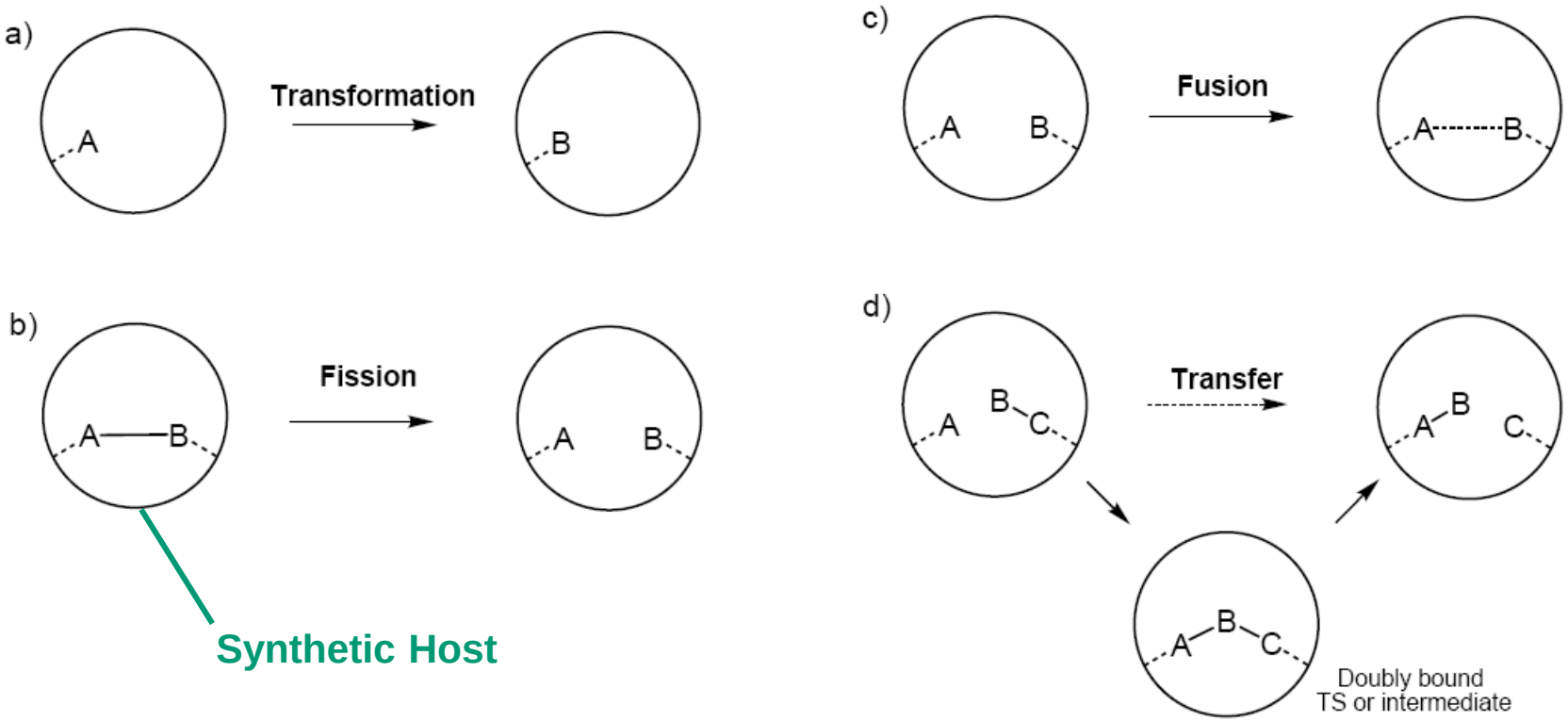
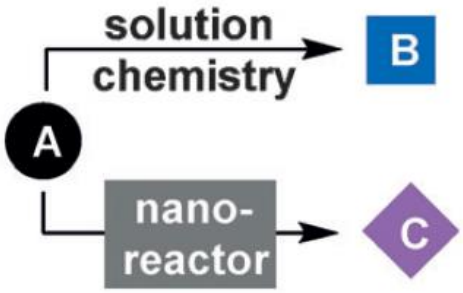
Supramolecular Catalysis



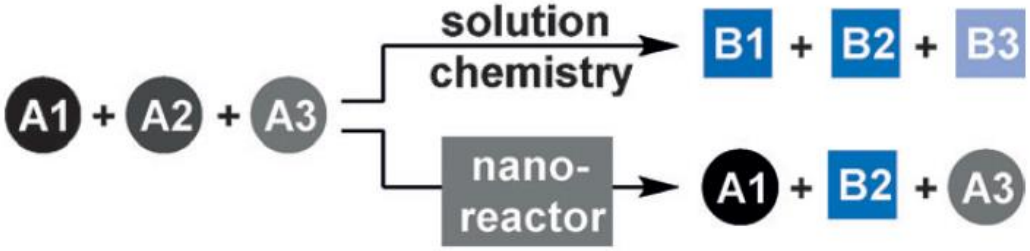
For the reactions c) and d), product inhibition can be a problem.

