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The art of compartment design for synthetic catalysts

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REVIEW

The art of compartment design for synthetic catalysts

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Confining synthetic catalysts in nanoscopic compartments has been gaining traction as a method to introduce additional levels of control in catalytic transformations. Running reactions inside of compartments is ubiquitous in biology, and recent attention has turned toward applying the same principles to synthetic systems. This perspective attempts to ellucidate compartment design principles and identify shortcomings of current methodologies. We start by using enzymes as an exemplar model system for biological compartments, extrapolate guiding principles, and apply them to organometallic catalysts. Structure and space are then explored as overarching design principles at work in compartmentalization. Finally, suggestions for future directions are provided. Compartmentalization has the potential to become a powerful synthetic tool, however, further work in understanding the fundamental principles at play is required. Herein, compartmentalization is presented as an important synthetic strategy guided by biomimicry.

Introduction

One of the goals of catalysis is to obtain a bio-like level of control over chemical transformations, which in chemical terms translates to highly active and selective catalysts.[1-4] Unfortunately, synthetic catalysts often fall short of their enzymatic counterparts by sacrificing selectivity and turnover number in favor of a broad substrate scope.[4] The superiority of enzymes in these categories can be attributed in part to their exquisite control over the chemical environment of the catalytic pocket. From a reductionist point of view, the tertiary structure of an enzyme confines the active site from the protein's external environment. This confinement offers an additional level of chemical definition often not considered when designing catalysts.[5] Confining the active site contributes to the enhanced properties of enzymatic catalysis, and in return, offers an additional synthetic tool to consider.

Intuitively, the easiest way to confine a catalyst is to place it inside a "compartment".[6] However, what defines a compartment is necessarily broad. As a starting point, we will consider a compartment to be any open system in which a chemical reaction takes place. Under this first iteration of the definition, a reaction taking place in an uncapped round bottom flask can be considered a reaction inside of a compartment; at the opposing extreme, astrochemical reactions have only energetically imposed physical limitations as to how they interact with the external environment.[7] In contrast, the reaction inside a flask is confined from mixing with its bulk external environment except through the opening at the top of the flask. This macroscopic example of a compartment exhibits how confinement is already well established in chemistry: compartments confine chemicals in an environment suited for us to study their reactivity. However, the more interesting frontiers of compartmentalization happen in nanoscopic systems.[8-12] These types of compartments offer the same benefits as their macroscopic counterparts in terms of studying reactivity, but they also introduce novel opportunities to study molecular control.

The increased levels of control that nanoscale compartments offer are the next step toward achieving biomimetic systems. Confined systems have been reviewed extensively in the literature,[13-25] therefore, we will only try to elucidate the main design principles at work in confinement chemistry. In this perspective, we will cover a set of unique catalysts in different types of confined environments and comment on how these systems are designed before providing suggestions regarding the utility of confinement.

A definitional example: cells & enzymes

Given that biomimetic catalysis is the ultimate goal, it is useful to take metalloenzymes as the exemplar case of organometallic confinement and create a top-down model of what makes a nanoscopic compartment. When a hypothetical enzyme A is inside a cell, the enzyme is naturally confined within the cell membrane.[26] However, cells are still open systems, and molecules of certain types are allowed to flow in and out. If one of those molecules is a substrate for enzyme A, we can consider the enzyme to be confined within the open system of the cell with limited access to potential substrates. Therefore, the principal function of the cell membrane, and thus of a compartment, is to control diffusion of substrates.[27] Confinement is useful because it introduces a form of control by limiting what species can access the catalyst. It should be noted that confinement of the catalyst in this manner is often not necessary for the catalyst to perform its synthetic duty, as enzymes still perform well in cell lysates.[28] However, confinement can be beneficial in limiting promiscuity and, therefore, fine tuning a catalyst's application.

