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THESIS TITLE:

SUPRAMOLECULAR CATALYSIS IN CONFINED NANO-SPACE

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INTRODUCTION

Catalysis

Catalysis plays a crucial role in chemical reactions and is at the heart of innumerable synthetic procedures, ranging from academia to research centers to chemical companies. By using catalytic reagents, one can lower the temperature of a reaction, reduce reagent-based waste, and improve the selectivity of a response, thus avoiding unpleasant side effects, resulting in a green invention. One of the most important concepts in green science is the structure and creation of the optimal catalyst. Reactant reagents (as specific as possible given the circumstances) are better than stoichiometric reagents, according to green science guidelines. Stoichiometric reagents are used in large quantities and only work once, whereas catalytic reagents are used in small quantities and can carry out a single reaction several times. The foundation of a large number of green scientific standards is to work more like nature. Nature has unmistakably shown us how to use microbes and enzymes to carry out environmentally favorable activities.

A variety of things such as pharmaceuticals, fine synthetics, polymers, textiles, fuels, paints, oils, and a slew of other value-added items required by humans would not be conceivable without catalyst. [1]

Catalyst

In general, a catalyst can accelerate a reaction in two ways: (i) opening a new mechanistic path that would not be possible in the absence of the catalyst, with a lower activation barrier than the uncatalyzed reaction (Fig. 1a); and (ii) lowering the activation barrier of the same mechanistic path of the uncatalyzed reaction by binding the transition state more strongly than the substrate (Fig. 1b)

Most of the supramolecular catalysts as well as several enzymes adopt the second strategy. [2]

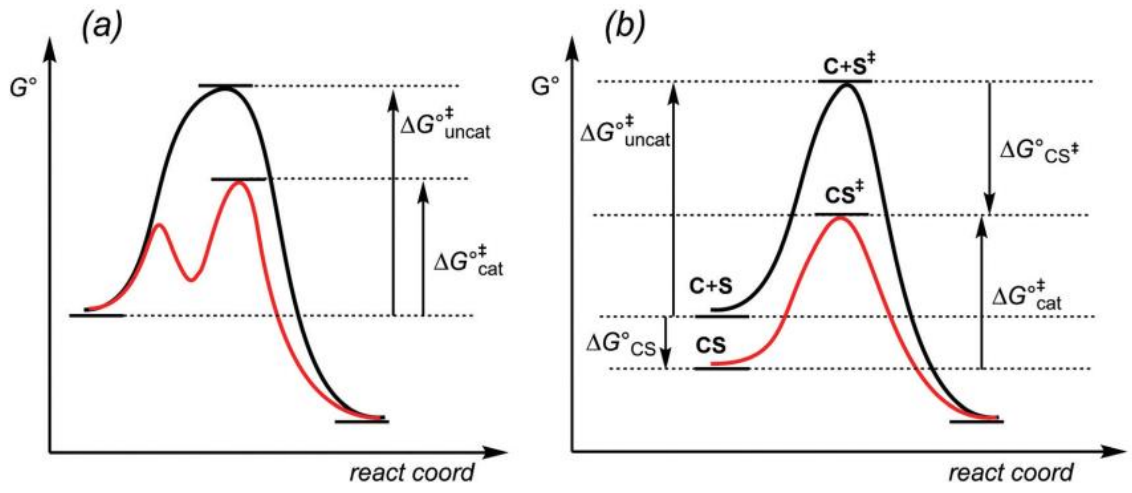


Figure 1: Two possible catalytic modalities: (a) the catalyst allows a new mechanistic path with a lower activation barrier, (b) the reaction mechanism remains the same but the catalyst binds the transition state more strongly than the initial state, lowering the activation barrier. Free energy variations are referred to 1 M standard states.

Types of catalysis

Among the three major types of catalysis, homogeneous, heterogeneous, and enzyme-based catalysis, enzyme-based catalysis is the most efficient and environmentally friendly. Both homogeneous and heterogeneous catalysis have their own set of benefits and drawbacks, necessitating the development of a new synergist framework that is dynamic like homogeneous catalysis and effectively recoverable like heterogeneous catalysts. The topics of interest of both homogeneous and heterogeneous catalytic frameworks have been combined in nano-catalysts.

The nano catalytic framework allows for faster, more precise chemical conversions with higher yields, as well as easier catalyst separation and recovery. The ability to recover a catalyst from its framework is one of the most important properties of any catalyst before it can be used in industrial green synthesis processes.

The interaction between reactants and catalysts increases dramatically at the nanoscale (this is near to homogeneous catalysis). Because of its insolubility in reactive solvents, the catalyst is heterogeneous and so can be successfully isolated from the reaction mixture (this is near to heterogeneous catalysis).

Nano catalysis

One of the first applications of nanoparticles was catalysis. In recent decades, several components and materials such as aluminum, iron, titanium dioxide, and silica have all been used as nanoscale

catalysts. In any event, the proper explanation of its massive synergist behavior manifested by NPs notwithstanding everything has yet to be fully appreciated. The large surface area of nanoparticles has a clear positive effect on reaction rate and may also be a useful explanation of its reactant mobility. The reactant movement of a material can be influenced by the structure and shape-dependent features of any substance at the nanoscale. In terms of synthesis, shape, and size, nano catalysts have been calibrated to obtain higher selectivity. The question here is how the physical qualities of nanoparticles influence their reactant properties, and how manufacturing boundaries can affect those physical properties.

A researcher can build and develop nano catalysts that are extremely dynamic, deeply specific, and extremely tough if they have a deeper understanding of them. Every one of these topics of interest will enable modern synthetic reactions to become more asset efficient, spend less energy, and produce less waste, all of which will assist to mitigate the environmental impact of our reliance on synthesis. Nanoparticles are often regarded as the most important modern catalyst, with uses ranging from chemical manufacture to energy transformation and storage. The essential distinction between homogeneous, heterogeneous, and nano catalysts is shown in Figure 2.

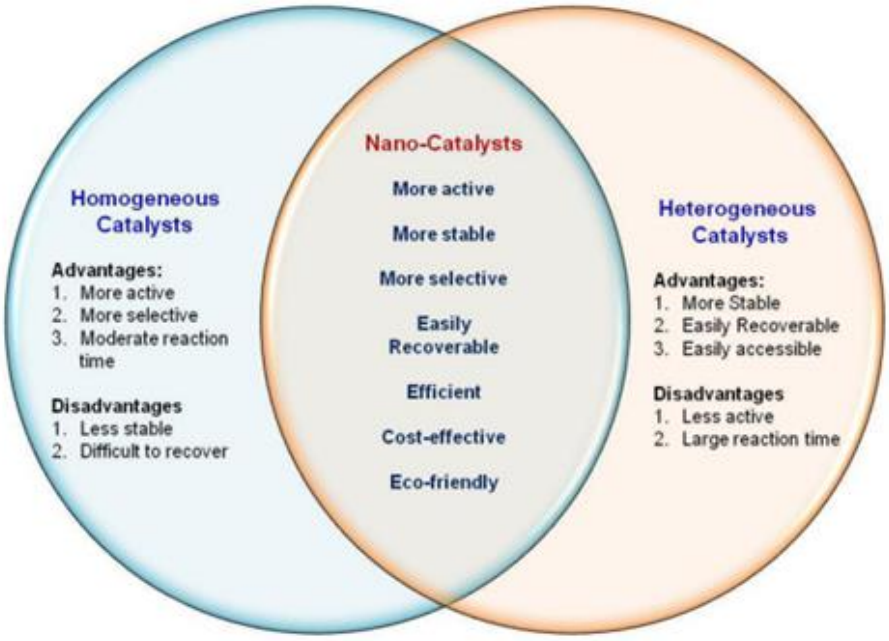


Figure 2: The difference between homogenous, heterogeneous and nano-catalysts

The concept behind nano catalysis may be understood by considering the effect of nanoparticles' characteristic properties on catalytic reaction. Characteristic properties of nanomaterials that have a significant impact on their synergist action can be classified as (i) amounts that are directly related to bond length, for example, the density, lattice parameter and binding energy; (ii) quantities that rely on cohesive energy; (iii) characteristics that vary with the density of binding energy; and (iv) properties resulting from the combined impact of density of atomic cohesive energy and binding energy.

The presence of an interatomic interface causes the performance of materials or a group of atoms to differ from that of a contained particle. The ability to control the properties of a nano catalyst in comparison to its bulk counterpart is enhanced by changing the relative quantity of the under constituted surface atoms. As a result, in chemical and physical demonstrations, contributions from

under-composed atoms and contributions from the interatomic interface might be the starting point for overcoming any difficulties between isolated atoms and bulk materials. In terms of bond unwinding and its effects on bond vitality, the effect of atomic coordination decrease is enormous, and it consistently brings together the exhibition of a surface, a nano-catalyst, and an amorphous state. [3]

Enzymes

Enzymes, nature's catalysts, have long inspired scientists working in the subject of catalysis. In order to impose high selectivity and activity, these systems often include numerous functionalities inside their catalytically relevant cavity. Despite the fact that the working principles of enzymes are still debated, improvements in transition state theory and computer simulations have enabled the formulation of broad principles that can be translated into synthetic systems. For a variety of reasons, maintaining a well-defined constrained region (second coordination sphere) surrounding the active center is critical in this scenario. First, it ensures that the substrate(s) and the catalyst active site are in close proximity, hence increasing overall reaction rates simply by pre-organization. Second, residues near the active site can influence substrate binding, allowing for substrate selectivity.

Finally, enzymes can pre-organize the substrate into a higher-energy conformation, increasing reactivity. Above all, according to transition state theory, the transition state's binding should be stronger than the substrate's, resulting in faster rates. In a similar vein, the cage can destabilize intermediates in order to minimize transition state barriers. These results show how the second

coordination sphere surrounding an enzyme's active site contributes to improved catalytic performance in general. Inspired by these natural instances, there is growing interest in concepts that enable the synthesis of well-defined second coordination spheres for the production of enzyme mimics. In addition, the use of catalysis in confined spaces to take advantage of the second coordination sphere effects has gotten a lot of interest. [4]

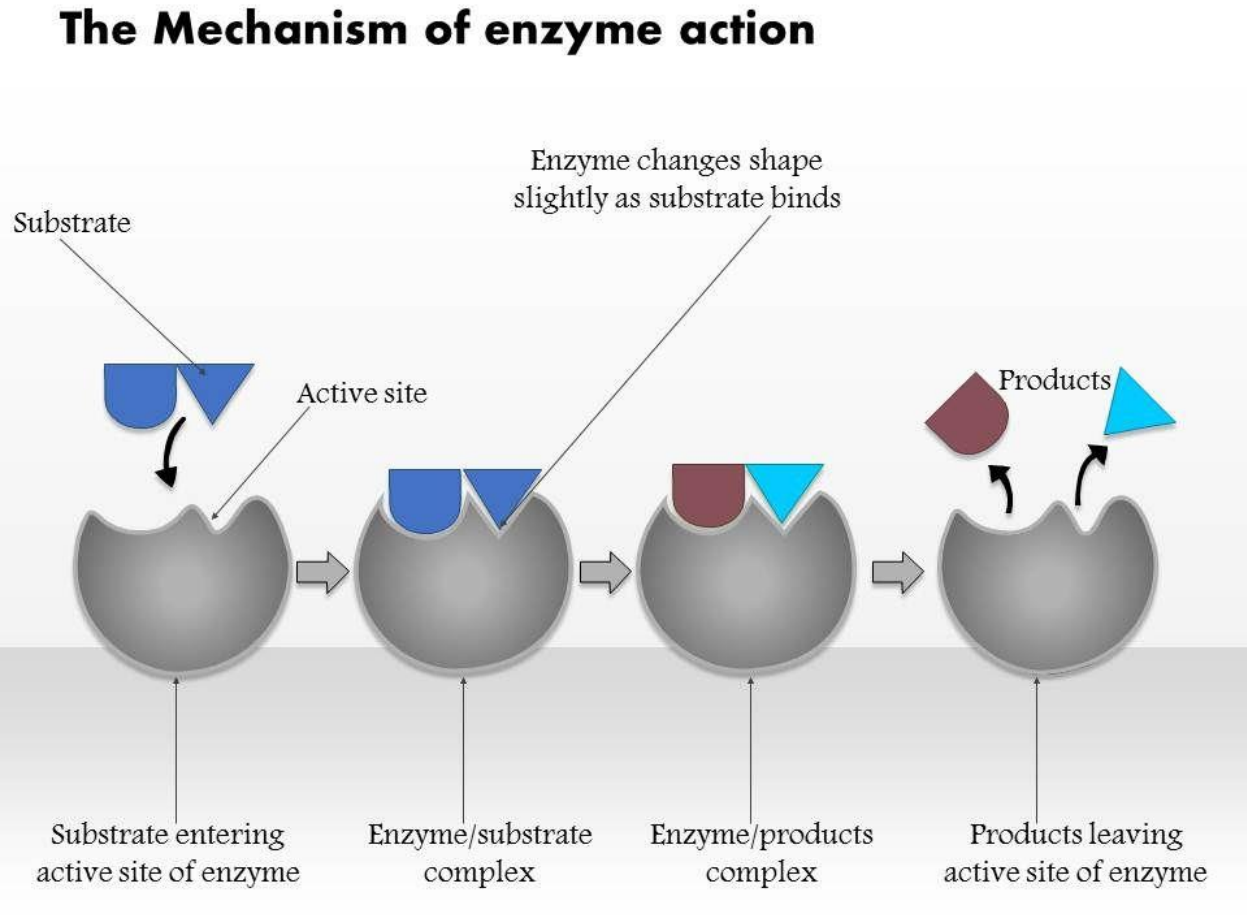


Figure 3: enzyme catalytic mechanism

Supramolecular catalysis

After a lengthy period of stable expansion, supramolecular catalysis has experienced exponential growth in the recent two decades. In summary, one could argue that the amount of attention paid to supramolecular phenomena and catalytic processes has skyrocketed in the field of chemistry. Supramolecular chemistry is presently used in a variety of fields, including data storage, sensor technology, light-to-energy conversion, materials science, selective complexation for extraction, medicine and catalysis.

Improvements in established commercial reactions, the invention of new reaction pathways, and the exponential growth of organo-catalysis have all made catalysis a keystone in chemical sciences. The rise of supramolecular catalysis can be attributed in part to the refocusing or renaming of research activities, as happened in the 1980s with supramolecular chemistry, which now encompasses selective complexation of metal ions and anions, host–guest chemistry, crown ether chemistry, self-assembly phenomena, encapsulation processes, self-recognition phenomena, and so on. Activities in the field of coordination chemistry are now referred to as supramolecular.

The observation and knowledge of enzyme catalysis provided a lot of inspiration for the creation of supramolecular catalytic systems. Synthetic models, on the other hand, usually only have one or a few of the properties seen in biologically enzymatic systems. Supramolecular enzyme model systems, on the other hand, are smaller and structurally simpler than enzymes. The fact that synthetic systems are simpler than biological systems does not limit the depth of topics that can be investigated; rather, it is possible to evaluate the relative relevance of diverse components that contribute to catalysis using these simpler systems.

Another advantage of using supramolecular models to research catalysis is that the compounds can be synthesized to investigate a specific feature. In the biological domain of catalysis, identifying a specific component responsible for an enzyme's catalytic effectiveness is a monumental task. Supramolecular systems might be thought of as current physical organic chemistry's newest instrument. The use of supramolecular model systems to research catalytic processes seeks to explain the observed rate enhancement in terms of structure and mechanism.

In some situations, the model systems may even provide a simplified simulation of an enzyme's action, allowing for a better understanding of the various mechanisms by which enzymes reach spectacular reaction rate accelerations and turnover numbers. Catalysis is a long-proposed use of supramolecular chemistry, and one of the ultimate goals of self-assembly research is to create supramolecular systems capable of emulating the catalytic capacity of real enzymes.

Supramolecular chemists have handled these difficult tasks from several angles. On the one hand, a number of model systems have been developed that use binding energy to catalyze reactions. Within this framework, two types of systems can be distinguished: (a) molecular receptors with a catalytic site close to a binding site that has been designed to bind selectively the reactant, and (b) molecular receptors that promote the reaction of two simultaneously complexed reactants, forming a multimolecular (ternary or higher order) complex held together by weak and reversible interactions.

The observed rate acceleration may be a simple effect due to an increase in the effective local concentration when two reacting functions are brought close together, such as through binding to a template/receptor or insertion into a molecular vessel. The effective molarity EM $= k_{intra}/k_{inter}$ can be used to calculate the entropic advantage of a "intramolecular" reaction over a

"intermolecular" reaction. In a system designed to bring functional groups together in close proximity, the EM value can tell us how catalytic performance relates to structure.

Although Page and Jenks estimated that entropy changes in solution have an effective concentration of about 6×10^8 M, and high EMs have been measured for simple cyclization reactions, synthetic supramolecular catalytic systems achieve rate accelerations that are tiny in comparison to enzymes (EM <10 M). Because the molecules of the bimolecular or ternary complexes are not tightly bonded, there is residual entropy in the complex due to vibrations, this mode of catalysis for two-substrate reactions has a low efficiency. When the molecules in the Transition state are linked, there is still a significant loss of entropy that is not mitigated by the binding energy.

The ability of enzymes to bind and thus stabilize the transition state and intermediates for a specific process is an important property. As a result, the challenge of catalysis can be characterized in terms of the recognition of transition states at the molecular level. Many supramolecular models fail to simulate enzyme turnover capabilities due to inhibition by firmly bound products.

Catalysis has been achieved not only by placing converging binding sites in such a way that reactant molecules are brought together in close proximity (entropy of activation is reduced or partially compensated by the favorable binding energy), but also by stabilization of the intermediate or transition state in more sophisticated synthetic hosts. Even from these increasingly complex structures, however, only a few effective supramolecular catalysts have developed.

