthesis of host octa acid (OA)[56] in 2004 for use as a reaction container.[57-63] Gibb and co-workers have summarized the early collaborative photochemical work on this topic and these will only be briefly mentioned here.[64-66] This article's main thrust is on the use of OA as a photochemical reaction container and does not deal with its binding properties, dynamics of the capsule etc. In this article photochemistry and photophysics of select organic molecules that bring out the unique properties of the host OA are highlighted. Despite its superior qualities as a reaction container very few reports have resulted from groups other ours on the excited state chemistry of OA encapsulated molecules.[67, 68] Therefore, the results covered here are only from the author's group.[1, 69] This article provides illustrative examples highlighting utility of the restricted space of the OA capsule in obtaining results desired but often unattainable in other reaction media. The OA capsule with its unique ability to form capsules in water has the potential to be a reaction container similar to crystals,[31] zeolites,[34-36, 70] micelles[4, 42] and cyclodextrins.[71, 72] Hope the results discussed here motivate others to pursue research on this topic.

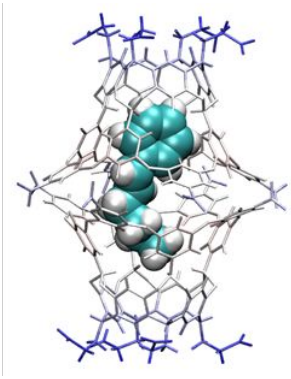
The host octa acid (OA), soluble in slightly basic aqueous medium (borate buffer, pH ~ 8.7) has a hollow cavity similar in dimensions to CB, CD and CA (Figure 2)[73] with one end very narrow for even an oxygen molecule to pass through. Two molecules of OA spontaneously form a capsuleplex surrounding one or two guest molecules. This capsule thus differs from hemicarcerand/carcerand of Cram where the reactant guest had to be included during the synthesis and the product released by dismantling the host.[48-50, 55] OA also differs from well-investigated cavitands such as CB, CD and CA that rarely form closed capsules. The inclusion of guests within OA is achieved by mild stirring/shaking the requisite amounts of OA and guest in borate buffer for 10-15 min. The OA capsuleplexes are defined in terms of the number of hosts (H, maximum two) and guests (G, maximum two) involved in the complexation. Depending on the size and polarity of the guests 1:1, 2:1, 1:2 and 2: 2 (H:G) complexes are formed. As illustrated in Figure 3, small aromatics like substituted benzene, naphthalene and anthracene form 2:2 complexes while larger ones such as tetracene and pyrene form 2:1

complexes; molecules longer than tetracene (length: 12° A) or bulkier than pyrene (width: 7° Å) do not form a complex. The inclusion of aromatic molecules within OA is generally is driven by hydrophobic factors. Hydrophobic aromatic molecules in general are not water-soluble and tend to aggregate in water. However, in presence of a hydrophobic cavity the aromatic molecules prefer the cavity over the solvent water.

The interior of the capsule has been established by emission and EPR probes to be non-polar and similar to benzene and dry without any water molecule when guest molecules are enclosed.[74, 75] Thus, while interpreting the observed excited state behavior one must keep in mind that the guest molecules solubilized in water with the help of OA remain in a hydrophobic, aromatic-like environment without any role from the bulk water molecules. OA absorbs in the region 230 to 320 nm and emits between 320 to 430 nm. The presence of multiple carbonyl chromophores facilitates intersystem crossing (ISC) of the excited OA enabling its triplet energy donor (E_T ~ 304 kJ/mole) role as illustrated by examples where it sensitizes triplet reactions of included guests.[76] Furthermore, OA is a good electron donor with an oxidation potential of ~1.5 eV. It also contains easily abstractable benzylic hydrogens projecting into the capsule. These properties make the reaction container provided by OA 'active'[13, 14] in the sense they can participate in photoreactions.[76] This feature is different from cyclodextrins, cucurbiturils and micelles where the reaction container is 'passive (not active)'; they do not directly participate in energy, electron and hydrogen atom transfer reactions. Therefore, while using OA as a reaction medium, direct excitation (230 to 320 nm) of the host should be avoided and for reaction involving electron transfer the acceptors should have oxidation potential lesser than ~1.5 eV. Also if one of the photoreactions of the guest is hydrogen abstraction one should be aware that the host itself can act as hydrogen donor. These features aside, to the knowledge of the author, OA is a reaction container for a large number of organic molecules in water unlike any other known thus far.

(a) (b)





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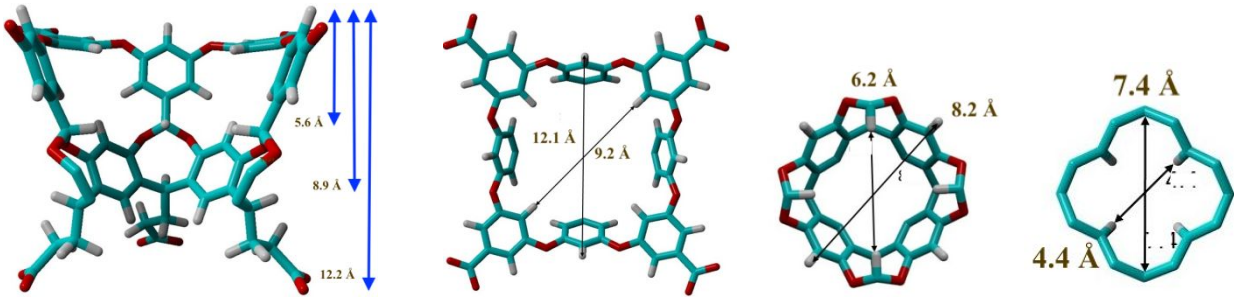


Figure 2. (a) Chemical and (b) MD simulated structures of 1:1 and 2:1 complexes known as cavitandplex and capsuleplex respectively. (c) Dimensions of octa acid cavity as generated by MD simulation.

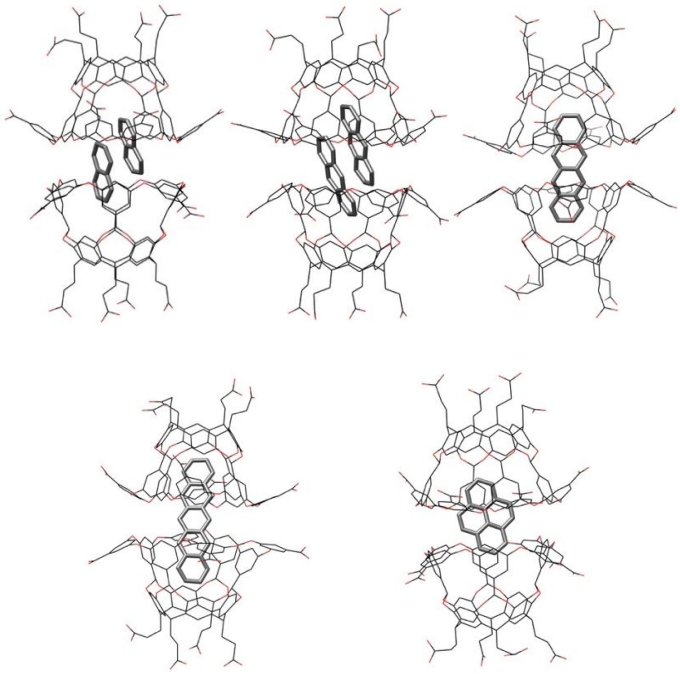


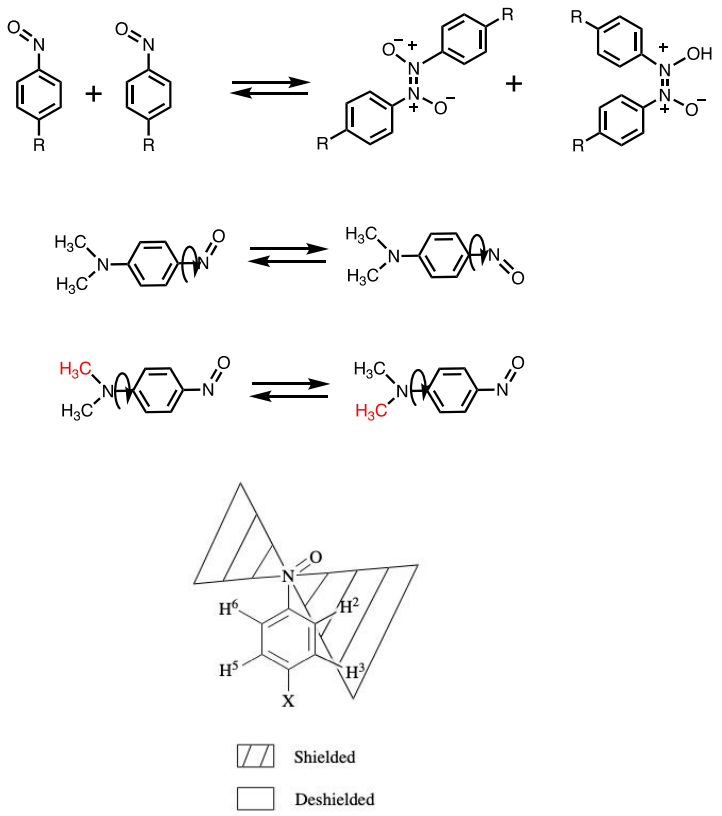
Figure 3. MD simulated structures of guest aromatics (naphthalene, anthracene, tetracene, pentacene and pyrene) within host octa acid to illustrate the type of aromatic molecules fitting in and the nature of the complex. Pentacene does not form the complex easily.