However, we must also consider why the active site of enzyme A is non-promiscuous even in the mixture of substrates that can access it. Ultimately, structure dictates function.[29-31] The folding of the protein creates a cavity that limits – beyond mere diffusion – how

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certain substrates reach the active site based on their size and shape. This limitation is so good that it can even cause stereoselective reactions to occur.[32] Consequently, the ultimate compartment for a catalyst is one that can control both diffusion of unwanted substrates and orient the correct ones. With this system in mind, we will categorize several examples found in literature working counter clockwise around Figure 1 in an attempt to elucidate design principles for creating confined catalysts.

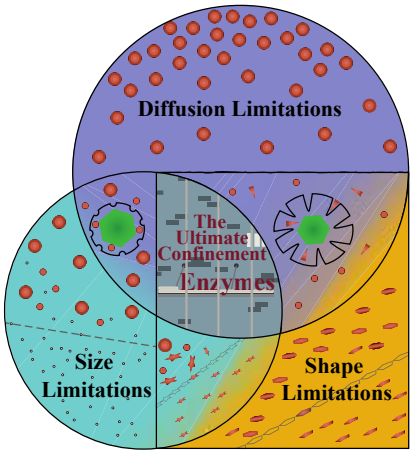

Figure 1 Venn diagram showing the three uses of confinement and how they overlap.

Guiding principles

Pure diffusion limitations

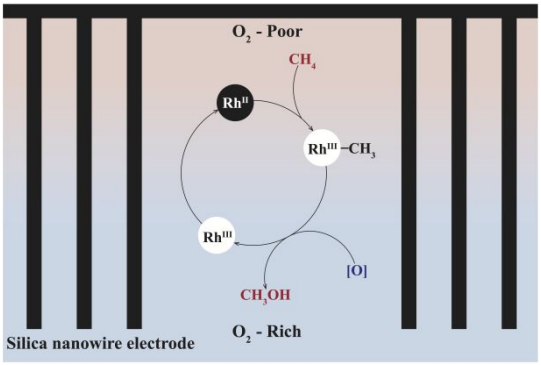

Figure 2 Silica nanowire array exemplifying diffusion limiting control. Adapted with permission from ref. 34. Copyright 2019, American Chemical Society.

Much like the case of a single cell, the properties of a compartment can help control the bulk diffusion of certain species. A practical use of controlling diffusion is the exclusion of potentially poisonous species from the reaction. In cases of catalytic poisoning, it is possible to design a compartment that allows just that.[33] Liu and coworkers were able to create an anoxic microenvironment that prevents oxygen poisoning of the catalyst, yet still allowed O_2 to be used in the oxidation of methane to methanol (Figure 2).[34, 35] In the presence of O_2, the oxidation of the Rh^{II} tetramesityl porphyrin metalloradical ((TMP)Rh^{II}) to form a Rh^{III} superoxo species is kinetically faster than the C-H activation step to form (TMP)Rh^{III}-CH_3. However, by applying a voltage to eliminate oxygen from the bottom of the compartment, (TMP)Rh^{III}-CH_3 is allowed to form and can react with the superoxo species to produce CH_3OH. Since oxygen is being consumed in the reaction, a gradient is created where there is less O_2 at the base of the array than at the top. This gradient allows the conversion of methane to methanol to proceed without complete formation of the kinetically favored Rh^{III} superoxo species. In this sense, (TMP)Rh^{II} is confined to the anoxic environment created by that array, and it is allowed to diffuse from the O_2-free to the O_2 rich environment as mechanistically necessary. By introducing diffusion limitations, kinetic factors could be manipulated, not possible to do in non-confined systems, and, in this instance, changing kinetic factors ultimately led to enhanced reaction rates and turnover numbers for the catalyst and, ultimately, being able to combine two otherwise incompatible reactions.[33]

Examples of purely diffusion limited systems are difficult to find because they are almost exclusively related to engineering issues. Diffusion is a bulk process, so there is a necessary level of abstraction from a chemical to a physical model where the approach of the substrate to the catalyst is no longer considered. Consequently, most diffusion limiting cases have a great emphasis on reactor design. In order to utilize diffusion limitations in confinement chemistry, the system ultimately needs to be thought of in physical terms – a point that most confinement literature misses.