According to Sanders, supramolecular chemists have gone too far in the direction of rigidity and preorganization due to their fear of entropy. Rigid structures with a small mismatch to the Transition state aren't going to work as catalysts. Furthermore, the employment of large and stiff

molecular components in catalytic supramolecular systems makes the sub-angström changes required for optimal Transition state stabilization difficult to obtain. To our knowledge, however, this argument has not yet been proven, owing to the arduous design and synthesis work required.

The creation of a self-assembled catalyst in which all recognition motifs are kinetically labile, both between catalyst subunits and between substrate and catalyst, should give a viable approximation to the issue of catalytic supramolecular system stiffness. When shifting from a non-rigid and conformationally unrestricted complex to the fixed geometry of the transition state, a flexible supramolecular system achieves a better fit to the transition state at the expense of a large loss of vibrational and rotational entropy. Desolvation of the reactive polar groups is another way for enzymes to achieve rate acceleration. The desolvation of functional groups occurs with the insertion of reactants into the active site's catalytic apparatus. This is another way of looking at the selective stabilization of the transition state in terms of a "specific" solvation of the reactants by the enzyme residues of the active site, which replaces the random solvation of the solvent molecules and the associated enthalpic and entropic cost of their reorganization in the transition state. [5]

Molecular capsule

Self-assembled molecular capsules were a big step forward in the development of supramolecular catalysts with enhanced characteristics and functions in this regard.

Secondary interactions cause the spontaneous and orderly aggregation of molecular components, resulting in self-assembled capsules.

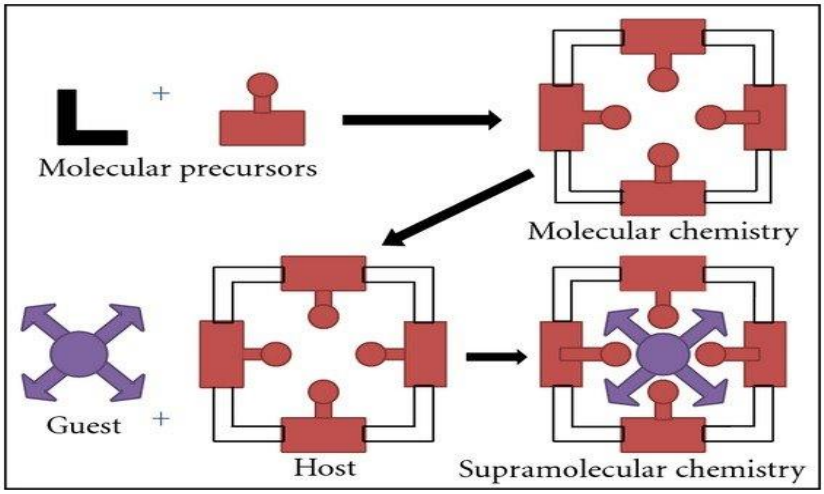


Figure 4: Lehn's comparison of the scopes of molecular and supramolecular chemistry. [6]

The nanoconfined area inside a self-assembled molecular capsule, similar to an enzyme pocket, allows the production of a microenvironment with different physical and chemical properties in comparison to the surrounding medium. In fact, confining the reactants inside an molecular capsule reduces their molecular mobility, resulting in a different stereo- and regiochemical outcome of the reaction than under bulk conditions. When reactants are housed inside an molecular capsule, the proximity effect between them, as well as the stability of intermediates and transition states, causes a reaction acceleration, similar to natural systems.

Rebek and Kang revealed a self-assembled hydrogen-bonded structure, the so-called "softball," in which two glycoluril units were sealed by 16 hydrogen bonds in a groundbreaking work. [7]

The "softball" which is made up of two multiring structures with a bridging bicyclic centerpiece and two glycoluril units on each extremities of the multiring, providing the essential rigidity,

curvature, and functional groups for capsule assembly (Fig. 5). Following the formation of a seam of sixteen hydrogen bonds, the self-complementary glycoluril-based building blocks dimerize in solution to form capsule B. "Softball" B is a closed-shell capsule with a roughly spherical form and an internal capacity of approximately 400 $Å^3$.

The "softball" can contain two distinct guests at the same time, for example, one molecule of deuterated benzene and one molecule of deuterated monofluorobenezene. Guests are encapsulated by the opening of two different flaps of the "softball," followed by the guest's exit when the incoming guest approaches, i.e. the gating mechanism

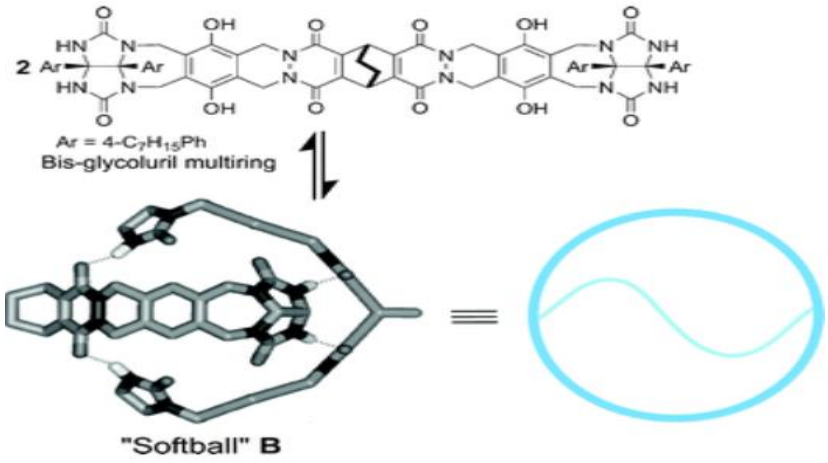


Figure 5: Structure of the monomer and the self-assembled dimer called "softball"B

- The Diels–Alder reaction between p-quinone and cyclohexadiene was catalyzed by the pseudospherical softball. The substrates inside the supramolecular architecture were stabilized by p–p stacking interactions in this case. The Diels–Alder reaction

was accelerated 170-fold relative to the bulk, yielding the encapsulated adduct [B 13a]

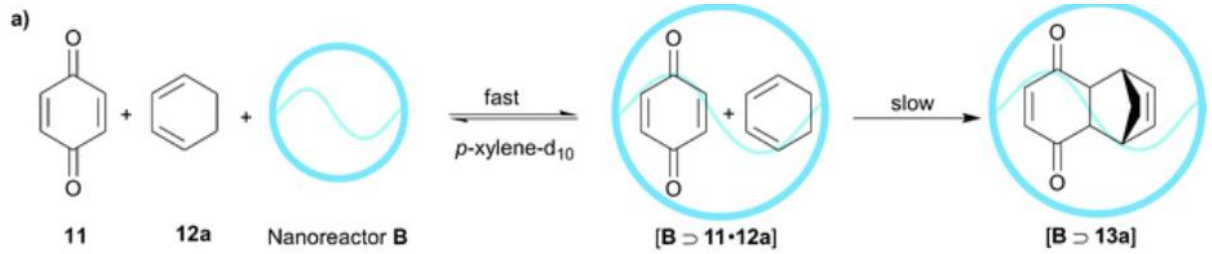


Fig. (6a) Diels–Alder reaction between p-benzoquinone **11** and cyclohexadiene**12a** within nanoreactor **B**.(softball)

- The Diels–Alder reaction between *p*-benzoquinone and the thiophene dioxide derivative within nanoreactor **B**, Despite the fact that nanoreactor B speeds up the encapsulating reaction, no real catalytic behavior was seen due to 13a product inhibition. When thiophene dioxide derivative 12b is employed as the diene, product inhibition is reduced (Fig.5b). This is due to the fact that the Diels–Alder product of the thiophene dioxide derivative 13b has a lower affinity for nanoreactor B than two equivalents of the p-benzoquinone 11, namely [B(11)2]. When two quinones11 are enclosed within B, one of them is periodically replaced by thiophene dioxide 12b, resulting in the encapsulated Diels–Alder product 13b. [8]

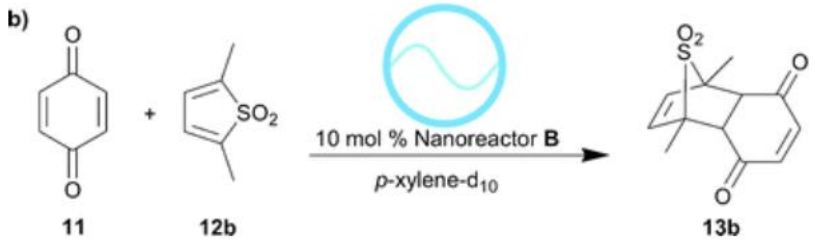


Fig.(6b) Catalytic Diels–Alder reaction between p-benzoquinone 11 and the thiophene dioxide derivative 12b within nanoreactor B.

Advantages of Catalysis inside Host structures

Conceptually, the main advantages of performing catalysis inside molecular capsules can be divided into three categories (Fig.7):

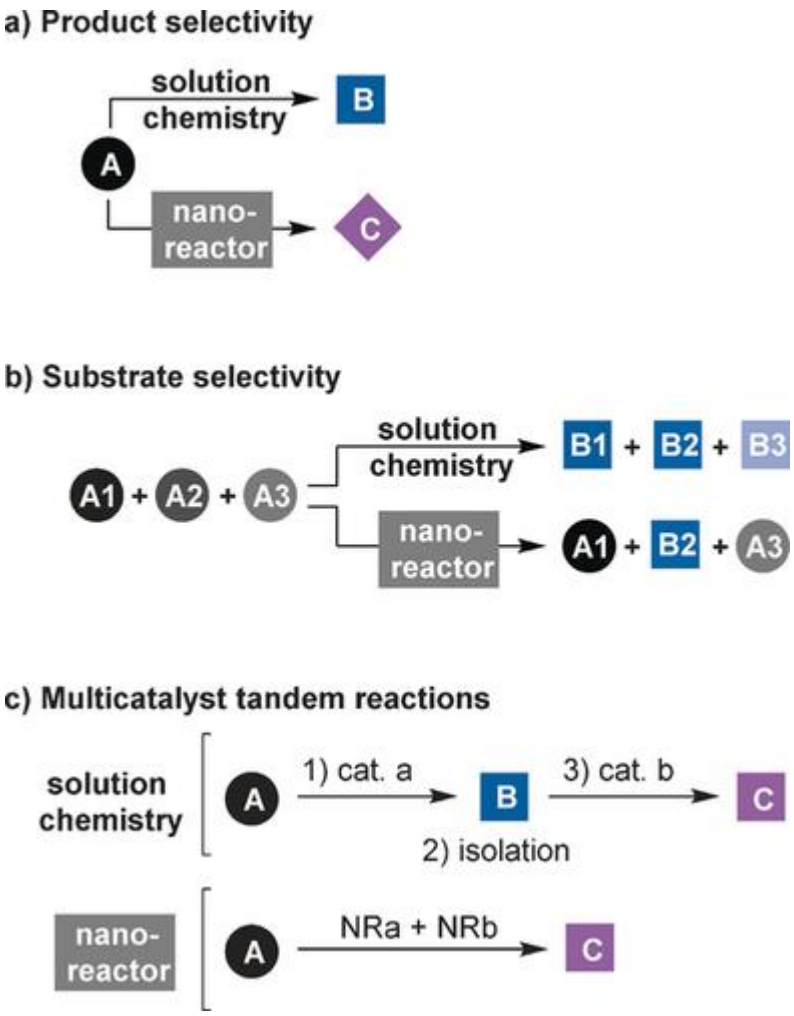


Figure 7: Advantages of molecular capsules in catalysis

a) Product selectivity: In this situation, the product created in a nanoreactor differs from the one formed in a bulk solvent. Alternative reaction pathways are accelerated due to (noncovalent) interactions between the encapsulated substrate and the host environment.

The products generated may be stereoisomers (diastereoisomers, enantiomers) or constitutional isomers of their counterparts in a solution experiment.

b) Substrate selectivity: Because of the limited environment within a molecular host, only substrates that fit the cavity space are preferentially transformed in the presence of additional substrates with similar reactivity but differing shape and/or size. In solution, such selectivity cannot be observed. In fact, size-selective conversions provide strong evidence that the reaction is occurring within the host system rather than outside in solution or on the host's outer surface.

c) Multicatalyst tandem reactions: It is typical in solution chemistry to build up the reaction mixture and purify the result after each separate synthetic step. Combining many catalytic cycles in one pot would be favorable from an economic standpoint, as it would reduce waste output and boost efficiency. Nature efficiently employs multienzymatic systems to produce complex compounds without the need for solvent changes or workups. However, due to the required compatibility of all catalysts, reagents, and intermediates generated throughout the reaction sequence, developing such multicatalytic tandem reactions in the laboratory remains extremely difficult. Furthermore, to avoid the creation of side products, each step of the tandem sequence must follow the proper order. In other words, the catalysts used must have high substrate selectivities.

Resorcin[4]arene

Amazing supramolecular designs capable of mimicking the mode of operation of natural enzymes have been constructed using the basic principles of supramolecular chemistry and the imagination of chemists. Self-assembled capsules, in particular, have gained popularity, owing to their ease of production. In fact, they spontaneously form in solution from smaller subunits, requiring less synthetic effort than traditional molecular catalysts. The self-assembled capsules can display essential working characteristics of natural enzymes, such as (i) the presence of a cavity capable of confining the reactants; (ii) substrate and product selectivity; and (iii) the stabilization of either the transition states or the reaction intermediates. [9]

Among self-assembled systems, the resorcin[4]arene-based hexameric capsule C is one of the most studied systems in supramolecular catalysis. For the first time, Atwood demonstrated that in the solid state, six resorcin[4]arene1 molecules and eight water molecules form a cube-shaped capsule sealed by 60 (O–HO) H-bonds.

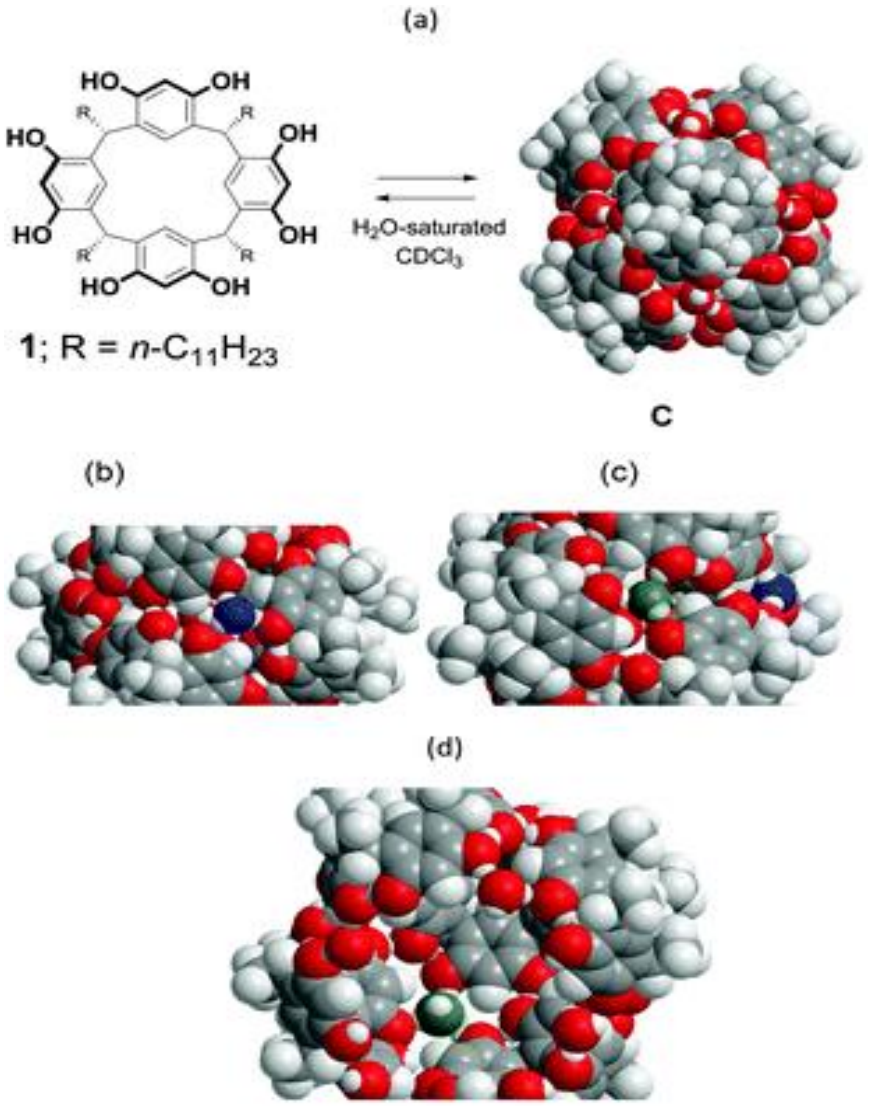


Fig.8 (a) Self-assembly of resorcin[4]arene 1 into hexameric resorcin[4]arene capsule C in a water-saturated CDCl3 solution. (b) Detailed view (external) of C in which one bridging-water molecule (in blue) saturates its H-bond-donating valences. Detailed views, external (c) and internal (d), of another bridging-water molecule (in green) with one free H-bond-donating valence.

The presence of an H-bond network involving eight bridging water molecules and six resorcin[4]arene molecules is clearly seen in the X-ray structure of C. The bridging-water molecules are situated in the cube's corners (Fig.8 1b–d), and each is involved in three different H-bonds (Fig. 8b–d). Four of these bridging-water molecules have completed their H-bond-

donating valences with neighboring resorcinol OH groups (Fig. 8b, in blue), but the other four molecules can only donate one H-bond (Fig. 8c and d, in green), leaving one free H-bond-donating valence. Cohen and coworkers demonstrated that the hexameric resorcin[4]arene capsule C self-assembles in solution. [10]

Many papers in the literature have highlighted the hexameric capsule's potential as a supramolecular catalyst for organic processes. Capsule C is easily created in wet apolar solvents such as chloroform and benzene and has an internal volume of 1375 $Å^3$ that may host approximately 6–8 chloroform or benzene molecules. According to evidence from the literature, capsule C can function as both a nano-reactor and a catalyst. In the first example, the catalyst and substrates are recognized and confined inside the nano-container C, resulting in an increase in reaction rate due to an overconcentration effect, substrate preorganization, and the stability of intermediates and/or transition states.

