

## The Chemistry of Confined Spaces

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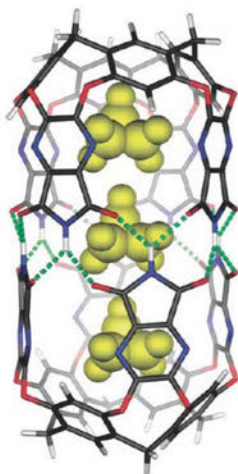
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**Abstract:** The reactivity in the confined spaces of zeolites, metal-organic frameworks, cage compounds and macrocycles differ in many aspects from those conducted in bulk solution. Cases of altered regioselectivity, enhanced stability and accelerated substrate reactivity are presented within the context of non-covalent interactions between host and guest molecules, which define much of supramolecular chemistry, being unique and imparting highly useful properties that are of interest for their intellectual merit as well as their immense commercial value.

**Keywords:** Catalysis, metal-organic frameworks, supramolecular, zeolite.

### 1. INTRODUCTION

Enzymatic behavior is often described [1] as a biological analogy to synthetic supramolecular chemistry - *i.e.* that a molecular host and guest are like a lock and key [2]. This analogy perhaps places too much emphasis on the shape complementarity of a lock and key, a position that has resulted in this model being further refined [3]. The chemistry that occurs within confined spaces - be they synthetic or enzymatic - is a product of the collective forces that go beyond singular factors such as shape complementarity of a host and guest, but arise precisely because the environment of a confined space is unlike the environment we envision [4, 5] for reactivity that occurs within a flask. To put this into perspective, in a memorable paper [6] by Jules Rebek, wherein the observation was made that gases are solubilized by a self-assembling cavitand at standard temperature and pressure (Fig. 1), a tongue-in-cheek use of the ideal gas law suggested these cavitands were holding back approximately 300 atmospheres worth of cyclopropane inside  $420 \text{ \AA}^3$  worth of space.



**Fig. (1).** The original cavitand containing 3 cyclopropane molecules. (Reproduced from Ajami, D.; Rebek, J. Gas behavior in self-assembled capsules. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6059).

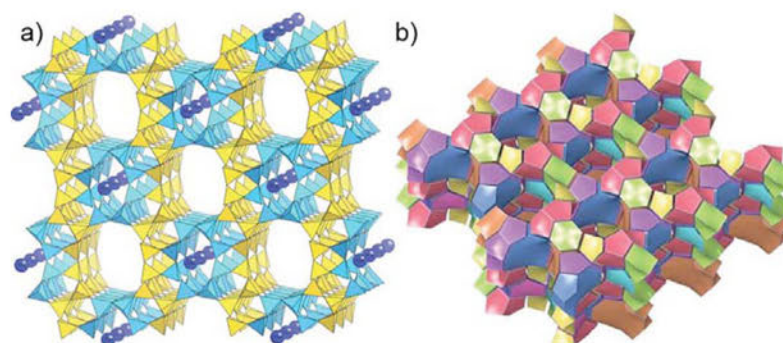
The spectacular failure of the ideal gas law (more so than typically) demonstrates first and foremost: different forces govern the behavior of molecular guests within the confines of only slightly larger molecular spaces - this is where the true power of supramolecular chemistry lies and this review hopes to illustrate a few case studies of these phenomena.

### 2. CONFINEMENT IN THE NATURAL WORLD

Zeolites [7, 8] are an interesting species to begin a discussion on the chemistry of confined spaces as they are naturally present with crystalline aluminosilicate minerals found in volcanic rocks. They consist of interconnected channels (Fig. 2) with a range of pore sizes, and many have an intrinsic pH that can be exploited to advance a number of synthetic reactions within these small cavities.

With an annual production of 4 million tons of natural zeolite material and an additional 1.5 million tons of synthetic material, they are - by a wide margin - the most ubiquitous small molecular reactors in the world. They are domestically found in water softeners as ion exchange media and they are employed on large scales in the cracking of petroleum products industrially. Their existence predates even alchemic chemistry and they have, therefore, been the subjects of much investigation [9] since the 1950's, when large deposits of naturally occurring zeolites were first found. Their natural occurrence and ion exchange characteristics [7] have made them popular reagents in green chemistry. Whilst these species are ubiquitous, the mechanisms by which they perform their chemistry are occasionally opaque. For instance, their use as catalytic agents in the cracking of petroleum has given rise to speculation [10] that they can behave as superacids [11] by promoting  $\sigma$ -bond protolysis. Further, it has been shown that they generate [12] so-called "super-electrophiles," thereby allowing chemistry to occur within their confines under much safer conditions than in solution. Super-electrophiles, a term suggested by G. Olah, [13] are generated from cationic electrophiles that become further protonated or coordinated by a Lewis Acid. Super-electrophiles are typically created in the presence of superacids or large excesses of powerful Lewis acids, and yet they are generated in substantially less acidic zeolites. This implies a structure-function relationship that promotes the stability of highly electron deficient species by forcing protonated reagents into close proximity with the acidic walls of a zeolite cage. For instance, Koltunov, Sommer and coworkers described [12] a series of Friedel-Crafts and cyclo-alkylations of aromatics that do not