Diffusion & size limitations

Diffusion and size are inherently linked concepts, classically related via the Stokes-Einstein equation.[36] As a result, a lot of diffusion limited confinement relies on bigger molecules diffusing at slower rates than smaller ones. However, diffusion limitations can also be based on the hydrophilicity of compounds, as the polarity of molecules has been shown to influence how molecules traverse surfaces.[37-39] As a working definition, we will consider a diffusion and size limited case to that combines both size and polarity of the compounds in its effect.

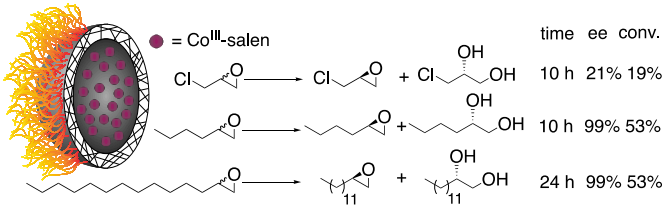

Figure 3 Micelle with a cross-linked inner core capable of discriminating between compounds based on both size and hydrophilicity. Adapted with permission from ref. 40. Copyright 2011, American Chemical Society.

Micelles are an interesting case study for diffusion limited systems as they closely mimic the ability of the cell membrane to dictate which molecules can cross. Weck and coworkers created a shell crosslinked micelle with a cobalt(III)-salen core that can selectively hydrolyze hydrophobic epoxides over hydrophilic ones (Figure 3).[40] Therefore, by confining the catalyst inside the micelle, the compartment introduces diffusion limitations on the basis of hydrophilicity. Additionally, within the scope of the hydrophobic epoxides they screened, smaller epoxides hydrolyzed faster than

larger epoxides. This phenomenon was not observed in the non-crosslinked version of the micelle and shows size discrimination due to the presence of crosslinks.[41] As a result, the micelle has a dual purpose in how it can discriminate between substrates on the basis of both diffusion and size.

Size limitations

While diffusion is mainly based on size, systems exploiting size differences do not have to rely on diffusion, but they can instead introduce physical blockages to restrict the flow of larger molecules. Size limitations are inherently different from diffusion limitations as the polarity of the substrate is not considered. Much of the current literature on confinement is based on substrate discrimination. From a research chemist's perspective, it is rare to deal with mixtures of undesirable substrates as the starting point for a reaction. Consequently, discrimination is only empirically useful when a mixture of those materials naturally exists. However, keeping the biomimetic goal in mind, the ability of enzymes to discriminate between substrates is essential for their function. Therefore, in order to achieve biomimetic catalysis, organometallic catalysts should be able to mimic substrate discrimination as closely as enzymes.

One of the most common starting places in studying discrimination is to limit the size of the substrates that can reach a catalytically active site. This type of chemistry is generally based on filtering substrates through a pore where only the smaller of two species can pass. As a result, examples of size limitations rely on the larger of substrates not being able to fit through the porous container due to steric constraints.[24] Substrate size filtering is fairly easy to implement and there are plenty of examples in cyclodextrin/cavitand chemistry, supramolecular host-guest chemistry, and ligand templating approaches.[13]

In a typical example of size filtering, a manganese porphyrin catalyst is constrained inside of a box comprised of zinc porphyrin complexes on the top and bottom and tin porphyrin complexes on the facial sides (Figure 4).[42] Epoxidation of a less sterically bulky alkene occurs preferentially to the epoxidation of a more sterically bulky alkene due to the accessibility of the manganese face. The main point being that the catalytically active metal must necessarily be protected on all sides to achieve discrimination. Regardless, confinement based on size limitations can be intuitively thought of as simple pore filtration. Size discrimination ultimately becomes a two-dimensional problem because these systems have no ability to distinguish between the depths of the molecule. All that matters at any given angle of approach is the size of the projection of the substrates shape onto a two-dimensional plane. The catalyst sits far enough away from the pore that the substrate's shape becomes inconsequential to the filtration. In pure size limitation cases, the size of the entrance to the compartment plays an essential role in the effects of confinement.