In the second situation, capsule C can operate as a catalyst by utilizing its capacity to stabilize cationic intermediates and transition states via cation–interactions, as well as its mild phenol-based Brønsted acidity with a pKa value of approximately 5.5–6.0. (measured in water-saturated CDCl3 relative to the reported aniline pKa value in water). [11]

The hexameric resorcin[4]arene capsule's inside resembles an enzyme pocket, with enough capacity to hold reagents and promote bimolecular reactions. When it comes to reactions in the bulk medium, the over concentration effect might cause a rate acceleration. The reactions between molecules crammed into the small space inside the resorcin[4]arene capsule frequently produce

unusual regiochemical and stereochemical results. As a result, the traditional reactivity restrictions that apply in a bulk media are frequently violated. The resorcin[4]arene capsule, mimicking a natural enzyme, can work selectively on the structural properties of reagents and products, resulting in a regio-, enantio-, and diastereoselective reaction. The hexameric capsule has been employed as a cyclase mimic to catalyze terpene cyclisation because of these features. In these circumstances, the capsule pocket chemically quenches the carbo cationic intermediates and stabilizes them via cation interactions. The water molecules in the capsule have a dual catalytic function: (1) they can operate as hydrogen-bonding donor groups in catalysis, and (2) they can be critical in Brønsted acid catalysis. Finally, in the presence of competing inhibitors with high affinities for the hexameric capsule's interior cavity, the catalytic activity of the hexameric capsule can be regulated, much as it can in natural systems. [12]

Encapsulation

Researchers interested to the concept of duplicating the catalytic qualities of an enzyme pocket have been inspired by the physicochemical properties of C. In fact, like an enzyme active site, the inner cavity of C can preferentially host substrates. They are able to react as a result of the confinement effect, resulting in the creation of intermediates and transition states that are stabilized by interactions with the capsule.

For the first time in 2001, Rebek and Shivanyuk reported NMR spectroscopy evidence of ammonium guests encapsulation inside the hexameric capsule in solution. The authors discovered that cation–p interactions between cationic guests and the p-electron-rich cavity of C are critical

for the stability of the complex +NR4@ C , in solution. It was convincingly demonstrated in this report that the internal volume of C was several times that of the tetrabutylammonium cation, resulting in the simultaneous encapsulation of both a cation and an anion within C. While ion-pair encapsulation was demonstrated with I and BF4 as counter anions of $^{+}N(nBu)_4$, no tetra-butylammonium cation complexes were detected with big tosylate and B(Ph)4 counter anions.

In a subsequent study, Cohen and Avram demonstrated that the presence of the cationic guest was not required for the synthesis of C in solution. In reality, they discovered that the capsule self-assembled in water saturated CHCl3(or CDCl3) or wet benzene using diffusion NMR spectroscopy in solution; in these circumstances, the empty space inside C was filled with solvent molecules. Surprisingly, alcohol molecules on the seam of the hydrogen bonds can replace water molecules at the corners of the hexameric capsule. 6/8 H2O molecules can be substituted by a ()-2-ethylhexanolinanhexameric structure sealed by 50 hydrogen-bonding connections, which is interesting.

Tiefenbacher's group made another breakthrough when they discovered that C behaved like a weak Brønsted acid with a pKa value of around 5.5–6.0.

The authors calculated this range of values by using the capsule C to explore the protonation equilibria of amines of decreasing basicity and integrating appropriate 1HNMR data to determine the percentage of protonated amine. Intriguingly, adding pyridine (pKa= 5.2) to a water saturated C solution resulted in 53 percent protonation. The hexameric capsule C has a pKa value of 5.6, which was derived using this value and the pKa of pyridine. The degree of protonation was reduced to 23 percent with aniline (p Ka= 4.6), resulting in a pKa value of 5.9 for C. [13]

Evolution of the Resorcin[4]arene in catalysis

Many papers in the field of supramolecular catalysis have proven that the Resorcin[4]arene hexameric capsule can catalyze chemical processes in the previous decade.

Some of the examples are listed below:

I. Hydrolysis and Hydration Reactions

Hydrolysis of acetals to its corresponding acetaldehyde with up to 85% yield in 1 h. The capsule acts as a supramolecular catalyst by the encapsulation of the substrate, to prove that the reaction occurred inside the capsule a control experiments were carried out in which a competitive cationic guest was used observing that no chemical transformation occurred due to the affinity of the guest that occupy the cavity. Furthermore, the capsule was observed to be size selective using a range of different lengths of acetals showing high selectivity to shorter ones. [14]

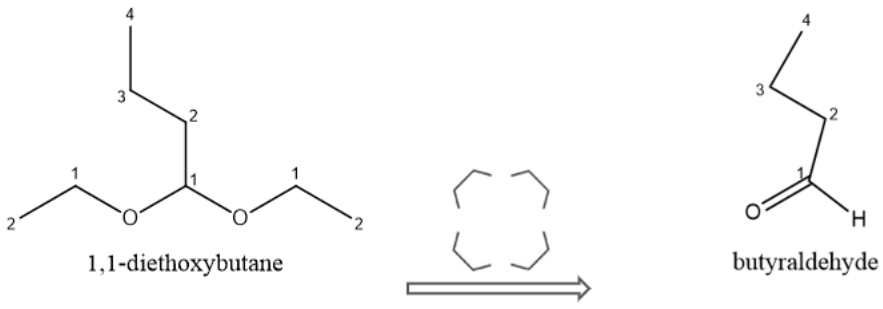


Figure 9(a): Hydrolysis of acetals to acetaldehyde mediated by C

Hydration of isonitrile was examined, the neutral substrate was encapsulated and converted to its corresponding formamides due to water addition. In the same previous way, a competitive cationic guest was used as a control experiment which proved the efficiency of the capsule. The catalytic activity of the capsule is due to its mild acidity and the stabilization effect. [15]

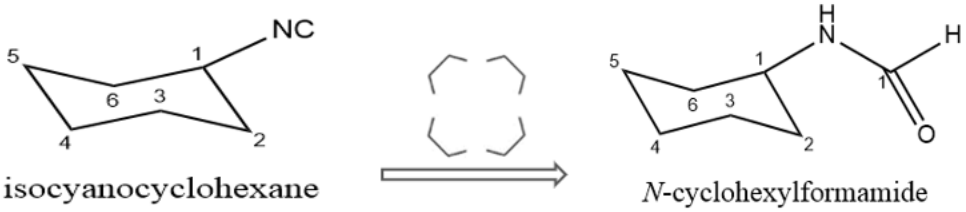


Figure 9(b): Hydration of isonitrile mediated by C

In the hydration of alkynes, the capsule catalyzed the reaction and convert alkynes to its corresponding ketones only after the addition of a strong Brønsted acid i.e. HBF4 & HCL with a timeframe of 1 h, while no reaction was observed when using the Brønsted acid alone. Likewise encapsulating the capsule with a tetraalkyl ammonium guest inhibited the catalytic activity of the capsule and no hydration reaction occurred. [16]

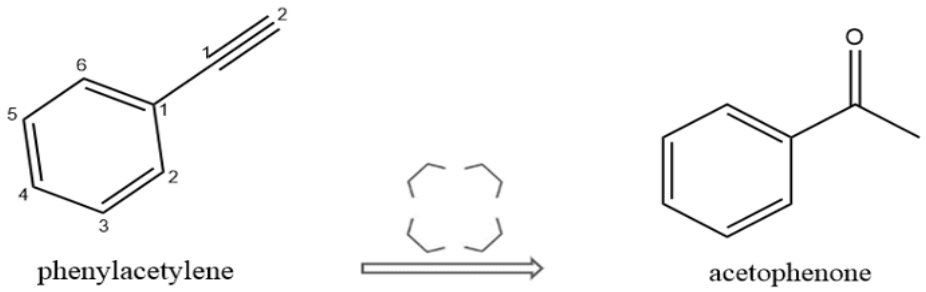


Figure 9(c): Hydration of Alkynes to form Ketones mediated by C

II. C─C Bond-Forming Reactions

The supramolecular catalytic ability of the self-assembly hexamer imparted by the electron rich cavity enabled c-c bond forming reactions like the cycloaddition of diazoacetate with electron poor alkenes forming pyrazole derivatives. To ascertain the reactivity of the diazoacetate in cycloaddition, the experiment was carried with acrolein in absence of the capsule showing a dramatic decrease in the product formation. In the same way filling the cavity with a cationic species inhibit the formation of the product. [17]

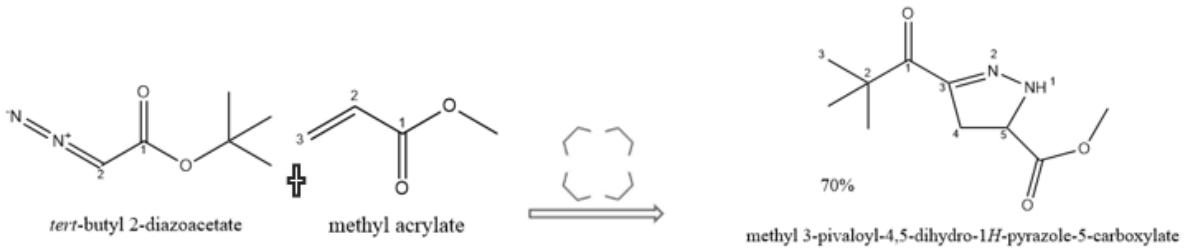


Figure 9(d): cycloaddition of diazoacetate with an alkene to form pyrazole mediated by C

III. C-heteroatom Bond-Forming Reactions

Other than the hydration reaction offered by isonitrile substrates, this substrates can also undergo C-heteroatom bond forming reactions by combining the isonitrile with a nucleophilic substrate like trimethylsilyl azide which should occur before the hydration process in order to avoid the formamides formation and to lead to the corresponding tetrazoles. To justify the catalytic activity of the capsule, several control experiments were performed. A Brønsted acid with comparable acidity of the capsule was used and the H bond bearing resorcinol similar to the capsule did not show any catalytic activity [18].

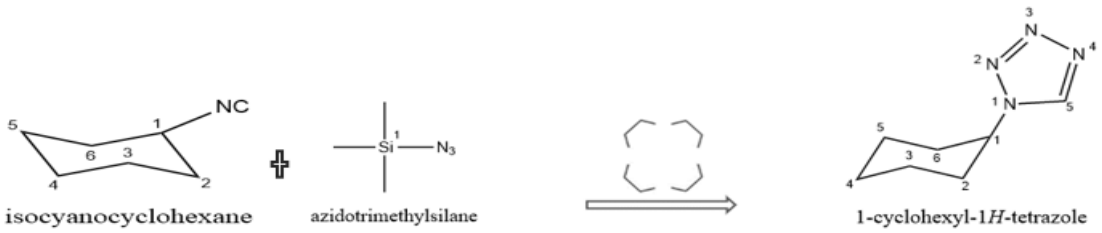


Figure 9(e): reaction of isonitrile with trimethylsilyl to form tetrazoles, mediated by C

IV. Cyclization Reactions

The weak acidity of the capsule and its ability to stabilize the carbonic intermediate enable the uptake of alcohols through H bonding this property help to catalyze the reaction and undergo intramolecular cyclization/hydroalkoxylation reactions following the encapsulation of the substrate, one of which are the unsaturated alcohols to its corresponding cyclic compound by breaking the double bond through protonation and further alkoxylation of the carbocation intermediate formed.

Other set of substrates that bear moieties like OH and acetates that are sensitive to the presence of acid can catalyze the cyclization reaction like for instance acyclic terpenes to form cyclic product mimicking the enzyme action more interestingly it was found to be more selective than the enzyme catalyzed reaction. [19]

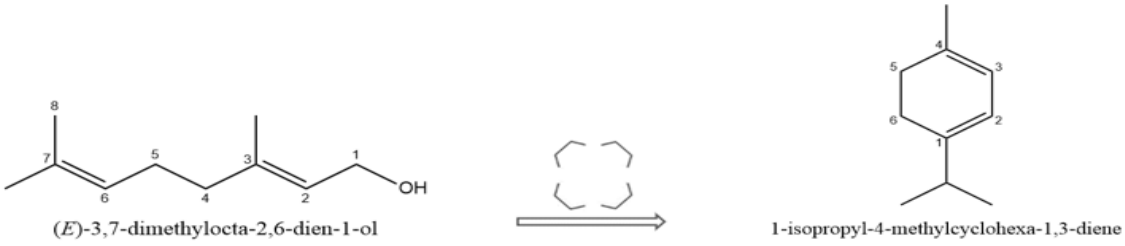


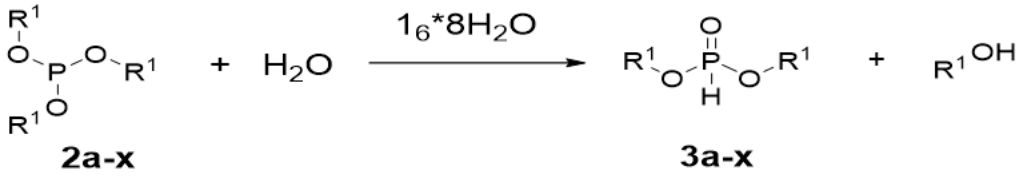
Figure 9(f): cyclization of acyclic terpenes, mediated by C

PURPOSE OF THE THESIS

The development of resorcin [4] arene as an organic supramolecular catalyst. The likelihood of responding by passing through a cationic transition state stabilized by the presence of the capsule is a common assumption among the examined substrates. Furthermore, nucleophilic compounds that could be encapsulated were employed to intercept this intermediate and attack the active site. Due to the fact that the resorcin [4] arene capsule catalyzes many reactions involving water addition for instance Alkynes and Isonitriles, we decided to investigate the phosphite to H-phosphonate hydrolysis reaction and to the fact that the organophosphorus compounds have a wide range of uses in medical and agricultural chemistry. Despite their importance there are few broad and effective ways for producing them. The methods known in the literature, the famous Michaelis–Arbuzov reaction based on the reaction of alkyl halides with trialkyl phosphites at high temperature obtaining a high yield product however, it has a significant drawbacks. In addition to the usage of hazardous alkyl halides, the simultaneous synthesis of an equivalent of low-boiling ethyl bromide is unavoidable, which can induce side reactions, reduce atom efficiency, and cause environmental issues. Discovering a method for the synthesis of phosphonates with less drastic conditions and high yield was a goal for many scientists, Wiemer, Mohanakrishnan, and Iranpoor's groups independently demonstrated ZnI2, ZnBr2, or PPh3/DDQ-mediated Michaelis–Arbuzov reactions of trivalent phosphorus esters with alcohols replacing the alkyl halides. These updated methods, however, are not without restrictions. The P(III) compounds used in the former method, for example, are not commercially available and require time-consuming preparation procedures; the latter methods, on the other hand, generally require anhydrous conditions and stoichiometric

amounts of activators, but are still limited to the more reactive benzyl and allylic alcohols. [20] Recently the groups of Qing Xu and Li-Biao Han has reported a new green alcohol version of the Michaelis–Arbuzov reaction for the formation of phosphonates via coupling of alcohol with phosphites catalyzed by n-Bu4NI. [21] Although the method is simpler and more environmental friendly compared to the conventional and modified Michaelis–Arbuzov reaction, the reaction time of 24 h and it's high temperature condition is still a limitation for large scale industrial production.

The purpose of this thesis is to elucidate the mechanism and scope of the conversion of phosphite to H-phosphonates in the presence of the hexameric resorcin[4]arene capsule. This reaction is known to be catalyzed by strong Brønsted acid and harsh conditions, but the mild conditions inside the cavity may offer new synthetic possibilities.

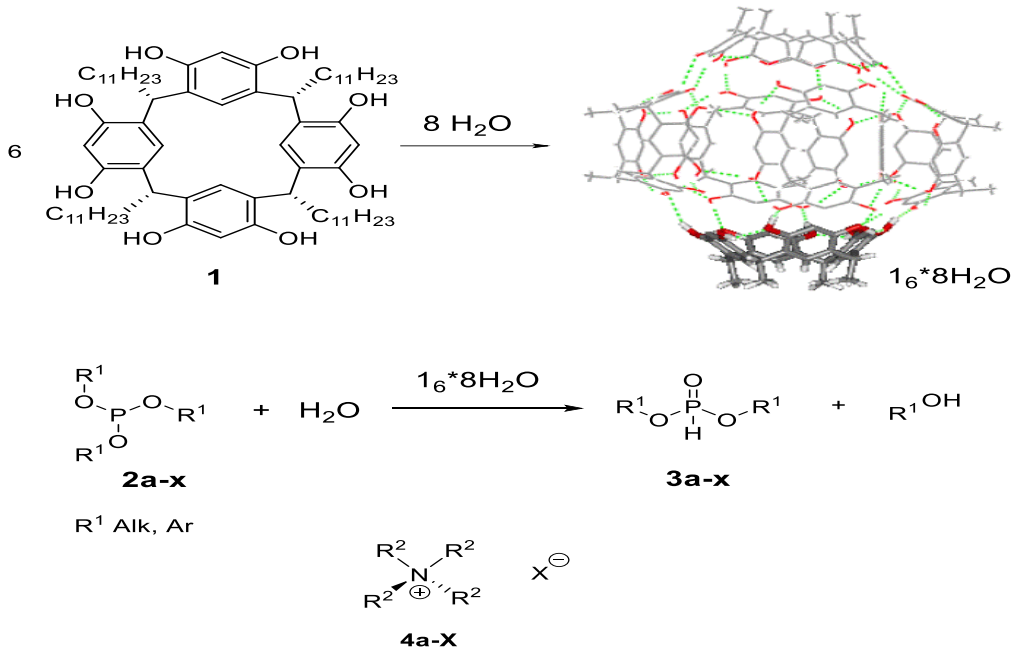


2a-x **3a-x**

RESULTS AND DISCUSSION

Recently we disclosed the high activation provided by $1_6 \cdot 8H_2O$ for a series of hydration reactions involving substrates like alkynes[22] and isonitriles[23] in which the supramolecular capsule stabilizes cationic intermediate protonated species thus accelerating the rate of the reactions. Herein we report about the supramolecular activation imparted by the resorcinarene hexameric capsule $1_6 \cdot 8H_2O$ in the phosphite reaction with water under Arbuzov conditions leading rapidly to the formation of the corresponding H-phosphonates and alcohols as side product.