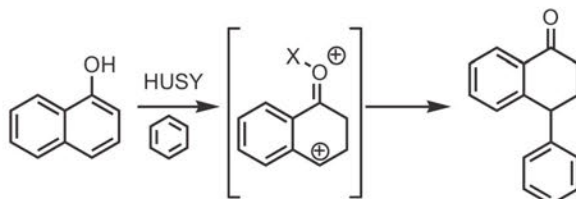
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**Fig. (2).** (A) The zeolite mineral mordenite (MOR): developed in the 1960's and widely used in the hydrocarbon cracking. SiO<sub>4</sub> polyhedra are represented as yellow tetrahedra and AlO<sub>4</sub> polyhedra are represented as aqua tetrahedra (B) The depicted framework is that of ZSM-5 zeolite (MFI), a commercially important material in the removal of "hard" minerals from water. (Reproduced from Townsend, R.P.; Coker, E.N. In: *Stud. Surf. Sci. Catal.*; van Bekkum, H.; Flanigen, E.M.; Jacobs, P.A.; Jansen, J.C. Eds.; Elsevier: **2001**; Vol. 137, pp. 467).

readily proceed in the absence of strong acids. In one particular experiment, depicted in (Fig. 3), they demonstrate the zeolite HUSY can induce the arylation of naphthol, which occurs only with the strongest superacid – fluoro-antimonic acid (apparently, failing even with triflic acid) [14].

The authors are quick to point out that this remarkable activation does not arise from free dicationic species but from stabilization of the intermediates by interactions with the zeolite framework. This capacity to stabilize intermediates [15], being one of the hallmarks of enzymatic activity and supramolecular reactions, is at the



**Fig. (3).** The reaction between naphthol and benzene in the zeolite HUSY occurs via a superelectrophilic intermediate stabilized by the zeolite surface.

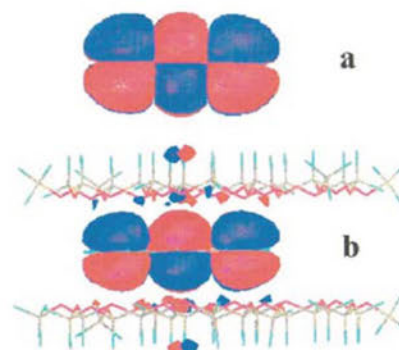


**Fig. (4).** An example of Lapis lazuli, and the brilliant blue color associated with the entrapped S<sub>3</sub><sup>-</sup> radical anion, intricately carved into a Chinese sailing junk. (Reproduced from Reinen, D.; Lindner, G.G. The nature of the chalcogen colour centres in ultramarine-type solids. *Chem. Soc. Rev.*, **1999**, 28, 75).

heart of supramolecular and enzymatic chemistry. For instance, the brilliant blue pigment, Ultramarine, is naturally formed [16, 17] as the semi-precious stone Lapis lazuli. Lapis Lazuli itself would be an unremarkable grey zeolite were it not for the persistent confinement of the S<sub>3</sub><sup>-</sup> radical anion, which simply cannot exist outside its zeolite matrix. In fact, many pigments have found enhanced stability [18] by residing in these structures and have been used by artisans for hundreds or even thousands of years (Fig. 4).

While the characteristic acidity and high surface area of these zeolite materials superficially explain much of their reactivity, these two phenomena fail to fully account for all of them. The so-called *confinement effect* [19, 20] is an interesting *electronic* property known to affect the diffusion of substances and the catalytic properties of these materials (Fig. 5).

The confinement effect is known to arise from the electronic interactions with the walls of the zeolite framework and is dependent upon these surface-based interactions. It is thus likely a more general phenomenon. For instance, very similar effects have been observed and are now receiving significant physical analysis [21-23] in synthetic solids coming on the scene, literally eons after the formation of zeolites, called Metal-Organic Frameworks (MOFs) - another breed of porous crystalline material.

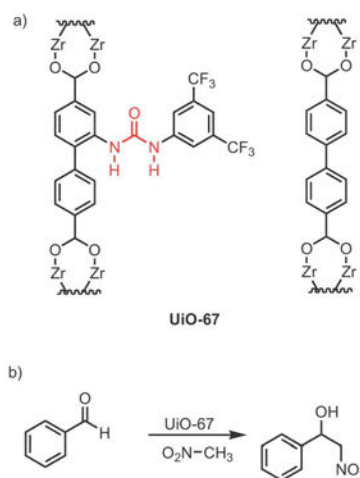


**Fig. (5).** (a) Calculated spatial extension of the anthracene HOMO in the gas phase and (b) calculated as confined between two sheets of mica. Notably, the HOMO of the anthracene is delocalized slightly in the sheets of mica and the overall size of the orbitals of anthracene decrease in the z axis. (Reproduced from Márquez, F.; García, H.; Palomares, E.; Fernández, L.; Corma, A. Spectroscopic evidence in support of the molecular orbital confinement concept: Case of anthracene incorporated in zeolites. *J. Am. Chem. Soc.*, **2000**, 122, 6520).