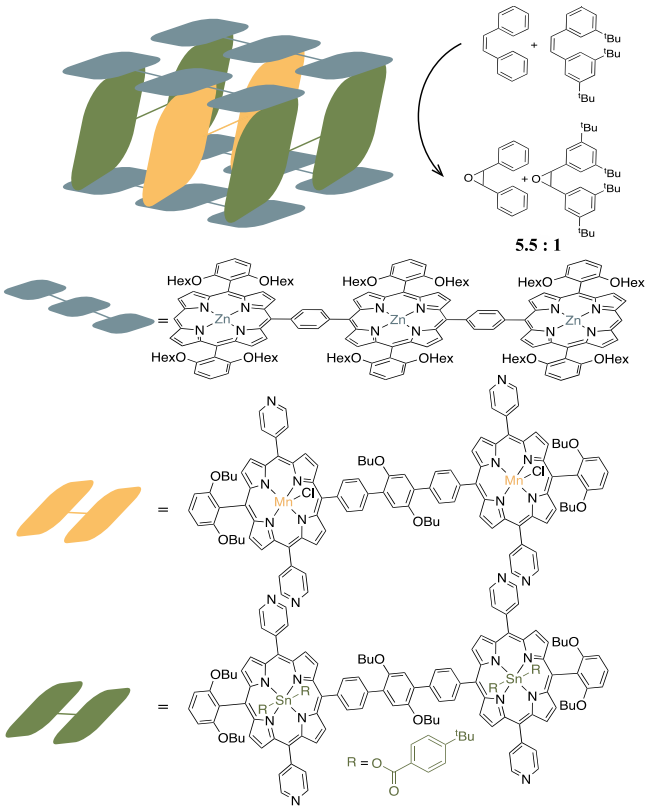

Figure 4 Ligand templated porphyrin box capable of discriminating based on size. Adapted with permission from ref. 42. Copyright 2011, American Chemical Society.

Shape & size limitations

Shape discrimination introduces increased selectivity into a confined system because the substrate now needs to approach the active site with a specific orientation. While shape discrimination alone can lead to stereo- or enantioselective reactions, incorporating a size component can further alter selectivities.[43, 44] Together, shape and size are the main aspects of enzymatic systems that affect the binding of the substrate, as they are directly related to the occupation of the binding site.[45] Therefore, the combination of these two limitations leads to a true microanalysis of substrate approach as they are inherently concerned with the chemical reaction at the active site itself rather than simple physical blockages.

One of the earliest successful examples that combines shape and size discrimination between substrates is a preferentially large substrate catalyst produced by Brauman and coworkers in 1990.[46] Using Mn(TTPPP(OAr)) ((5,10,15,20-tetrakis(2',4',6'-triphenylphenyl)porphyrinato)manganese(III), OAr = 3,5-di-*tert*-butyl-phenoxide) as a catalyst and iodosylbenzene as a stoichiometric oxidant in dry acetonitrile, they were able to achieve a >1000:1 preference for the epoxidation of large disubstituted alkenes over smaller trisubstituted alkenes, exclusively forming the *S*,*R*-stereoisomer from internal alkenes (Figure 5). Importantly, when the X-type axial ligand was replaced with an L-type ligand such as a 3,5-disubstitued imidazole, this selectivity disappeared suggesting that the reactivity in the X-type ligand case proceeds inside the cavity and not at the open face.[47] These results indicate that confinement

based on both shape and size limitations can alter the orientation of substrates toward a catalyst lending itself to selective reactivity.