Remarkably, the interaction with different tetraalkylammonium salts altered the catalytic activity, in some cases accelerating the reaction and in others completely inhibiting substrate conversion, as function of the size of the ammonium species and the nature of the counter-anion.



Scheme 1: Molecular structure of the hexameric resorcin[4]arene capsule $\mathbf{1}_6.(H_2O)_8$, representative phosphite **2a-x** hydrolysis to the corresponding H-phosphonate **3a-x** and alcohol and tetraalkylammonium cations **4a-x** as potential guests for the capsule.

Seeking for new classes of neutral compounds as suitable guests for the hexameric capsule, we investigated the addition of a tenfold excess of triethyl phosphite **2a** and diethyl phosphite **3a** to the capsule $1_6.(H_2O)_8$. By ^1H NMR it was observed that right after mixing, even though **2a** did not show the formation of new resonances attributed to encapsulated **2a**, **3a** showed clearly to be a suitable guest for the capsule (Figure 10) observing a series of new resonances attributed to the encapsulated guest at 6.56 and 4.80 ppm for the P-H hydrogen atom of the encapsulated **3a** ($\Delta\delta$= -1.16 ppm), at 2.6 ppm for the encapsulated methylene units of 3a ($\Delta\delta$= -1.60 ppm), and at -0.41 ppm for the methyl resonances of the encapsulated **3a** that experience the largest shielding effect ($\Delta\delta$= -1.78 ppm) imparted by the aromatic inner surfaces of the cavity of the capsule. Moreover, with 10 equivalents of **3a** with respect to $1_6 \cdot 8H_2O$, the integration demonstrated that two molecules of **3a** were accommodated within each capsule by making titration of capsule with increasing amounts of 3a.

Pseudo 2D DOSY NMR spectrum further confirmed the encapsulation of **3a** within the capsule and NOESY spectrum showed exchange cross-peaks between XXX and the XXX for the free **3a**, together with some cross-peaks involving the resonances XX of encapsulated **3a** and the XXX of the capsules, further confirming the hosting of the P compound within the cavity. In consideration of the variation of the resonances attributed to the OH residues of the capsule at about 9-10 ppm in the presence of **3a**, it is likely that the latter compound binds with the P=O moiety within the cavity acting as a H-bond donor with respect to the four dangling OH units that are known to adorn the inner cavity of the capsule. [24,25]

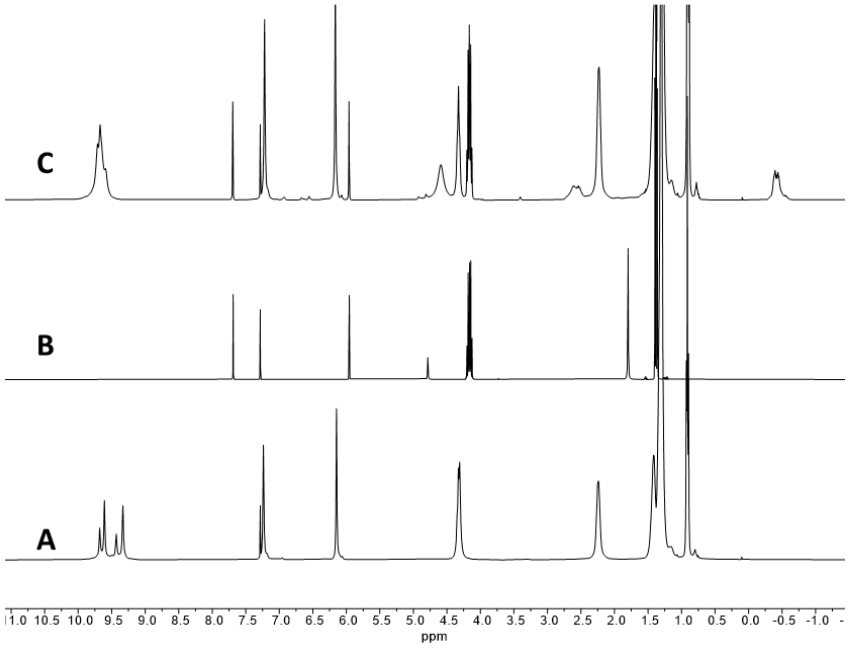


Figure 10. ^{1}H NMR spectra in chloroform-d of a) **1**$_6$.$(H_2O)_8$ 5 mM; b) **3a** 50 mM; c) **3a** 50 mM and **1**$_6$.$(H_2O)_8$ 5 mM.

Same effect was observed considering the $^{31}P(^{1}H)$ spectra for **3a** in the presence of **1**$_6$.$(H_2O)_8$ leading to the formation of new broad resonances in the range 4.3-5.3 ppm attributed to encapsulated molecules of **3a** while the remaining excess of free **3a** in solution was clearly evidenced by the singlet at 7.31 ppm. Free and encapsulated **3a** showed distinct resonances confirming the slow in-out exchange of the phosphorous compound on the NMR timescale.

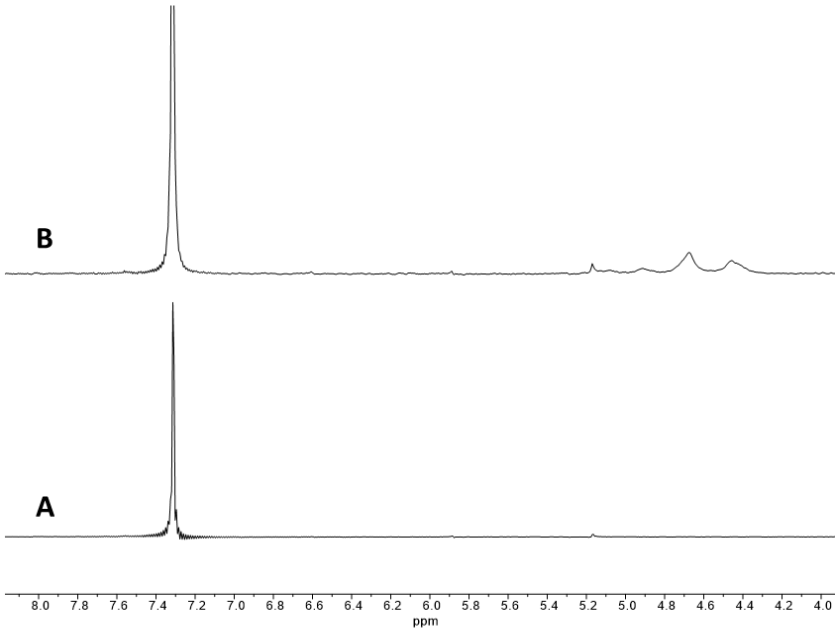


Figure 11**.** $^{31}P(^{1}H)$ NMR spectra in chloroform-d of a) **3a** 50 mM; c) **3a** 50 mM and $\mathbf{1}_6.(H_2O)_8$ 5 mM.

Remarkably, even if **2a** did not provide direct evidence of encapsulation, in the presence of the capsule it rapidly showed the formation of new resonances both in the $^{31}P(^{1}H)$ and ^{1}H NMR spectra due to its conversion into **3a** at room temperature. More specifically, 80% yield of **3a** was observed after 200 min of reaction with 10 mol% of capsules as supramolecular organocatalyst (Table 1, entry 2). The reaction was repeated monitoring the product formation by GC using bromobenzene as an internal standard. The correct assignment of the product obtained was confirmed by ^{1}H NMR and GC-MS analysis.

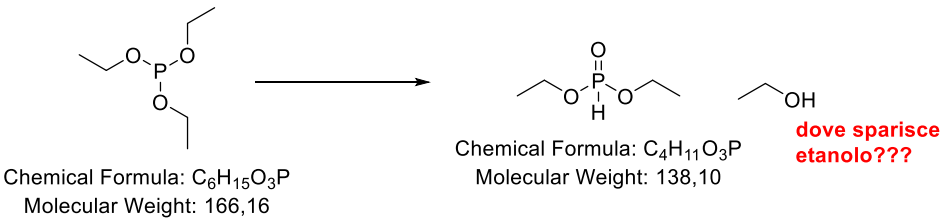
Table 1. Catalytic tests for hydrolysis of **2a** mediated by $\mathbf{1}_6\cdot(H_2O)_8$ and control experiments.

#	$\mathbf{1}_6\cdot(H_2O)_8$	**Additive**	**3a** (%)[a]
1	-	-	2
2	+	-	80
3	-	4-*n*-hexyl-resorcinol	16
4	-	HAc 10 mol%	37
5	+	2% v/v dmso	2
6	-	$N(n\text{Bu})_4Br$ **4a**	3
7	+	$N(n\text{Bu})_4Br$ **4a**	5

[**1**]= 30 mM corresponding to [$\mathbf{1}_6\cdot(H_2O)_8$]= 5 mM, [**2a**]= 50 mM, , water saturated chloroform-d 0.6 mL, T= rt, time 200 min. +: presence; -: absence; a) Determined by GC; b) [additive] = 120 mM (24 eq. with respect to $\mathbf{1}_6\cdot(H_2O)_8$).

To shed light onto the reaction, a series of control experiments were carried out. The reaction using 24 equivalents of 4-*n*-hexyl-resorcinol with respect to the capsule to mimic the H-bonding properties of **1** led to much lower product formation **3a** (Table 1, entry 3). Similarly, the reaction in the presence of 10 mol% of acetic acid to mimic the known Brønsted acidity of the capsule led to only 37% of **3a** (Table 1, entry 4). It is therefore possible to exclude just a simple H-bonding activation imparted by the resorcinol units of the capsule as well as a simple Brønsted acid catalysis. The reaction in the presence of capsule and with 10% v/v of dmso-d_6 as H-bonding

solvent able to disrupt the hexameric supramolecular assembly $\mathbf{1}_6.(H_2O)_8$ did not show significant product formation (Table 1, entry 5), further confirming the importance of the presence of the cavity of the capsule for the reaction under investigation and not only the presence of the resorcinarene moiety. Ammonium cations are known to be suitable guest for the capsule and in most cases have demonstrated to act as competitive guests for the cavity leading to complete or partial deactivation of the catalytic activity of the hexameric capsule. The reaction in the presence of the capsule and ten equivalents of tetrabutylammonium bromide **4a** as a typical competitive guest for the cavity led to a marked decrease of activity, comparable to that observed with the ammonium salt alone (Table 1, entries 6 and 7). This is an evidence of the importance of an accessible cavity to promote the reaction.

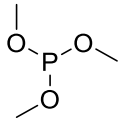
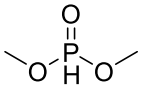
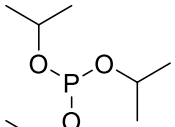
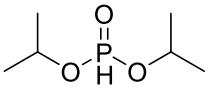
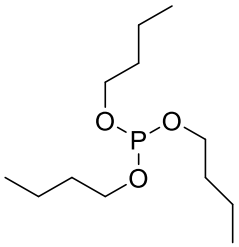
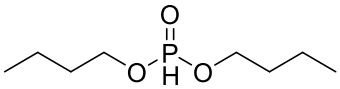
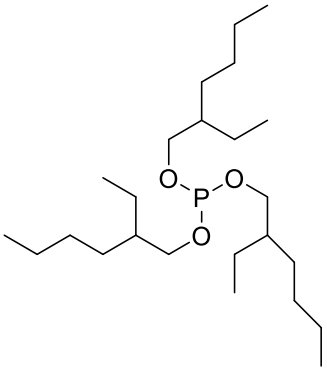
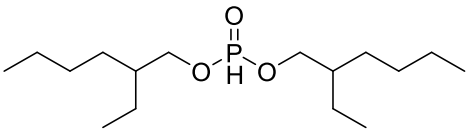


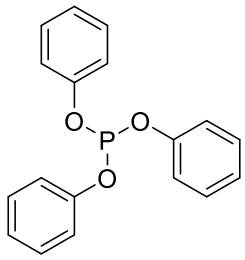
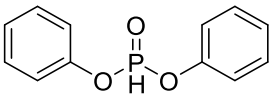
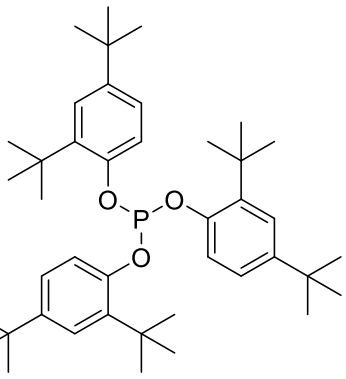
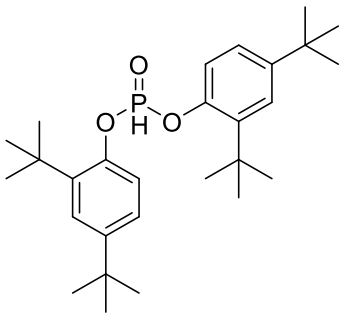
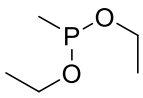
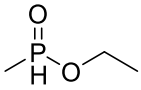
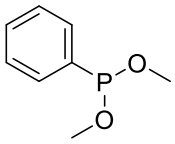
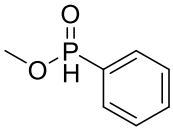
The reaction of **2a** in the presence of benzyl bromide, methyl iodide and other halogenated alkylating aliphatic derivatives did not provide the formation of the corresponding alkyl phosphonates through classical Michaelis-Arbuzov which have been reported in the literature to be promoted at 50-150 °C under flow conditions [26] or using a Lewis acid to operate at room temperature. [27]

It is worth to note that the high yield conversion of **2a** into **3a** catalyzed by 10 mol% of the organocatalytic supramolecular capsule at room temperature in 200 min is an important result

compared to recent literature in which the same reaction is carried out with much stronger Lewis or Brønsted acids under harsher experimental conditions. For instance, the reaction between **2a** and D_2O in place of H_2O with no catalyst provides **3a** in 89% yield after 3 h at reflux temperature above 150°C. [28] The same product can be obtained at room temperature using the stronger *p*-toluenesulfonic acid with 98% yield after 24 h but employing an equimolar amount with respect to **2a** (100 mol% of catalyst). [29] It is also worth to note in this case that the pKa of the *p*-toluenesulfonic acid is -2.8[30] compared to ca. 5 for the hexameric capsule. [31] Alternatively, **2a** can be converted into **3a** in only 55% yield after 42 h at 160 °C with 1 mol% of $NiCl_2 \cdot 6H_2O$. [32] Other publications report the conversion of *tris*-isopropyl phosphite **2c** to the corresponding H-phosphonate **3c** for instance with no catalyst at room temperature with 95% yield only after 48 h, [33] or with 2 mol% of strong Brønsted acids or alkylsulfonic acids like butyl and octyl (pKa<2), trifluoroacetic (pKa 0.52) or trifluoromethanesulfonic acid (pKa -14.7) leading to quantitative yield in 5 min. [34]

Table 2: Substrate scope for phosphite 2a-x hydrolysis mediated by $\mathbf{1}_6 \cdot (H_2O)_8$ and control experiments.

#	Substrate	$N(Bu)_4Br$	Time (min)	Product	Yield (%)[a]
1		-			XX
2	**2b**	+		**3b**	XX
3		-	125		96
4	**2c**	+	125	**3c**	5
5		-	125		90
6	**2d**	+	125	**3d**	15
7		-	138		95
8	**2e**	+	138	**3e**	28

9		-	1200		19
			1200		0
10		+			
	2f			**3f**	
11		-	1200		0
			1200		0
12		+			
	2g			**3g**	
	2g				
13		-	-		Xin progressX
	2i			**3i**	
14		+	-		Xin progressX
15		-	60		100
			60		50
16		+			
	2j			**3j**	

[**1**]= 30 mM corresponding to [$\mathbf{1}_6$·$(H_2O)_8$]= 5 mM, [**2b-x**]= 50 mM, water saturated chloroform-d 0.6 mL, T= rt. +: presence; -: absence; a)Determined by GC

The substrate scope of the reaction was investigated as reported in Table 2. Trimethyl phosphite **2b** is intrinsically very active due to good electronic properties and small steric hindrance of the methyl units. The reaction was promoted even in the absence of the capsule, with XX% of the dimethyl phosphite formed in XX minutes at room temperature. In the presence of 10 mol% of capsule the reaction was complete after only XX minutes (Table 2 entries 1 and 2). The reaction on **2c** led to 96% yield of the corresponding h-phosphate product **3c** in slightly more than 2 h (Table 2 entry 3). Increasing the length of the alkyl substituents of the tris-alkyl phosphite like in **2d** the catalyst still maintained a good conversion forming the corresponding product **3d** in 90% yield after 125 minutes (Table 2 entry 5). Even the highly branched substrate **2e** bearing three 2-ethyl-hexyl residues in the presence of 10 mol% of the capsule led to the formation of the corresponding H-phosphonate product **3e** in 90% yield after 138 minutes (Table 2 entry 7). Overall, the capsule turned out to efficiently convert even hindered tris-alkyl phosphites with comparable yields in few hours. As a further class of potential substrates for the capsule, we investigated the reaction on dimethyl phenyl phosphonite **2j** that was quantitatively converted into the product methyl phenyl phosphinate **3j** in just 60 minutes. We then moved to less electron rich phosphites and investigated the reaction of triphenyl phosphite **2f** and the *tris*(2,4-di-*tert*-butylphenyl) phosphite **2g** that could provide extra information about the maximum size allowed by the capsule for the conversion into products. The reaction on both substrates did not lead to the formation of the corresponding **3f** and **3g** product at room temperature for 72 h. We then increase the temperature to 75 °C monitoring the progress of the reaction by 31p NMR. We observed that in the presence of 10 mol% of capsule, the yield for the product **3f** was 12% after 2h and 19% after 20 h, indicating a certain level of inactivation of the catalyst over time. For the highly sterically hindered substrate **2g** no product formation was observed even after 20 h and even though this

reagent is more electron rich compared to **2f**. This could be explained by its very large size and steric hindrance that hampers the accommodation of such substrate within the cavity of the capsule. It is also worth to note that control experiments for all the tested substrates with the capsule in the presence of tetrabutylammonium bromide as competitive guest led to marked decrease of catalytic activity, confirming for all of them that the reaction takes place within the cavity of the capsule.