Advantages of Catalysis Inside Host Structures

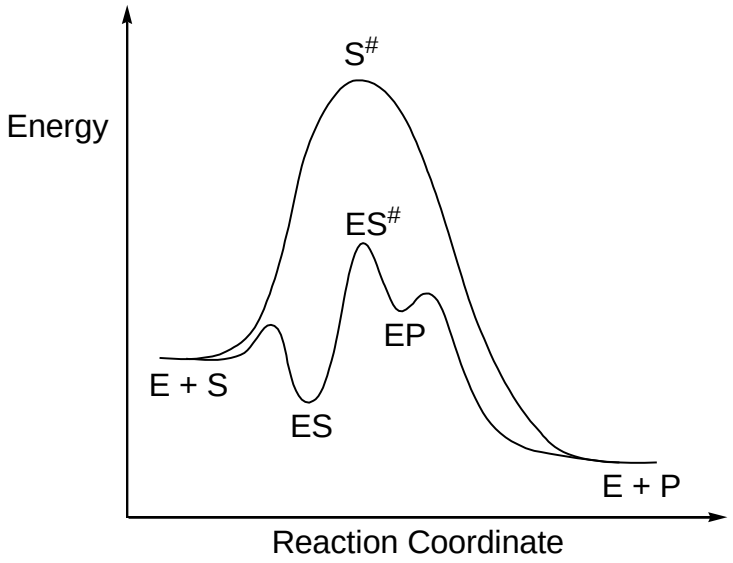
a) Product selectivity



b) Substrate selectivity

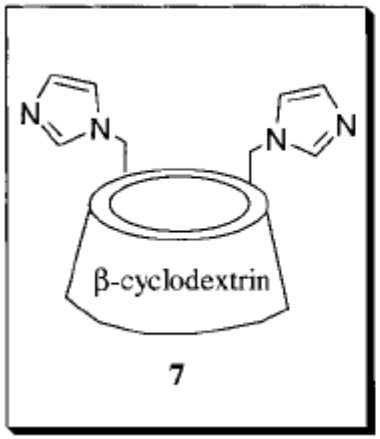


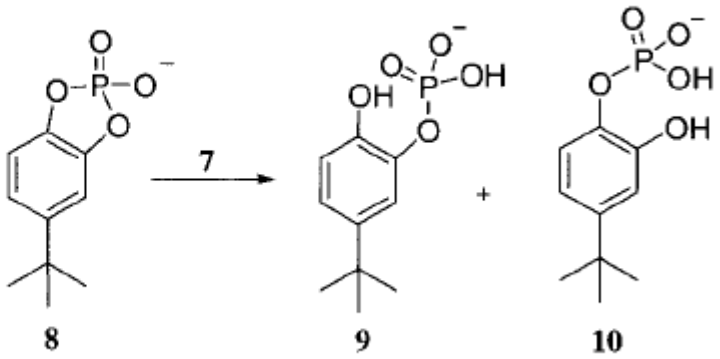
The Energetics of Enyzme Catalysis

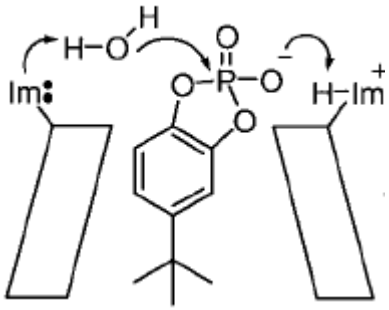


For a unimolecular reaction (S → P) the simplified energy profile is depicted. The activation barrier of the uncatalyzed reaction is represented by the energy difference of the substrate S and the transition state S#. In the presence of an enzyme (E), a complex ES is formed initially. During the course of the reaction, the enzyme is bound to the transition state ($ES^{\#}$) and to the product (EP). For catalysis to work, the difference in energy between ES and $ES^{\#}$ has to be smaller than the activation energy of the uncatalyzed reaction, meaning that the enzyme **preferentially stabilizes the transition state** of the reaction. To achieve catalytic turnover it is furthermore important that the complex between the enzyme and the substrate (ES) is thermodynamically more stable than the complex with the product (EP)