One of the great advantages of size and shape limited systems is their ability to alter catalytic pathways by changing transition state barriers.[48] These systems can give access to different catalytic outcomes that would not be accessible without confinement just by altering substrate approach. However, *de novo* construction of a confined system for a specific synthetic problem is rarely worth the effort, and the best bet is probably an *ab initio* guided design from known synthetic systems.[49] Nevertheless, all design of shape and size limited systems need to consider the space within the cavity and consider critically the effects different spaces will have. By altering the type and amount of space a catalyst is confined within, control in both substrate approach and substrate release can be introduced, and this is even more useful if the desired product is an intermediate in a catalytic cycle.[50-52] Controlling the space inside a compartment is an important aspect of confinement design.

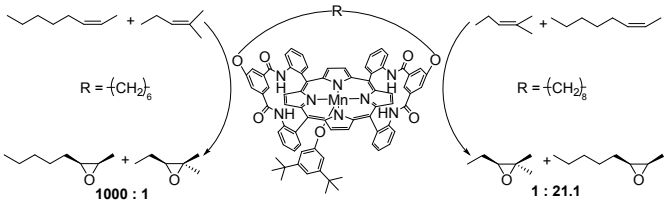

Figure 5 Porphyrin picnic basket compound showing shape and size discrimination. Adapted with permission from ref. 46. Copyright 1990, American Chemical Society.

Shape limitations

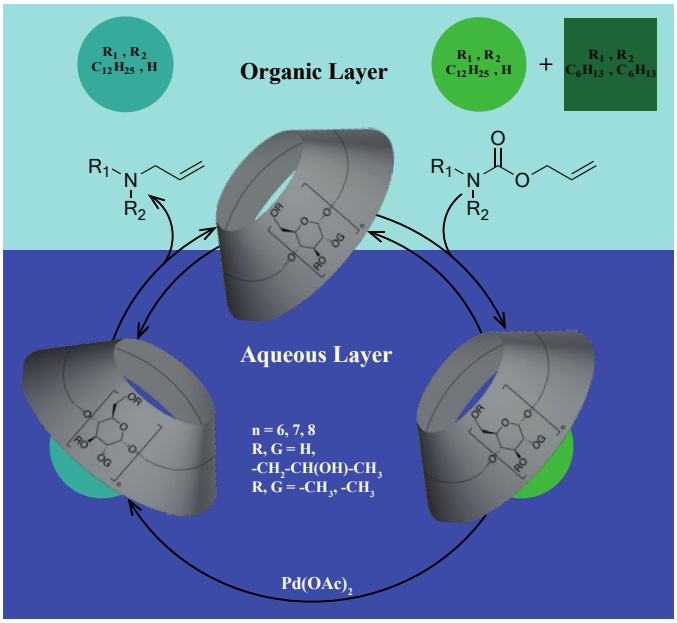

Figure 6 Cyclodextrins transporters selecting based on substrate shape. Adapted from ref. 54 with permission from Elsevier.

In general, shape limitations refer to the overall physical shape of the substrate from a steric viewpoint. Consequently, shape selectivity is one of the main ways enzymes are able to discriminate between different substrates. Molecular recognition is a key aspect to consider when trying to design biomimetic systems. Enzymes are able to achieve molecular recognition through a variety of ways such as modifying pocket size, or introducing new hydrogen bonding or salt bridge interactions.[53] However, engineering these moieties into catalytic containers is time consuming and costly, and as a result, most examples of shape discrimination in organometallic compartments are fairly rudimentary.

