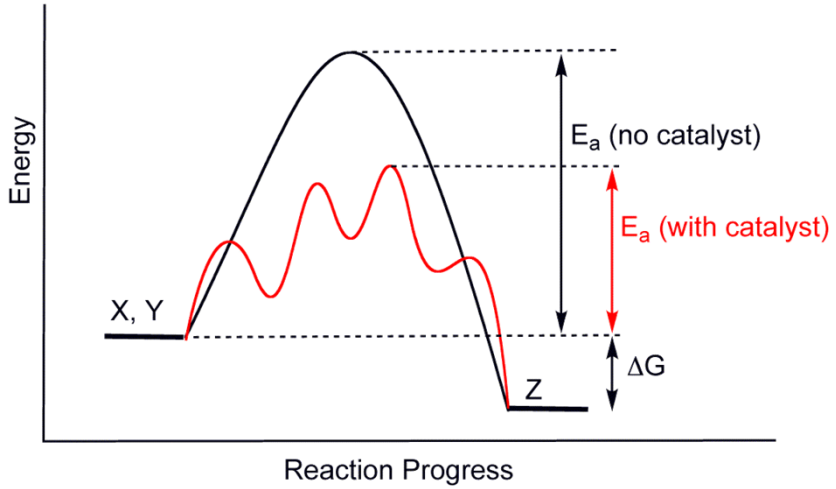
Supramolecular catalysis

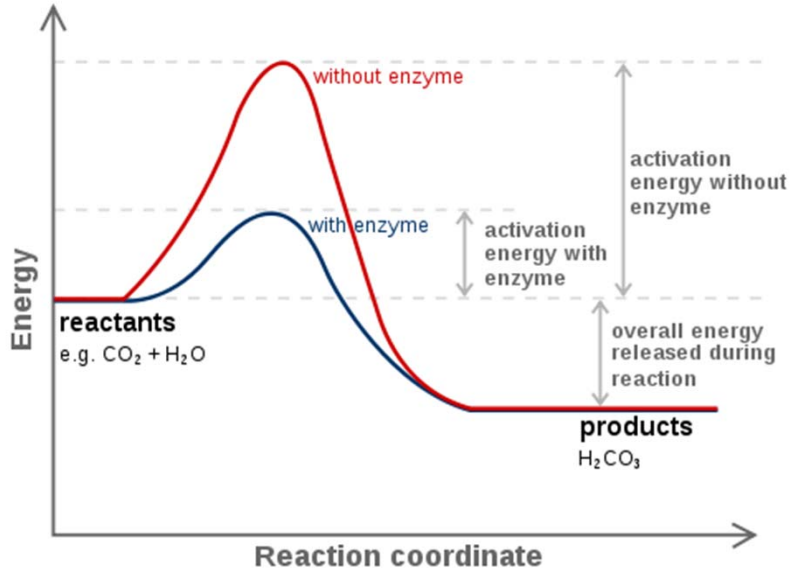
***Catalyst**: a chemical species that accelerates a chemical reactions without being consumed*

***Organometallic catalyst**: soluble metal complex with organic ligands that accelerates the reaction by changing the reaction pathway and the substrate reactivity*

***Enzyme**: protein that selectively **binds** the substrate and causes its chemical transformation by stabilizing the transition state*

Receptor → ***Catalysts***





Biomimetic chemistry

"The design, synthesis and study of artificial systems that reproduce, in a simplified manner, some aspects of the features of the equivalent biological systems"

R. Breslow, 1972

"…is the field in which chemists invent new substances and reactions that imitate biological chemistry"

R. Breslow, 1998

"…inventing new things inspired by what Nature does"

R. Breslow, 2008

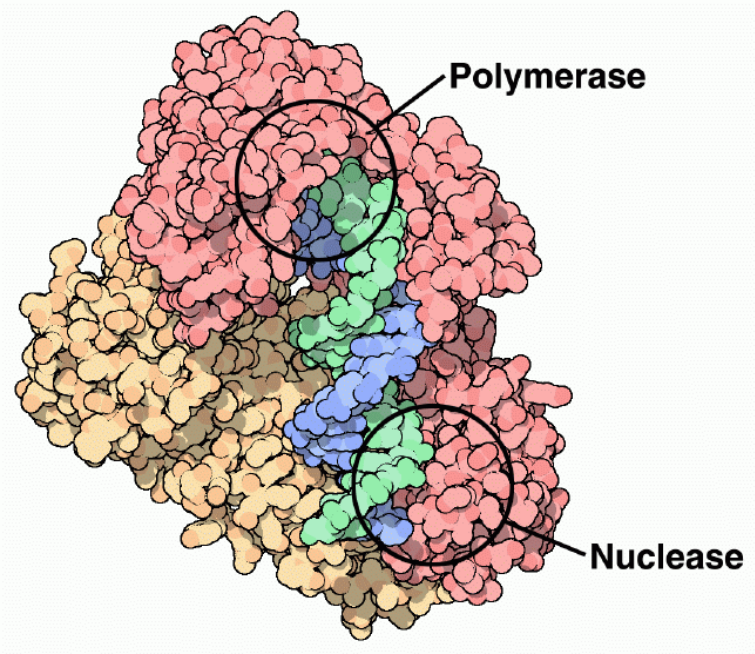
Biomimetic chemistry

"…inventing new things inspired by what Nature does"

Why being inspired by enzymes?

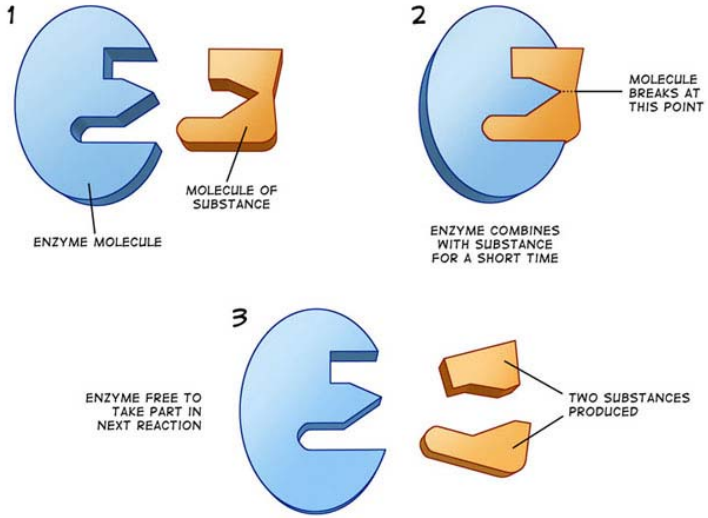
They are astonishing catalyst.

Enzyme catalysis



Reverse transcriptase

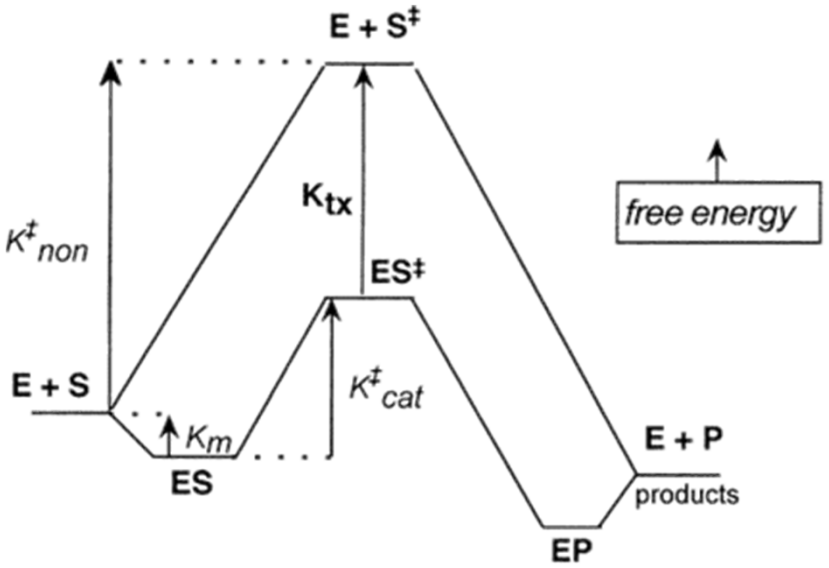
Large macromolecules (proteins) made by aminoacids and some prostetic group, with a binding pocket (active site) where the substrate is selectively recognized and transformed.

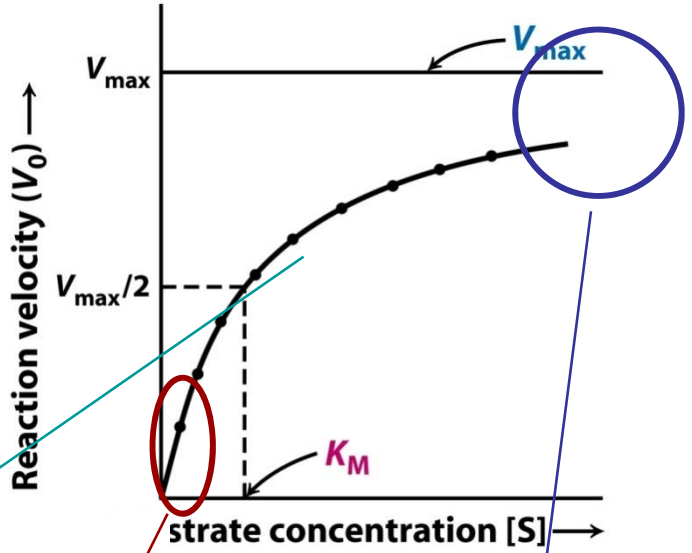


The substrate form a complex with the enzyme, undergoes the chemical reaction then the products are released and the enzyme is ready to transform another substrate molecule