Restrictions of molecular dynamics within a confined capsule

We begin the presentation with examples where the well-known dynamics of guest molecules in the ground and excited states are altered within OA capsule. The two ground state examples discussed first, although not directly relevant to the excited state chemistry, highlight the possibilities and opportunities. One of the two examples deals with restriction on intramolecular, single bond rotation whereas the other involves conformational restriction within OA capsule.[77, 78]

Ground State: Nitrosobenzene exists as an equilibrium mixture of monomeric and dimeric forms (azodioxide dimers) in solution (Scheme 1).[77, 79, 80] In the monomer, rotation about the C−N=O bond, fast on the NMR time scale is slowed when the 4- position is substituted with electron-donating groups as in 4-(N,N-dimethylamino)nitrosobenzene (DMANB). The –N=O chromophore with a large magnetic anisotropy helps follow the rotational dynamics of C–N=O bond as well as the bond attached at the 4-position of the benzene ring by variable temperature

NMR (VT-NMR). The two freely rotating σ bonds, C–N=O and C–N$(CH_3)_2$ of DMANB , are ideal to probe the effect of confinement on the dynamics of intramolecular rotation of two groups of different sizes.



Scheme 1. Properties of arylnitroso molecules illustrated: tendency to exist in equilibrium with dimers; restricted rotation of the s bonds and large magnetic isotropy of the nitroso group. (Scheme adopted from R. Varadharajan, S. A. Kelley, V. M. Jayasinghe-Arachchige, R. Prabhakar, V. Ramamurthy and S. C. Blackstock, *ACS Organic & Inorganic Au* 2022 ***2***,175-185

The VT-NMR spectra (2-52° C) of DMANB in D_2O as well as within the OA capsule in D_2O are shown in Figure 3.[77] At 2° C, both in presence and absence of OA, independent signals for all four aromatic hydrogens are observed, while the sharp, singlet -NMe_2 signal in the absence of OA splits into two in its presence. Apparently, rotation of C−N=O bond is frozen at 2° C both within and outside OA. On the other hand, C–NMe_2 bond rotation is frozen within the

OA capsule while freely rotating in D_2O at 2° C. The above difference is the consequence of confinement and lack of free space needed for C–NMe_2 bond rotation within OA capsule. From the VT-NMR recorded between 2° and 52° C the values of barrier for C–N=O rotation in D_2O, toluene and within OA were estimated to be 61.1 kJ/mol, 52.4 kJ/mol and 60.2 kJ/mol respectively. The difference in the barrier between water (61.1 kJ/mol) and toluene (52.4 kJ/mol) confirms the role of polarity in the process. Based on the micro-polarity of the capsule one would expect the barrier within OA capsule to be closer to that in toluene (52.4 kJ/mol). However, the higher than expected value (60.2 kJ/mol) suggests role of other factors in restricting the rotation of C−N=O within OA capsule. Most likely the lack of free space restricts the C–N=O rotation. Rotational behavior of C–NMe_2 bond is different. Rotation of this bond in D_2O has very little barrier as evident from the sharp signals for NMe_2 in the temperature range 2° C to 52° C (Figure 4a) while within OA the barrier is estimated to be 59.8 kJ/mol from the coalescence temperature (Figure 4b). Clearly, the C–NMe_2 bond with no significant barrier outside OA faces a large barrier for rotation within the OA capsule.

Yet another example of the effect of OA capsule on the restriction of conformational flexibility of cyclic systems is provided by the behavior of the piperidine derivative shown in Figure 5.[78] This molecule as expected, exists in solution in two conformations with O-propyl either in the axial or equatorial positions. In contrast to the conformer with O-propyl in the equatorial position in D_2O solution as ascertained from NMR, within OA capsule the conformer with the group in the axial position dominates. Such reversal of conformer selectivity while not unexpected when the space available for the molecule is restricted, are not available within common hosts such as CD, CB and CA, to the author's knowledge.[81, 82] As shown in Figure 4, the NMR spectrum of the 1:2 capsuleplex of the piperidine derivative is more complex than in an organic solvent. The ^1H NMR spectra reveal four signals for each of the H-d and H-f of the host OA and two signals for each of the guest methyl groups marked 2-a and 2-e, and CH_3-7. Extensive 2-D NMR experiments confirmed these signals to be consistent with the formation of two independent OA complexes with the two conformers shown: two H-d, two H-f, and one CH_3-7 belonging to one complex and the other set to the second complex. The two conformers seem frozen within OA in the NMR time scale; were they interconverting the two sets of independent signals would have merged or broadened. The most important conclusion to be drawn is the control exerted by the capsule on which isomer dominates. Clearly, even the less

stable conformer could dominate when the space demands. The above two examples clearly caution on extending the knowledge gained from solution chemistry to OA capsule without taking the 'free space' surrounding the guest into account.

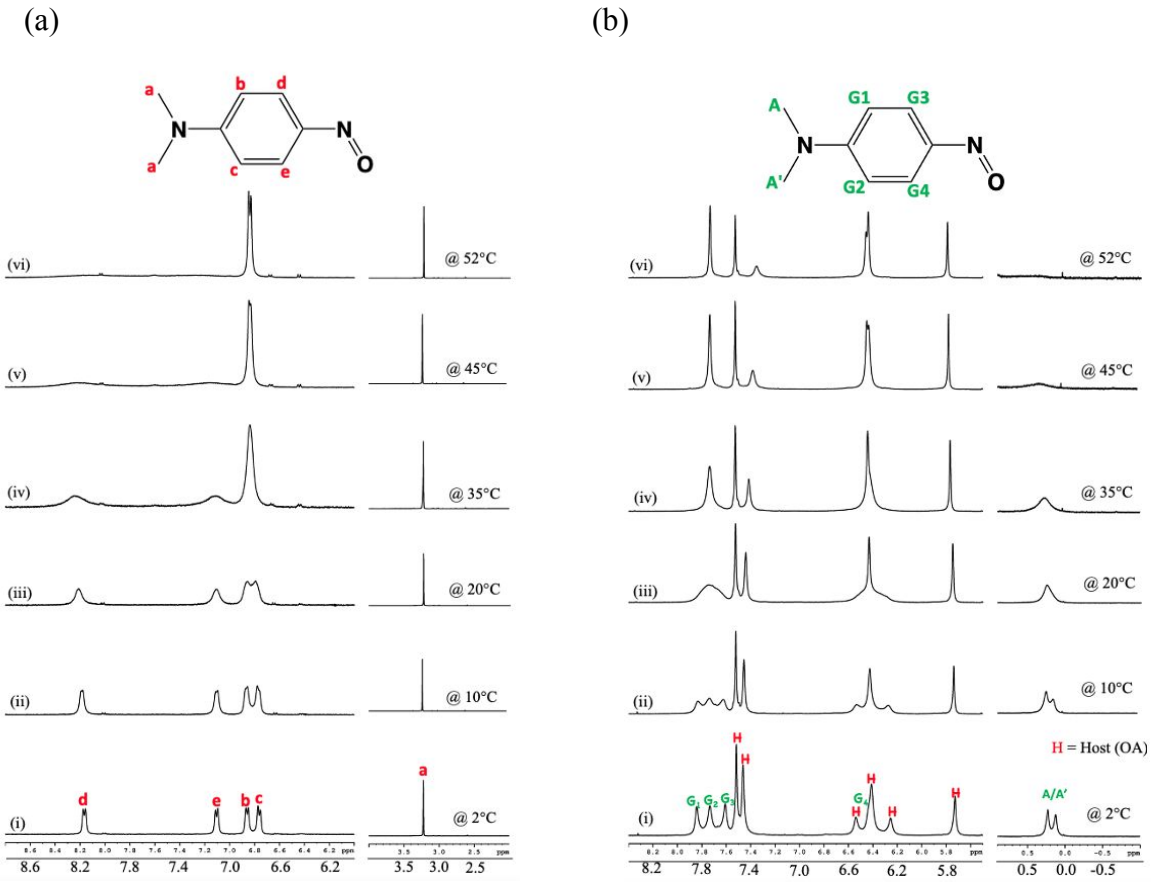


Figure 4. ^{1}H NMR spectra of (a) DMANB in D_2O and (b) 2:2 complex of DMANB with OA in D_2O at various temperatures. Note the difference in spectra, especially that of dimethyl group and aromatic signals of the guest with and without OA. (Adopted from R. Varadharajan, S. A. Kelley, V. M. Jayasinghe-Arachchige, R. Prabhakar, V. Ramamurthy and S. C. Blackstock, *ACS Org. Inorg. Au*, 2022, **2**, 175-185.