Mechanism for phosphite hydrolysis to H-phosphonates

Michaelis and Arbuzov [35] proposed that phosphite hydrolysis occurs through the electrophilic attack of the lone electron pair of phosphorus on water hydrogen and the subsequent nucleophilic attack of the water oxygen on the carbon in α-position, which subsequently breaks the O–C bond (Fig. 12a).

However, based on the analysis of the phosphite hydrolysis product and data obtained using infrared spectroscopy and ^{18}O labelled water, Aksnes [36] suggested that the phosphite hydrolysis preferentially occurs via a nucleophilic attack on the phosphorus atom and the consequential breakage of the P–O bond (Fig. 12b).

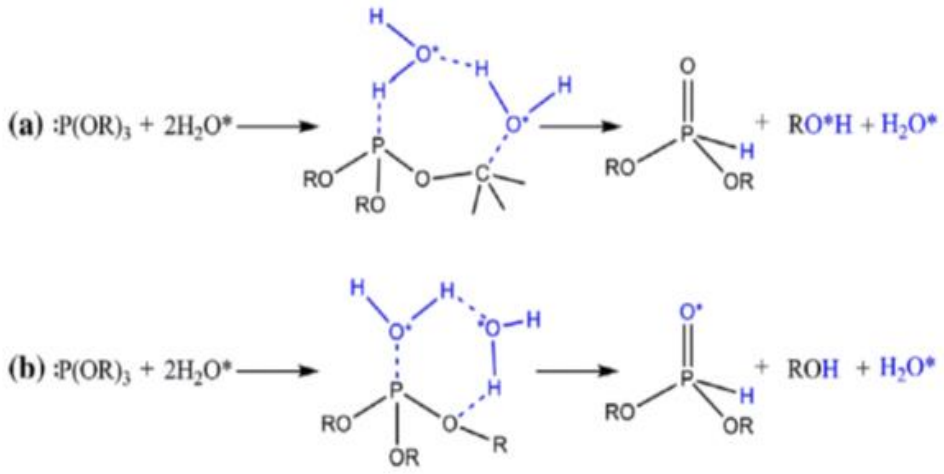


Figure 12:Mechanism of phosphite hydrolysis: (a) Michaelis and Arbuzov and (b) Alksnes (similar to organic ester hydrolysis)O*=O[18].

In order to shed light into the mechanism of the reaction and to ascertain the role of the water molecules involved in the seam of H-bonds of the capsule we repeated the reactions with $\mathbf{1}_6 \cdot (H_2O)_8$ under conditions of Table 1 entry 2 using D_2O saturated chloroform-d as solvent observing the formation of the deuterated H-phosphonate **3a** (Figure 13). More specifically the product showed a weak peak at m/z 139 corresponding to the monodeuterated **3a** and a very clear fragment at m/z 94 corresponding to the loss of the $CH_3CH_2O^{\cdot}$ radical leaving the cation $CH_3CH_2OPOD^+$. Similarly, the reaction was repeated using $H_2{}^{18}O$ saturated chloroform-d observing the formation of the corresponding ^{18}O isotopically labelled product **3a** with a weak peak at m/z 140 (Figure. 13) and a very clear fragment at m/z 95 corresponding to the loss of the $CH_3CH_2O^{\cdot}$ radical leaving the cation $CH_3CH_2OP^{18}OH^+$.

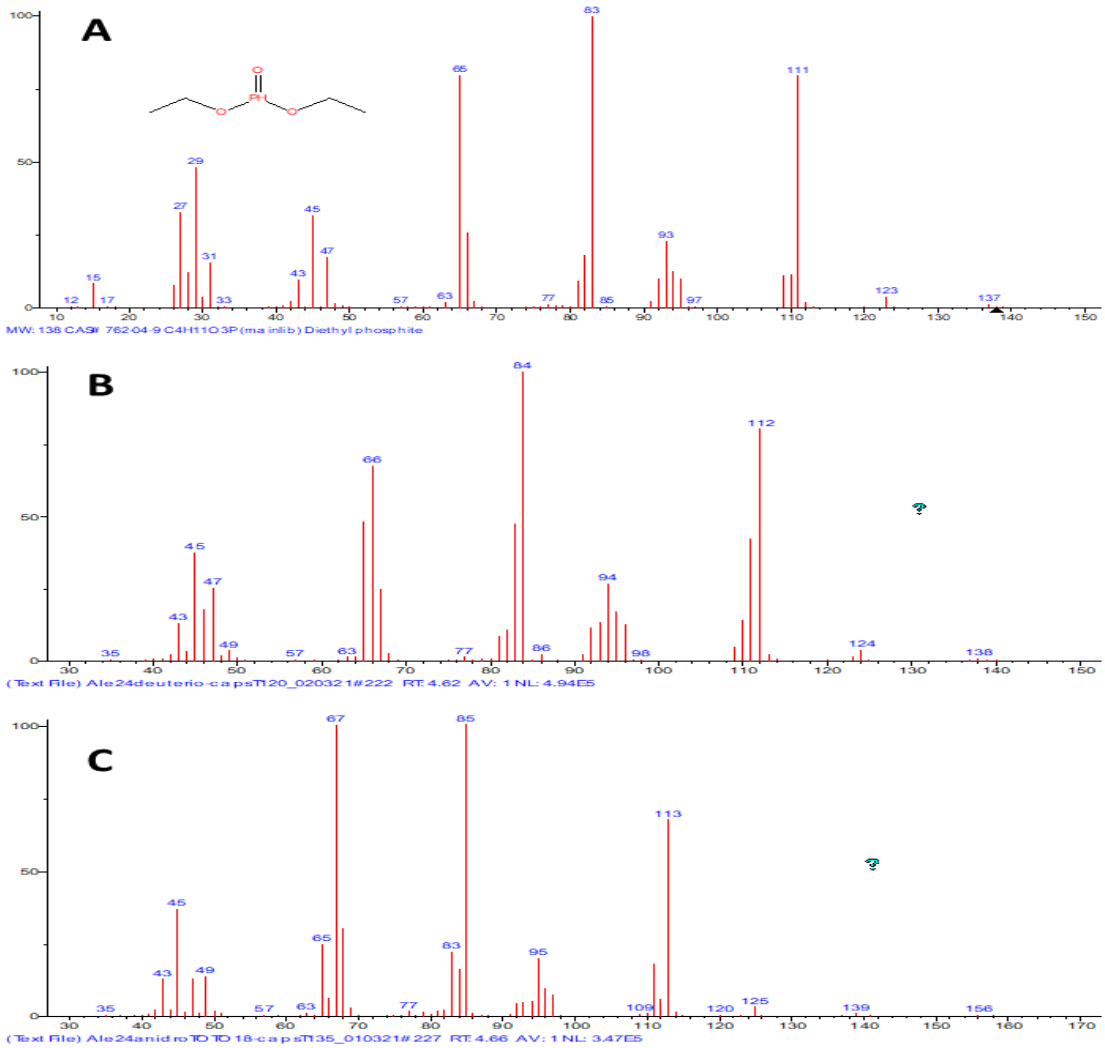


Figure 13. EI MS spectra of the diethyl H-phosphonate 3a obtained by reaction with $1_6 \cdot (H_2O)_8$ with a) normal water saturated chloroform-d, b) with D_2O saturated chloroform-d and c)$H_2{}^{18}O$ saturated chloroform-d.

The latter experiments ensures that the reaction catalyzed by the capsule occurs with nucleophilic attack of water on the phosphite. The evidence that the reaction occurs within the capsule finds a possible explanation in the activation of the phosphite by H-bonding of the O atoms [37] to one of the four dangling OH moieties arising from the eight water molecules part of the H-bond seam of the hexameric capsule. Similar activation pathways have been prosed for a wide range of reactions in which the electrophilic unit is activated within the cavity of the capsule. [38.39] This electrophilic activation favors the nucleophilic attack of a water molecule on the P atom, liberating the corresponding alcohol, and forming **3a**.

A further experiment to confirm the requirement of having the cavity of the capsule accessible for the substrate was carried out repeating the test on **2a** in the presence of $\mathbf{1}_6 \cdot (H_2O)_8$ and adding 10 equivalents of the competitive N(*n*Bu)$_4$Br after 30 min of reaction observing in the first part of the reaction the increase of the conversion that remained almost constant to 30% after 30 minutes due to the blocking of the cavity caused by the ammonium competitive guest.

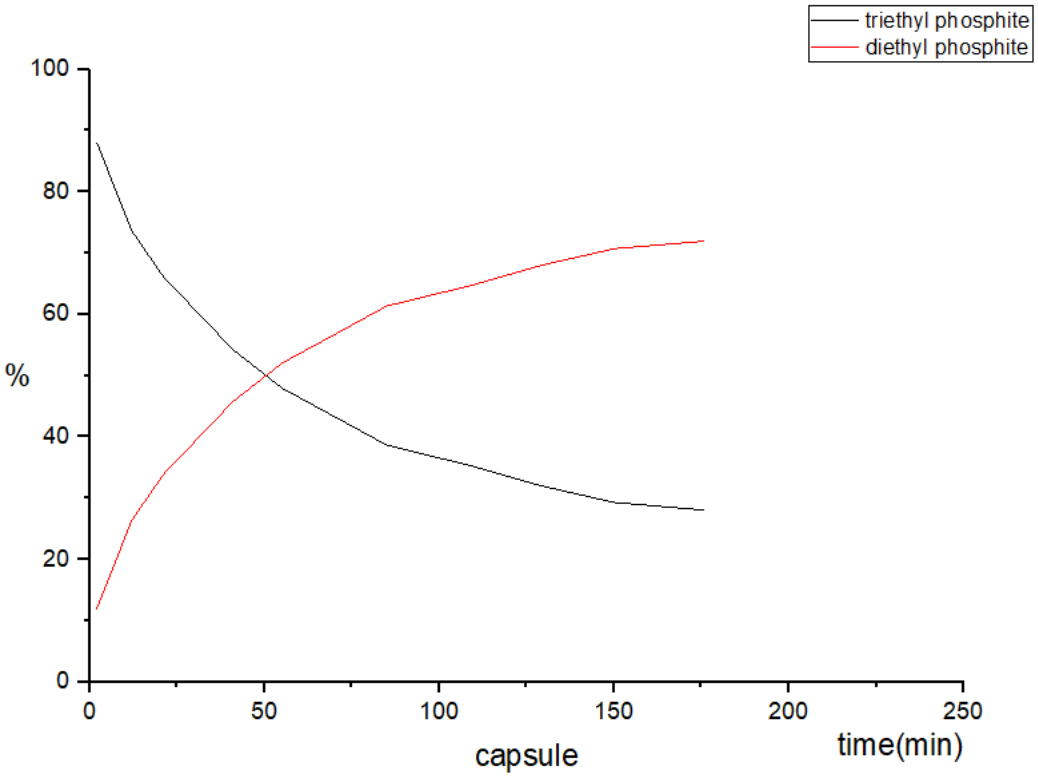


Figure 14. (table 1, entry 2) reaction of 5mM $\mathbf{1}_6\cdot(H_2O)_8$ with 10 eq of **2a**

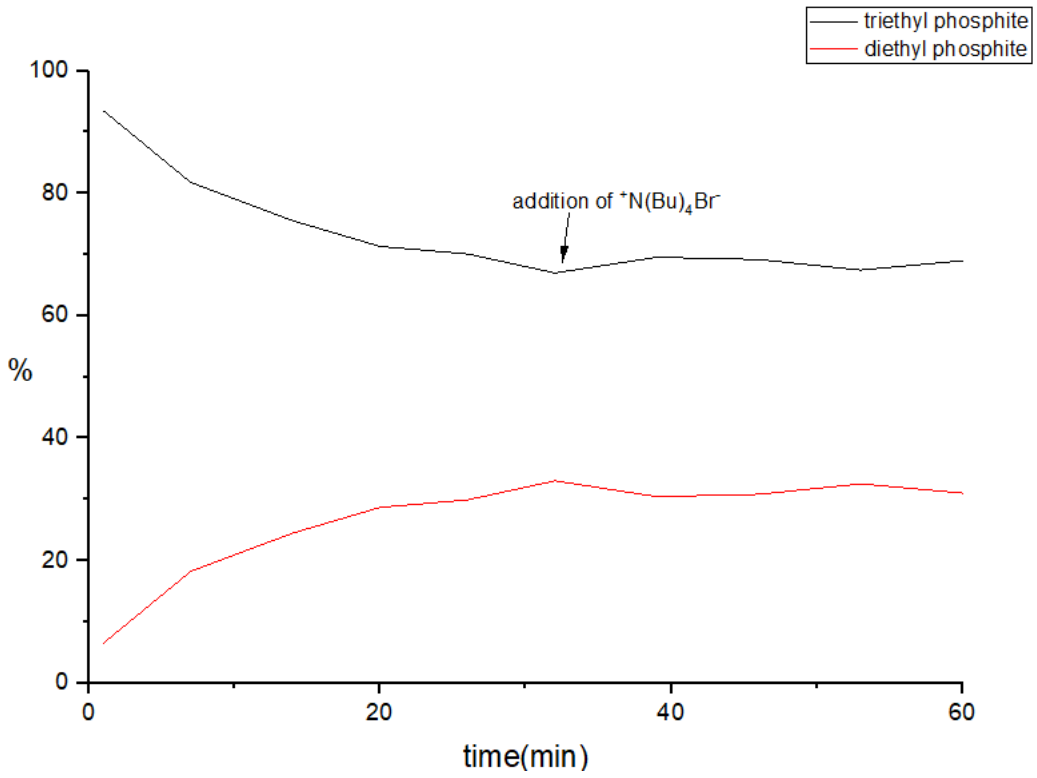


Figure 15. (table 1, entry 2) reaction with the addition of $N(nBu)_4Br$ after 30 min.

A competitive experiment was also carried out using equimolar amounts of the substrates **2a** and **2d** corresponding to 10 equivalents each with respect to the capsule. The two substrates can be considered very similar in terms of electronic properties but differ in the length of the alkyl chain and therefore in the steric hindrance and on the overall volume. The reaction in the presence of the capsule showed a modest preference for the smaller substrate especially in the first time period, while for longer reaction times the longer ones turned out to be faster in the reaction.

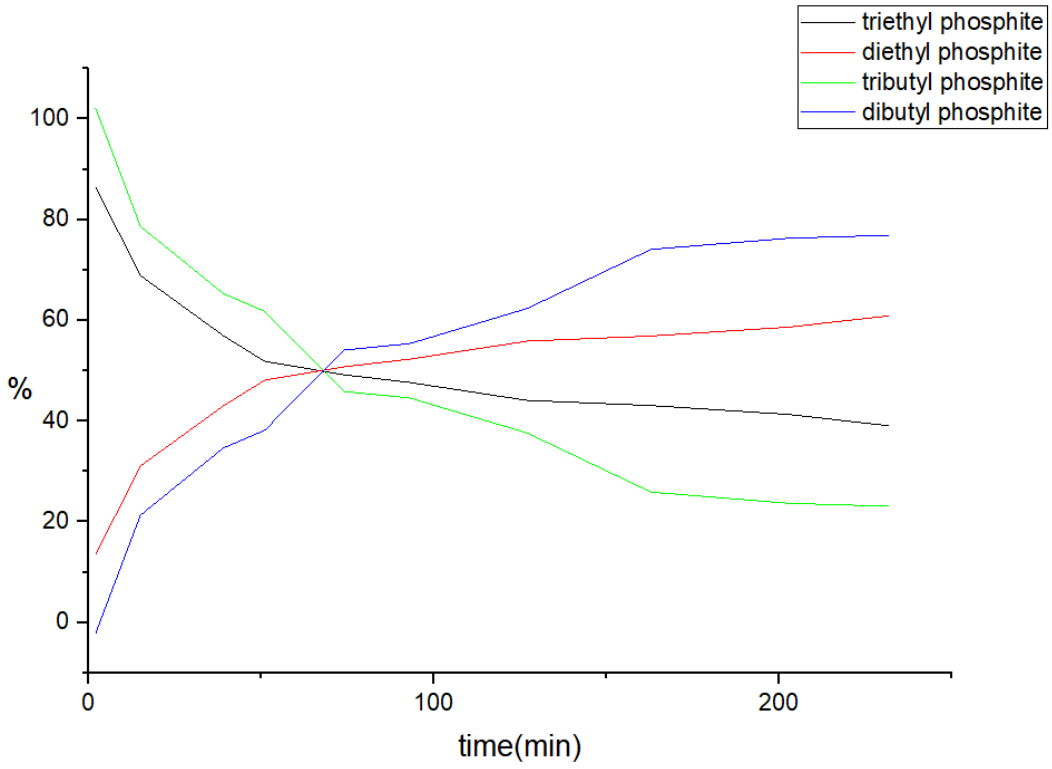


Figure 16. 5mM $\mathbf{1}_6\cdot(H_2O)_8$ with 50mM of **2a** & **2d.**

Investigation of the effect of the ammonium salt and corresponding counter-anion:

Tetraalkylammonium salts are usually exploited as competitive guests with inhibiting properties to prove the importance of the cavity of the capsule in supramolecular catalytic reactions. [40] Unexpectedly, for **2a** a much more intriguing scenario was observed, with both the nature of the ammonium cation and that of the counter-anion playing a crucial role. In particular, with 10 mol% of capsule and 10 equivalents of tetrabutylammonium tetrafluoroborate **4b**, the conversion of **2a** was unexpectedly even faster compared to just the capsule $\mathbf{1}_6.(H_2O)_8$ (Table 2, entry 2). ^{1}H NMR demonstrated that the capsule fully hosts the cationic species observing clear new up-field shifted resonances whose relative integration corresponds to a XX:XX ratio between capsule and cation.