Enzyme catalysis

Michaelis-Menten equation





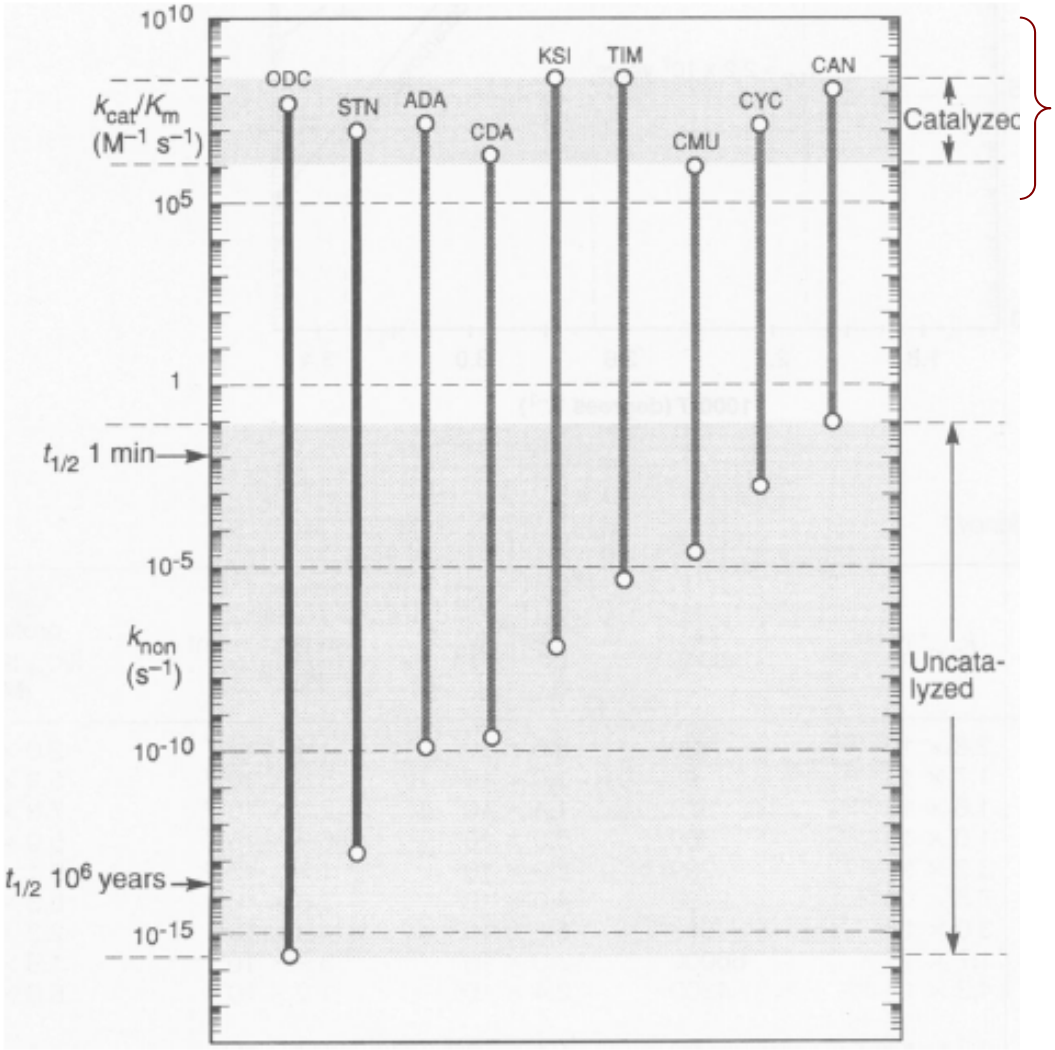
$$V_0 = \frac{k_{cat}[E_t][S]}{K_m + [S]}$$

$$k_2 = \frac{k_{cat}}{K_M}$$

$$V_{\max} = k_{cat}[E_t]$$

Why enzymes are so special?

Activity: accelerate reactions close to the diffusion limit



Micro- to milliseconds

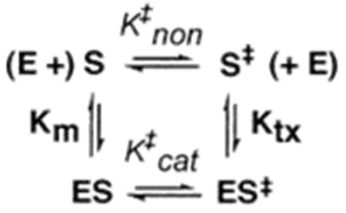
Why enzymes are so special?

Proficiency: transition state binding

Table 1. Enzymes listed in order of decreasing catalytic proficiency.*

Enzyme	Nonenzymatic $t_{1/2}$*	k_{non}* (s^{-1})	k_{cat}† (s^{-1})	k_{cat}/K_m† ($s^{-1}\ M^{-1}$)	Rate enhancement (k_{cat}/k_{non})	Catalytic proficiency $[(k_{cat}/K_m)/k_{non}]$ (M^{-1})
OMP decarboxylase	78,000,000 years	2.8×10^{-16}	39	5.6×10^{7}	1.4×10^{17}	2.0×10^{23}
Staphylococcal nuclease	130,000 years	1.7×10^{-13}	95	1.0×10^{7}	5.6×10^{14}	5.9×10^{19}
Adenosine deaminase	120 years	1.8×10^{-10}	370	1.4×10^{7}	2.1×10^{12}	7.8×10^{16}
AMP nucleosidase	69,000 years	1.0×10^{-11}	60	5.0×10^{5}	6.0×10^{12}	5.0×10^{16}
Cytidine deaminase	69 years	3.2×10^{-10}	299	2.9×10^{6}	1.2×10^{12}	9.1×10^{15}
Phosphotriesterase	2.9 years	7.5×10^{-9}	2100	4.0×10^{7}	2.8×10^{11}	5.3×10^{15}
Carboxypeptidase A	7.3 years	3.0×10^{-9}	578	6.6×10^{6}	1.9×10^{11}	2.2×10^{15}
Ketosteroid isomerase	7 weeks	1.7×10^{-7}	66000	3.0×10^{8}	3.9×10^{11}	1.8×10^{15}
Triosephosphate isomerase	1.9 days	4.3×10^{-6}	4300	2.4×10^{8}	1.0×10^{9}	5.6×10^{13}
Chorismate mutase	7.4 hours	2.6×10^{-5}	50	1.1×10^{6}	1.9×10^{6}	4.2×10^{10}
Carbonic anhydrase	5 s	1.3×10^{-1}	1×10^{6}	1.2×10^{8}	7.7×10^{6}	9.2×10^{8}
Cyclophilin, human	23 s	2.8×10^{-2}	13000	1.5×10^{7}	4.6×10^{5}	5.3×10^{8}

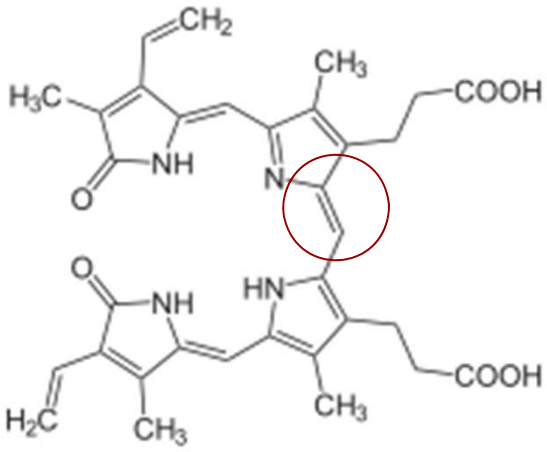
*Nonenzymatic reaction rate constants were obtained for OMP decarboxylase and staphylococcal nuclease from the present work, for adenosine and cytidine deaminases from (*5*), for AMP nucleosidase from (*25*), for phosphotriesterase from (*26*), for carboxypeptidase A from (*3*), for ketosteroid isomerase from (*27*), for triosephosphate isomerase from (*28*), for chorismate mutase from (*4*), for carbonic anhydrase from (*2*), and for cyclophilin from (*3*). †Enzyme reaction rate constants were obtained for OMP decarboxylase from (*7*), for staphylococcal nuclease from (*29*), for adenosine deaminase from (*30*), for AMP nucleosidase from (*31*), for phosphotriesterase from (*26*), for carboxypeptidase A from (*32*), for ketosteroid isomerase from (*33*), for triosephosphate isomerase from (*34*), for chorismate mutase from (*4*), for carbonic anhydrase from (*35*), and for cyclophilin from (*36*).



$$K_{tx} = K_m \cdot \frac{K^{\ddagger}_{non}}{K^{\ddagger}_{cat}} = K_m \cdot \frac{k_{non}}{k_{cat}}$$

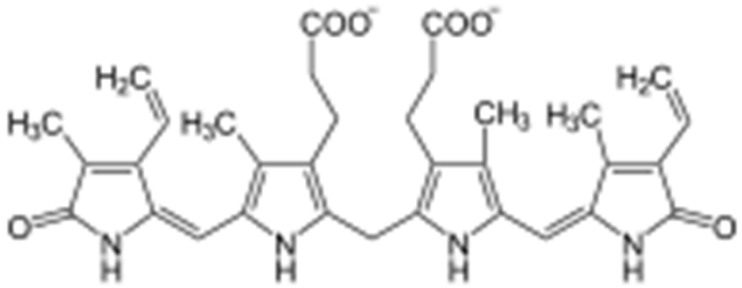
Why enzymes are so special?

Chemoselectivity



Biliverdin

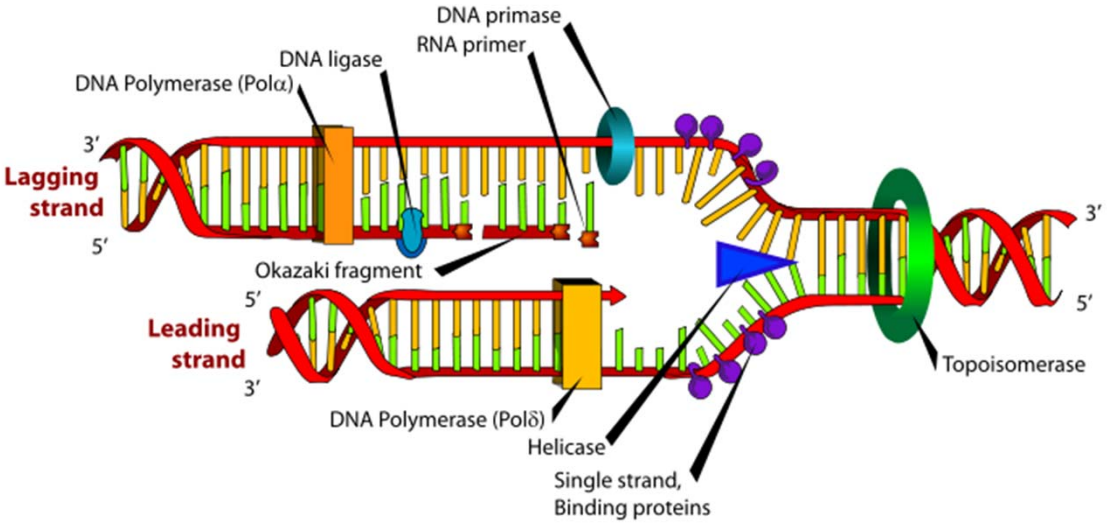
Biliverdin reductase

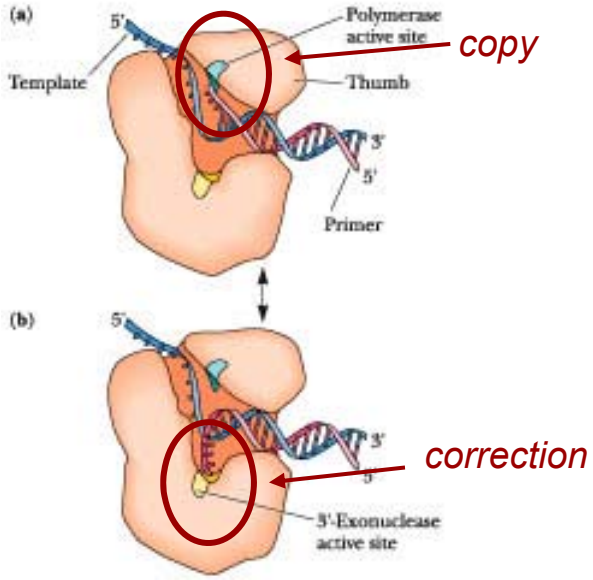


Birilubin

Why enzymes are so special?