### 3. INDUCING REACTIVITY IN THE SOLID STATE BY METAL ORGANIC FRAMEWORKS

MOFs are crystalline materials [24-26] consisting of an organic linker held in place *and separated from each other* by metal ions or metal clusters to produce a three dimensional porous solid. The strength of the metal-organic bond allows these pores to be emptied of solvent without a loss of crystallinity, such that the material becomes a large, solid “sponge”. This quality has received significant attention for their gas inclusion capabilities and how tunable their functionality can be. By judicious choice of organic linker, an MOF can be tuned for different properties and the separation of the individual organic linkers (struts) by the inorganic nodes prevent their mutual interaction.



**Fig. (6).** Catalysis of nitro-aldol reactions (also called the Henry reaction) can be conducted using an appropriate hydrogen bond donating group. To facilitate these reactions, (a) urea based struts were spatially separated *via* strong directional zirconium clusters producing large 23 and 12 Å diameter pores. Test reactions (b) using excess of nitromethane were then performed demonstrating superior product yield when the ureas were in fixed positions as opposed to in solution.

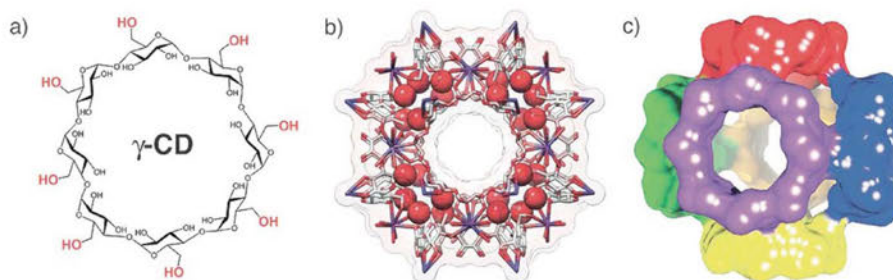
This property has allowed for interesting catalytic reactivity [27]. For instance, in a communication [28] by Scheidt, Hupp and Farha the use of hydrogen bond donating catalysis was investigated in a nitro-aldol reaction using a urea catalyst. Urea is well known to hydrogen bond to itself, thereby deactivating any potential hydro-

gen bond donating or accepting properties. To avoid this limitation, the team’s approach was to confine the urea catalyst to a strut within an MOF, thereby separating each urea in space. The team also employed a “mixed strut” strategy to increase reactive volume at the expense of reactive functional groups by mixing both the urea functionalized biphenyl dicarboxylate and an unfunctionalized biphenyl dicarboxylate (bpdc). While counter-intuitive, decreasing the amount of the bulky catalytic strut in the MOF actually increases the efficacy of the catalyst by opening up more interstitial space for chemistry. The synthesis of the MOF dubbed UiO-67-Urea/bpdc was performed under solvothermal conditions in the presence of HCl by mixing a urea functionalized biphenyl and an unfunctionalized biphenyl dicarboxylate (Fig. 6a) with zirconium chloride. Ultimately, the team saw an order of magnitude increase in yield when the reaction was conducted using the mixed strut variety of UiO-67-Urea/bpdc as compared to control. This example takes advantage of the voluminous pore space and spatial separation permitted in 3D crystalline matrices. These properties permitted catalytic activity an order of magnitude higher than if the catalysts were allowed to intermingle in solution. This provides an interesting juxtaposition to a second example illustrated below wherein reactivity is observed *because* MOF architectures permit a significant amount of functionality to be located very close by. In each case, however, porosity remains imperative.

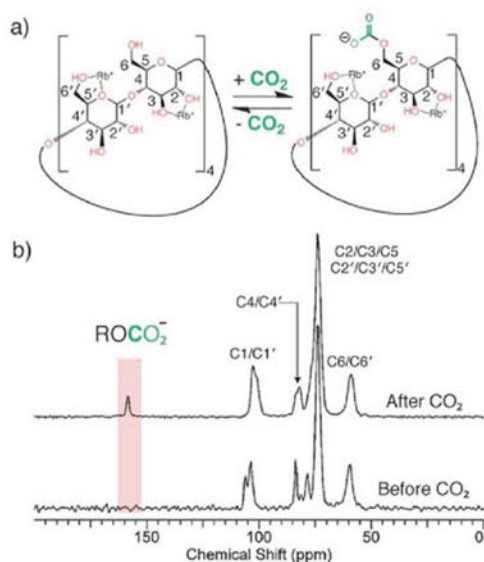
Several years ago, Stoddart and coworkers published a communication [29] detailing the rapid and chemisorptive uptake of carbon dioxide in a MOF (Fig. 7) composed of  $\gamma$ -cyclodextrin ( $\gamma$ -CD) - a tubular arrangement comprised of eight glucose unit (Fig. 7a) - and held together in a cubic framework by coordinating rubidium metal ions the authors called “CD-MOF-2”.