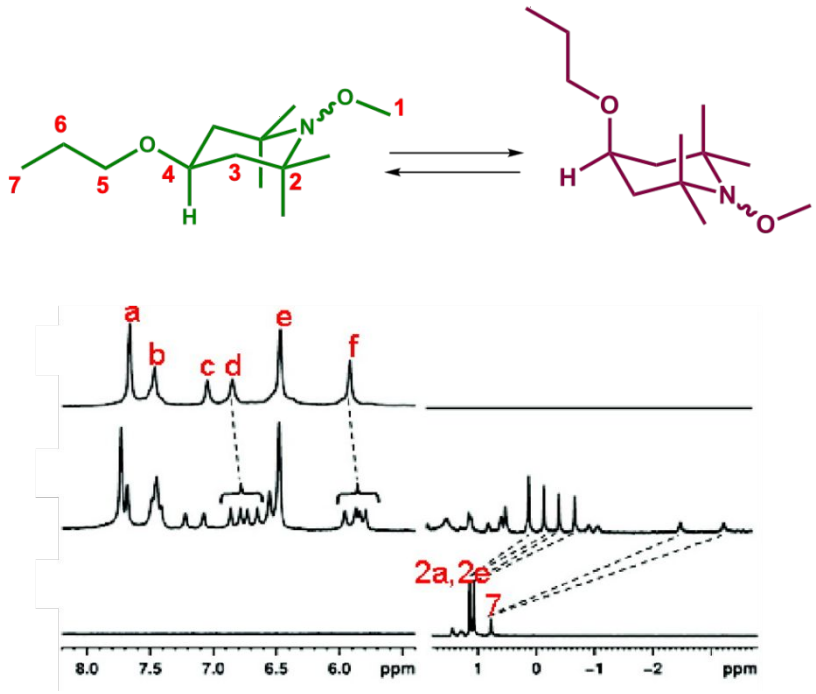


Figure 5. The NMR spectra confirming the presence of two conformations of piperidine derivative within OA capsule. Partial ^{1}H NMR spectra of OA (top) and the guest (bottom) and 2:1 OA-piperidine complex (middle). Host resonances are labeled "a−f", and guest resonances are labeled in numbers. (Adopted from M. Porel, N. Jayaraj, S. Raghothama and V. Ramamurthy, *Org. Lett.*, 2010, **12**, 4544-4547).

Excited state: As illustrated below, restriction on the dynamics of molecules in the ground state can extend to excited state. While the ground state complexation is based on 'complementarity'[83] and 'lock and key'[84, 85] for ground state structures, any change in the molecular structure requiring additional space around the reactant molecule would require this free space be available at the time of complexation, especially in the case of hard reaction containers such as octa acid capsule. Therefore, presence of free space around the guest molecule is essential for a reaction requiring a change in shape of the molecule. This is consistent with Rebek's 0.55 host-guest packing co-efficient requirement.[86] Control of this free space can lead to changes in excited state dynamics compared to that in solution. Example discussed below illustrates this feature.[87]

Aromatic molecules are well known to show excimer (excited state non-covalent dimer complex) emission in solution.[88] However, anthracene is an exception to not do so in solution.[89] The parent anthracene failed to show any excimer emission even when substituted anthracenes showed it at room temperature and at very low concentrations in cyclodextrin. In this context the OA capsule is unique and able to alter the excited state chemistry of anthracene. The emission attributable to monomer's on excitation of the transparent solution formed from water-insoluble anthracene aggregates on addition of OA was replaced with a broad one (Figure 6a) with a lifetime of 263 ns (Figure 6b). In the case of anthracene, the excimer lifetime at 77° is reported to be above 250 ns while that for the monomer emission in solution is known to be ~4 ns. The measured long (263 ns) lifetime is consistent with the long-sought excimer emission.[90, 91] The restricted space in the OA capsuleplex obviously hindered dimer formation to steer the anthracene molecules to a path towards anthracene excimer. This change in the excited state behavior unequivocally proves the power of the 'confined space' in altering the dynamics of encapsulated molecules singling out OA capsule and differentiating it from the other CD, CB and CA cavitands.

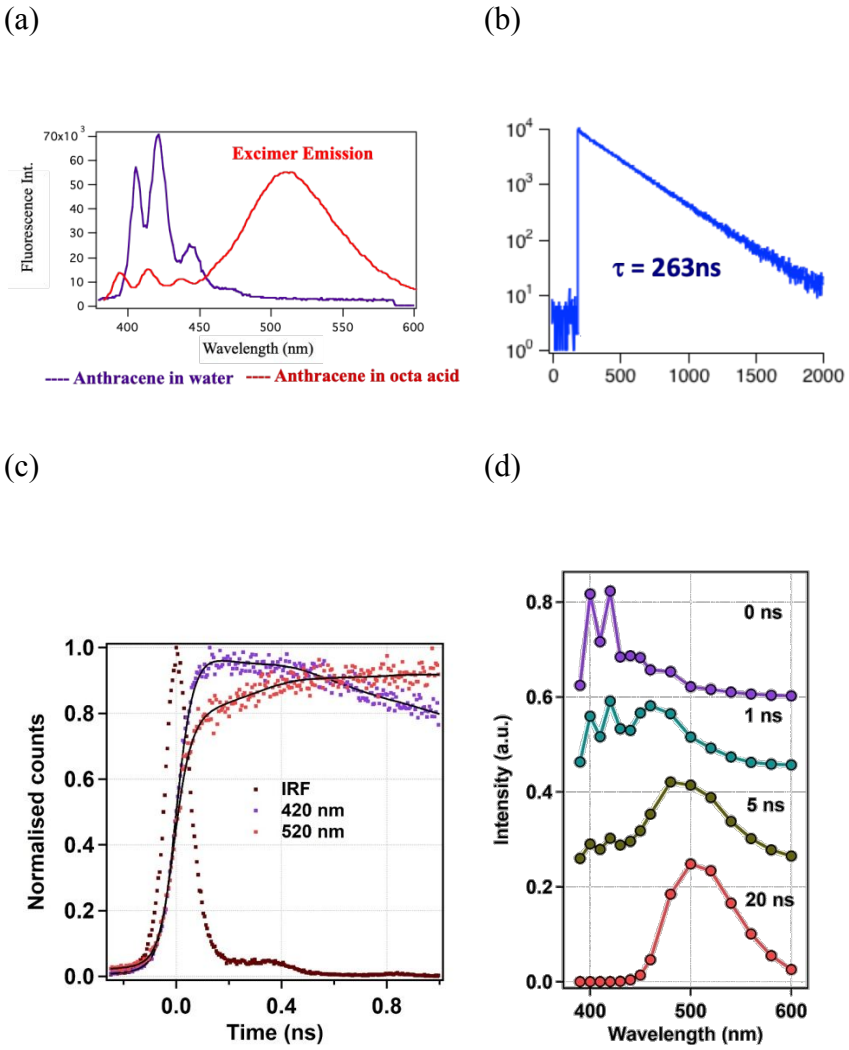


Figure 6. Photophysics of anthracene included within OA capsule. (a) The emission spectra of anthracene (10^{-7} M; pH ~ 8.7) in water in presence and absence of OA. (b) The lifetime of the emission in presence of OA. (c) The rise time of the two emissions with 420 and 520 nm maxima. (d) Time resolved emission spectra in presence of OA at various delay times. (Adopted from A. Das, A. Danao, S. Banerjee, A. M. Raj, G. Sharma, R. Prabhakar, V. Srinivasan, V. Ramamurthy and P. Sen, *J. Am. Chem. Soc.*, 2021, **143**, 2025-2036).