Complexity



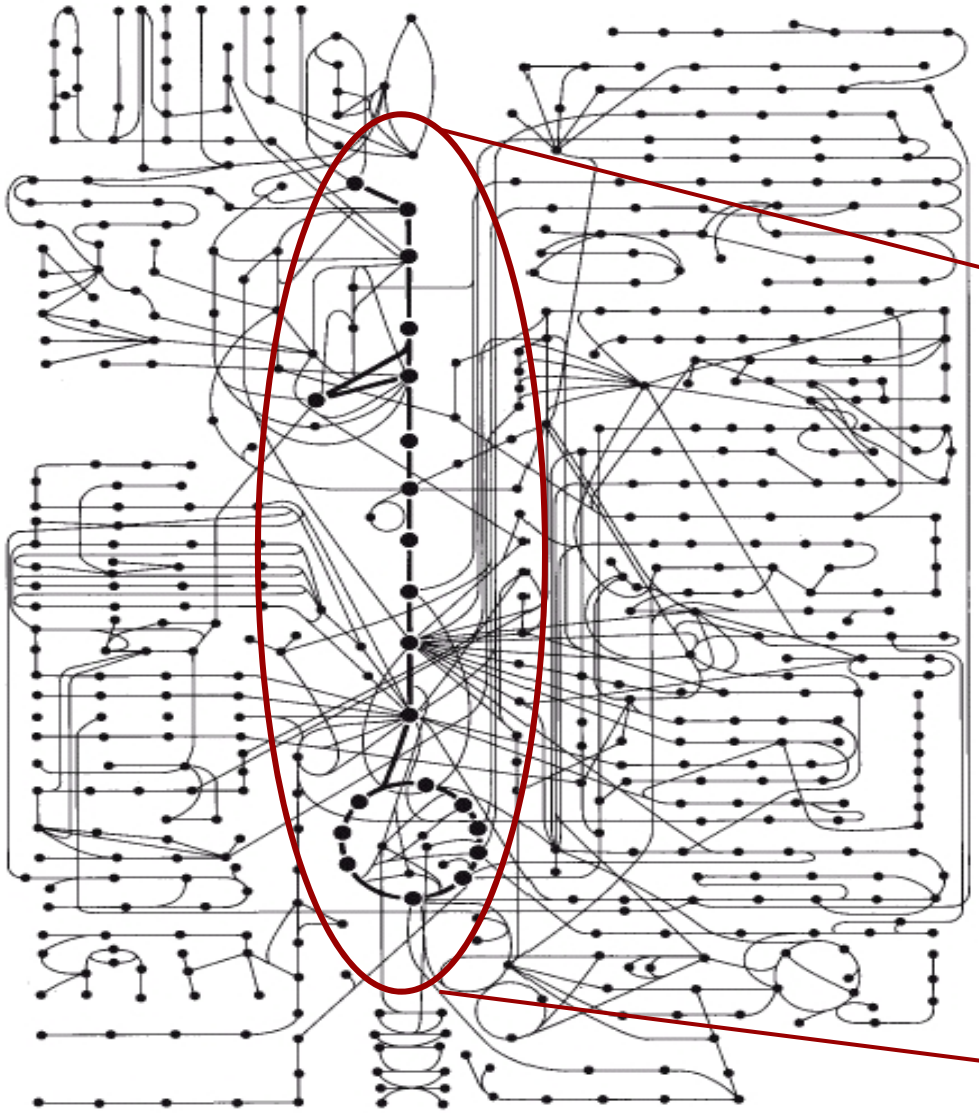


DNA polymerase

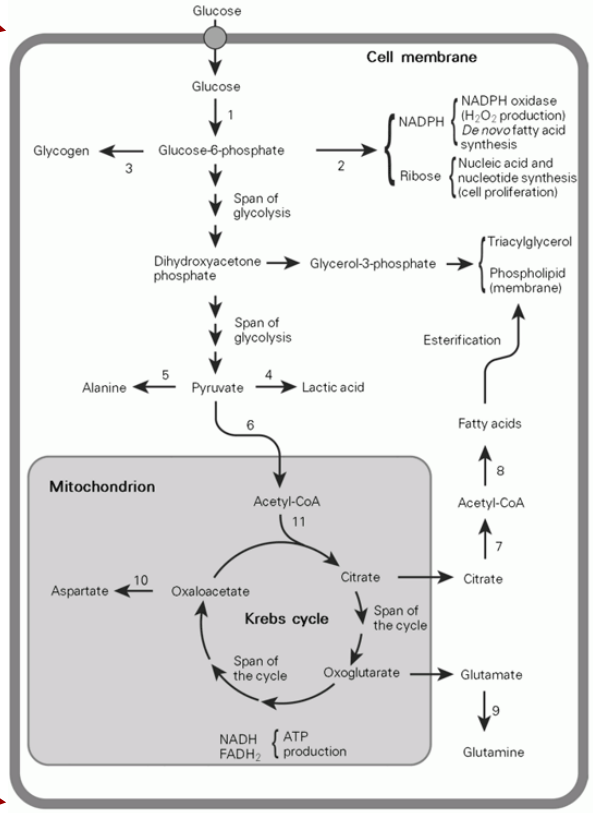
In DNA replication, several enymes cooperate to unwind the double helix, separate the strands, copy a new strand on each of the two.
Errors are detected and corrected by a double proof-reading exherted by the same enzyme (DNA polymerase) that perform the replication.

Why enzymes are so special?

Complexity



Map of the biotransformations occurring in a cell: each point represents a compound and each line an enzyme-catalyzed reaction



Why enzymes are so special?

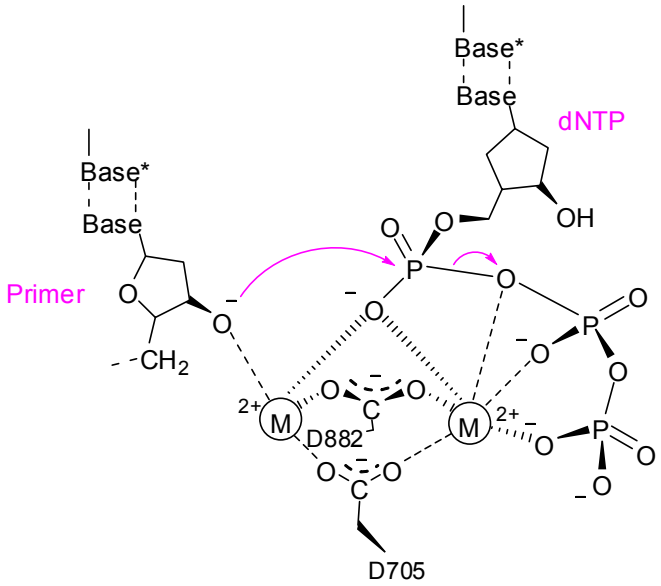
- **Universal**: each class of reactions (included redox and photochemical reactions, C-C bond formation, transposition) is catalyzed by enzymes.
- **Efficient**, acceleration reported reach 10^{18}-fold over the background reaction.
- **Selective**: target substrate is selectively picked up in a complex mixture (biological fluid) and transformed at the desired site with the desired geometry.
- **Mild**: reactions occur at 36 °C, in water at pH 7

- **Not easy to make, purify and store**
- **Not general**: they work on the substrates that are important for nature
- **Delicate**: denaturation alters they activity

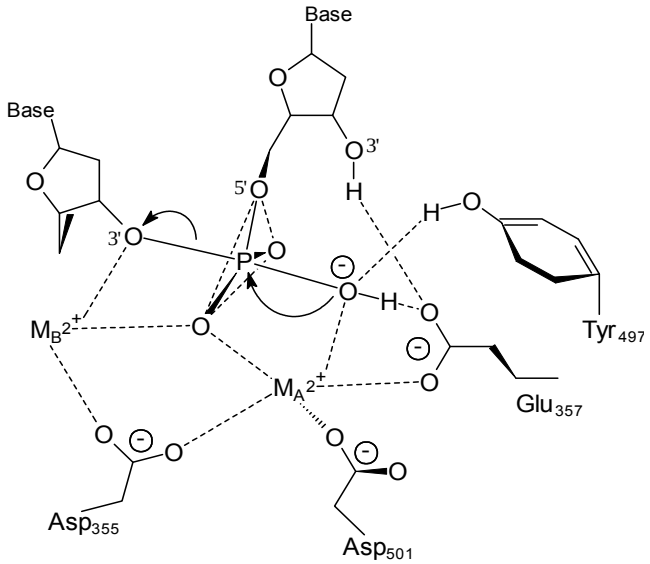
- **Understand**: only if can do the same we can really say we got it
- **Use**: new catalysts, new selectivity (against “the functional groups tyranny”)

Enzyme catalysis: how do they work?