Cyclodextrins as Catalysts – Histidine Derivatives



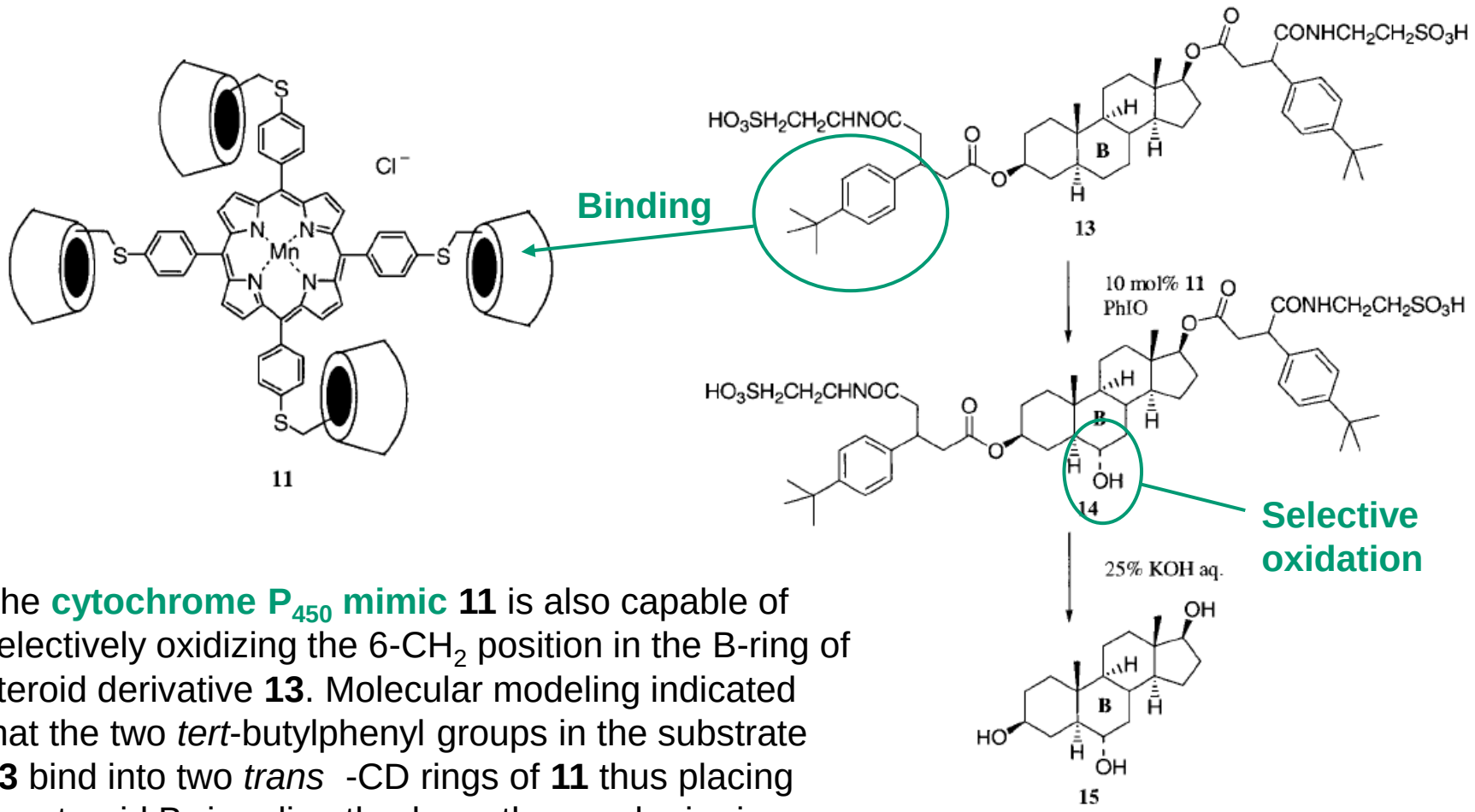




To mimic the enzyme ribonuclease A two imidazole rings were attached to the primary face of β-cyclodextrin. This mimic catalyses the hydrolysis of the cyclic phosphate **8** with a k_{cat} 120×10^{-5} s^{-1} compared to k_{uncat} 1×10^{-5} s^{-1} for the uncatalyzed reaction and shows greater than 99:1 selectivity for **9**. This is in comparison to the simple solution reaction with NaOH which gives a 1:1 mixture of both products.

R. Breslow and C. Schmuck *J. Am. Chem. Soc.* **1996**, *118*, 6601.

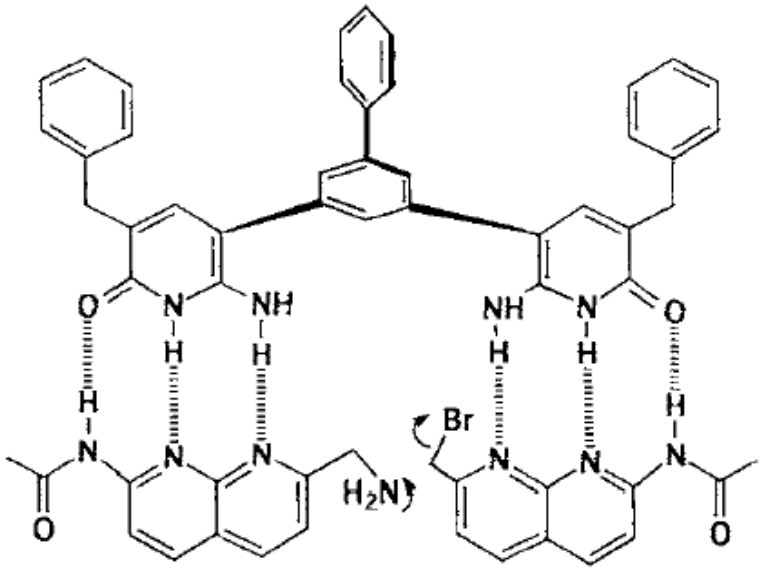
Cyclodextrins as Catalysts – a Cytochrome P_{450} Mimic



The **cytochrome P_{450} mimic 11** is also capable of selectively oxidizing the 6-CH_2 position in the B-ring of steroid derivative **13**. Molecular modeling indicated that the two *tert*-butylphenyl groups in the substrate **13** bind into two *trans* -CD rings of **11** thus placing the steroid B-ring directly above the porphyrin ring.