A good example of a shape discrimination system was reported in 2005 by Monflier and coworkers (Figure 6). Various cyclodextrins were used as phase transfer reagents to transport *N*-dodecyl-*O*-allylurethane over *N*,*N*-dihexyl-*O*-allylurethane preferentially from an organic phase to a water soluble organometallic catalyst resulting in decarboxylation.[54] In the absence of cyclodextrins, the reaction rate was relatively slow at only 0.03 h^{-1}. However, it could be increased by over 150-fold in the presence of methyl-α-cyclodextrin with a 7:1 preference for *N*-dodecyl-*O*-allylurethane, and the preference could be increased to 20:1 if small amines such as diethyl amine were added. Interestingly, both the shape and size of the cyclodextrin was important for discriminating between the urethanes. Larger cyclodextrins and those containing 2-hydroxylpropyl instead of methyl groups showed decreases in selectivity with only around a 4:1 preference for *N*-dodecyl-*O*-allylurethane. This difference in selectivity implies that the cyclodextrins are capable of discriminating between the two molecules based on shape, and that some optimum cavity design exists for facilitating the discrimination.

In reality, cyclodextrins are frequently used to discriminate based on shape in confinement issues although the catalyst is normally confined inside the cavity of the cyclodextrin.[55, 56] While they do not necessarily provide a well-defined shape recognition, cyclodextrins introduce a three-dimensional argument in confinement. Unlike confinement that limits the size of molecules through pores, confinement that limits shape must consider the depth of the compartment as a fundamental tool in shape recognition. While current shape limitation systems are not as sophisticated as enzymatic regulation, compartment depth is an important design element to consider in confinement.

Diffusion & shape limitations

Considering compartment depth on a larger scale than just the microenvironment of the catalyst allows the incorporation of diffusion limitations along with shape limitations. The linking of these two concepts is how cells control what materials reach an enzyme in order to limit promiscuity. As a crude example, secluding DNA synthetase inside of the nucleus ensures access to template DNA strands while still being selective for deoxyribonucleic acids over ribonucleic acids.[57] In 2012, Song and coworkers reported a diffusion-induced shape-selective Suzuki coupling reaction inside the pores of a mesoporous palladium nanoreactor (Figure 7).[58] In this system, palladium nanoparticles sit at the bottom of silica pores, and various phenylboronic acids adsorb onto the silica walls, effectively creating tunable pore diameters. When larger phenylboronic acids are used, iodobenzene is not able to reach palladium, and only a trace of product is observed. However, upon mixing small and large phenyl boronic acids, the conversion of both acids to the coupled

product is observed. The authors suggest the conversion of both acids is a consequence of the formation of an incomplete diffusion barrier, i.e., mixing the adsorption of both small and large phenyl boronic acids allows iodobenzene to pass through because of the open pores left by the adsorbed small acids. Shape selectivity of the catalyst is also observed with *ortho*-carboxyphenylboronic acid after only achieving a trace conversion to the coupled product after 3 hours of residence time but *para* and *meta*-carboxyphenylboronic acids achieved ca. 60% conversion after only 3 minutes. This difference was not observed in the Pd/C model system, and, therefore, it was considered an emergent property resulting from the confinement.[59]

Mesoporous silica nanoparticles are a good example of a system capable of regulating both shape and diffusion. The cavity depth employed is longer than what is used in shape limiting cases alone and allows for diffusion aspects to be incorporated into the confinement. While the mechanism for the shape limitation observed is unknown, it is not unreasonable to assume it stems from an orientation issue. Overall, even though this example is relatively complicated, it offers proof of concept that diffusion and shape limitations can exist in smaller and slightly more defined systems than purely diffusion or purely shape limited systems alone.