The rise time of the excimer emission of 400 ps (Figure 6c) indicating only one of the two anthracene molecules in the capsule is excited provided an insight on the dynamics of the

reaction. The excimer emission should be prompt (0 rise time), if both molecules (ground state complex) are excited at the same time. That of the two adjacently placed molecules only one of them is excited prior to excimer emission is an unforeseen opportunity to examine the dynamics of excimer formation without the involvement of diffusion. This allowed monitoring the needed structural adjustments for the formation of excimer from the pre-arranged pair within the capsule. As per the MD simulated and quantum chemical calculated structures the two molecules have to adjust themselves along all three co-ordinates (a, b and c in Figure 7) for maximum overlap of the orbitals. The ultrafast time resolved emission spectra with time dependent maxima shown in Figure 6d suggest that movement along the excimer coordinate is slow in the ultrafast time scale and emission is able to compete with the forward movement to the excimer. Such a time dependent excimer emission maxima is not expected from text book display of the excimer evolution.

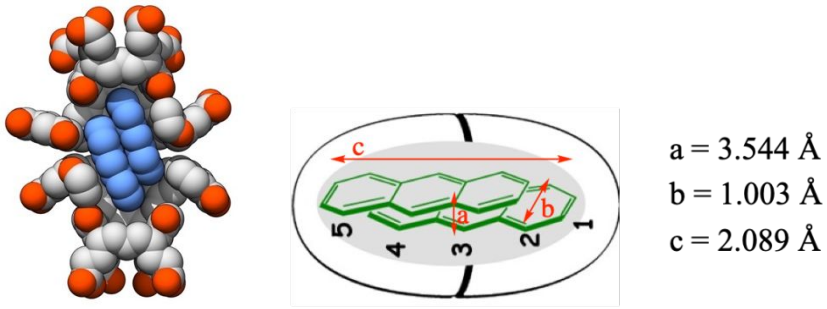
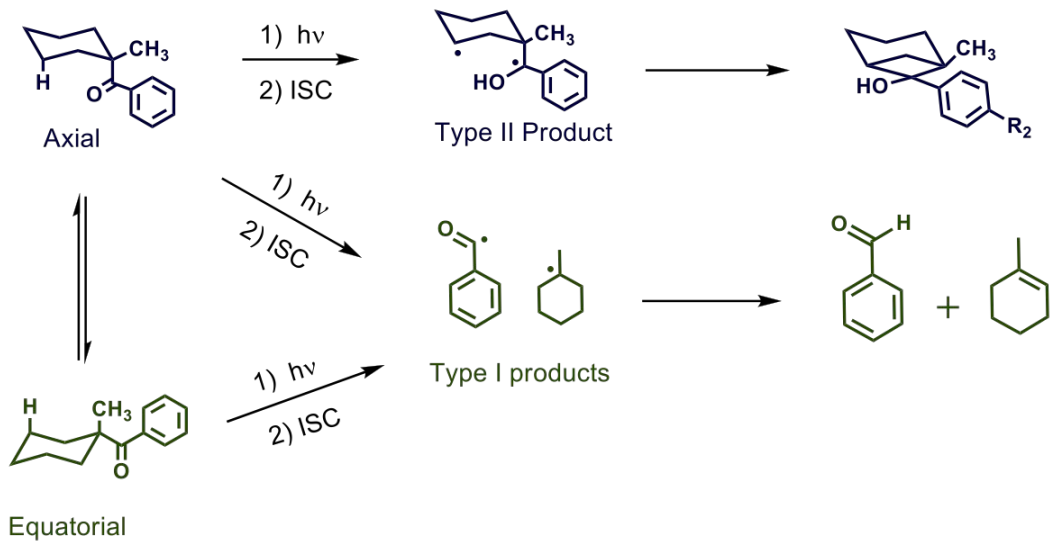


Figure 7. Molecular dynamics (MD) equilibrated structures of the 2:2 OA complex of anthracene in space-filling model. The displacement of the two anthracene molecules within OA capsule is illustrated with the extent of displacement along 3-axes included. The numbers on the anthracene ring represents the carbon numbers. **(**Adopted from A. Das, A. Danao, S. Banerjee, A. M. Raj, G. Sharma, R. Prabhakar, V. Srinivasan, V. Ramamurthy and P. Sen, *J. Am. Chem. Soc.*, 2021, **143**, 2025-2036).

Additional examples of consequences of restrictions on the dynamics of guest molecules within OA capsule is found in the excited state chemistry of phenyl alkyl (cyclic and acyclic)

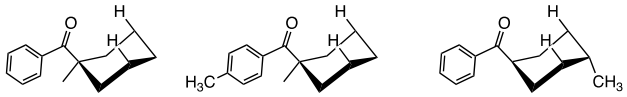
ketones that undergo competitive Norrish Type I and Type II reactions.[26] The Norrish Type II (γ-hydrogen abstraction) reaction depends on the γ-hydrogen being accessible to the excited carbonyl chromophore while no such requirement exists for the Type I (α-cleavage). Further, the Type I reaction is reversible, *i.e.*, the primary radical pair formed by the α-cleavage process can recombine to give back the starting ketone either with or without rearrangement. Significantly different products distribution obtained from excited cyclohexyl phenyl ketones[92] and α-alkyldeoxybenzoins[93] within OA capsule compared to that in isotropic solution is a reflection of the restriction on conformational, translational and rotational motions experienced by the excited molecule in a restricted space.

Cyclohexyl phenyl ketone shown in Scheme 2 similar to the previously discussed piperidine derivatives (Figure 5) exists in two conformations and shows conformer specific photochemistry in solution.[92] As shown in Table 1 the photoproducts distribution of cyclohexyl phenyl ketones **1**-**3** is different within OA capsule (2:1 complex) from that in acetonitrile. Importantly, the difference in behavior on the excited state is understandable on the basis of the control of the rotational- and conformational mobility of the reactant ketone within the OA capsule. Extensive NMR experiments and MD simulations have identified the ketones to reside within the OA in a single conformer (Figure 8) with the phenyl ketone part in the axial position. While in solution both conformers are present, preference for a single conformer within OA capsule is likely driven by the host-guest complementarity. Based on Scheme 2, from the axial conformer one would expect the γ-hydrogen abstraction to dominate and yield the cyclobutanol as the major product. But this product was not formed within OA capsule in all three ketones. Closer look at the structure of the complex from MD simulations explains why only products of Norrish Type I are isolated (Figure 8 and Table 1) from OA capsule. For Norrish Type II reaction to occur the γ-hydrogens present on the cyclohexyl ring and the carbonyl chromophore should be close (< 2.8 Å) but as seen in the figure the carbonyl chromophore is turned away from the γ-hydrogens. While in solution the rotational flexibility of the –(C=O)Ph would bring the γ-hydrogen closer and yield the Norrish Type II products, such rotation is hindered within the restricted environment of the capsule. It is important to note that the dynamics of excited molecules within a confined space need not be the same as in solution.



Scheme 2. Photoreactions of 1-methyl cyclohexyl phenyl ketone that can exist in two conformations. Type II reaction occurs only from the conformer in which the Ph C=O is axial. (Adopted from R. Kulasekharan, R. Choudhury, R. Prabhakar and V. Ramamurthy, *Chem. Comm.,* 2011, **47**, 2841-2843).

Table 1. Products upon irradiation of 1-methylcyclohexyl phenyl ketones in solution and within OA capsule. Note the absence of Type II products within OA capsule.