R. Breslow et al., *J. Am. Chem. Soc.* **1997**, *119*, 4535.

Preorganizing Substrates via H-Bonding



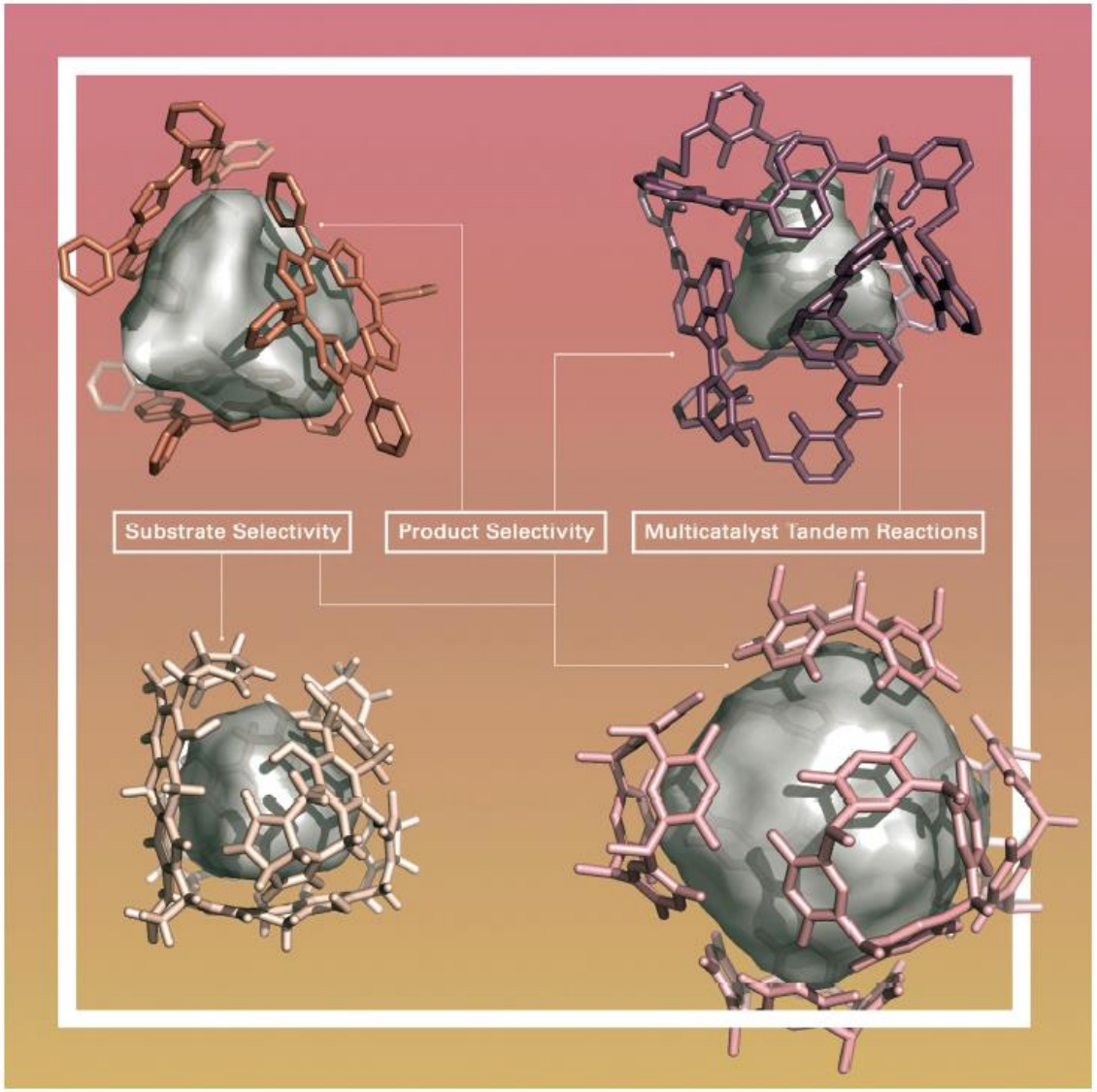
Reaction rate enhancement: only 6 times

Problems :

- No tunover
- Identical binding sites for two different substrates
- Host does not bind the transition state

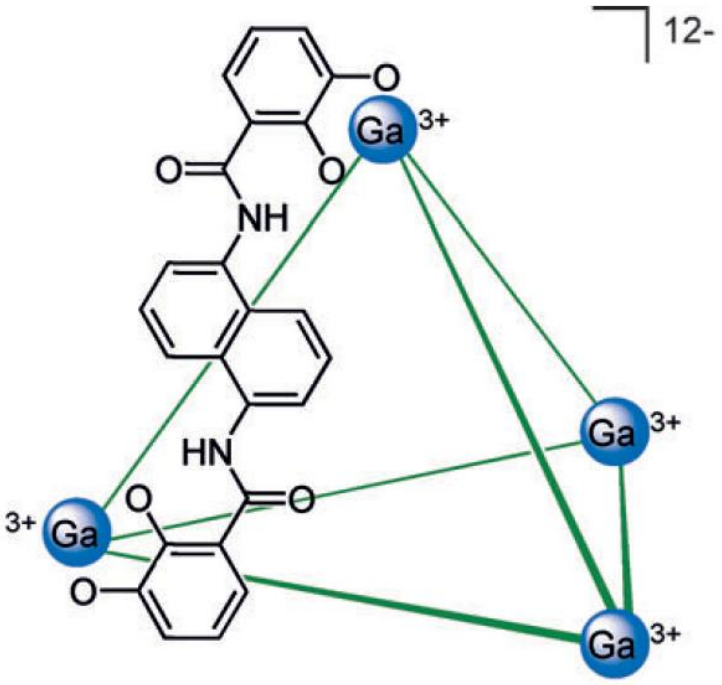
T. R. Kelly, et al. *J. Am. Chem. Soc.* **1990**, *112*, 8024.