In addition to this being a very “green” MOF comprised of non-toxic reagents, this communication focused upon the unanticipated formation of carboxylic acid functions when CD-MOF-2 was exposed to high concentrations of CO<sub>2</sub>. These carboxylic functional groups were made evident, as shown in (Fig. 8), by characteristic resonances in CP/MAS <sup>13</sup>C NMR. The authors were further able to demonstrate a pH change within the local environment of the structure by incorporating a commercial colorimetric pH indicator. Two more tests to demonstrate if this effect was unique to the structure of the MOF were then performed: Firstly they demonstrated that  $\gamma$ -CD on its own was incapable of forming the carboxylic acid moieties by again employing CP/MAS <sup>13</sup>C NMR.

They further demonstrated that, after intense milling of the pH indicator imbued CD-MOF-2 material into an amorphous powder;



**Fig. (7).** (a) Structural formula of  $\gamma$ -cyclodextrin ( $\gamma$ -CD) with the primary hydroxyl groups colored red. (b) Crystallographic representation of a single cubic ( $\gamma$ -CD)<sub>6</sub> unit of the extended framework of CD-MOF-2. The primary faces of the six  $\gamma$ -CD tori are coordinated by 24 Rb<sup>+</sup> cations to another six ( $\gamma$ -CD)<sub>6</sub> units, forming a 3D extended bcc structure. (c) Space-filling representation of the ( $\gamma$ -CD)<sub>6</sub> unit with the six  $\gamma$ -CD rings forming the sides of the cube colored differently to show the six sides of the cube. (Reproduced from Gassensmith, J.J.; Furukawa, H.; Smaldone, R.A.; Forgan, R.S.; Botros, Y.Y.; Yaghi, O.M.; Stoddart, J.F. Strong and reversible binding of carbon dioxide in a green metal-organic framework. *J. Am. Chem. Soc.*, **2011**, *133*, 15312).

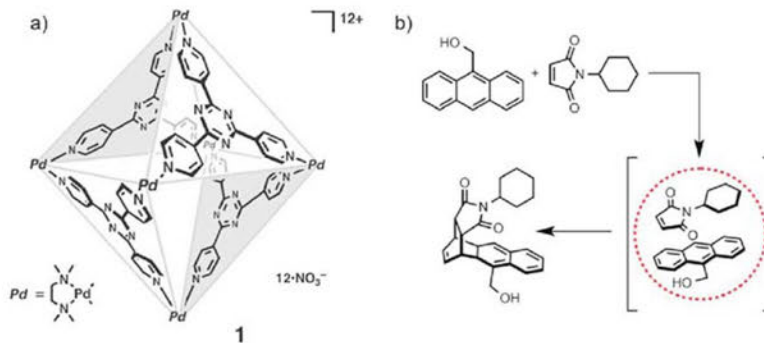


**Fig. (8).** (a) Schematic diagram illustrating the equilibrium during the chemisorption of  $\text{CO}_2$  by CD-MOF-2 (b) CP/MAS  $^{13}\text{C}$  NMR spectra (400 MHz, room temperature) of activated CD-MOF-2 before (bottom) and after (top) exposure to  $\text{CO}_2$ . Upon exposure to  $\text{CO}_2$ , CD-MOF-2 shows a new resonance at 158 ppm from the formation of carbonic acid functions is observed. (Reproduced from Gassensmith, J.J.; Furukawa, H.; Smaldone, R.A.; Forgan, R.S.; Botros, Y.Y.; Yaghi, O.M.; Stoddart, J.F. Strong and Reversible binding of carbon dioxide in a green metal-organic framework. *J. Am. Chem. Soc.*, **2011**, *133*, 15312).

no evident formation of carboxylate functionalities arose. The consensus result from multiple reports [29-33] is that a high concentration of  $\text{CO}_2$  finds itself within the pores of the MOF owing to the strong dipole-quadrupole interactions associated with the sugars and the  $\text{CO}_2$ . This evident high concentration of the weak electrophile  $\text{CO}_2$  around a surfeit of protonated alcohols induces covalent bond formation through equilibrium pressure, vis-à-vis Le Châtelier's principle.

#### 4. CAGES AND MACROCYCLES

Several synthetic systems have emerged as reactive vessels for interesting chemistry, often catalyzing unfavorable processes by bringing two (or more) reactants together within confined space.



**Fig. (9).** (a) The Self-assembled coordination cage prepared by mixing of an exo-tridentate organic ligand and an end-capped Pd(II) ion in a 4:6 ratio in water is used in the (b) encapsulation of 9-hydroxymethylanthracene and N-cyclohexylphthalimide. Within the cage complex (illustrated as a red circle), the subsequent Diels-Alder reaction leads to the *syn* isomer of a 1,4-adduct. (Part a Reproduced from Yoshizawa, M.; Tamura, M.; Fujita, M. Diels-Alder in aqueous molecular hosts: Unusual regioselectivity and efficient catalysis. *Science*, **2006**, *312*, 251).