1 **2** **3**

Molecule	**Medium**	**Type II products** (%)	**Type I products** (%)
1	Acetonitrile	80	20
1	@OA_2-Buffer	0	100
2	Acetonitrile	80	20
2	@OA_2-Buffer	0	100
3	Acetonitrile	100	0
3	@OA_2-Buffer	0	100

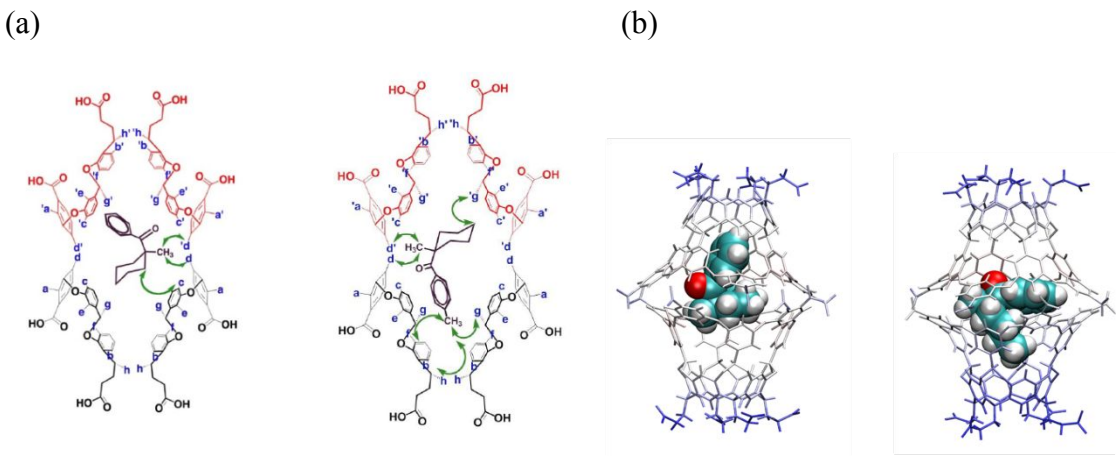
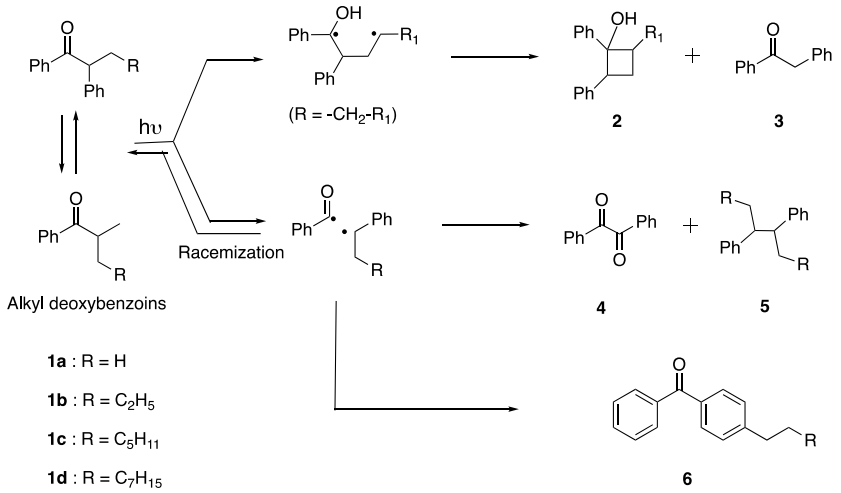


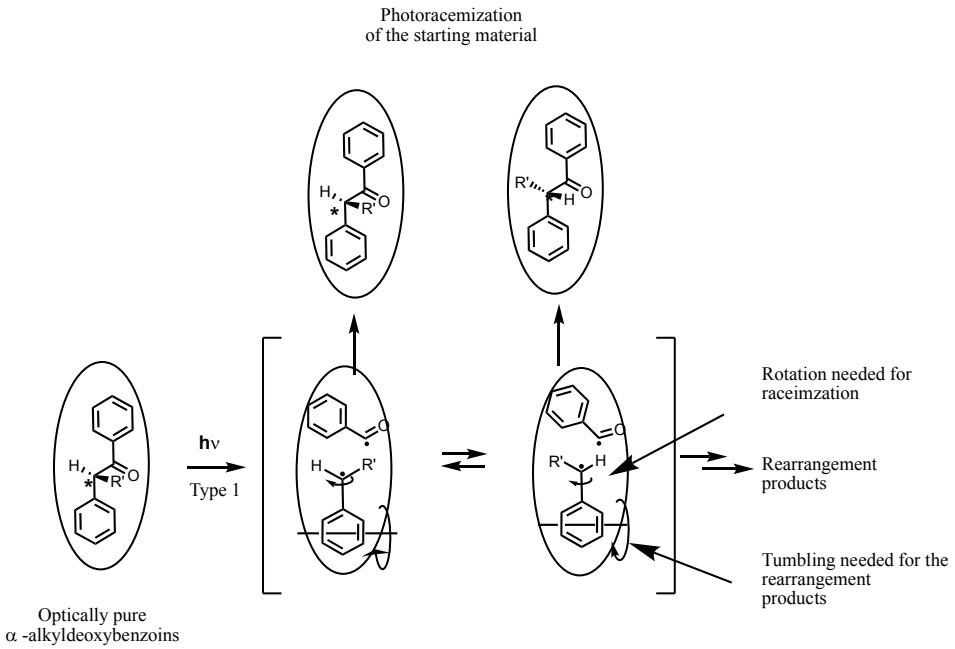
Figure 8. Structures of 1-methyl cyclohexyl phenyl ketone-OA (1:2) complexes based on (a) NOESY correlations and (b) MD simulations. (Adopted from R. Kulasekharan, R. Choudhury, R. Prabhakar and V. Ramamurthy, *Chem. Comm.,* 2011, **47**, 2841-2843).

One other example where the confinement alters the excited state dynamics is provided by optically pure α-alkyldeoxybenzoins (Scheme 3).[93] These molecules upon excitation undergo both Norrish Type I and Type II reactions both in solution and within OA capsule (Scheme 3 and Table 2). In this example, we focus mainly on the Norrish Type I products. In solution, since the cage lifetime is short the radical pair resulting from Type I process separates quickly. The caged radical pair in OA having long lifetime results in racemization and formation of the rearranged ketone a process unique to OA environment. As shown in Scheme 4 formation of these sets of products involves different types of rotational motions requiring different amounts of free space around them. As seen in Table 2 within OA, racemization and rearrangement product **6** (Scheme 3) are isolated with their yields dependent on the chain length of the α-alkyl group, decreasing with increasing alkyl length (methyl to octyl) in both reactions. As one would expect, the yields of these to decrease with lesser available space to the radical pair, the yield of the S isomer (the product of racemization) decreases as the alkyl chain length increases from methyl to octyl (25, 20, 16 and 12%, Table 2). The yield of the rearranged product dramatically

reduces from 100% to 0% as the alkyl group size is increased from methyl to hexyl. These are the resultants of shrinking free space as the guest gets larger in size.



Scheme 3. Photoreactions of α-alkyldeoxybenzoins that can exist in multiple conformations. Type II reaction occurs only from the conformer in which the Ph C=O is within 3 Å of the abstractable hydrogens. The primary radical pair resulting from Type I can return to starting ketone. (Adopted from R. Kulasekharan, M. V. S. N. Maddipatla, A. Parthasarathy and V. Ramamurthy, *J. Org. Chem.*, 2013, **78**, 942-949).



Scheme 4. Spatial need for racemization and rearrangement product formation within OA capsule. The free space depends on the alkyl chain length. (Adopted from R. Kulasekharan, M. V. S. N. Maddipatla, A. Parthasarathy and V. Ramamurthy, *J. Org. Chem.*, 2013, **78**, 942-949).

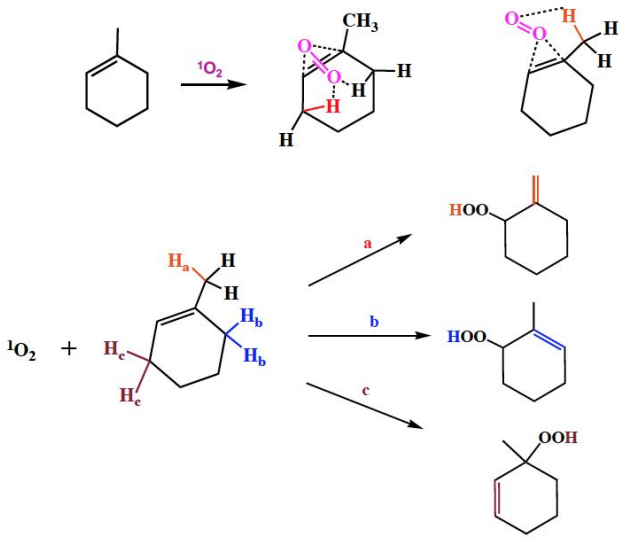
Table 2. Product distribution upon photolysis of α-alkyldeoxybenzoins in benzene and as complexes within the OA capsule (see Scheme 4 for product numbering).