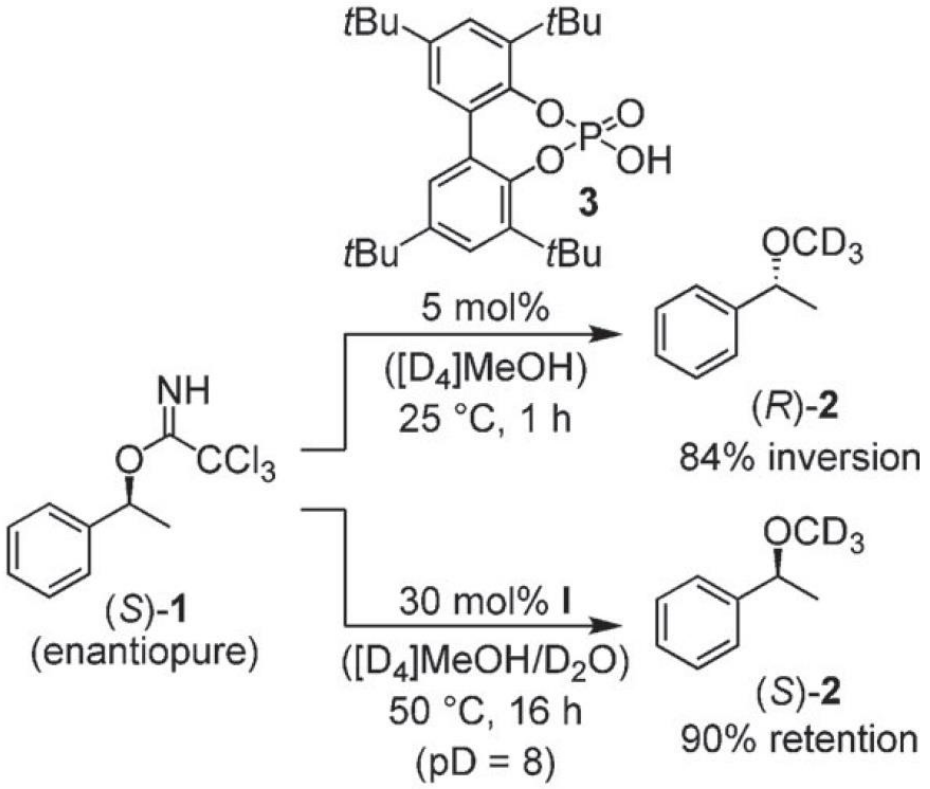
Catalysis in Self-Assembled Molecular Capsules



K. Tiefenbacher et al.
Chem. Eur. J. **2016**, *22*, 9060.

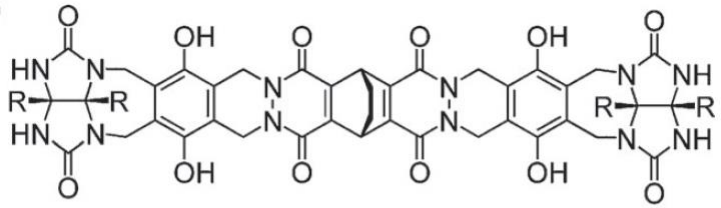
Product Selectivity



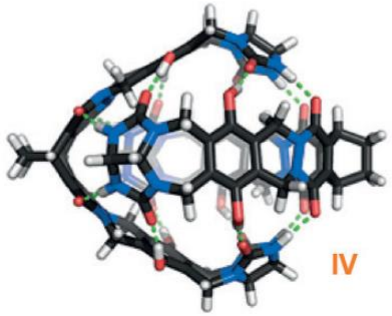


R. G. Bergman et al. *J. Am. Chem. Soc.* **2014**, *136*, 14409.

Substrate Selectivity

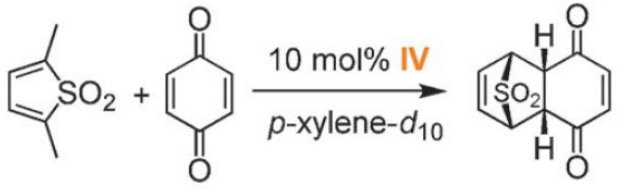


20 (R = 4-*n*-heptylphenyl)