This result was completely unexpected in consideration of the vast literature on the subject reporting typical inhibiting properties by ammonium species as competitive guests for the cavity of $\mathbf{1}_6.(H_2O)_8$. [40] The reaction of **2a** with just **4b** in solution did not show a rapid product formation thus excluding any direct activation of the substrate by the ammonium species (Table 2, entry 1,).

The effect of the size of the ammonium species was investigated observing that with tetrahexylammonium tetrafluoroborate **4c** the reaction showed exactly the same profile as for the free capsule.

With a larger ammonium species like Hexadecyltrioctadecylammonium bromide **4d** the reaction showed exactly the same profile compared to the free capsule. In fact, ^{1}H NMR spectra showed that the latter large ammonium species was not encapsulated within the cavity of the capsule due to its size larger than the cavity. Because of this the presence of the **4d** in solution did not affect at all the catalytic properties of the capsule.

Bromide tends to be co-encapsulated with the cation (therefore mitigating its acidity or that of the capsule) while the larger anions remain outside.

The effect of the counter-anion was investigated repeating the experiments with tetrabutylammonium bromide **4a** observing that neither the reaction with just the ammonium species, nor the one with ammonium and capsule, showed any product formation within hours (Table 1, entries 6 and 7). In the latter cases it is possible to imagine that the nature and position assumed by the anion is fundamental for the reaction. Specifically, from the literature it is known that tetraalkylammonium cations of suitable size compared to the hexameric capsule are

encapsulated alongside the bromide counter-anion. In the latter case the Br probably kills the activation properties imparted by the ammonium and the reaction did not occur either with or without capsule. Conversely, with tetrabutylammonium tetrafluoroborate **4b** the anion is known to remain outside the cavity and the tetrabutylammonium cation is hosted alone in the cavity. It is likely that under such conditions there is a complementary effect due to the capsule and the ammonium leading to a faster reaction compared to just the capsule. As a comparison, the reaction with the larger tetrahexylammonium bromide **4e** and tetrafluoroborate **4c** were carried out observing in both cases that only the ammonium species did not provide any catalytic effect, similarly to what observed for the smaller tetrabutylammonium. In the presence of the capsule, the reaction with BF_4 anion was good. Unexpectedly, with the bromide counter-anion and the encapsulated tetrahexylammonium, conversely to tetrabutylammonium, the reaction was good. With tetrabutylammonium iodide **4g** the reaction did not work, while with salt and capsule the reaction was good. Same for tetrabutylammonium hexafluorophosphate **4f**.

From the ^{1}H NMR spectra it is evident that the α methylene units in the tetrabutylammonium bromide are more de-shielded with respect to the tetrabutylammonium tetrafluoroborate with a difference in chemical shift of about XX ppm. Same effect was observed for the tetrahexylammonium derivatives XX.

Table 3:Catalytic tests for hydrolysis of **2a** mediated by $\mathbf{1}_6\cdot(H_2O)_8$ and control experiments.

#	$\mathbf{1}_6\cdot(H_2O)_8$	**Additive 4a-x**	**Time (min)**	**Encapsulation**	**3b (%)[a]**
1	-	$N(n\text{Bu})_4BF_4$ **4b**	200	-	20
2	+	$N(n\text{Bu})_4BF_4$ **4b**	200	Yes	80
3	-	$N(n\text{Hex})_4BF_4$ **4c**	200	-	2
4	+	$N(n\text{Hex})_4BF_4$ **4c**	200	No	71
5	-	$C_{70}H_{144}NBr$ **4d**	200	-	2
6	+	$C_{70}H_{144}NBr$ **4d**	200	No	70
7	-	$N(n\text{Hex})_4Br$ **4e**	200	-	4
8	+	$N(n\text{Hex})_4Br$ **4e**	200	Yes	61
9	-	$N(n\text{Bu})_4PF_6$ **4f**	200	-	15
10	+	$N(n\text{Bu})_4PF_6$ **4f**	200	Weak binding	70

11	-	N(*nBu*)$_4$I **4g**	200	-	2
12	+	N(*nBu*)$_4$I **4g**	200	Yes	61

1]= 30 mM corresponding to [16·(H2O)8]= 5 mM, [2a-c]= 50 mM, , water saturated chloroform-d 0.6 mL, T= rt, time 200 min. +: presence; -: absence; a) Determined by GC; b) [additive] = 120 mM (24 eq. with respect to 1_6·$(H2O)_8$).

In particular, with small counter anions such as *Cl^-, Br^-, I^-, NO_2^- and NO_3^-, the cationic Ir(III)* complex was accommodated within the capsule alongside the anion, which interacts positively with the inwardly oriented hydroxyl groups of the water molecules present on the seam of H-bonds. This led to enhanced luminescent properties, with increase of the quantum yield (Φ) and the lifetime (τ) of the emission, characterized also by a marked blue shift thanks to the inhibition of the non-radiative pathways provided by the cavity protecting the excited guest. Moving to larger, less coordinating anions like *ClO_4^-, PF_6^- and OTf^-* that are characterized by lower H-bonding properties, a decreasing affinity of the ion pair for the cavity was observed, with no encapsulation taking place. This was reflected by the luminescent properties of the metal complex being more reminiscent of those of the free complex in solution [41]

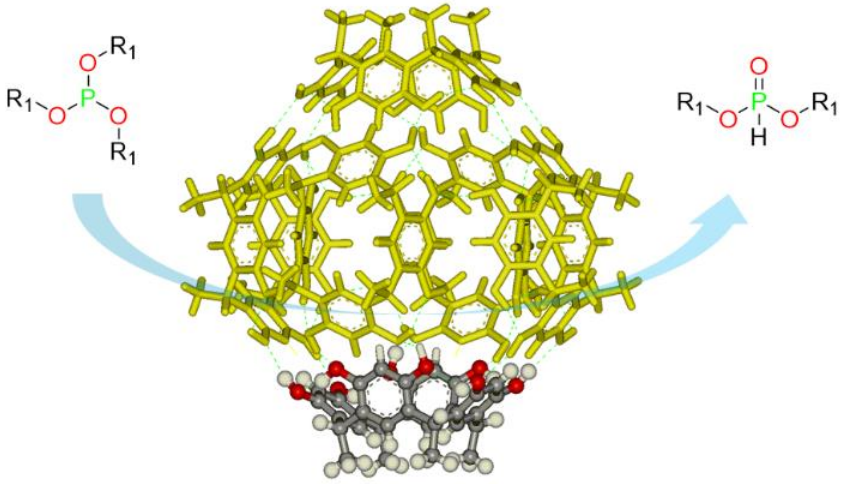
Paper Rebek Shivanyuk. [42]

A very complex spectrum was observed for the tetraoctylammonium cation. Because the pattern depended on the concentration of guest, it was not possible to assign the signals of the encapsulated guest or accurately determine the host-guest stoichiometry. The tetrahexadecylammonium cation was not complexed under these conditions.

Alkylammonium salts as hydrogen bonding catalysts [43]

N(*n*Hex)$_4$BF$_4$ and $C_{70}H_{144}NBr$ they both show the same kinetic profile compared to the sole capsule; therefore both need to be analyzed with the capsule to understand whether: a) both they are NOT guests for the capsule (hexyl with Br as counter-anion was reported as perfect guest by Rebek) but maybe with BF4 something different occurs? Otherwise, if hexyl goes in but the catalysis is the same it means that there is not a cooperative effect and that probably the H-bonding Ch are masked or too buried inside (from n-heptylammonium the chain is folded)

Graphical Abstract



CONCLUSION

The hydrogen bonded resorcinarene capsule was found to promote rapid hydrolysis of phosphites to the corresponding H-phosphonates providing a high yield product in few hours with formation of the alcohols as by-products through activation of water by a seam of H-bonds, opening a new green synthetic pathway for the formation of organophosphates that overcome the drawbacks of other synthetic methods mentioned in the literature.

Tetralkylammonium salts was found to provid inhibition or cooperative activation of the reaction based on the size of the cation and the nature of the counter-anion, with the smaller alkyl cation enhancing the catalytic activity of the capsule with an exception of the Br^- counter anion i.e.$^+N(Bu)_4Br^-$ acting as an comptetive inhibtor. Conversely, the $BF4^-$ anion promoted the activity of the capsule to twofold.

EXPERIMENTAL PART

Instrumentation and operating conditions

General Methods

All the reactions were followed with TLC Polygram® Sil G/UV254, 0.25 mm thickness. ^{1}H NMR, ^{13}C NMR, and DOSY spectra were recorded with a Bruker Avance 300 and Ascend 400 spectrometers, working at 300-400 and 75-100 MHz respectively. ^{19}F NMR spectra were recorded with an Ascend 400 spectrometer, working at 376 MHz. Resonance frequencies are referred to tetramethylsilane. IR spectra were recorded with a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were recorded on a Waters ZQ2000 spectrometer equipped with ESI Ion Polarity Positive source, with the following conditions: Set Nebuliser: 0.3 Bar, Focus Active Set Capillary: 4500 V, Set Dry Heater: 200 °C, Scan begins at 50 m/z and ends at 800 m/z, Set End Plate Offset: –500 V, Set Dry Gas: 3.5 L/min, Set Collision Cell RF: 2500.0 Vpp. A 1 mg/mL solution of sample in water was diluted 1:1000 into methanol containing 0.1 % trifluoroacetic acid and the solution injected by syringe pump. GC-MS analyses were carried out on a MSD Agilent Technologies EI source, injected by GC System Agilent Technologies equipped with HP-5MS column, with the following temperature programming: 50 °C for 2 minutes, then ramping 10 °C/min up to 300 °C, then 300 °C for 10 minutes, solvent delay: 4 minutes. Reagents and solvents with high purity degree purchased by the providers were used as given. Otherwise, they were purified following the procedures reported in literature. Anhydrous solvents were prepared by adding activated 3 and

4 Å molecular sieves to the solvent under inert atmosphere. Molecular sieves were activated shortly before the use by continuous heating under vacuum. Flash chromatography were done with silica gel Merk 60, 230-400 mesh, following procedures reported in literature.[i]

General

^{1}H NMR, $^{31}P\{^{1}H\}$ NMR, $^{13}C\{^{1}H\}$ NMR spectra were run on:

Bruker Avance 300 spectrometer operating at 300, 122, 75 MHz, respectively, at 298 K.

Bruker Avance 400 spectrometer operating at 400, 162, 101 MHz, respectively, at 298 K.

δ values are reported in ppm relative to $Si(CH_3)_4$ or 85% H_3PO_4.

GC-MS analyses were performed on a GC Trace GC 2000 coupled with a quadrupole MS Thermo Finnigan Trace MS with *Full Scan* method. Experimental conditions are reported in the following table.

Experimental conditions for GC-MS analyses	
Capillary column:	HP5-MS 30 m, 0.25 mm x 0.25 μm
Initial T, °C:	80°C for 5 min
Rate, °C/min:	30°C/min
Final T, °C:	280°C for 30 min

Injector T (split), °C:	280°C
Gas carrier flow, mL/min.	0.8 mL/min
Injected volume, μL	0.8-1 μL
Solvent delay, min.	4 min.
Mass range, amu:	35-500 amu
Detector voltage, V:	350 V
Interface T, °C	300°C
Source T, °C:	200°C

Low resolution mass spectra (LRMS) were recorded on a Finningan LCQ Deca XP Max mass spectrometer coupled to electrospray ionisation source (ESI) in positive or negative mode.

Substances used

The chemicals used are commercially available and have been used without further purification. The following solvents and reagents were purchased from Sigma-Aldrich:

Triethyl phosphite purity>98%

Tetrabutylammonium hexafluro phosphate >99%

Tetrahexylammonium tetrafluroborate >97%

Tetradodecylammonium bromide >86%

Tetrahexylammonium bromide

Trimethyl phosphite

Tertabutyl ammonium bromide

Dimethyl phenyl phosphite

Tetrabutylammonium iodide

Triisopropyl phosphite

Dimethylphenyl phosphite

Dimethyl sulfoxide (DMSO)

Tris(2,4-di-tert-butylphenyl) phosphite >98% from TCI (tokyo chemical industry)

4-n-hexyl-resorcinol were purchased from Alpha Aesar

Tetrabutylammonium tetrafluoroborate from Fluka

Acetic acid from J. T. Baker.

The CDCl3 was prepared by passing it through aluminum oxide, at room temperature and the addition of 3 drops(150µl) of double-distilled water to a (100ml) bottle containing deuterated chloroform.

Catalyst used

Resorcin [4]arene is a product available in the laboratory that has been synthesized previously according to a process reported in the literature. [44]

Method

0.875 g of resorcinol in 5 ml EtOH and 1.25 ml of 37% HCl were dissolved in a flask stirred then placed in a water and ice bath, within the flask 1.45 g of dodecanal was slowly added within 2 hrs. The solution was bought to room temperature by cooling and then was refluxed for 17 h, after cooling it was washed with cold methanol, then washed with acetonitrile to remove methanol residues and dried under vacuum for 6 hrs.

Hydrolysis of triethyl phosphite to diethyl phosphite

- Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. Subsequently, triethyl phosphite (10 eq;50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

- Conrol Experiment of triethyl phosphite with +N(Bu)4Br- encapsulated as a competitive guest: Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. $^{+}N(Bu)_4Br^{-}$ (5 eq compared to the capsule; 25mM) was added and sample was gently mixed. Subsequently, triethyl

phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

Experiments with encapsulation of ammonium salts and its affect on hydrolysis of triethylphosphite:

A set of six experiments were conducted using a different ammonium salt. For each experiment a 5mM of resorcin [4]arene was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. 5 eq compared to the capsule; for each experiment a 25mM of one of the following ammonium salts ($N(nBu)_4BF_4$, $N(nBu)_4PF_6$, $N(n\text{Hex})_4Br$, $N(n\text{Hex})_4BF_4$, $N(nBu)_4I$, $C_{70}H_{144}NBr$) were added respectively, and samples were gently mixed. Subsequently, triethyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

Hydrolysis of tributyl phosphite to dibutyl phosphite

- Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. Subsequently, tributyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

- Conrol Experiment of tributyl phosphite with +N(Bu)4Br- encapsulated as a competitive guest: Resorcin[4]arene (5mM) was dissolved in an NMR tube containing

0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. $^{+}N(Bu)_4Br^{-}$ (5 eq compared to the capsule; 25mM) was added and sample was gently mixed. Subsequently, tributyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

Hydrolysis of triisopropyl phosphite to diisopropyl phosphite

- Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution Subsequently, tributyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

- Conrol Experiment of triisopropyl phosphite with +N(Bu)4Br- encapsulated as a competitive guest: Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. $^{+}N(Bu)_4Br^{-}$ (5 eq compared to the capsule; 25mM) was added and sample was gently mixed. Subsequently, triisopropyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

Hydrolysis of dimethylphenyl phosphite to methylphenyl phosphonate

- Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. Subsequently, dimethylphenyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

- Conrol Experiment of dimethylphenyl phosphite with +N(Bu)4Br- encapsulated as a competitive guest: Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. $^{+}N(Bu)_4Br^{-}$ (5 eq compared to the capsule; 25mM) was added and sample was gently mixed. Subsequently, dimethylphenyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

Hydrolysis of tris(2-ethylhexyl)phosphite to bis(2-ethylhexyl) phosphite

- Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. Subsequently, trisethylhexyl phosphite (10 eq compared to the capsule; 50 mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

- Conrol Experiment of trisethylhexyl phosphite with +N(Bu)4Br- encapsulated as a competitive guest:

Resorcin[4]arene (5mM) was dissolved in an NMR tube containing 0.6 mL of $CDCl_3$ saturated with water. sample was homogenized by sonication , gentle heating with a heat gun and agitation to give a clear solution. $^{+}N(Bu)_4Br^{-}$ (5 eq compared to the capsule; 25mM) was added and sample was gently mixed. Subsequently, trisethylhexyl phosphite (10 eq compared to the capsule; 50mM) was added. The course of the reaction was monitored by recording the GC every 15 min.

Control Experiment with n-hexylresorcinol

4-n-hexylresorcinol (24 eq compared to capsule, 120 mM) was dissolved in an NMR tube containing 0.6 mL of water-saturated deuterated $CDCl_3$. Subsequently, (10 eq compared to the capsule;50 mM) of triethyl phosphite(**3a**) were introduced and the tube was shaken. The course of the reaction was monitored by recording the GC every 15 min.