Alkyldeoxybenzoin (Alkyl DB)/Medium	**Type I products**			**Type II products**		**Composition of optical isomers**	
	(4)	**(5)**	**(6)**	**(2)**	**(3)**	**R isomer**	**S isomer**
Methyl DB/Benzene (**1a**)	26	74	-	-	-	95	5
Methyl DB @OA_2/Buffer	-	-	100	-	-	75	25
Propyl DB /Benzene (**1b**)	12	17	-	54	17	96	4
Propyl DB @OA_2/Buffer	-	-	60	34	6	80	20
Hexyl DB /Benzene (**1c**)	12	24	-	36	32	96	4
Hexyl DB @OA_2/Buffer	-	-	-	83	17	84	16
Octyl DB /Benzene (**1d**)	6	49	-	24	21	96	4
Octyl DB @OA_2/Buffer	-	-	-	46	54	88	12

Enzyme analogy: Limitations of nano-containers

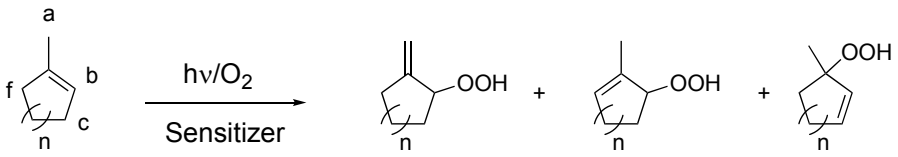
Chemistry in a laboratory is built on the principle that analogous molecules behave similarly. On the other hand, biological chemistry is built on specifics (exceptions) – for example even small changes in enzymes acting on specific molecules result in 'inaction'.[44, 83-85, 94] Photochemistry in nano-containers adopting the principles of both organic chemistry and biological chemistry aims to develop strategies that would help to understand the origin of specificity by examining a number of related systems under identical conditions. The two examples discussed below reveal that generalizations based on one or two examples can be misleading. But the specificity noted with one or two molecules of the whole class could be valuable as is the case with 11-*cis* retinal in the vision process.

The first reaction to discuss in this context is the oxidation of cyclic olefins by singlet oxygen by a reaction known as 'ene reaction'.[95] It involves a concerted addition of singlet oxygen to π and allylic σ bonds in the geometry as shown in Scheme 5. When there is more than one allylic hydrogen multiple products would result. Owing to the small size of singlet oxygen the product distribution cannot be controlled in solution and a mixture controlled by electronic factors results (see Table 3 for distribution in acetonitrile). Confinement of the olefin in OA capsule amplifies the steric factors and results in product selectivity.[61] For example, the oxidation of 1-methylcycloalkenes carried out within OA resulted in a different product distribution and selectivity from that in solution (Table 3). This selectivity is readily rationalized based on the host-guest structure deduced from NMR spectra (Figure 9). The figure includes the Δδ values (the chemical shift difference between within OA and in $CDCl_3$) which indirectly indicate the location of the three allylic hydrogens within the OA capsule; larger the difference deeper the penetration (closer to the narrower end). From the Δδ values it is clear that of the three allylic hydrogens H_c is closer to the wider entrance of OA cavitand and has the most free space around it and the H_a (the methyl) (present at the tapered end of the capsule) has the least. In isotropic solution there is no obvious difference between the three allylic hydrogens. The observed selectivity in Table 3 is consistent with the singlet oxygen abstracting the allylic hydrogen with the most free space around it. Thus while in solution singlet oxygen is unable to distinguish between the three allylic hydrogens, within OA it is able to preferably attack the less hindered H_c. The first three molecules chosen to explore the OA capsule as a reaction container to test its effectiveness were the 1-methylcycloalkens listed in Table 3. The unusual selectivity in OA was unfortunately limited only to these three olefins. The selectivity in none of the other twenty alkylcycloalkenes was as high.[96] The products of oxidation of eight 1-alkylcycloalkenes in acetonitrile and OA capsule summarized in Table 4 show the high selectivity with 1-methylcycloalkens was nowhere close to that obtained with the other alkylcycloalkenes. The strategy of manipulating the products of singlet oxygen oxidation with OA capsule is evidently specific and not general. The observed unique selectivity with one system (methyl) among eight closely related cycloalkenes reveals that OA exhibits specificity resembling enzymes. Thus the similar chemical behavior of analogous groups in isotropic solution need not be true within a confined space.



Scheme 5. Singlet oxygen oxidation (ene reaction) of 1-methyl cyclohexene. Possible three hydroperoxides are shown.

Table 3. Products of singlet oxygen oxidation of 1-methylcycloalkenes in acetonitrile and within OA capsule. (Adopted from A. Natarajan, L. S. Kaanumalle, S. Jockusch, C. L. D. Gibb, B. C. Gibb, N. J. Turro and V. Ramamurthy, *J. Am. Chem. Soc.*, 2007, **129**, 4132-4133).



Molecule	Condition	% yield of oxidation products		
n=1	CH_3CN / Rose bengal	4	43%	53%
	Octa acid / Rose bengal	-	5%	95%
n=2	CH_3CN / Rose bengal	44	20%	36%
	Octa acid / Rose bengal	10	-	90%
n=3	CH_3CN / Rose bengal	4	48%	48%
	Octa acid / Rose bengal	4	6%	90%

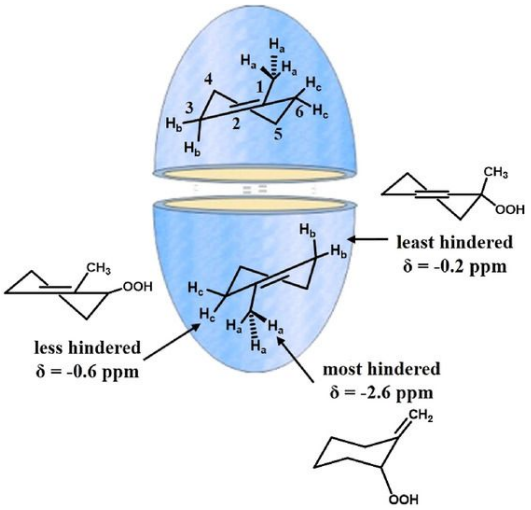
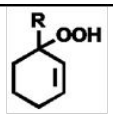
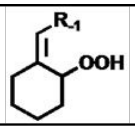
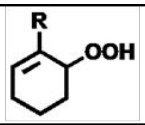


Figure 9. Cartoon illustration of the inclusion of methyl cyclohexene within OA capsule and the difference in accessibility of the three allylic hydrogens. (Adopted from S. Gupta and V. Ramamurthy, *ChemPhotoChem*, 2018, **2**, 655-666).

Table 4. Alkyl chain length dependent product distribution upon oxidation of 1-alkyl-cycloalkenes.

Relative Percentages (based on GC analysis)				
1-methylcyclohexene[#](G_1)	Solution	36	44	20
	Octa Acid	**90**	**10**	**-**
1-ethylcyclohexene (G_2)	Solution	42	43	15
	Octa Acid	**52**	**40**	**8**
1-propylcyclohexene(G_3)	Solution	37	35	28
	Octa Acid	**58**	**9**	**33**
1-butylcyclohexene (G_4)	Solution	39	34	26
	Octa Acid	**55**	**10**	**36**
1-hexylcyclohexene (G_6)	Solution	41	21	40
	Octa Acid	**56**	**3**	**42**
1-octylcyclohexene (G_8)	Solution	41	20	39
	Octa Acid	**48**	**4**	**49**
1-decylcyclohexene G_{10})	Solution	39	21	40
	Octa Acid	**50**	**0.0**	**50**
1-dodecylcyclohexene(G_{11})	Solution	40	22	38
	Octa Acid	**50**	**2**	**48**

Another system that displays the specificity is the alkyl stilbenes.[97-99] Here again only two of the several systems investigated showed unusual selectivity. Of the eight closely analogues stilbenes listed in Table 5 only two (4,4'-dimethylstilbene and 4-propylstilbene) behaved differently from that in acetonitrile solution. Prolonged irradiation of either *trans* or *cis*- 4,4'-dimethyl stilbene (DMS) included in OA established a photostationary state consisting of 80% *trans* and 20% *cis* and a quantum yield of isomerization from *trans* to *cis* of 0.06, distinctly different from the photostationary state mixture of 17% *trans* and 79% *cis* and quantum yield of 0.39 in hexane. Such dramatic dependence of photostationary state composition and the quantum yield of isomerization on the medium, to the knowledge of the author, is not common. The observed selectivity in the case of 4,4'-dimethylstilbene is attributed to anchoring of the two

ends of the stilbene via CH---π interaction between the CH_3 groups and the phenyl groups of the OA capsule present at the two poles of the capsule. In contrast to the behavior of 4,4'-dimethylstilbene, 4-propylstilbene gave *cis* enriched photostationary state mixture within OA. This seems to be the result of better fit of the *cis* rather than *trans* within OA. The calculated binding energies for *cis* and *trans* with OA (-212 vs -148 kJ/mol) supports this interpretation. Thus photochemistry within confined spaces is still challenging and interesting. Prediction is not still within reach. Without going into the details of selectivity we conclude that OA capsule can alter the dynamics of the excited state geometric isomerization of olefins and is specific to the olefin. The effect of confinement is not universal. It is likely to be guest dependent.