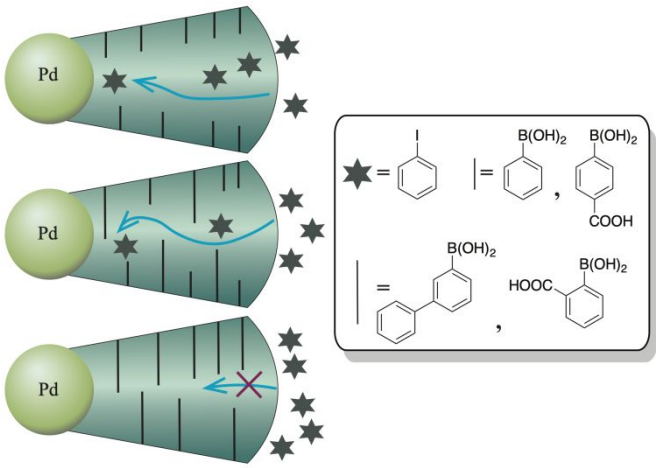

Figure 7 Pores of mesoporous silica nanoparticles with different phenyl boronic acids adsorbed as a way to tune substrate accessibility to a palladium catalyst. Adapted with permission from ref. 58. Copyright 2012, American Chemical Society.

Design aspects

Up to this point we covered a silica nanowire array, micelles, porphyrin boxes, basket handle compounds, cyclodextrins, and nanoparticles as examples of different categories of confined catalysts, and some clear trends are apparent. In order to design a successful compartment, the two biggest aspects to consider are its physical structure and space within. In this section, we break down how to consider those two aspects when designing compartments (Figure 8).

Most physical structures do not need to have strict chemically defined components since the main role that structure plays is limiting *what* has access to the catalytically active site. This lack of strict definition can be beneficial since it prevents catalysts from having too narrow of a reaction scope. Structural aspects can be applied to both diffusion and size problems. For diffusion issues, the material the structure is made from can have a profound impact on what can access the catalyst such as the micelles selecting for hydrophobic molecules as discussed earlier. Size problems are even easier to consider since all they necessitate is tuning of pore size. However, it needs to be stressed that physicality is a compartment construction problem, and it needs to be thought of separately from the space it creates. Multiple components need to be present in a system, but if they are not arranged the right way, the compartment will not have the desired effects. The best structures have additional layers of modification that can be woven into their construction (i.e., passing a current through a nanowire array or crosslinking the micelles) to increase the amount of control over chemical transformations. However, construction aspects will only be able to modulate bulk properties owing to their lack of atomistic definition.

Space, on the other hand, deals with *how* a substrate has access to a catalyst. Space is considered on much smaller terms than physical aspects because with proper space control, one can also control the orientation of the substrate. Space can be easily affected by minor chemical changes, such as substituting a methyl with a *tert*-butyl to force substrate orientation into a different direction. Space mainly encompasses shape limitations and is necessarily atomistic. In that way, space becomes important in altering catalytic pathways by forcing alternate orientations.[48] Space is ultimately a fine tuning issue, and likely will require some aspect of trial and error for figuring out how to trim cavities, and what contributions small changes have on the final reaction outcome.

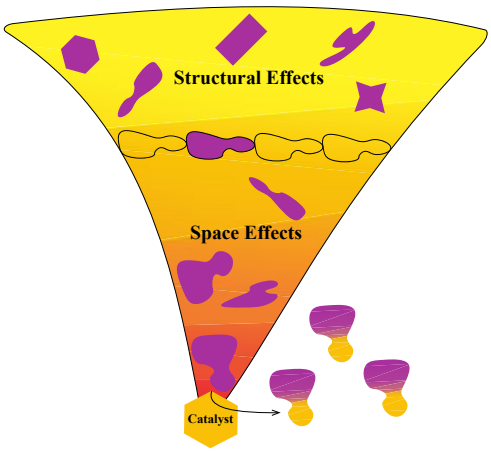

Figure 8 Design of compartments must take both structural and space effects into account.