Active site



polymerase site

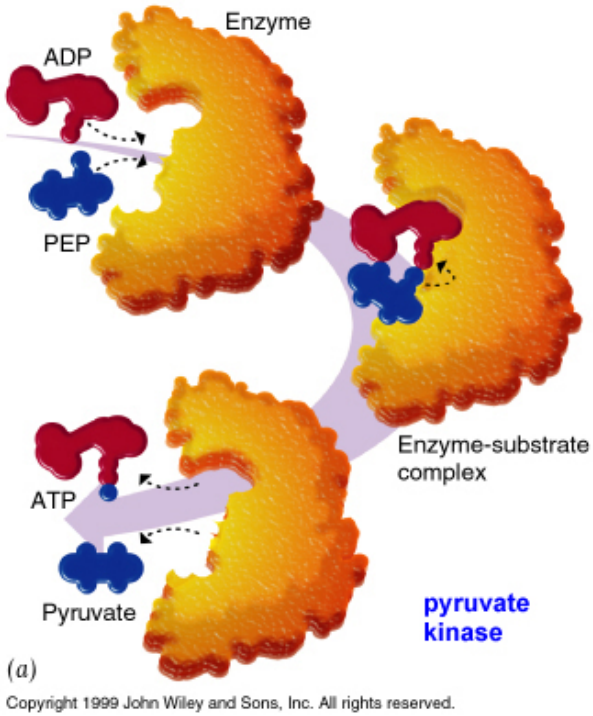


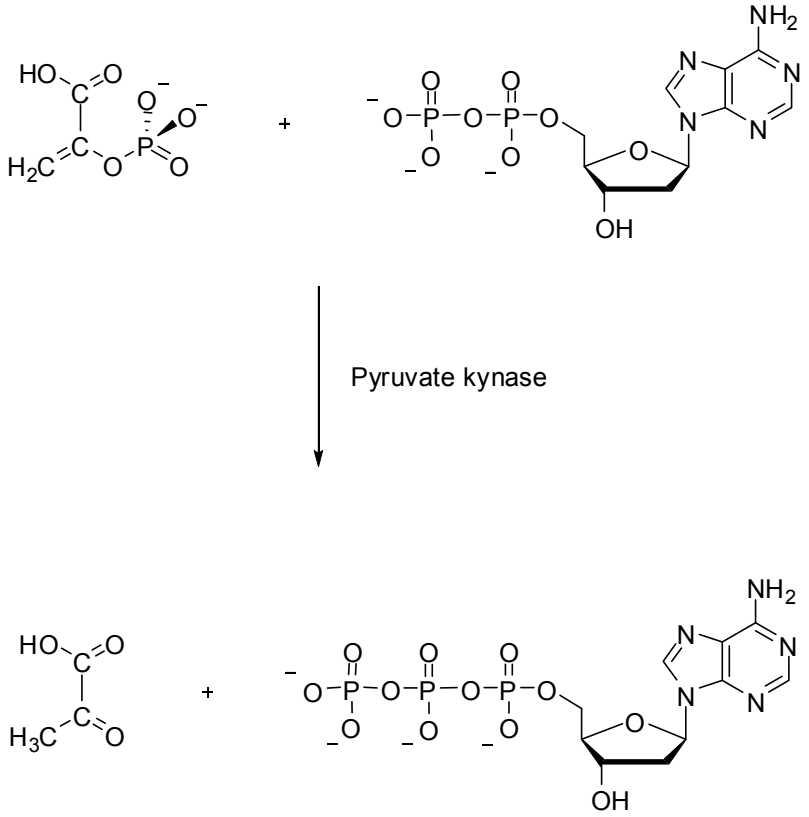
3'-5' exonuclease site

- Reactants are brought in close proximity
- Transition state is stabilized by non-covalent and even covalent interactions
- Solvatation modified

Enzyme catalysis: how do they work?

Putting the reagent close togheter

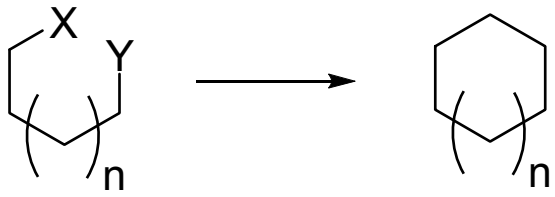




Effective Molarity (EM) = k (intra) / k_2 (inter)

Reactants in close proximity experience an higher concentration that the analytical one

Effective Molarity



5-fold rate increase per rotor

Table 4. Entropy Changes and Effective Molarities[a] in the Cyclization of Bifunctional Chains as a Function of the Number of Skeletal Single Bonds (*r*)

r	$\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}$ [a]	EMs (M)	*r*	$\Delta S^{\ddagger}_{intra} - \Delta S^{\ddagger}_{inter}$ [a]	EMs (M)
0	30	3.6×10^{6}	10	−1.5	4.7×10^{-1}
1	26	4.8×10^{5}	12	−2.7	2.6×10^{-1}
2	22	6.4×10^{4}	14	−3.7	1.6×10^{-1}
3	18	8.6×10^{3}	16	−4.3	1.1×10^{-1}
4	14	1.1×10^{3}	20	−5.3	6.9×10^{-2}
5	10	1.5×10^{2}	25	−6.0	4.9×10^{-2}
6	6	2.0×10	30	−6.5	3.8×10^{-2}
7	2	2.7	40	−7.3	2.5×10^{-2}
8	0	1.0	50	−8.0	1.8×10^{-2}
9	−0.8	6.7×10^{-1}			

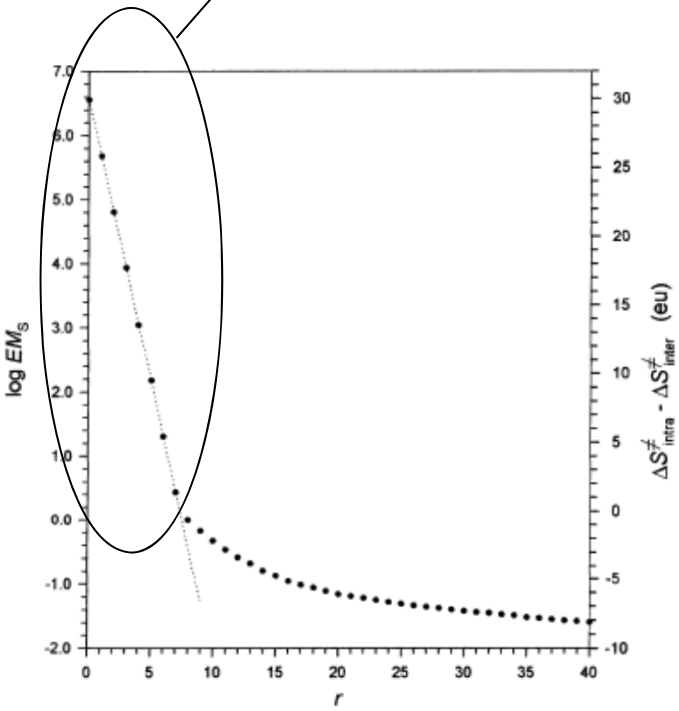
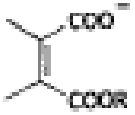


FIGURE 1. Log EMs vs number of rotatable bonds (*r*) in the bifunctional chain undergoing cyclization.

L. Mandolini et al., *Acc. Chem. Res.* **2004,** 37, 113-122

Effective Molarity

Table 1. Strength of dynamic binding based on effective molarities for intramolecular cyclizations.

	EM [M]	$\Delta\Delta G^{\neq}$ [kJ mol^{-1}]
	1	0
	220	13
	5×10^4	27
	3×10^9	54
	4×10^{13}	(73)

EM can be greater that that calculated on the basis of the number of rotors

A. J. Kirby, *Angew. Chem. Int. Ed.* **1996,** 35, 707-724

Enzyme catalysis: how do they work?

Transition state binding

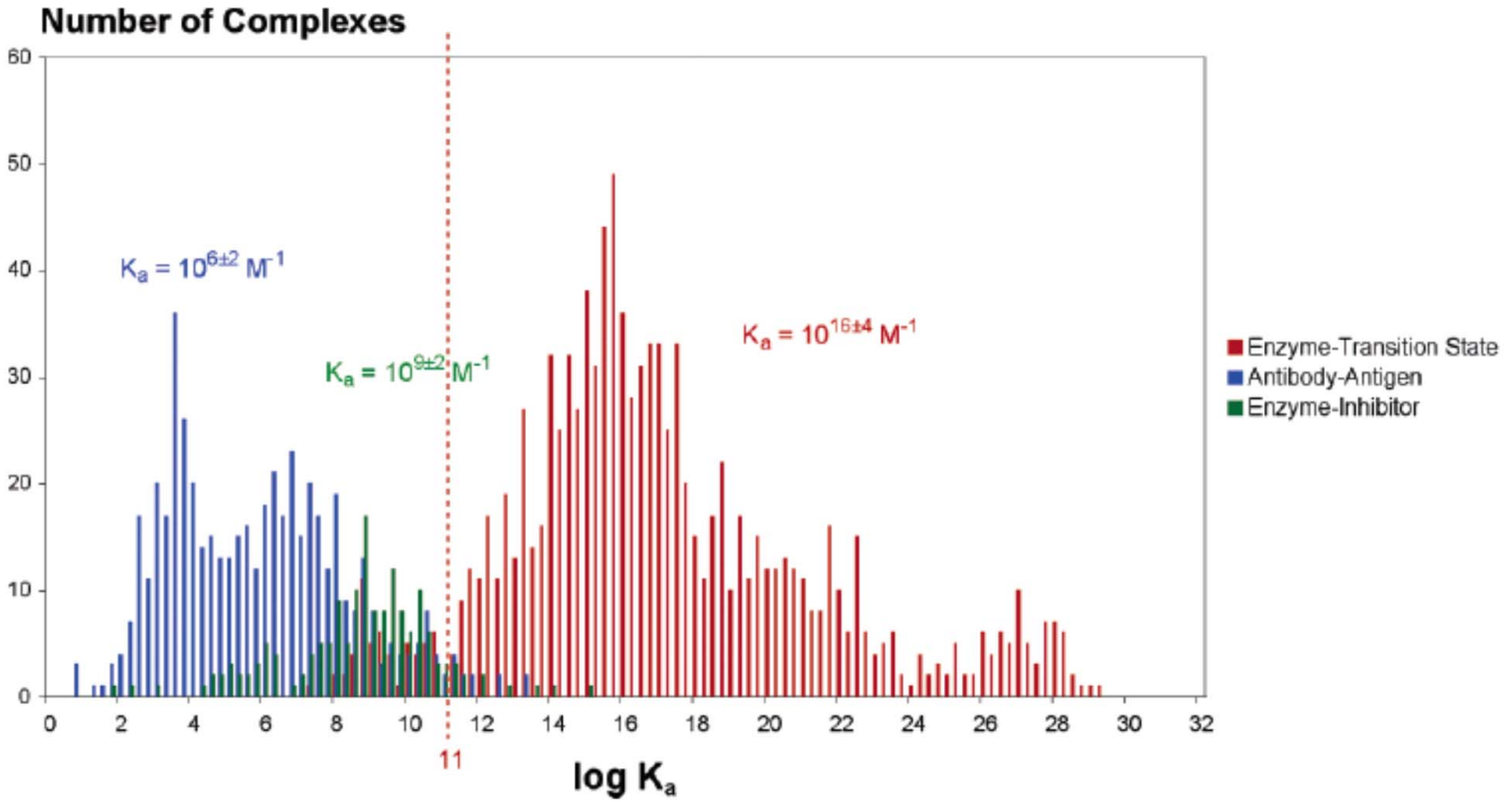


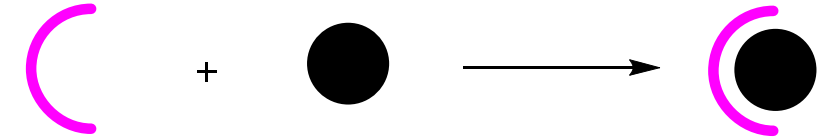
FIGURE 4. Frequency plot of association constant for 507 antibody–antigen complexes, 160 enzyme–inhibitor complexes, and 1017 measurements of enzyme–transition state complex.