Control Experiment with Acetic acid

In an NMR tube with 0.6 mL of $CDCl_3$. Acetic acid (25 mM) was added, an acid of strength comparable to resorcin[4]arenas. Subsequently, (10 eq compared to the capsule ;50 mM) of triethyl phosphite(**3a**) were introduced. The tube was shaken, the course of the reaction was monitored by recording GC every 15 min.

Control Experiment with substrate alone

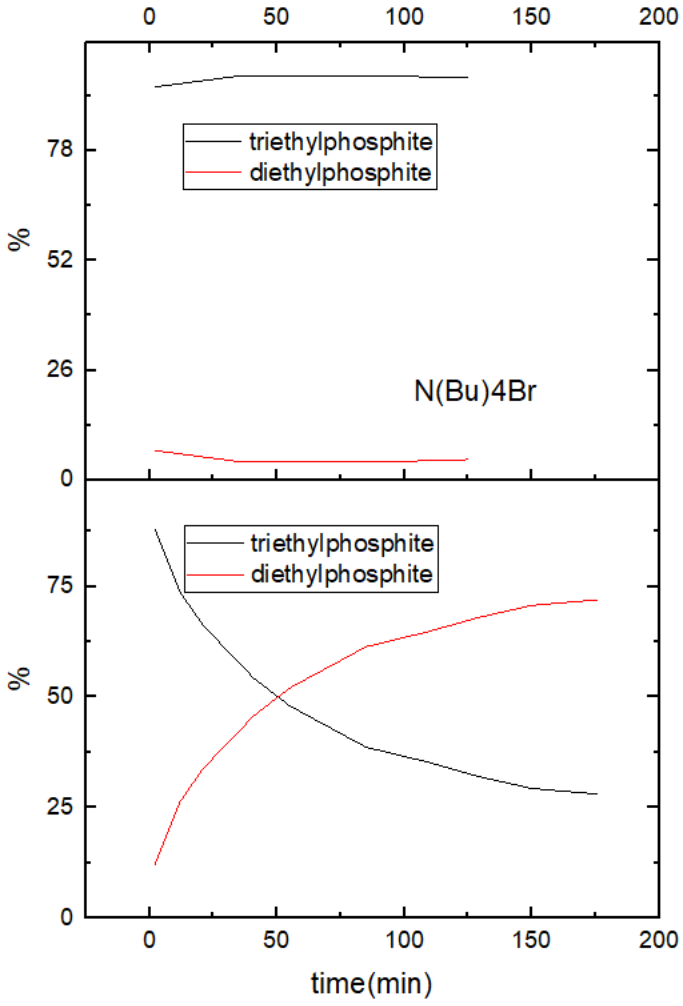
In an NMR tube containing 0.6 mL of water-saturated $CDCl_3$, (10 eq compared to the capsule; 50 mM) of triethyl phosphite(**3a**) were introduced. The tube is shaken the course of the reaction was monitored by recording GC every 30 min.

Control Experiment with DMSO

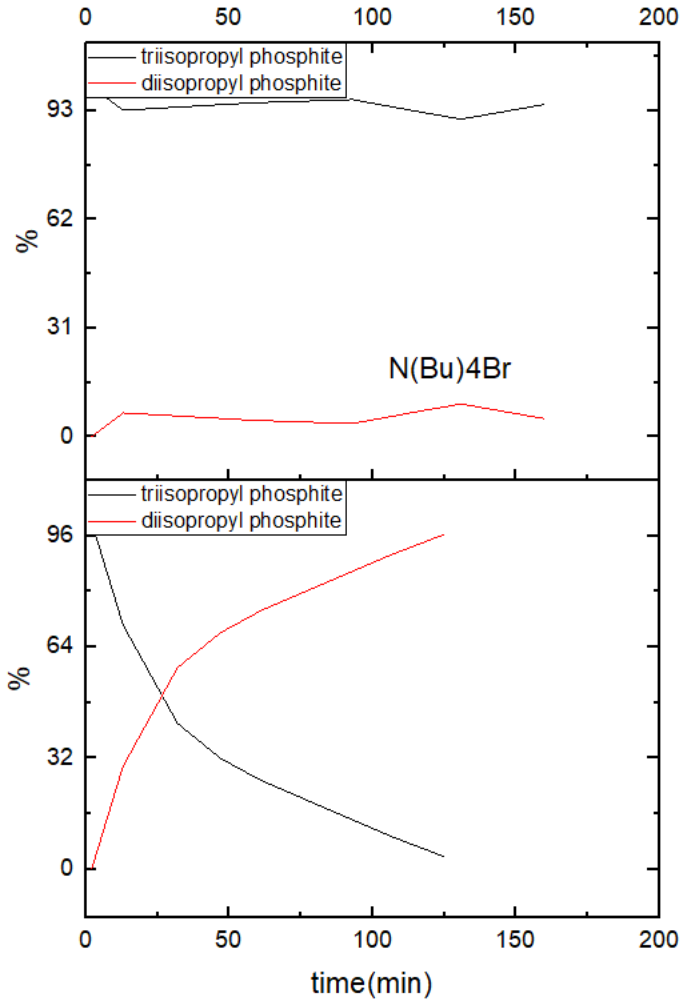
In an NMR tube containing 0.6 mL of water-saturated $CDCl_3$, resorcin[4]arenas (5mM) was dissolved. DMSO(20 eq compared to the capsule, 100 mM) was added and the tube is shaken. Subsequently, (10eq compared to the capsule ;50 mM) of triethyl phosphite(**3a**) were introduced. The tube is shaken and the course of the reaction was monitored by recording GC every 15 min.

SUPPORTING INFORMATION

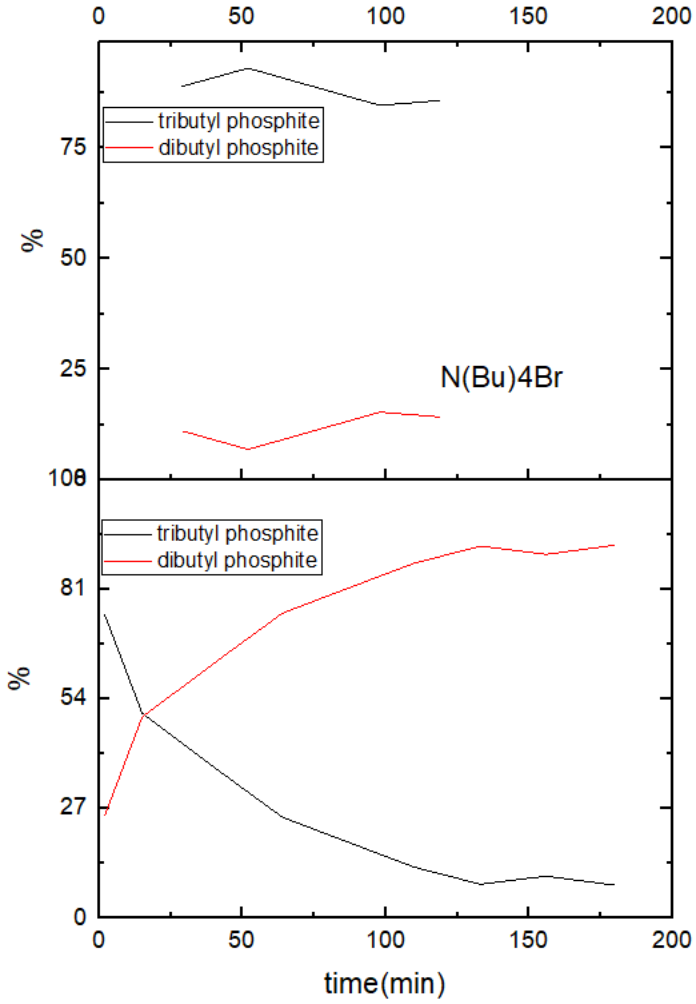
The graphs of phosphites conversion mediated by $1_6.(H2O)_8$ and control experiments



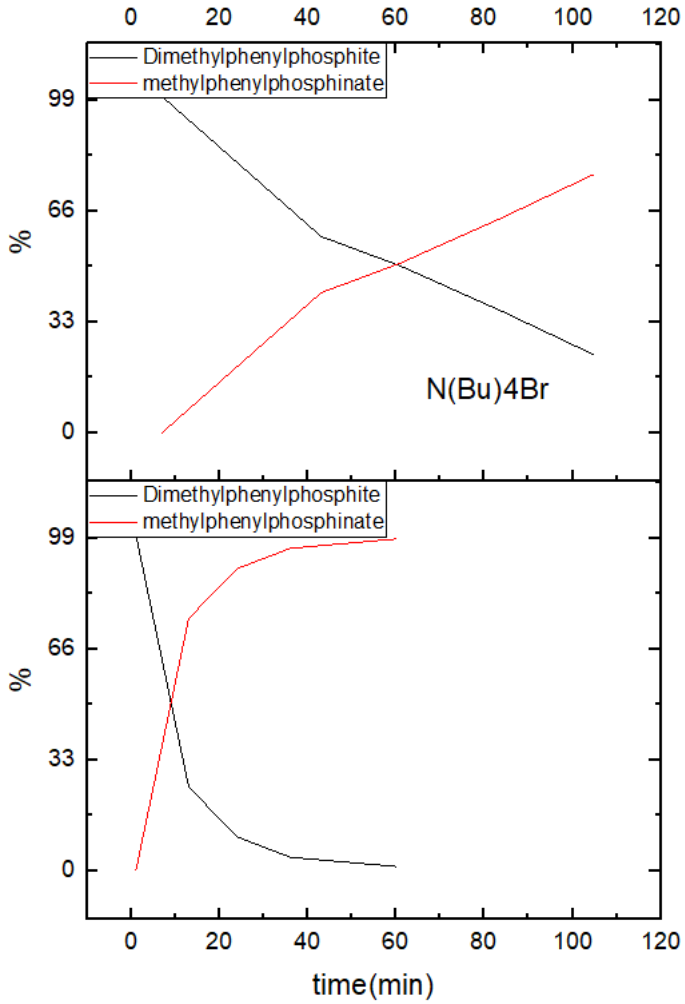
Conversion and product formation for the reaction of **2a** in chloroform-d at rt; bottom) **1**$_6$.$(H2O)_8$ 5 mM **2a** 50 mM ; top) **1**$_6$.$(H2O)_8$ 5 mM **2a** 50 mM and $^{+}N(Bu)_4Br^{-}$ 25 mM.



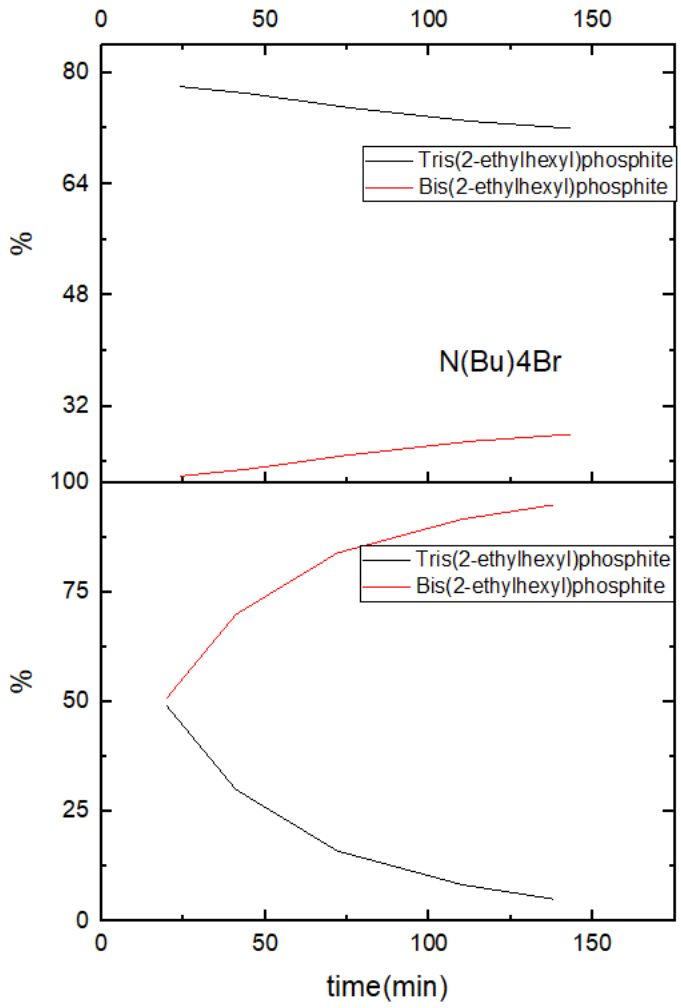
Conversion and product formation for the reaction of **2c** in chloroform-d at rt; bottom) **1**$_6$.(H2O)$_8$ 5 mM **2c** 50 mM ; top) **1**$_6$.(H2O)$_8$ 5 mM **2c** 50 mM and $^{+}$N(Bu)$_4$Br^{-} 25 mM.



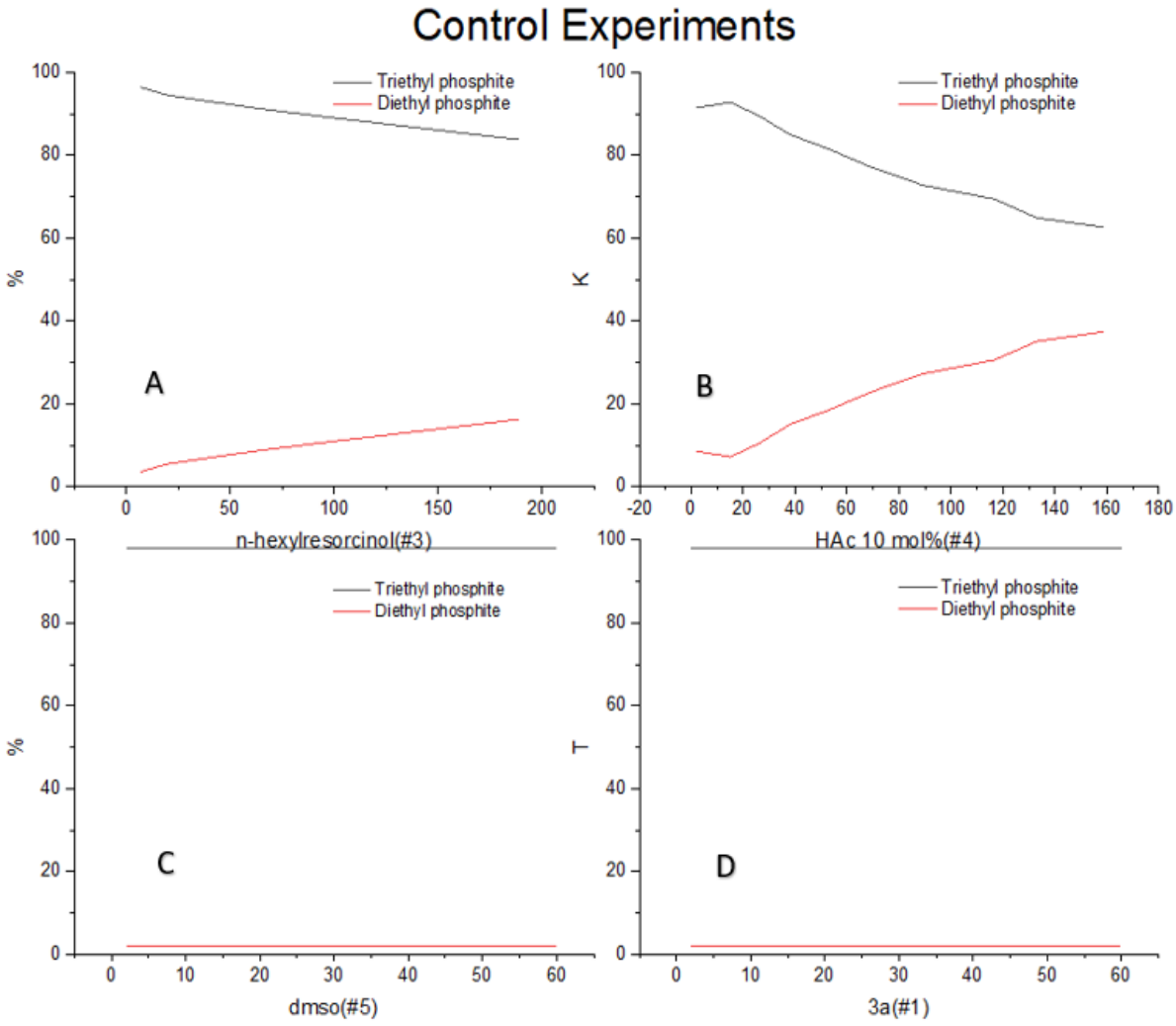
Conversion and product formation for the reaction of **2d** in chloroform-d at rt; bottom) **1**$_6$.(H2O)$_8$ 5 mM **2d** 50 mM ; top) **1**$_6$.(H2O)$_8$ 5 mM **2d** 50 mM and $^{+}$N(Bu)$_4$Br^{-} 25 mM.



Conversion and product formation for the reaction of **2j** in chloroform-d at rt; bottom) $\mathbf{1}_6.(H2O)_8$ 5 mM **2j** 50 mM ; top) $\mathbf{1}_6.(H2O)_8$ 5 mM **2j** 50 mM and $^{+}N(Bu)_4Br^{-}$ 25 mM.