This naturally leaves the question of *when* and *how* to implement these strategies in deciding whether to pursue compartmentalization as a synthetic methodology. As a reflection of the literature, the majority of the examples provided here focus on substrate discrimination between large organic molecules.[13] However, in our opinion, the future of the field lies in applying the lessons learned from organic molecule discrimination to small molecule discrimination and activation, for example, in simultaneous gas separation and catalysis. Compartmentalization presents a tangible method both to circumvent the poisoning of catalysts – as

noted in the pure diffusion case – as well as to discriminate between different molecule types. The combination of these strategies relies heavily on engineering additional functionality into the compartment beyond pure structural considerations. To be explicit, the space within a structure already has inherent definition, but the functionality of that space is often ignored. To make a biological analogy, ignoring functional aspects of a space is akin to putting metal oxide nanoparticles into a cell and expecting them to exhibit wildly different properties merely because they occupy a different location.[60] This way of thinking fails to incorporate *how* the nanoparticle interacts with the intracellular environment. In truth, we do not explicitly present *how* to implement these strategies, as implementation is highly dependent on the goals at hand, as reflected by the diverse breadth of the literature surveyed. We merely come to the conclusion that there are in fact unifying themes in designing a compartment that correlate to biological motifs. The use of this work therefore lies in explicitly defining what those motifs are to give other researchers a framework in which to consider compartmentalization in catalysis.

The one thing nature has been able to do rather well that humans have not quite been able to match is combining structure and space effects in catalysts. The scaffold of the cell membrane and the scaffold of the enzyme work synergistically to ensure only certain substrates have access to the active site. Cell membranes help with bulk diffusion and amino acids control the space around the active site. Active site control is so important that mutations in an amino acid sequence close to the active site have a major impact on catalytic activity.[61] Future work in compartments needs to start taking a critical look at how to incorporate both structure and space together to mimic enzymatic catalysis closely.

Conclusion

True atomistic control over compartment space as is observed in enzymatic reactions has yet to be achieved, but that begs the question of whether it is necessary. Enzymes are hyper specific in their substrate scope, something that historically has not been important in chemistry.[62-64] What has been important is gaining a basic understanding of how certain substrates can be manipulated. Since the molecular chemist can afford to employ much harsher conditions than nature, the need for control over certain transformations does not exist. However, there is a green chemistry argument to be made in favor of compartmentalization.[65] Namely, being able to create the same harsh conditions – anoxic and water free environments – but on the nanoscale would lessen the required amount of energy and environmental taxation.

However, the barrier for creating widely accessible synthetic systems that operate at the nanoscale is currently too high.[66] As a consequence of how much effort needs to be put into creating a compartment, confinement chemistry currently only has two practical uses: altering reactivity and niche industrial applications (most often in the form of zeolites).[67] For the synthetic research chemist, being able to alter the energetics of catalytic pathways to reach different products will always be inherently interesting. Unfortunately, the vast portion of confinement research only considers discrimination between substrates and not changing catalytic pathways. Steric properties that alter pathways exist on the angstrom scale, but when the space of a compartment has to be designed to that precision, substrate scope becomes limited. Therefore, as an immediate grand solution, we see confinement as an answer to sustainability problems. A lot of effort needs to be put into designing compartments for catalytic problems, yet as long as fabrication techniques are not too harsh, confinement can introduce new and/or green ways to make certain compounds. If research efforts are going to be placed on creating novel confined systems, the systems need to be designed with specific end goals in mind rather than mere investigations of the effects small changes have.

Going back to the premise that our collective goal as a research community is to surpass biological systems, confinement of catalysts needs to be done with a purpose, and we believe a good starting place is to revisit reactions that nature has worked on for millennia.[68] For example, tackling small molecule activation problems — such as carbon dioxide reduction — and then designing a system with tangible confinement effects compared to no confinement, while simultaneously benchmarking the reactivity against nature, could be a beginning. Once truly biomimetic catalysis has been achieved under benign conditions, then compartmentalization in chemistry will have enough of a theoretical backing to push into other industrially and synthetically meaningful avenues. Hopefully, we have been able to shed some light on what to consider when creating compartments, by defining universal motifs such as the physical structure and the space the catalyst sits in, and are able to provide some directionality to the field for the future.

Conflicts of interest

There are no conflicts to declare.

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