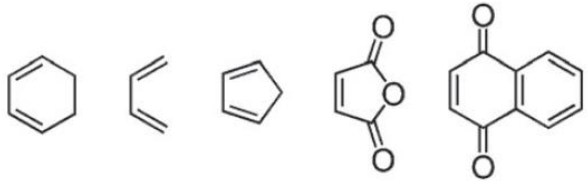


IV

Not bound well
→ catalytic turnover



21 **22** **23**

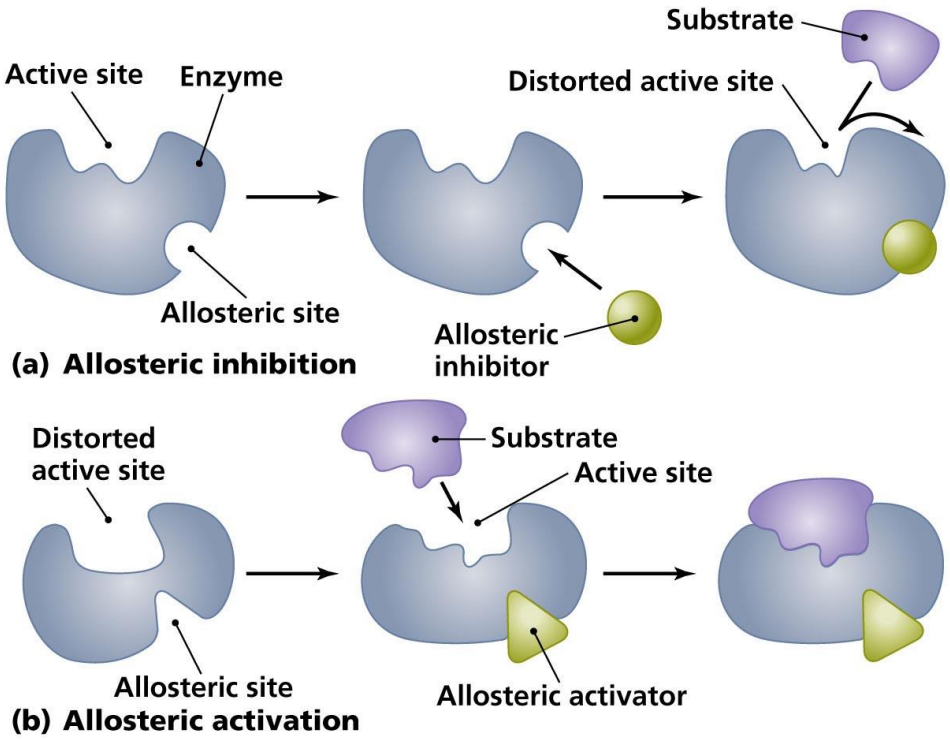


24 **25** **26** **27** **28**

other substrates either too large (28) or product inhibition

J. Rebek, et al. *J. Am. Chem. Soc.* **1998**, *120*, 3650.

Allosteric Proteins



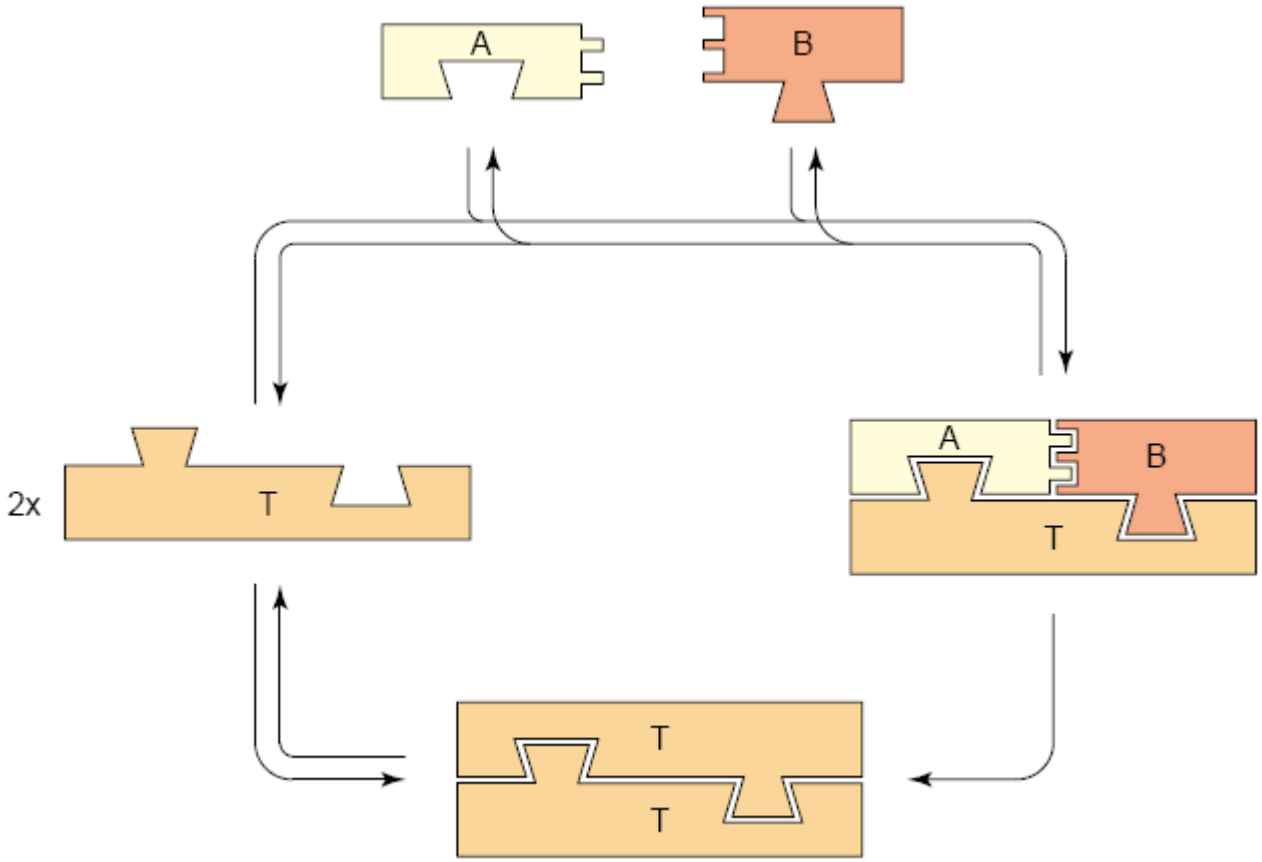
The concept of allosteric proteins was developed in the early 1960s by Monod and Koshland. The binding of a regulatory molecule or ion to a specific allosteric site of the protein, structurally distinct from the active site, brings about an alteration of the conformation of the protein that indirectly modifies the properties of the biologically active site. The effector can either enhance (*allosteric activation*) or decrease (*allosteric inhibition*) the binding or catalytic efficiency of the protein.

Molecular Self-Replication

Nature's ability to generate identical copies of the macromolecules necessary for life is a complex process, involving multiple reaction steps that must be tightly coordinated for efficient copying to occur.