The overlapping of reactive geometries to manipulate the outcome of otherwise unfavorable chemistry is one of the hallmarks of enzymatic systems and here we present a handful of such systems.

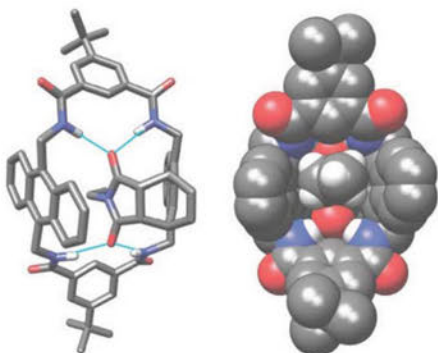
The reactivity of anthracene under Diels-Alder conditions is dominated by 9,10 addition across the central arene ring with reactivity at the peripheral rings in the 1,4 position being rare. This chemistry can be facilitated, however, by forcing the geometries of the diene and dienophile into positions where orbital overlap nevertheless produces the less favored 1,4 adduct exclusively. For example, Fujita and coworkers have utilized [34, 35] an octahedral  $M_6L_4$  coordination complex self-assembled from an admixture of *cis* coordinating or  $\text{Pd}^{2+}$  (e.g.  $[\text{Pd}(\text{en})]^{2+}$ ) with the C3-symmetric tripodal ligand 2,4,6-tris(3-pyridyl)-1,3,5-triazine in a 6 : 4 ratio. The resulting highly charged and aqueous soluble octahedral "cage" (Fig. 9) contains a large internal cavity capable of accommodating hydrophobic guests. The cavity is large enough to accommodate the judicious choice of diene (a cyclohexylmaleimide) and dienophile (9-methoxy anthracene) where, upon modest heating, the unlikely formation of a 1,4-substituted anthracene diels alder adduct is formed in excess of 98%!

The reaction in (Fig. 9b), when done in organic solvent and in the absence of the  $M_6L_4$  coordination complex, yields typical 9,10 adducts. This result strongly suggests that the regioselectivity is set by the interactions between adducts and the cage structure. The explanation lies in the way the two reactants are forced by steric crowding into a preorganized arrangement that yields the energetically less favorable of the two potential regioisomers with their inclusion owed to the entropic effects afforded by hydrophobic driven assembly inside the cage.

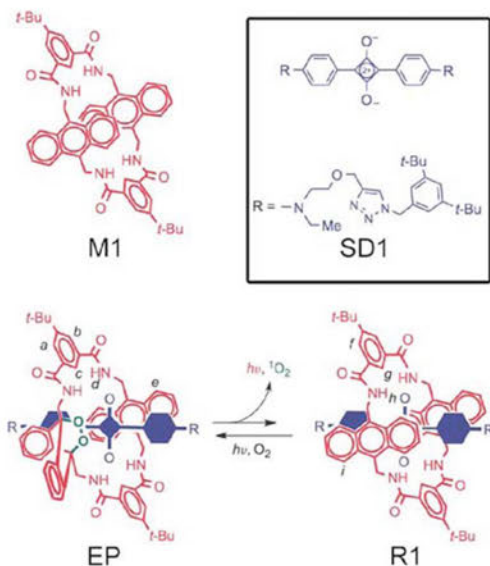
This steric approach contrasts nicely with a second means of obtaining a similar product through the use of positional arrangement by hydrogen bonding. Smith and coworkers reported [36] the observation of quantitative 1,4 substrate addition to the anthracene constituents of a tetralactam cyclophane (Fig. 10). Using N-ethylmaleimide as the diene in chloroform media, under mild heating, the reaction gave exclusively the *endo*-1,4 regioisomer.

This outcome appears attributed to restraining hydrogen bonding from the four amide hydrogens located around the macrocycle, which is sufficiently rigid to enforce overlap between the ethylmaleimide and the 1,4 position of the anthracene within the macrocycle. Interestingly, the group also reported the addition of singlet oxygen across the 9,10 position to produce endoperoxides, indicating the 9,10 position of their anthracene macrocycle is indeed receptive to [4+2] reactions. This endoperoxide formation is interest-





**Fig. 10.** The (left) stick model highlighting intramolecular hydrogen bonding and (right) space-filling model highlighting the N-ethyl group inside the macrocyclic cavity. (Reproduced from Gassensmith, J.J.; Baumes, J.M.; Eberhard, J.; Smith, B.D. Cycloaddition to an anthracene-derived macrocyclic receptor with supramolecular control of regioselectivity. *Chem. Commun.*, 2009, 2517).