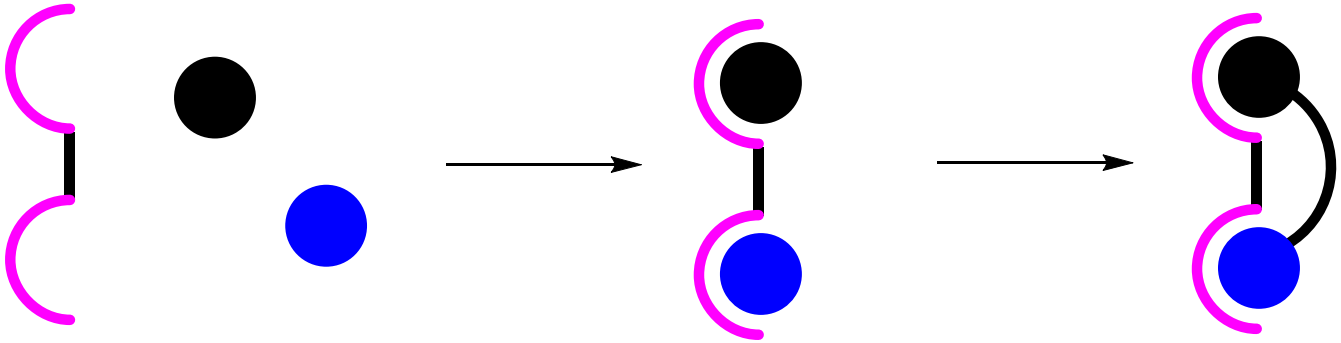
K. N. Houk et al., *Acc. Chem. Res.* **2005,** 38, 379-385

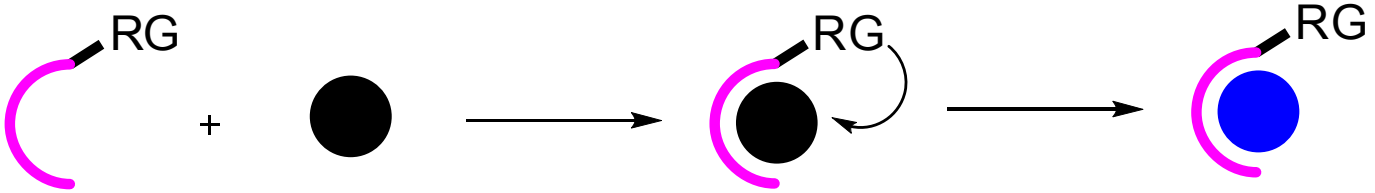
Outline

1. Enzyme catalysis
2. Enzyme models: successes and thing to do
3. Case study 1: Artificial nucleases – the classical approach
4. Case study 2: Artificial nucleases – the ARCUT system

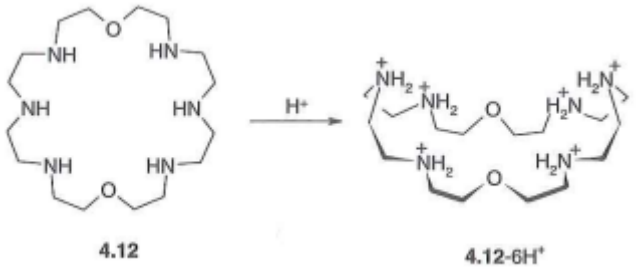
Artificial enzymes: design

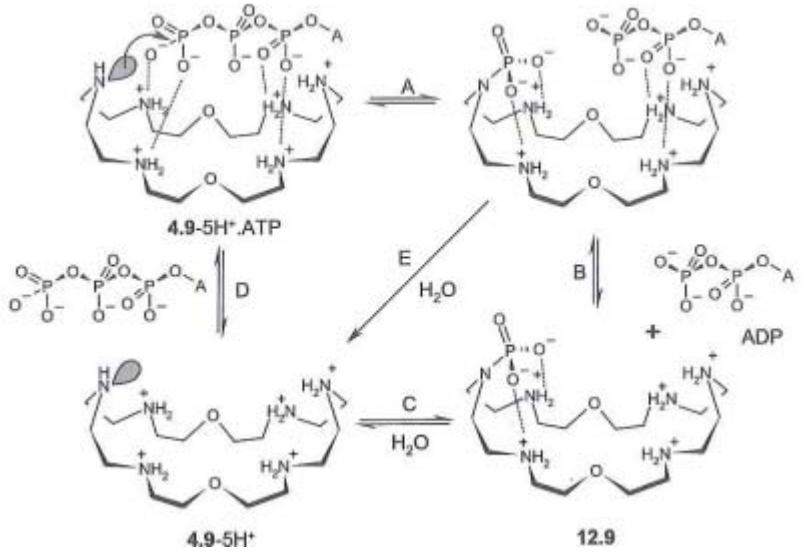


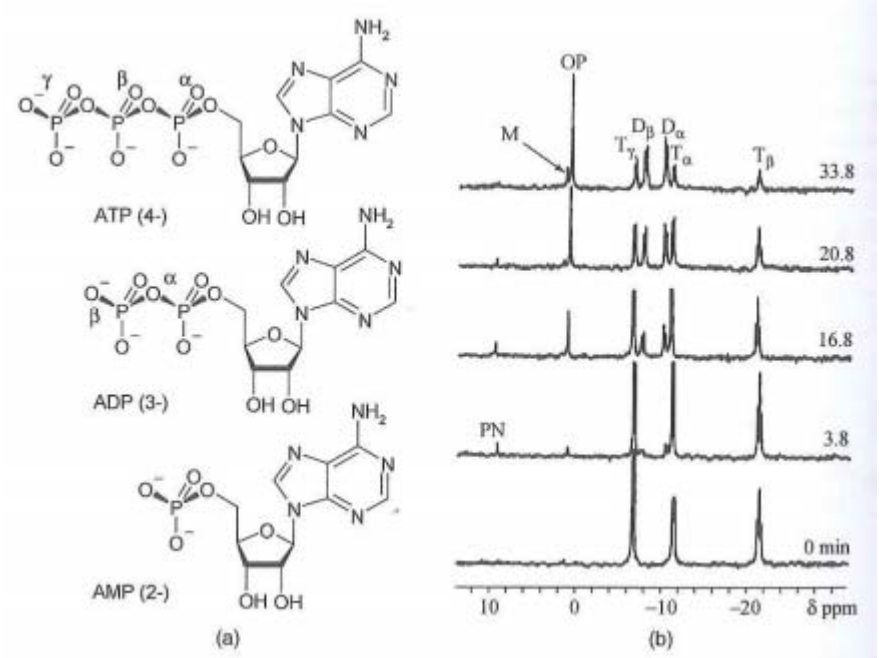




Corands



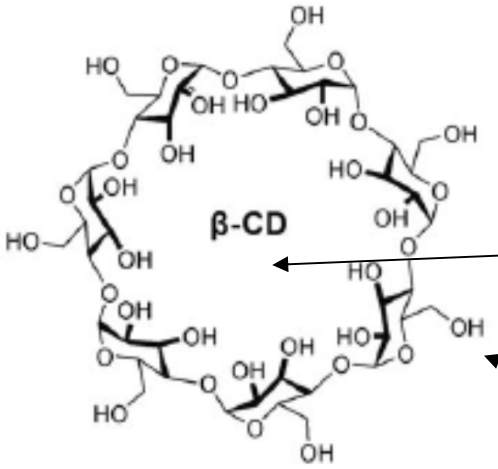




100-fold acceleration

No product inhibition

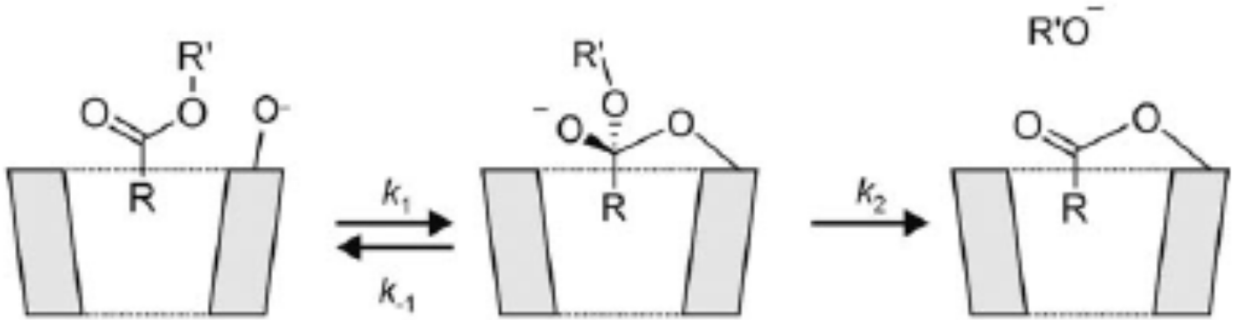
Cyclodextrins



Water soluble host

Tunable hydrophobic pocket (α–, β–, γ-cyclodextrins)

Nucleophilic hydroxyls (pK_a ~ 12.5)

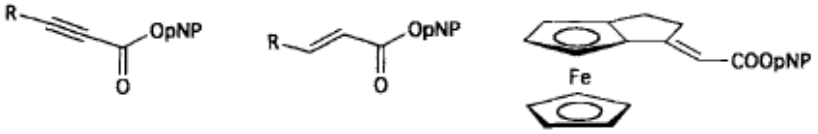


- Michaelis-Menten like kinetics
- Low, if any, turnover
- Product inhibition

Cyclodextrins

Table 3. Reactivity and transition state binding data for reactions conducted in the presence of cyclodextrins (CDs).