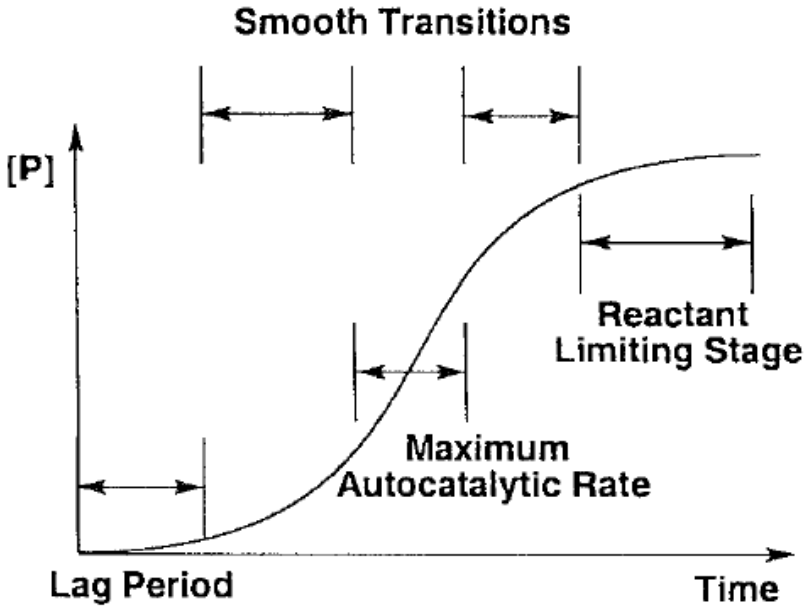
A simplified version of this system might employ a single template molecule that also functions as a catalyst. The system is considered to be self-replicating if the product, formed from two or more component substrates, is identical to the template.

Minimal Self-Replicating Systems



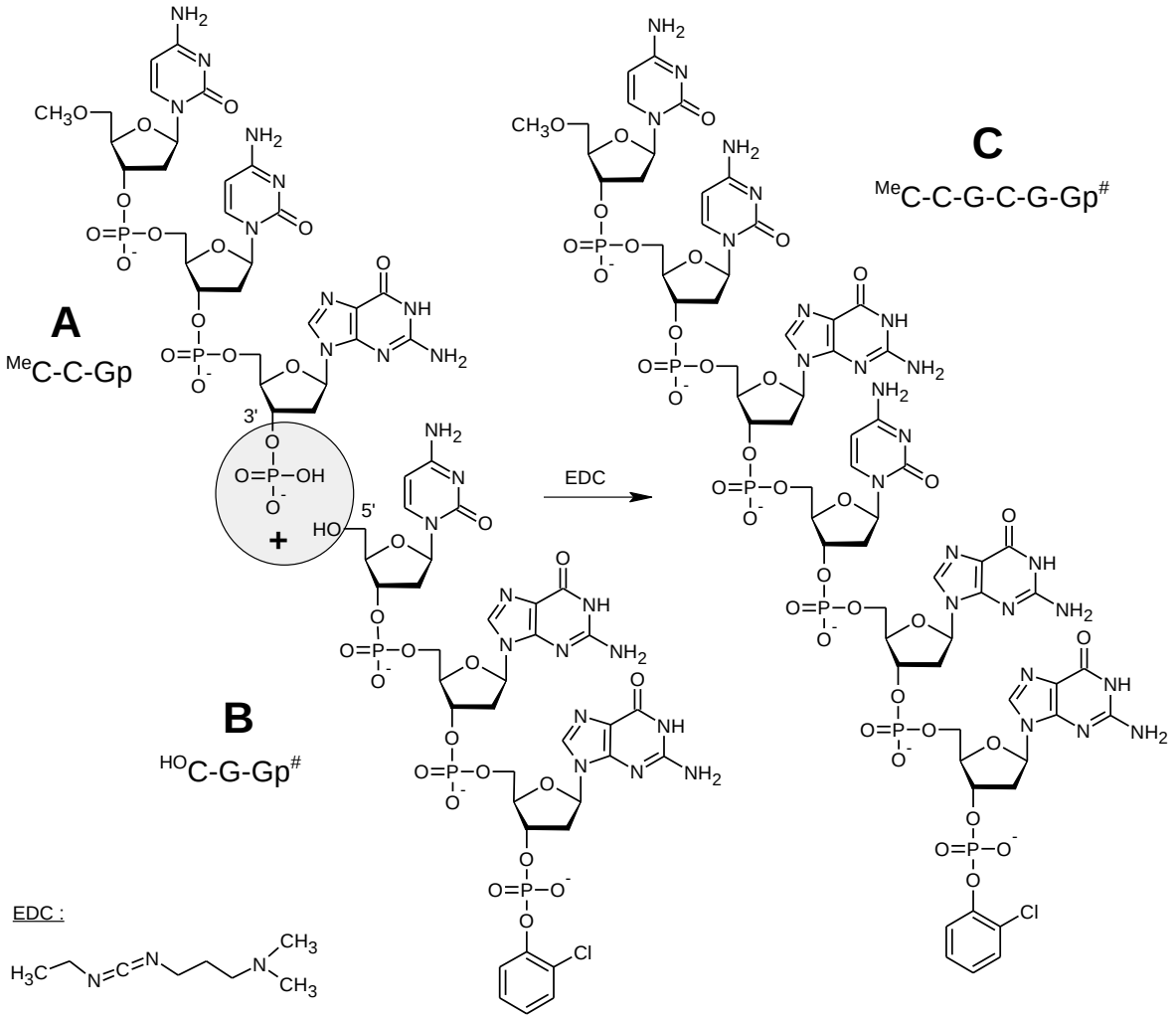
The template (**T**) binds two substrates (**A** and **B**), which become joined to form another copy of **T**. Following dissociation of the template–product complex, each copy of **T** can enter another replication cycle.