**Fig. 11.** The anthracene based macrocycle M1 and squaraine dye SD1 form a permanently interlocked rotaxane R1 that is reversibly oxidized from dissolved oxygen to form endoperoxide EP. The reverse reaction liberates oxygen and produces a photon, which is detected as Near-infrared radiation ( $\lambda_{\text{max}}$  733 nm). (Reproduced from Baumes, J.M.; Gassensmith, J.J.; Giblin, J.; Lee, J.J.; White, A.G.; Culligan, W.J.; Leevy, W.M.; Kuno, M.; Smith, B.D. Singlet oxygen release and cell toxicity of a chemiluminescent squaraine rotaxane dye: Implications for molecular imaging. *Nature Chem.*, 2010, 2, 1025.)

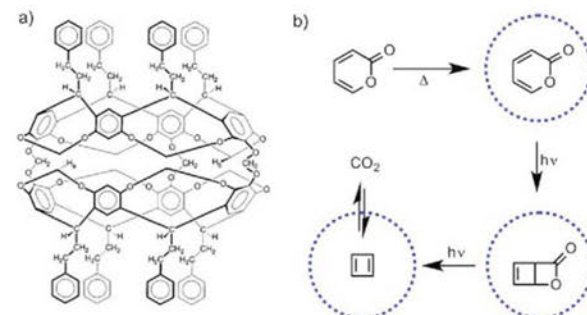
ing in its own right, however, when the guest is a mechanically [37] entrapped dye, as opposed to an alky maleimide, a unique hybrid of hydrogen bonding assisted by steric interactions interplay to produce a unique chemiluminescent effect.

Briefly, squaraine dyes [38–40] (SD1, top, Fig. 11) are typically near-infrared fluorescing molecules possessing a unique structure that serves as a competent guest to the same tetralactam macrocycle (Fig. 11 M1). An interesting property of squaraines, in addition to their high quantum yield, is their capacity to generate small amounts of singlet oxygen [40]. After the macrocycle host M1 and squaraine guest SD1 are permanently interlocked to form [2]rotaxane R1, exposure to light in an oxygenated organic solvent results [41] in a [4+2] cycloaddition between singlet oxygen ( $^1\Delta$ )

and the 9,10 position of one of the two anthracene moieties of M1 (Fig. 11). The thermally unstable endoperoxide produces significant steric strain on the system such that the overall geometry of the ordinarily rigid anthracene yaws outward whilst the rigid squaraine dye (locally fixed *via* hydrogen bonding) bends in the opposing direction. This steric strain induces a retro [4+2] reaction, which induces a chemiluminescent response. In this particular instance, the nature of R1 facilitates a geometry capable of forming a reactive intermediate that decomposes to produce chemiluminescence. It is worth mentioning, however, that this intermediate endoperoxide product, whilst thermally stable, can be fully characterized by a suite of analytical methods at lower temperatures. Indeed, the chemiluminescent materials can be stored indefinitely at  $-20\text{ }^\circ\text{C}$  until further needed. While it is interesting that the reactive endoperoxide species can be trapped at lower temperatures, other systems have shown equally or more impressive capacities to trap transient intermediates.

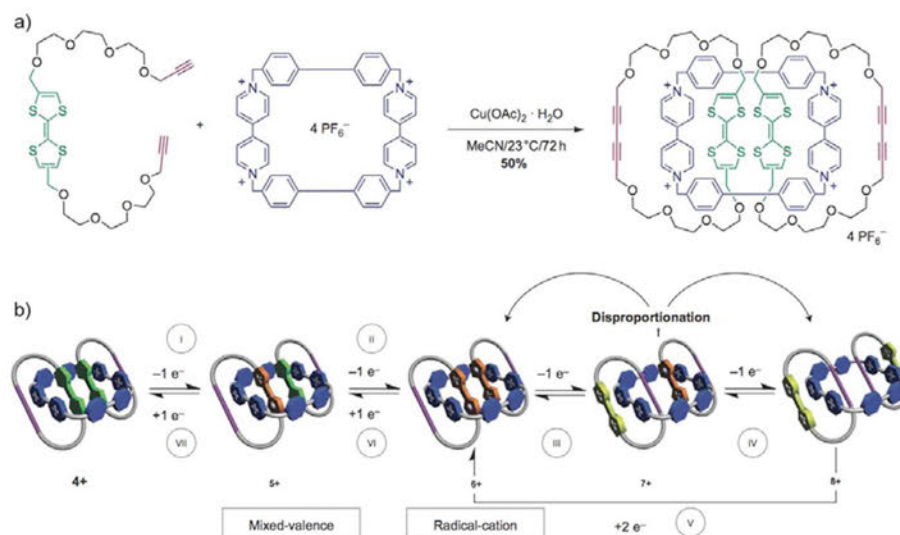
## 5. CONFINEMENT OF REACTIVE INTERMEDIATES

A fascinating example [42] of trapping cyclobutadiene, an extremely reactive anti-aromatic compound, stands out as a unique combination of reactivity within a confined system as well as maintained stability. Cram and coworkers utilized a large hemicarcerand (Fig. 12) containing an inner cavity large enough to accommodate small molecules yet is *not* porous enough at room temperature to allow any exchange equilibrium with external solvent. Only upon heating will the hemicarcerand expand and allow for exchange with guests. In this manner, the Cram group was able to utilize a hemicarcerand to entrap  $\alpha$ -pyrone at high temperatures followed by cooling, which inhibited further exchange or contact with external solvent.