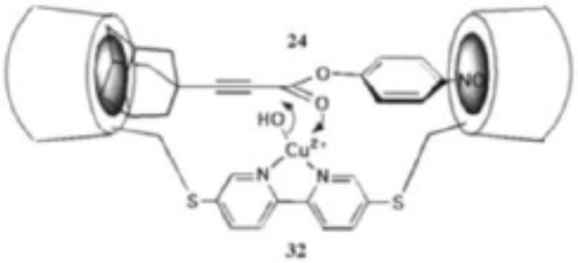
CD	Substrate	k_{cat} [s^{-1}]	EM [M]	K_{ass} [M^{-1}]	k_{cat}/k_{uncat}
α	pNB-CH_2CF_3 [a]	8.8×10^{-4}	<0.1 [b]	294	4.4
α	*m*-*t*BuC_6H_4OAc [c]	0.13	0.4	500	260
β	*m*-*t*BuC_6H_4OAc [c]	0.12	0.3	7700	250
β	**24** [d]	8.4×10^{-2}	7 [e]	3300	2150
β	**25** [d]	0.4	480 [e]	200	1.4×10^5
β	**26** [d]	0.21	1100 [e]	143	7.5×10^5
β	**27** [d]	9.2×10^{-2}	2×10^4 [e]	175	5.9×10^6
32	**24** [d]	6.8×10^{-3}	–	7×10^4	2.2×10^5
30	**29** [f]	1.4×10^{-3}	7 [g]	5555	360



24, R = 1-adamantyl
25, R = ferrocenyl (Fc)

26, R = Fc

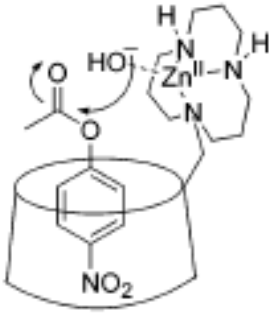
27

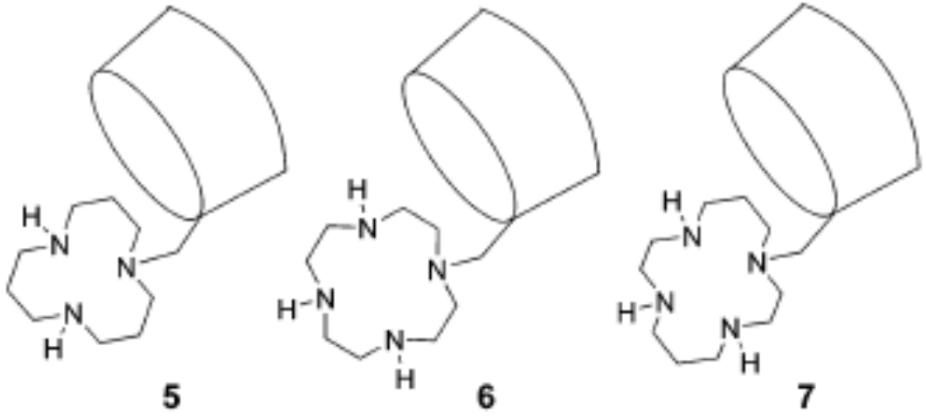


R. Breslow, data from *Angew. Chem. Int. Ed.* **1996,** 35, 707-724

Cyclodextrins

Effective molarity?



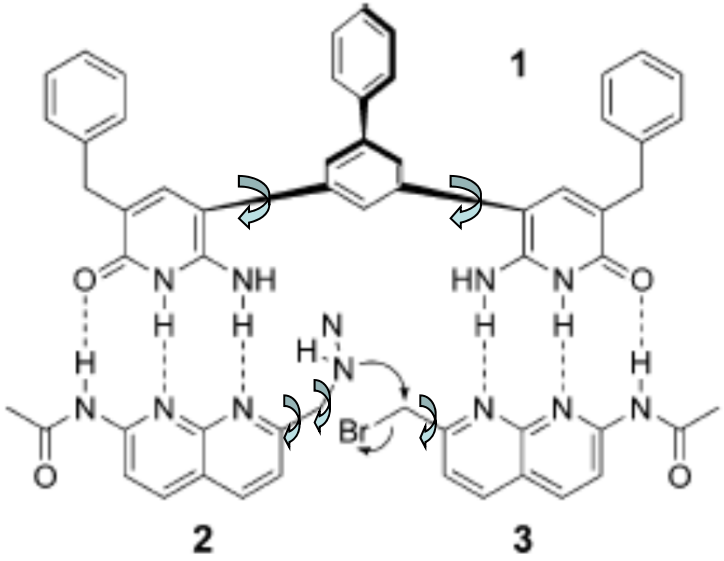


5 6 7

EM = 0.21 M EM = 0.17 M EM = 0.34 M

S. S. Lee et al., *Bioorg. Med. Chem*. **2000**, 8, 647-652.

Synthetic receptors

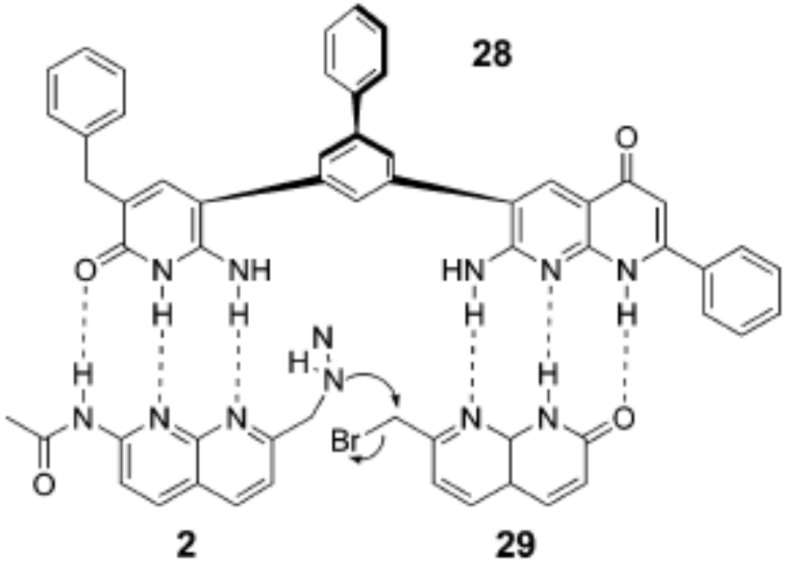


K_{ass} > 1x10^4 M^{-1} (each site)

k_{cat}/k_{uncat} = 6

EM = 0.14 M (EM_{teor} = 150 M)

Identical binding sites may lead to improductive binding.



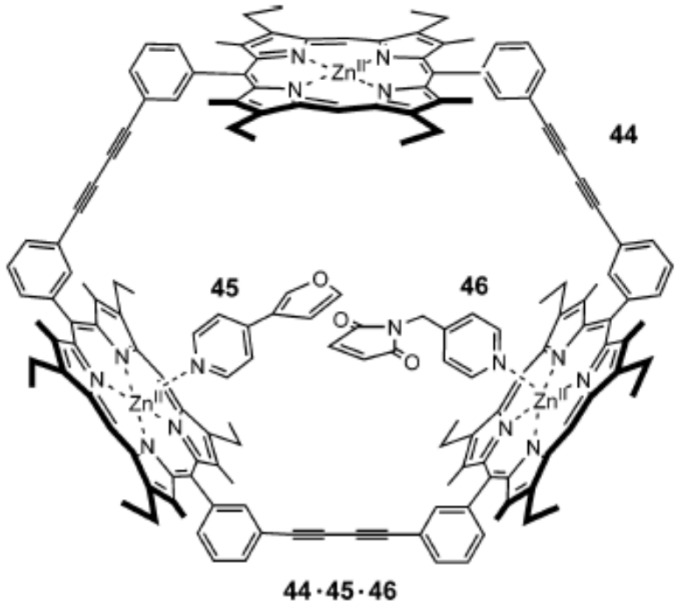
K_{ass} > 1x10^4 M^{-1} (each site)

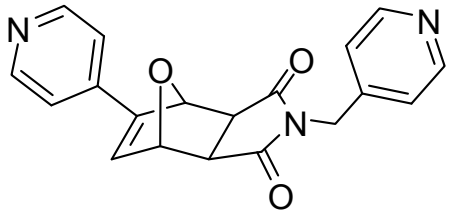
k_{cat}/k_{uncat} = 12

EM = 0.11 M (EM_{teor} = 150 M)

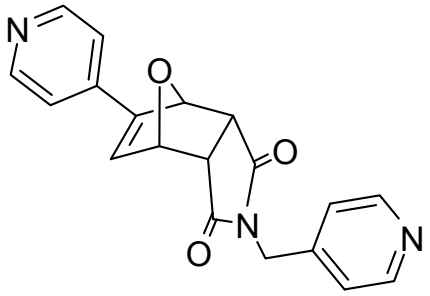
T. R. Kelly et al. *J. Am. Chem. Soc*. **1990**, 112, 8024-8034

Synthetic receptors





eso



endo

K_{ass} ~ 2×10^3 M^{-1} (each site)

k_{cat}/k_{uncat} = not measured

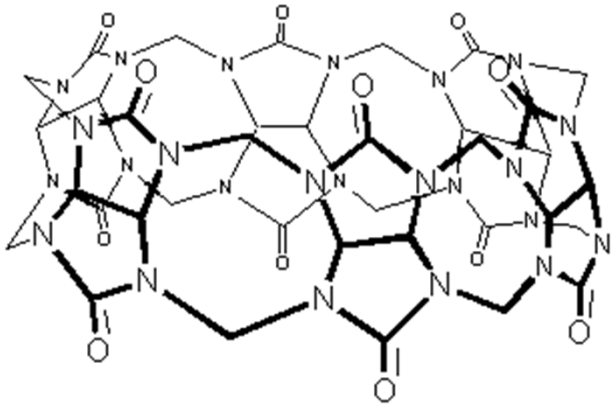
EM = 8 M (EM_{teor} = 150 M)

Product inhibition

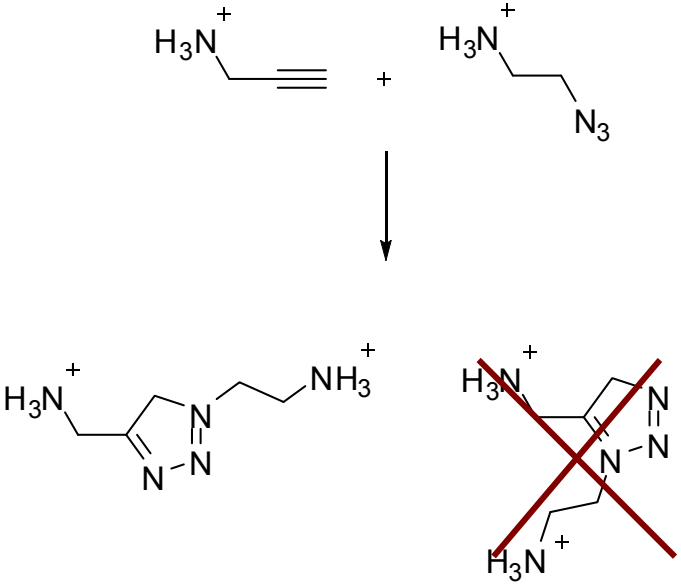
[eso]/[endo]=1000

J. K. M. Sanders, Chem. Commun. **1993**, 458-460.

Cavitands and capsules



cucurbit[6]uril
(cavity volume 164 A^3)