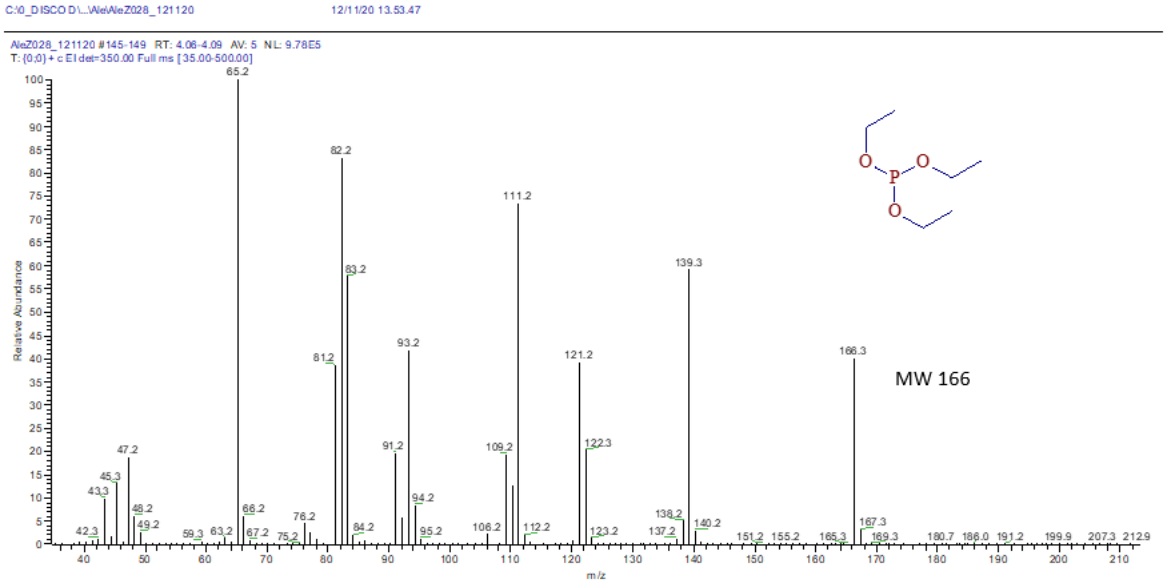


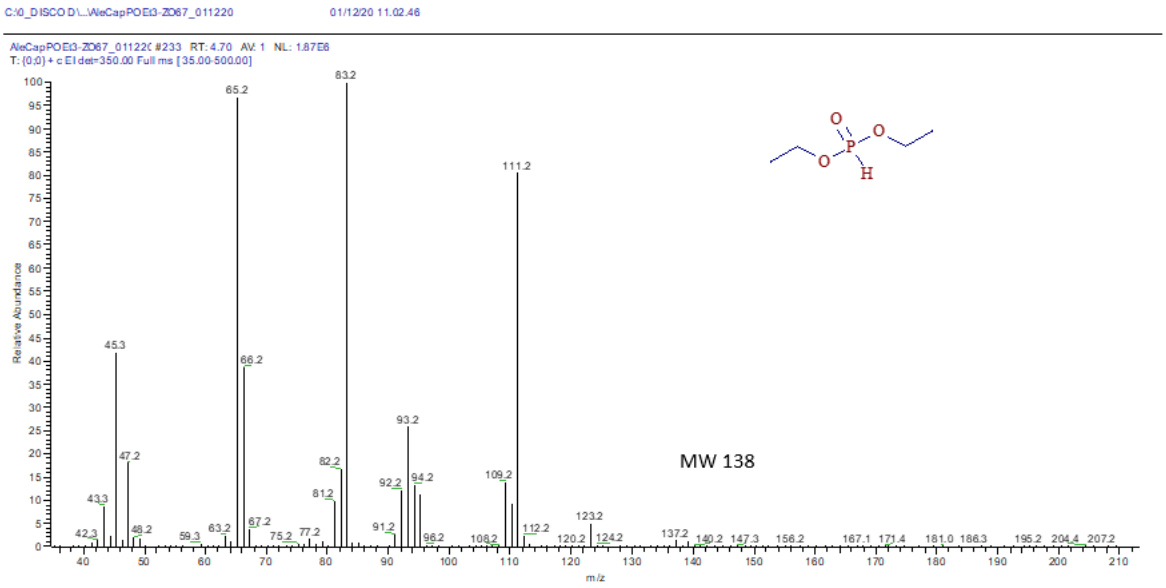
Conversion and product formation for the reaction of **2e** in chloroform-d at rt; bottom) **1**$_6$.(H2O)$_8$ 5 mM **2e** 50 mM ; top) **1**$_6$.(H2O)$_8$ 5 mM **2e** 50 mM and $^{+}$N(Bu)$_4$Br^{-} 25 mM.

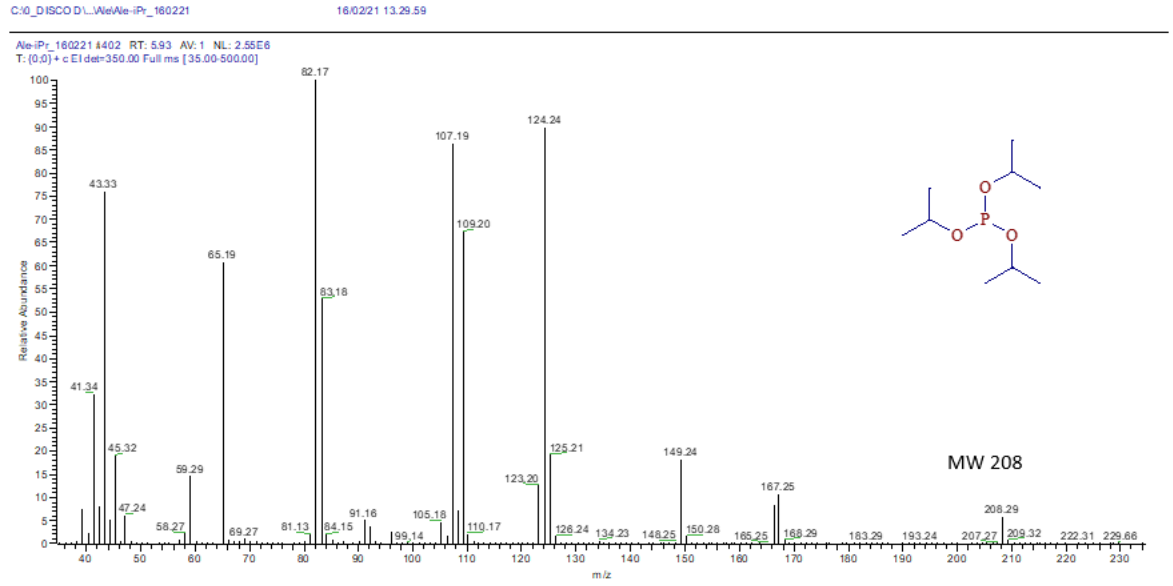


Control experiments A) table 1, entry 3;B) table 1, entry 4; C) table 1, entry 5; D) table 1, entry 1

GC/MS characterization



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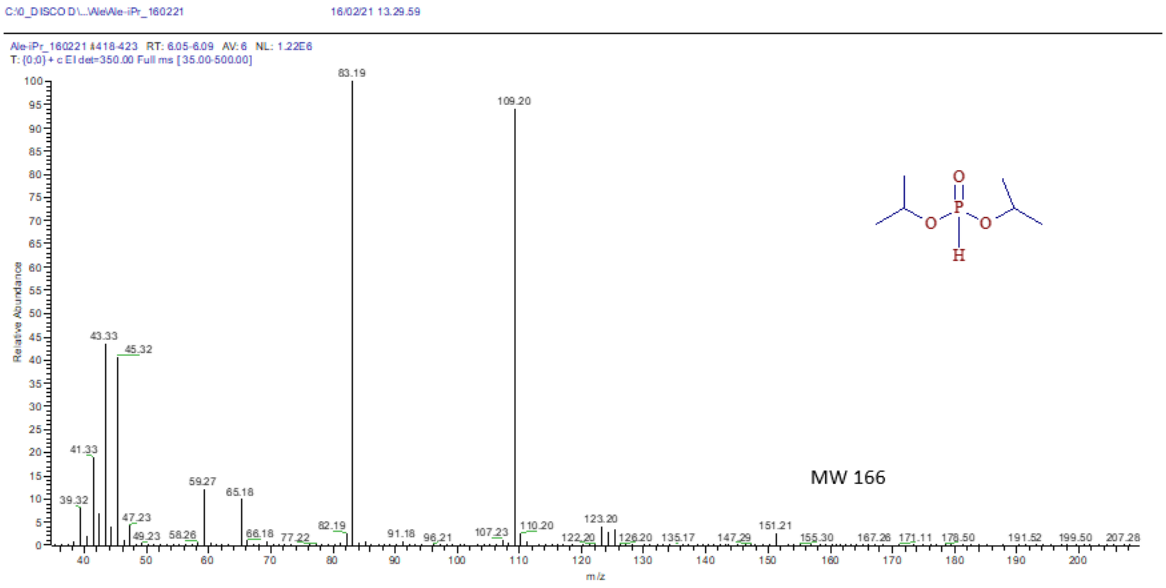
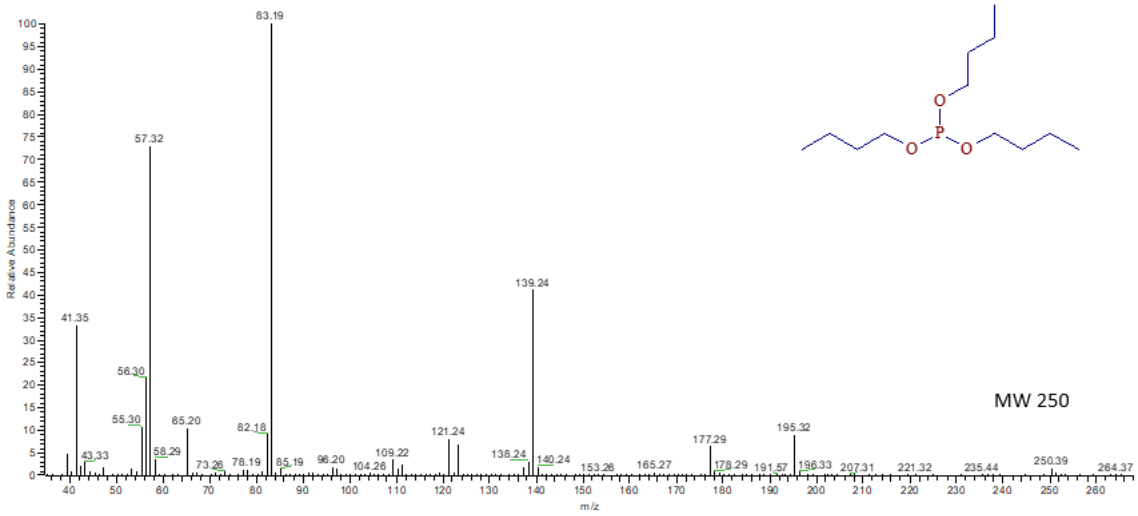
Relative Abundance
m/z
MW 208


C:\0_DISCO D\...\Ale\Ale-iPr_160221
16/02/21 13.29.59
Ale-iPr_160221 #418-423 RT: 6.05-6.09 AV: 6 NL: 1.22E6
T: {0;0} + c EI det=350.00 Full ms [35.00-500.00]
Relative Abundance
m/z
MW 166

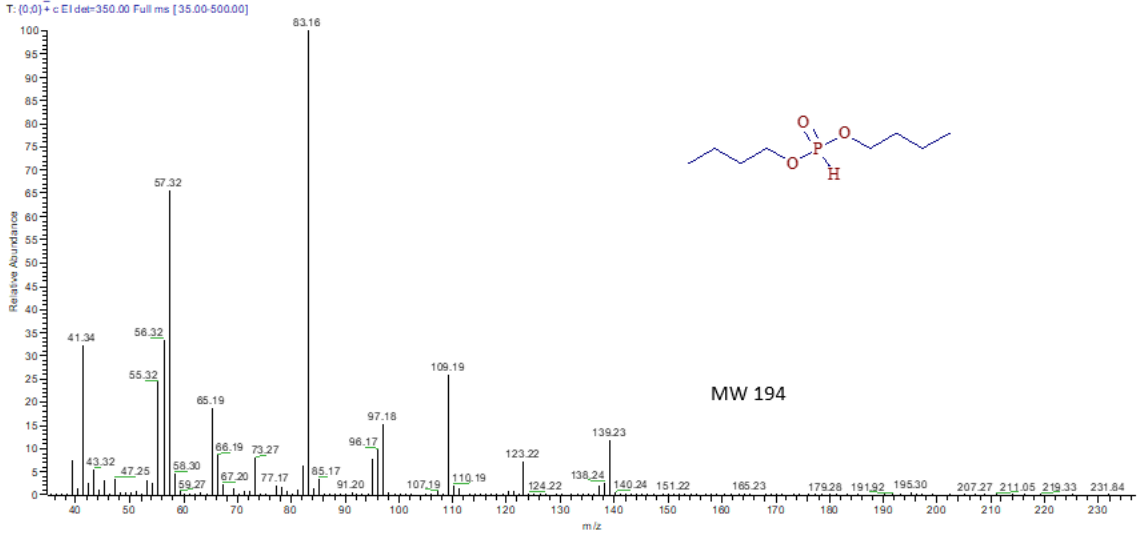
C:\0_DISCO D\...\Ale\Ale-Bu_160221 16/02/21 14.07.04

Ale-Bu_160221 #864 RT: 9.31 AV: 1 NL: 2.28E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



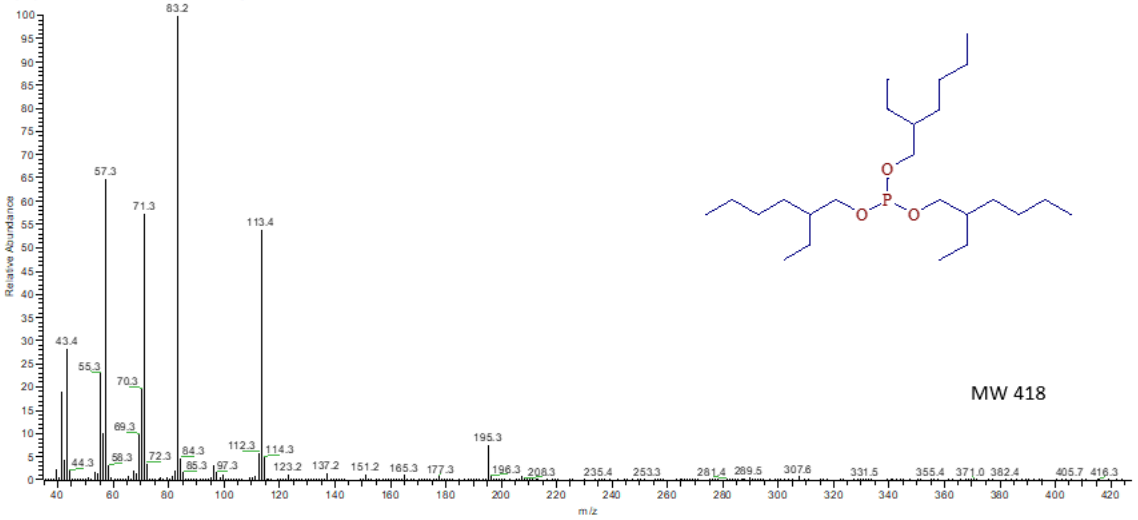
c:\0_disco d\...\ale\ale-buc_160221 16/02/21 14.24.10

ale-buc_160221 #790 RT: 8.77 AV: 1 NL: 2.81E6
T: {0,0} + c EI det=350.00 Full ms [35.00-500.00]



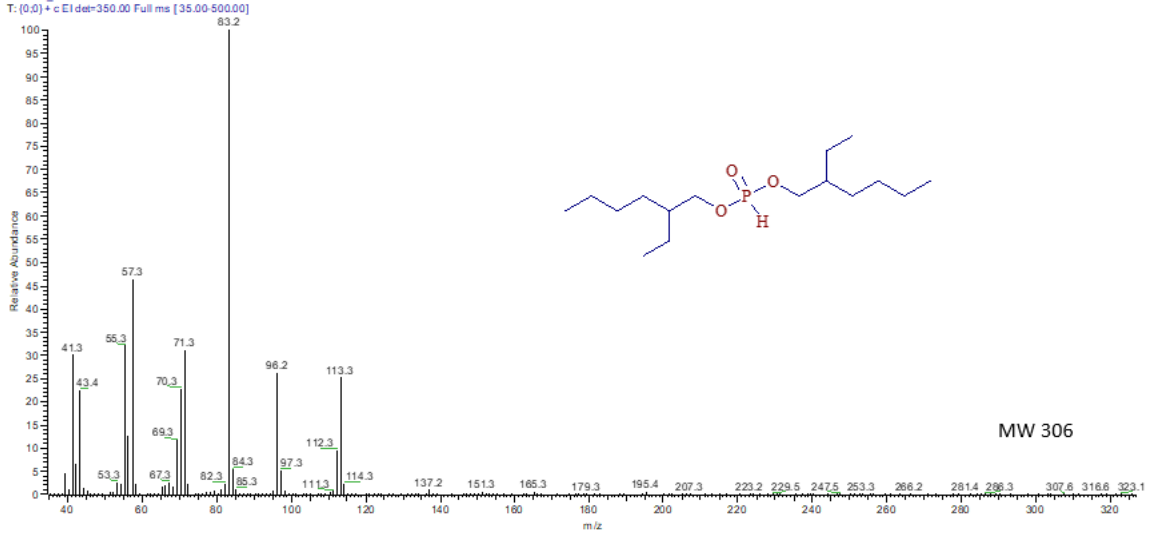
C:\0_DISCO D\...\Ale\Ale-2EH_160221 16/02/21 14.41.52

Ale-2EH_160221 #1277-1281 RT: 12.32-12.35 AV: 5 SB: 3 11.40-11.41 NL: 8.72E5
T: {0;0} + c EI det=350.00 Full ms [35.00-500.00]



C:\0_DISCO D\...\Ale\Ale-2EH_160221 16/02/21 14.41.52

Ale-2EH_160221 #1155-1157 RT: 11.43-11.45 AV: 3 SB: 3 11.40-11.41 NL: 3.35E5
T: {0;0} + c EI det=350.00 Full ms [35.00-500.00]



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