**Fig. 12.** a) The hemicarcerand depicted can entrap small molecules reversibly at high temperature. Upon cooling, the trapped molecules are unable to exchange with their environment and *visa-versa*. In this way,  $\alpha$ -pyrone (b) was entrapped by the hemicarcerand (blue circle) and subsequently photochemically converted to cyclobutadiene. (Part a reproduced from Cram, D.J.; Tanner, M.E.; Thomas, R. The taming of cyclobutadiene. *Angew. Chem. Int. Ed. Engl.*, 1991, 30, 1024).

A solution of the  $\alpha$ -pyrone hemicarcerand complex was degassed and photocatalytically decomposed to produce cyclohexabutene through a two-step process, which resulted in the elimination of  $\text{CO}_2$ , a molecule small enough to exit the pores of the hemicarcerand under ambient conditions. This unique environment and reactivity provided for three things making this particular isolation of an intermediate a success: (i) the hemicarcerand was inert toward its reactive guest, (ii) the guest was only able to exist as a 1:1 complex with the hemicarcerand, preventing dimerization and (iii) other molecular species, except small gases such as oxygen and carbon dioxide, were unable to penetrate the hemicarcerand, thereby leaving the complex stable.



**Fig. (13).** a) The synthesis of the [3]catenane structure begins with a TTF functionalized alkyne and a tetracationic cyclophane used in these experiments and the b) five redox states. The  $6^+$  structure is a stable radical-cation complex. (Reproduced from Spruell, J.M.; Coskun, A.; Friedman, D.C.; Forgan, R.S.; Sarjeant, A.A.; Trabolsi, A.; Fahrenbach, A.C.; Barin, G.; Paxton, W.F.; Dey, S.K.; Olson, M.A.; Benitez, D.; Tkatchouk, E.; Colvin, M.T.; Carmielli, R.; Caldwell, S.T.; Rosair, G.M.; Hewage, S.G.; Duclairioir, F.; Seymour, J.L.; Slawin, A.M.Z.; Goddard, I.; William A.; Wasielewski, M.R.; Cooke, G.; Stoddart, J.F. Highly stable tetrathiafulvalene radical dimers in [3]catenanes. *Nature Chem.*, **2010**, *2*, 870).

In the case of cyclobutadiene, such measures are to protect the guest from the environment. Occasionally, however, the host plays a more active role allowing reactive intermediates, normally unobservable in solution, to form and remain persistent even if they are exposed-however marginally-to the remainder of solution. For instance, a recent publication [43, 44] demonstrated the ability to trap, at room temperature, radical dimer complexes of tetrathiofulvalene (TTF), an inherently good  $\pi$ -donor, within a strong  $\pi$ -accepting tetracationic viologen-based cyclophane. While trapping radical species within host systems is known [5, 12], this example merits particular interest, as the conditions required to produce the trapped radicals do not preclude interactions of the radical species with the solution.

Ordinarily (Fig. 13a) the cyclophane used in this example and TTF have a high 2:1 association constant; however, TTF is capably oxidized into a radical cation state causing coulombic repulsion from the cyclophane's four cationic charges. The work by Spruell and Coskun *et al.*, however, challenged that in a remarkable way by demonstrating stabilization of TTF radical cations within a cationic host as a [3]catenane (affinity *umpolung* - a term the authors borrowed from more conventional chemical systems). Hitherto, TTF radical dimers (TTF $^+$ )<sub>2</sub> have been observed only in anaerobic, high concentration and low temperature environments [45], safely protected from reduction or disproportionation. Through the formation of an interlocked [3]catenane system, the group was able to demonstrate by EPR, NMR and in the solid state crystallographic analysis, that such mixed radical systems could indeed coexist in solution so long as (i) they were mechanically bound as a [3]catenane and (ii) they were confined to the interstitial gap within the cationic cyclophane.