Table 5. Isomerization ratio of stilbenes within OA and in organic solvents.

Compound	**Acetonitrile Solution**	**OA complex**
	trans : cis	***trans : cis***
4,4'-dimethylstilbene	20 : 80	80 : 20
3,3-dimethylstilbene	17 : 79	15 : 85
2,2-dimethylstilbene	9 : 91	15 : 85
4- methylstilbene	15 : 85	15 : 85
3- methylstilbene	9 : 91	10 : 90
2- methylstilbene	8 : 92	8 : 92
4-propylstilbene	15 : 85	3 : 97

Confined molecules can be reached from outside

A number of photoreactions require activation of the reactive molecule indirectly by a second molecule often known as photosensitizer (or photocatalyst).[26] Sensitizers in principle activate the molecule of interest by energy- (triplet-triplet) or electron transfer processes that require close contact between the acceptor (reactant) and the donor (sensitizer).[26] Confinement

of a molecule in a small organic molecular container raises the doubt if such activation can occur across the capsular wall (reactant within the capsule and the sensitizer in the surrounding solution). Examples discussed in this section demonstrate this possibility.

As illustrated in Figure 10b fluorescence of OA encapsulated *trans*-4,4'-dimethyl stilbene (DMS) is quenched by the electron acceptor methyl-viologen (MV^{2+}) stationed in the water surrounding OA.[100] The Stern-Volmer plots based on emission and lifetime quenching shown in Figure 10c suggest that the quenching is static ruling out the need for diffusion for the two to get close. The transient spectra recorded for $DMS^{+\circ}$ and $MV^{+\circ}$ upon quenching (Figure 10d and e) confirm that it occurs via electron transfer (eT). While the rate constant for eT for this particular pair could not be measured due to experimental difficulties, based on the numbers measured for coumarins– viologens pairs it is estimated to be in the range of 0.4 to 4 x 10^9 s^{-1}.[101-104] These experiments suggest that photoinduced eT reactions of confined molecules can be performed. One such example is discussed below.[105] In this experiment the excited *bis*-N-methylacridinium nitrate (BMAN) is used as the electron acceptor and encapsulated *cis*-stilbenes (Table 6) as donors. It is known that the *cis*-stilbenes are quantitatively converted to the *trans* isomers while the latter is stable under electron transfer conditions.[106] As shown in Table 6 the *cis*-stilbenes are quantitatively converted to the *trans* isomers when BMAN was excited with light >375 nm while less than 5% isomerization was observed in the control experiments (without BMAN). This result unequivocally established that the radical cations of stilbenes can be generated by eT across the OA capsule wall. The details of the mechanism of eT across the OA wall is under investigation.[100]

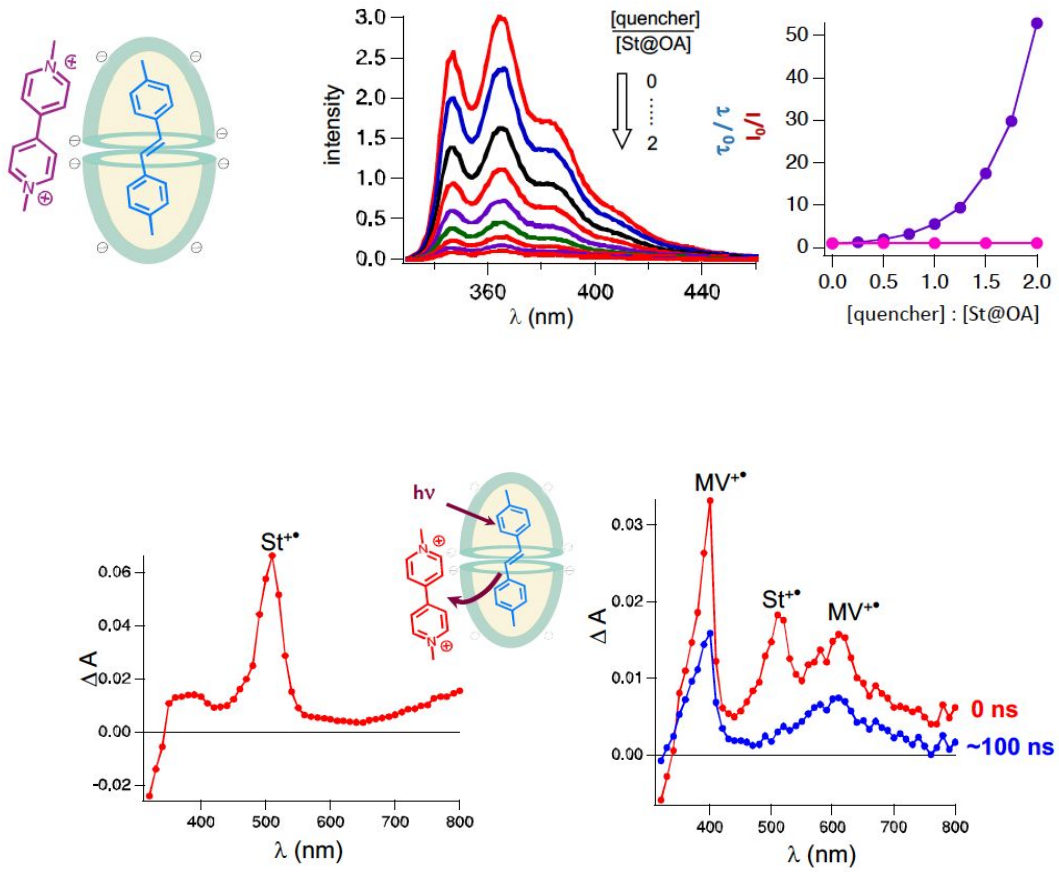
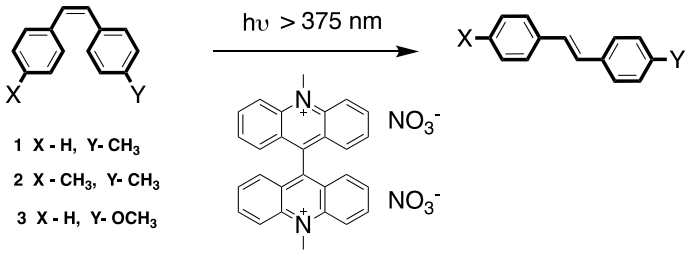


Figure 10. (a) Fluorescence spectra of 4,4'-dimetlstilbene@OA_2 at different amounts of MV^{2+}. Top left: Stern–Volmer plots of fluorescence quenching with MV^{2+} using steady-state fluorescence intensity and fluorescence lifetime. Top right: A cartoon representation of 4,4'-dimetlstilbene@OA_2 and Columbically attached MV^{2+}. (b) Transient absorption spectra after laser excitation of 4,4'-dimetlstilbene@OA_2 in the presence of MV^{2+}. (Adopted from M. Porel, S. Jockusch, A. Parthasarathy, V. Jayathirtha Rao, N. J. Turro and V. Ramamurthy, *Chem. Commun.*, 2012, **48**, 2710-2712).