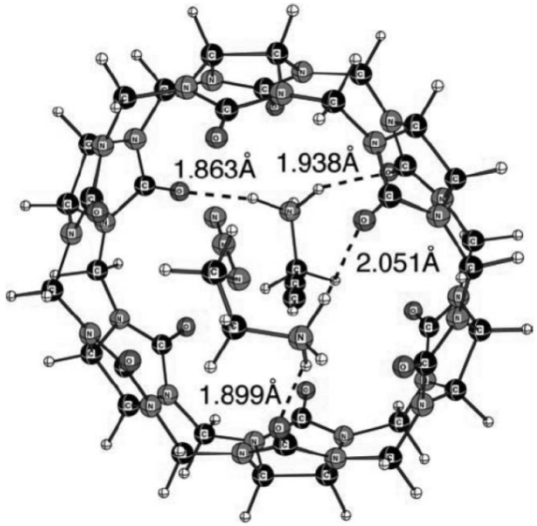


K_{ass} ~ 1.5×10^3 M^{-1} , 4×10^2 M^{-1}

k_{cat}/k_{uncat} ~ 10^5

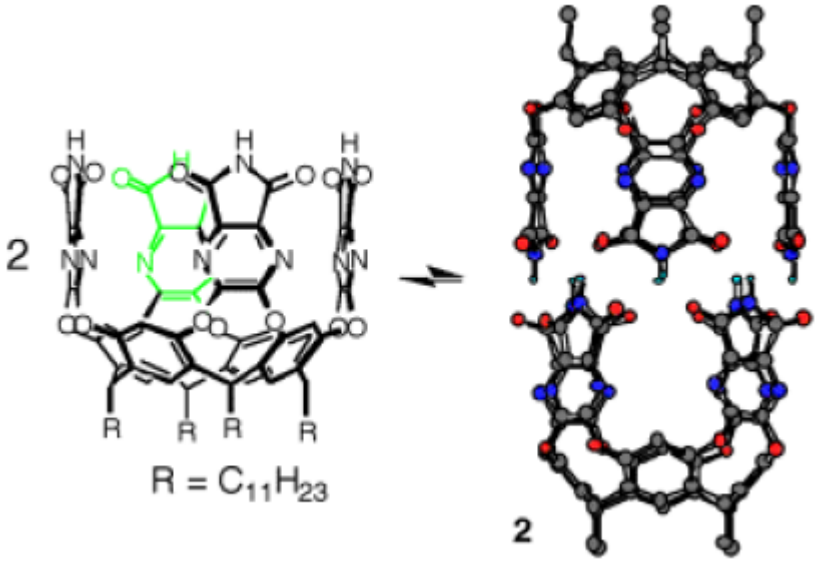
EM = 1.6×10^4 M (EM_{teor} = 3.6×10^6 M)

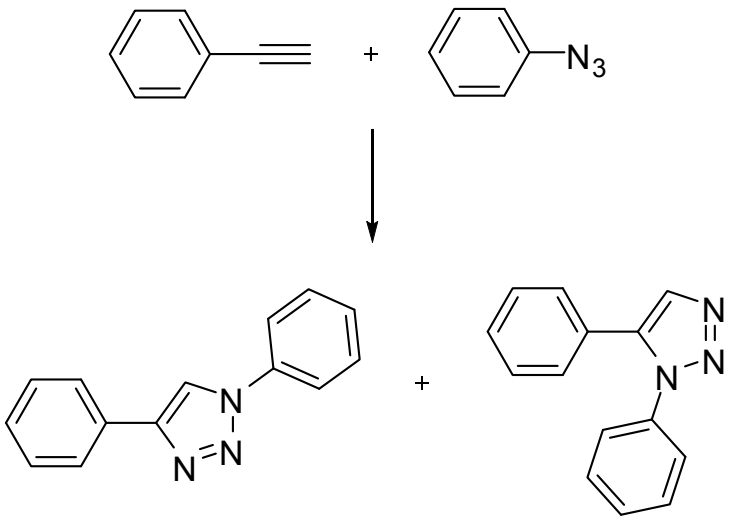
Turnover (slow)!



W. L. Mock et al. *J. Org. Chem.*, 1989, 54, 5302

Cavitands and capsules



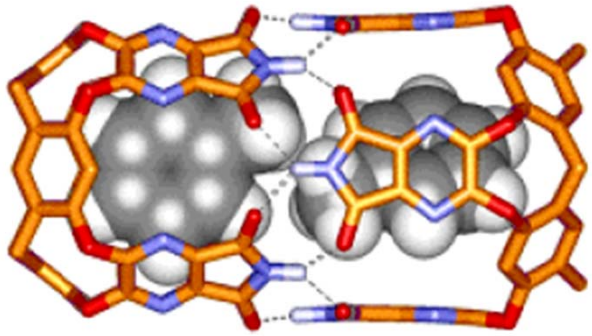


K_{ass} ~ 0.5 M^{-1}

k_{cat}/k_{uncat} ~ 240

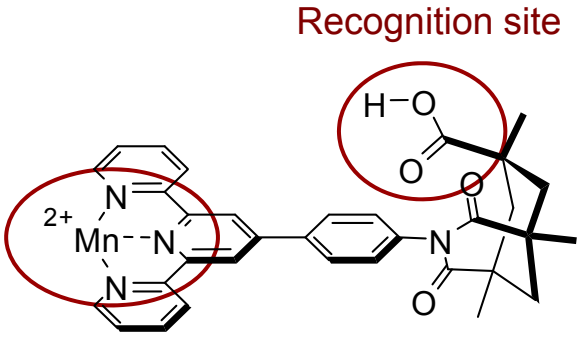
EM = 120 M (EM_{teor} = 3.6×10^6 M)

Turnover (slow)!

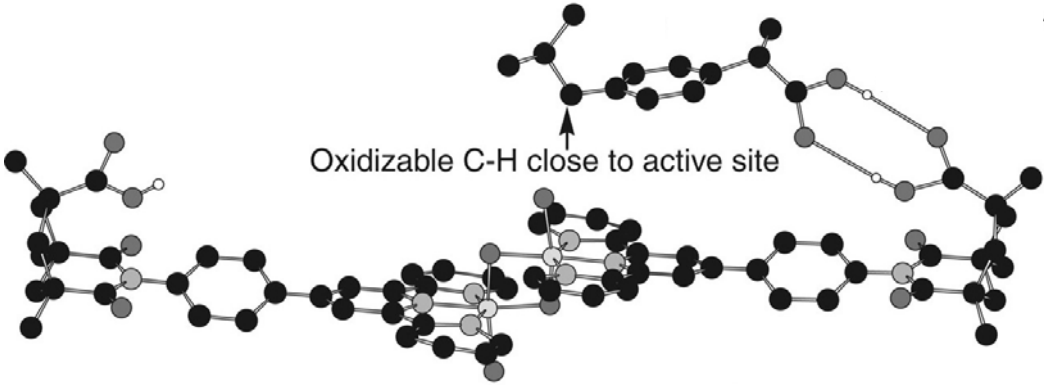


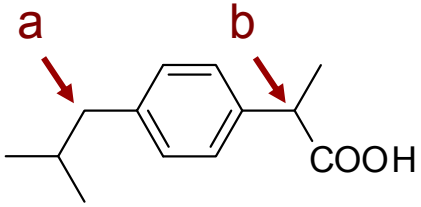
J. Rebek, *Org. Lett.* **2002**, 4, 327-329.

Selectivity induction by recognition



Reactive site (oxidation)