General Characteristics of Self-Replicating Systems



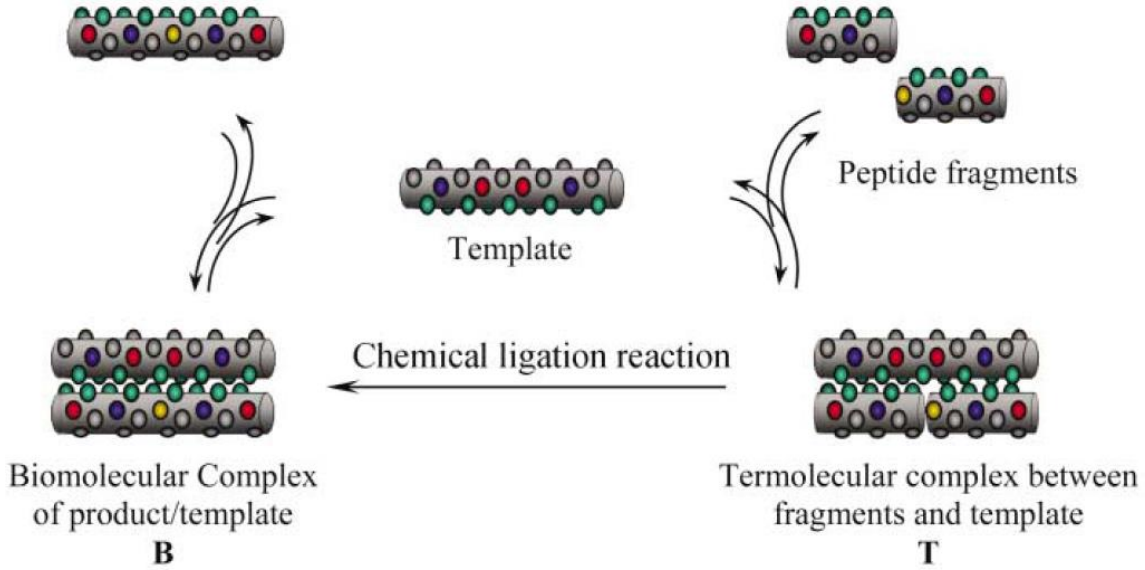
The characteristic **sigmoidal time course** of an autocatalytic reaction. [P] represents the concentration of product.

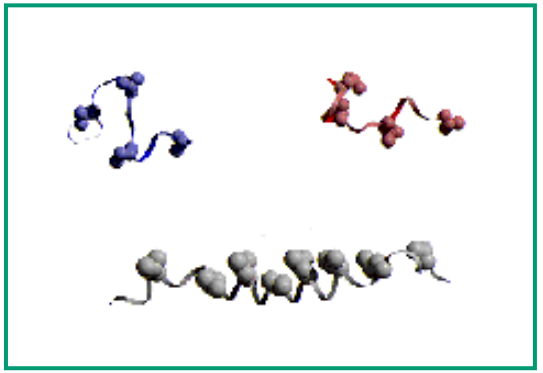
The First Example – A Self-Replicating Hexanucleotide



G. von Kiedrowski, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 932.

A Self-Replicating Peptide

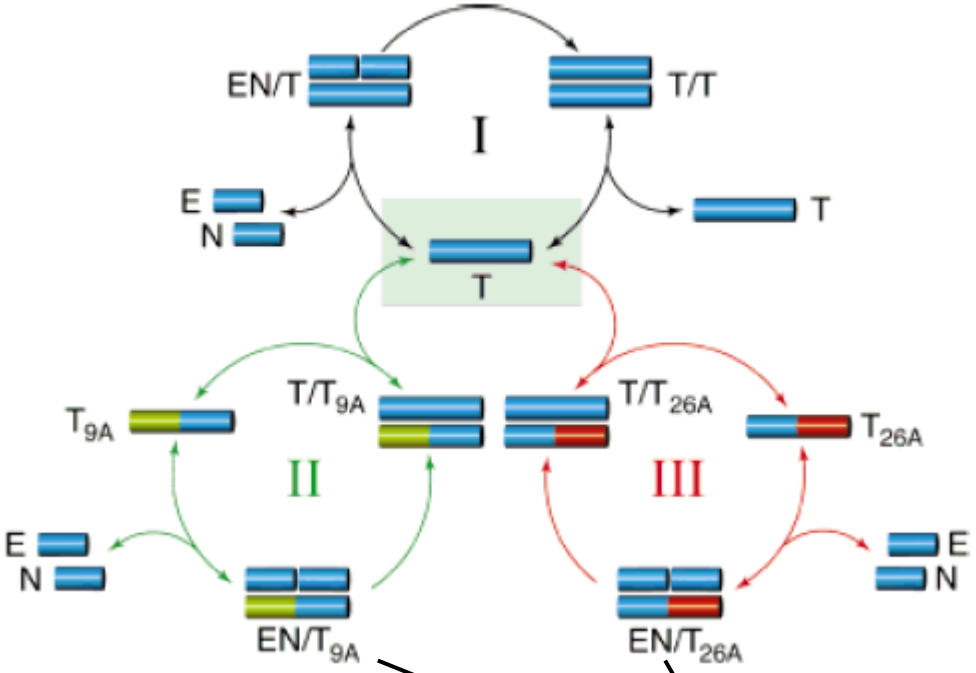




An animated cartoon showing the self-replication process with the 32 residue peptidic template.

M. R. Ghadiri et al., *Nature* **1996**, *382*, 525.

More Complex Systems



I: Autocatalytic cycle

II: Crosscatalytic cycle

III: Crosscatalytic cycle

Peptides with Ala mutations

M. R. Ghadiri et al., *Angew. Chem. Int. Ed.* **1998**, *37*, 126.

Future Challenges

- Artificial self-replicating systems with truly exponential growth rates.
- Self-replicating systems with new types of building blocks.
- Stereoselective self-replicating systems (first examples are known).
- Design and study of complex autocatalytic networks (mixtures of self-replicating molecules with cross-catalytic pathways).
- Ultimately: artificial life ?!?