

MOLECULAR FLASKS: CHEMICAL REACTIONS IN SUPRAMOLECULAR HOSTS

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INTRODUCTION

Inspired by the ability of enzymes to catalyze reactions under mild conditions with remarkable catalyst turnover, synthetic chemists have sought to identify low molecular weight macromolecular hosts that possess similar attributes.¹ Recent work has focused on supramolecular hosts formed via self-assembly through noncovalent interactions.² Much like enzymes, supramolecular hosts can encapsulate guest molecules and; in certain systems, act as molecular flasks facilitating synthetic transformations in the unique steric and electronic environment of the host cavity.³

FUNCTIONAL MOLECULAR FLASKS

Similar to enzymatic binding sites, the steric and electronic environment of the cavity influence reactivity in molecular flasks.³ In 1997, Rebek and coworkers reported the first self-assembled host that could serve as a reaction vessel, identifying a 200-fold rate increase in the Diels-Alder reaction between *p*-benzoquinone and cyclohexadiene when encapsulated in host **1**.⁴ Expanding on this work, Fujita and coworkers synthesized supramolecular host **2** via self-assembly through metal-ligand interactions.³ Host **2** was able to facilitate Diels-Alder reactions of several aromatic dienes including substituted anthracenes and naphthalenes.⁵ Steric constriction inside molecular flask **2** oriented substrates to lower activation energy and alter regioselectivity.

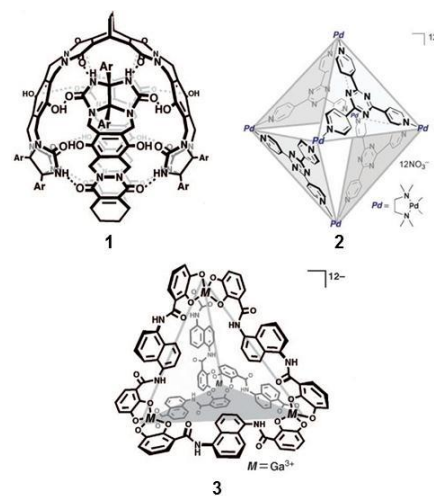


Figure 1. Self-assembled hosts developed by Rebek (1), Fujita (2), and Raymond (3).²

CATALYTIC TURNOVER IN SELF-ASSEMBLED MOLECULAR FLASKS

The greatest obstacle in achieving catalysis in supramolecular hosts is product inhibition since the products often have higher binding affinities and have lower solubility in water.³ Rebek and coworkers were able to modulate product binding affinity in the Diels-Alder reaction to achieve catalytic turnover.⁶ Raymond and coworkers have exploited the preference of host **3** to bind cationic guests to achieve catalysis in a variety of different ways.⁷ Initial studies focused on catalytic unimolecular rearrangements such as the cationic 3-aza-Cope rearrangement.⁸ The mechanism of this rearrangement has been extensively studied and an enantioselective variant has been reported.⁹ Expanding the scope of reactivity inside host **3**, Raymond and coworkers have also been able to achieve the acid catalyzed

Nazarov cyclization in basic media.¹⁰

One attractive feature of enzymes is their ability to sequester transition metal catalysts and prevent decomposition. Raymond and coworkers have successfully sequestered Ru and Au catalysts in host **3** that retain catalytic activity and are capable of high turnover numbers.^{11,12} This strategy enables transition metal catalysis in aqueous media of reactions that have previously only been possible in organic solvents.

CONCLUSION AND OUTLOOK

Self-assembly allows for rapid generation of complex supramolecular hosts that can act as nanoscale reaction vessels. Increased local concentration and molecular preorganization in supramolecular host cavities can result in increased reaction rate and unique regioselectivity. Overcoming product inhibition to achieve catalysis is a major concern yet has been accomplished by decreasing product affinity for the host and phase-transfer catalysis. Furthermore, incorporation of transition metal catalysts in supramolecular hosts prevents catalyst decomposition and allows for catalytic transformations in aqueous media. Expansion of the substrate scope of reactions in molecular flasks will facilitate acceptance of supramolecular catalysis as a viable strategy in organic synthesis.

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