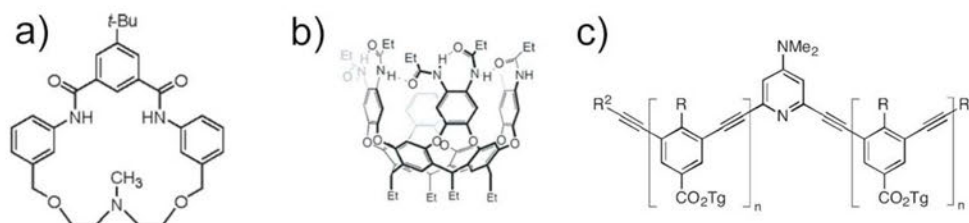
## 6. REACTIVITY OF CONFINED INTERMEDIATES AND MOLECULAR SIEVING

The enhancement of reactivity between two substrates using host-guest chemistry has a very rich history under the auspices of

enzyme mimicry. In a few instances, it was found that the stabilization of reactive intermediates, as discussed above, provided a significant impetus for rate enhancement. For instance, the groups of Moore, Smith and Rebek found that they could accelerate the nucleophilic substitution of alkyl groups to modestly nucleophilic amines by multiple orders of magnitude (as high as 150,000 fold relative to control systems). Each group employed a slightly different strategy to effectively accomplish the same task: accelerate the Menshutkin reaction [46], an S<sub>N</sub>2 process that trivially involves the formation of a quaternary ammonium salt, usually by an alkyl halide, reacting with a tertiary amine.

The Smith group utilized [47, 48] a macrocyclic structure (Fig. 14a) containing a tertiary amine transversely located to meta substituted amide groups. This created a reactive pocket that was serendipitously ideal for the stabilization of dichloromethane. With the amide hydrogens coordinating to a single chloride atom acting as Lewis acids, and the tertiary amine positioned very favorably, the activated intermediate complex underwent S<sub>N</sub>2 substitutions at rates 4-5 orders of magnitude above background. [Clearly, S<sub>N</sub>2 reactions do not have intermediates; however, the process of a guest binding to the host produces a distinct molecular intermediate, it is this species to which is referred]. The Rebek group's focus, on the other hand, utilized a self-folding cavitand system [49] (Fig. 14b) capable of trapping the tertiary amine, quinuclidine, as a guest under solvophobic conditions. The reactivity enhancement in this system likely arises from a very favorable juxtaposition between a transiently forming cation on the guest quinuclidine nitrogen and periphery amide groups on the host; in other words, the host and guest act synergistically to enhance the rate of the Menshutkin reaction. In both of these instances, a stabilization and induced geometric positioning of the reactive intermediate by complexation with Lewis acids creates drastic rate enhancements. It is worth noting that it is not necessarily imperative that the intermediate be restrained or activated by Lewis acids in these host-guest systems and that merely increasing local concentration is sufficient for rate enhancement. For instance, the Moore group's approach was to utilize





**Fig. (14).** The three Menshutkin reactors above, each enhance the reactivity of alkylhalides with tertiary amines. Macrocycle **a**) utilizes the isophthalamide NH groups as Lewis acids and the distal tertiary amine as the nucleophile. Cavitand **b**) utilizes its ethyl-amides to solvophobically capture tertiary-amines from a quinuclidine (not shown). These ethyl-amides are also believed to play a role in the stabilization of the leaving group just like macrocycle **a**). Foldamer **c**) uses its extended phenylene-ethylene subunits and pyridine's tertiary amine to form a discrete bundle that provides for a more optimal environment for the reaction and a means of excluding guests by molecular sieving.

a pyridine moiety as the reactive nitrogen placed within a phenylene ethylene oligomer [50-52] (Fig. **14c**). These oligomers adopt a conformation akin to a helix with an open, hydrophobic center by dint of a solvophobic conformational transition. This structure-function relationship was made clear by the obvious rate enhancements of methylation in solvents of differing polarity. For instance, in pyridine functionalized foldamers of identical length, rate enhancements of methylation we found to be 400 fold greater with methyl-iodine in acetonitrile than chloroform, with the authors ultimately speculating that the reactivity is related to solvophobicity and the foldamer's unique hydrophobic core accommodating the methylating agents. In follow up work, it was made further clear that the conditions necessary do indeed have to satisfy an induced fit model with the foldamer architecture, thereby making the foldamer approach substrate specific - in other words, it does not merely produce a hydrophobic pocket that will satisfy the conditions necessary to perform any Menshutkin-like reaction, but behaves as a molecular sieve (50, 51) - not surprisingly an observation made by all three groups with each of their systems.

## 7. CONCLUSION

The chemistry within confined spaces, be they engineered or natural, produces some fascinating phenomena. In the short-term future, it appears the field is moving more toward solid-state and naturally porous systems; in particular, catalysis and reactivity within porous solids will likely dominate the landscape. From the naturally occurring host-guest stabilized pigment Ultramarine to the very synthetic square cages of Fujita and co-workers, it is obviated that the chemistry within these small spaces does not reflect the chemistry in a flask. Unfortunately, this review is unable to do justice to the huge mountain of equally compelling examples in vesicles [53], micelles [54], dendrimers [54-57], cyclodextrins [58] and the vast number of other cage and macrocyclic structures [14]. Though, through analysis, their behavior seems to clearly spell out the simple fact: while we can describe the chemistry of these systems in classical kinetic and thermodynamic terms, as researchers, we are often surprised by how drastically those terms differ from what occurs in bulk solution. It illustrates just how far "beyond the molecule" supramolecular chemistry (*I*) truly can be.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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