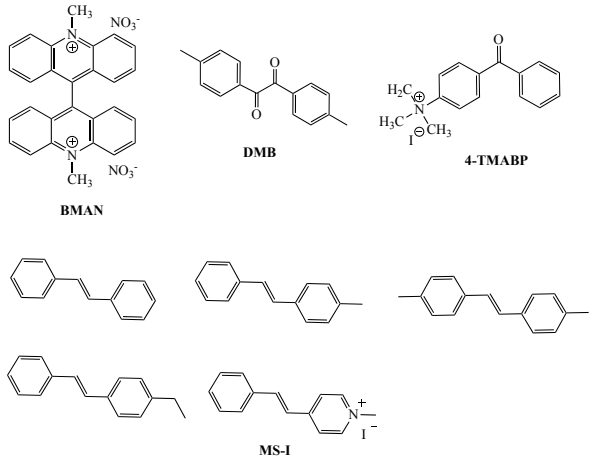
Table 6. Photoisomerization of *cis*-stilbenes included within OA capsule sensitized by *bis*-N-methylacridinium nitrate.[105]



Compound	Product distribution during electron transfer sensitization by BMAN[a, b]	
	Starting isomer: 100% *cis*	
	cis	*trans*
1@$(OA)_2$	10	90
1@$(OA)_2$-control	90	10
2@$(OA)_2$	0	100
2@$(OA)_2$-control	85	15
3@$(OA)_2$	73	27
3@$(OA)_2$-control	100	0

The final set of examples deals with triplet-triplet energy transfer (ET) across the OA wall. Triplet-triplet ET across Cram's hemicarcerand's wall established decades ago[107-109] could not be extended to larger molecules and reactions owing to the hemicarcerand's limited ability to include guest molecules. Feasibility of triplet-triplet ET across OA wall was established with neutral 4,4'dimethylbenzil (DMB) and cationic N, N, N-trimethyl-4-(phenylcarbonyl)benzene

amminium iodide (4-BMAP) (Scheme 6) as triplet energy donors. DMB and 4-BMAP stay within the OA capsule and outside closer to the wall of the capsule respectively due to their hydrophobic and charged nature and therefore, their corresponding acceptors would be located accordingly. ET across the wall was established with two acceptors, ground state oxygen and methylstilbazolium iodide (MS-I; Scheme 6) in the case of DMB[110, 111] and stilbenes enclosed within OA for cationic 4-BMAP.[105] Phosphorescence quenching of DMB by ground state oxygen resulted in singlet oxygen as confirmed by its emission. While the above results established the occurrence of triplet-triplet ET across the OA wall, the long triplet lifetime DMB (234 μs) gave rise to the suspicion of it occurring when the capsule is slightly open. To establish that ET can occur across the wall of a closed capsule even when the capsule is fully closed, the phosphorescence of OA encapsulated DMB was quenched by the cationic olefin MS-I (Scheme 6) that would stay closer to the OA exterior and is much larger than oxygen. As shown in Figure 11, the emission was quenched by the cationic MS-I giving rise to a linear Stern-Volmer plot and estimated ET rate constant of $3.1 \times 10^9\ M^{-1}sec^{-1}$. The faster quenching rate confirmed that the ET is occurring before the capsule has the time to open.[110, 112, 113] Consistent with the occurrence of triplet-triplet ET, geometric isomerization of *trans*-MS-I resulted in a photostationary state mixture of 69:31 *trans* to *cis* isomers, same as that in solution. Triplet sensitization of encapsulated stilbenes with 4-BMAP was also accomplished confirming guest molecules trapped within OA capsules can be reached from outside.



Scheme 6. Electron and energy transfer sensitizers and acceptors used for remote sensitization across OA wall.

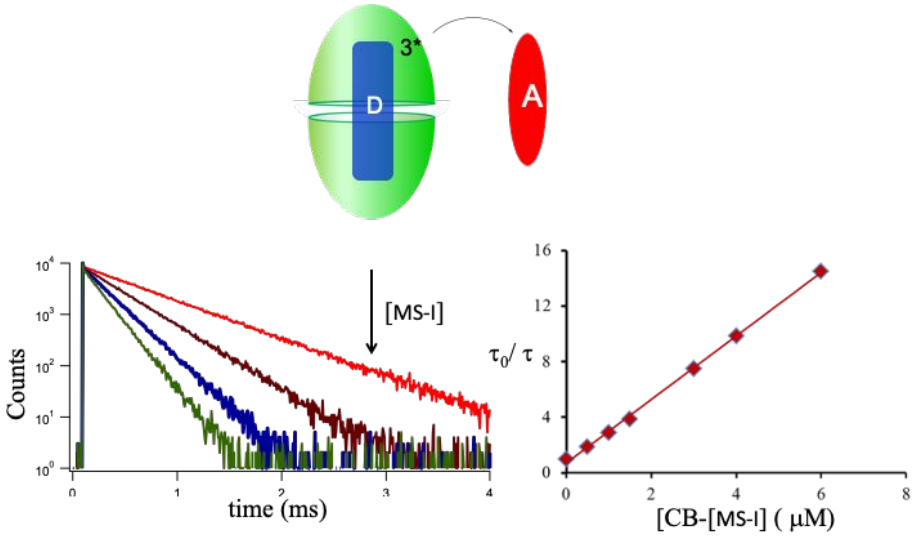


Figure 11. (left) Plot showing the quenching of triplet lifetime of **DMB**@OA_2 with gradual increment of concentration of *trans*-methylstilbazolium salt. (right) Stern-Volmer plot for phosphorescence quenching of **DMB**@OA_2 by *trans*-methylstilbazolium salt. (S. R. Samanta, A. Parthasarathy and V. Ramamurthy, *Photochemical & Photobiological Sciences*, 2012, **11**, 1652-1660).

Summary

Living systems are fastidious in terms of rate, and chemo-, regio- and stereo-selectivities of the various reactions accomplished through transformations in an aqueous environment by confining molecules and restricting their mobility through weak interactions (entropic control). Nature utilizes less reagents but more pre-organization and confinement to synthesize complex molecules with much less wastage. Recent availability of a large number of synthetic hosts provides an unprecedented opportunity to exploit confinement as a strategy to alter the dynamics of molecules both in the ground and on excited state surfaces. This review has highlighted the possibilities that exist for exploring the chemistry of molecules in synthetic confined cavities with features akin to a natural system.

Recent thrust in green and sustainable chemistry has led to surge in interest to perform photoreactions in water using photon as the non-toxic and sustainable reagent. To reduce waste in chemical reactions finding new ways to achieve ‘selectivity’ in product formation has become a goal. In this context concepts based on supramolecular chemistry are employed to perform

light initiated reactions. Over a period of time two approaches has evolved: (a) well defined hosts are used as reaction containers and (b) carefully crafted synthetic templates are used to hold molecules in a desired arrangement/geometry. While the latter makes use of weak interactions to hold molecules in select conformations, the former depends on hydrophobic effects to bring guest molecules to the container. Judicial implementation of the second approach requires well defined hosts with sufficient free space for the guest molecule to reside and undergo structural changes upon excitation. In this context it is important to keep the prophetic words of Lao-tzu (ca. 4th century BC) in mind: "*We shape clays into a pot, but it is the emptiness inside that holds whetever we want*". As emphasized in this article, not only the size of the container but also the extent of emptiness within should be considered while choosing the host.

For over more than four decades water soluble micelles, cyclodextrins, cucurbiturils, calixarenes, metal-organic cages, etc. have been explored as reaction containers. Although each one is unique and serve a function, none provides total encapsulation of the reactant molecule that would provide better selectivity than the above partially open containers. The host octa acid discussed here, in presence of a guest molecule, forms a capsule that remains closed in nanosecond time scales during which time most photoprocesses, especially from excited singlet states occur. The container chemistry is exciting provided we have containers of several sizes and shapes. At the moment the choice is limited and water-soluble hosts that can encapsulate and solubilize organic molecules of different sizes in water are in great demand. The synthetic challenge is worth undertaking. Finally, to reduce waste it is important to design systems that are photocatalytic. Thus supramolecular photocatalysis is an exciting topic with plenty of opportunities and challenges.

Conflicts of interest

There are no conflicts to declare.

Acknowledgement: The author is grateful to US National Science Foundation for generously supporting the program. He is thankful to the past and current members of the group as well as collaborators especially Professors Pratik Sen, Christopher Elles, Varadharajan Srinivasan, Rajeev Prabhakar and Silas Blackstock whose experimental and intellectual contributions

enhanced the quality of the research outcome . Rajee Ramamurthy provided support by carefully reading, commenting and copyediting this as well as most articles this review has summarized.

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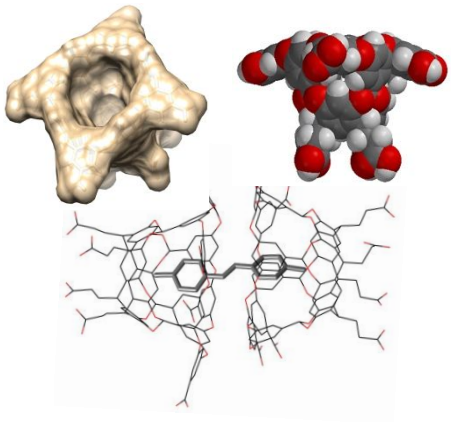
Table of Contents Graphic



The free space within an organic capsule following the occupation by the guest can be exploited to control the dynamics of molecules on excited state surfaces. The extent and shape decide the observed selectivity.