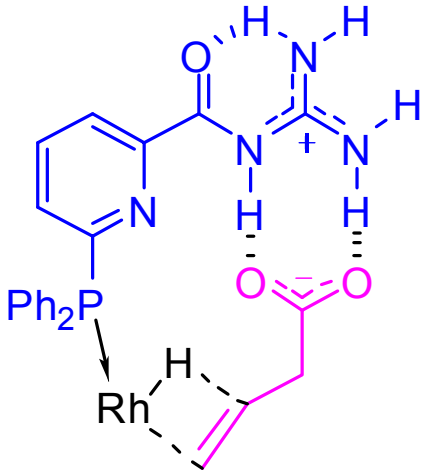
Ibuprofen

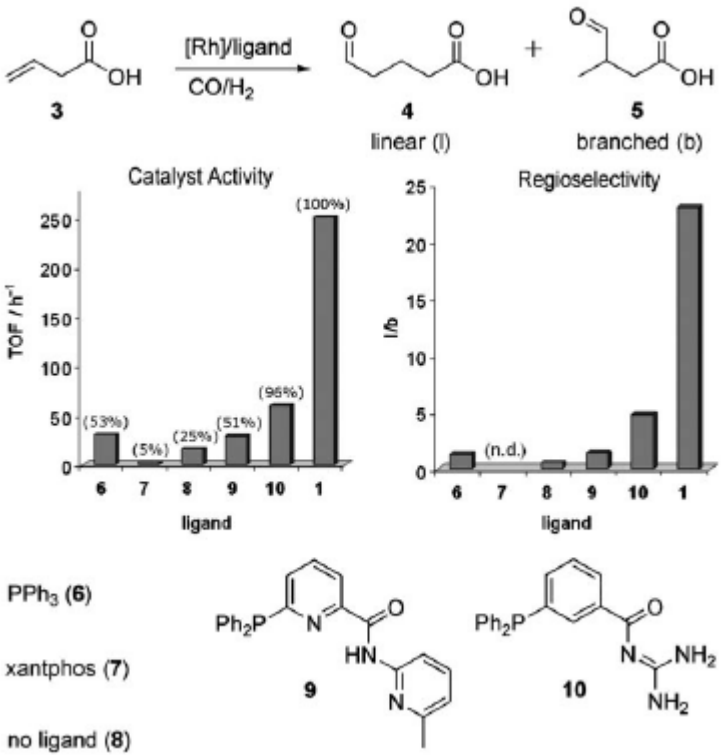
No recognition site a:b = 77 : 23

With recognition site a:b = 97.5:2.5

R. H. Crabtree, G. W. Brudvig et al. *Science*, **2006**, 312, 1941-1943

Selectivity induction by recognition



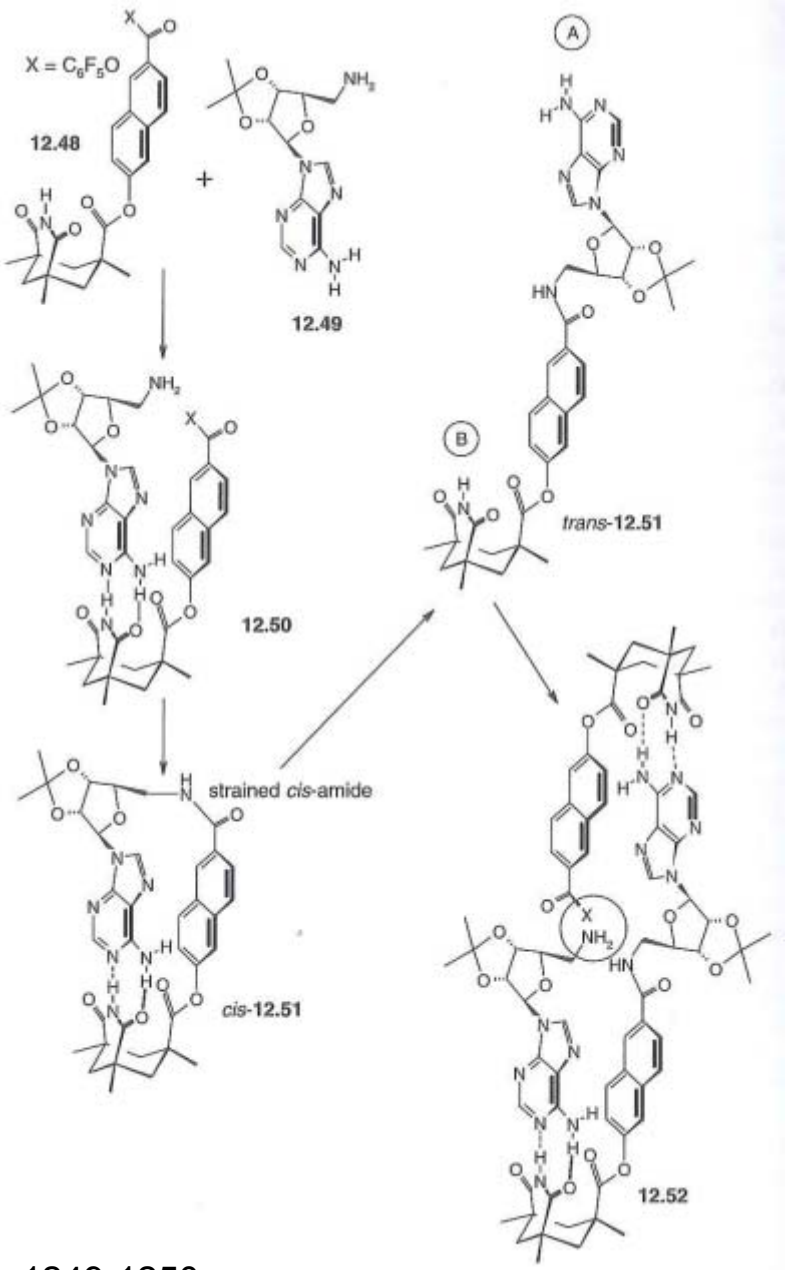


B. Breit et al., *Angew. Chem. Int. Ed.* **2008**, 47, 311 –315

Self-replication

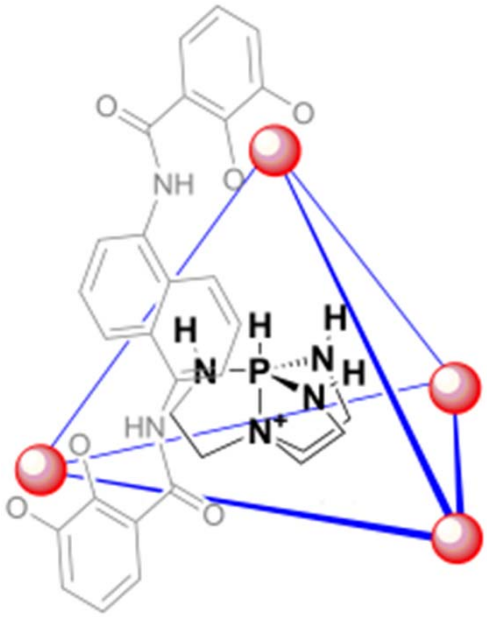
$K_{ass} = 8 \cdot 10^4\ M^{-1}$ *in 12.52*

Strong self-poisoning

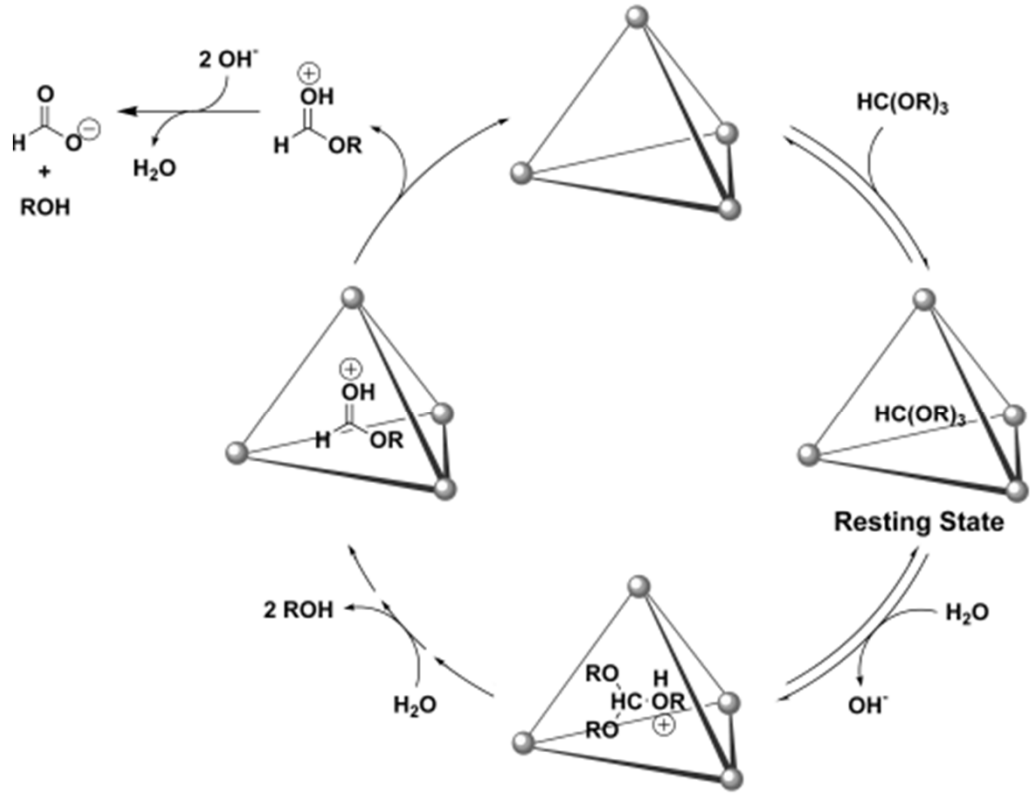


J. Rebek, Jr.et al., *J. Am. Chem. Soc*. **1990**, 112, 1249-1250

Transition state recognition



6 N,N′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene units and 4 Ga(III) ions self-assemble to form a tetrahedral cluster that strongly binds cationic guests.
Weakly basic molecules can be protonated inside the cativity even in basic conditions



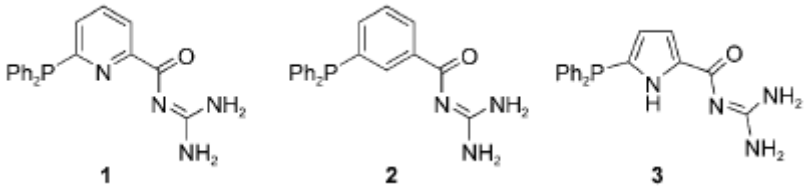
K_{ass} ~ 130 M^{-1}

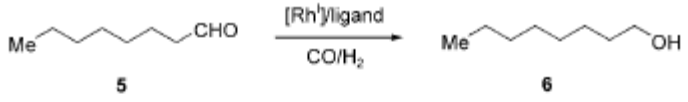
k_{cat}/k_{uncat} ~ 240

Turnover!

R. G. Bergman, K. N. Raymond et al. *Science*, **2007**, 316, 85-88

Transition state recognition

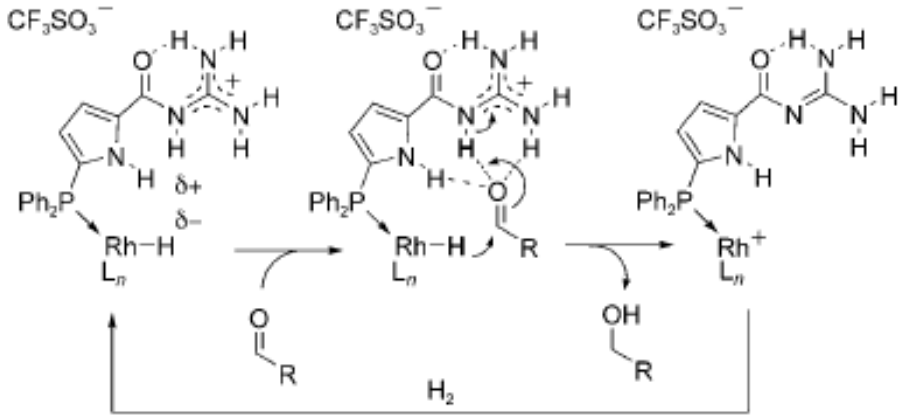


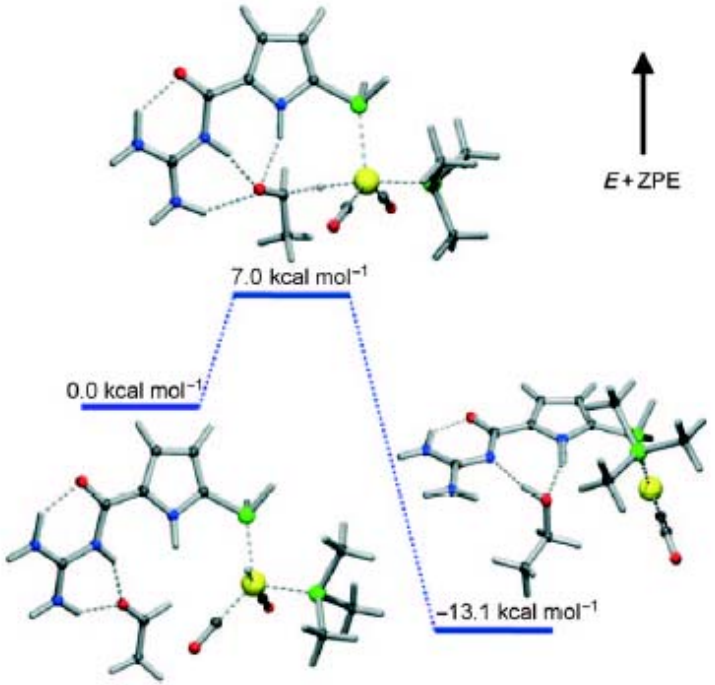


Entry	Ligand	Conversion [%]	Yield [%]
1	PPh_3	0	0
2	**1**	3	3
3	**2**	97	95
4	**3**	100	97
5[b]	**3**	27	27
6[c]	**3**	89	79

[a] Reaction conditions: $[Rh(CO)_2acac]$/ligand/substrate/CF_3SO_3H (1:10:500:5), CH_2Cl_2 (2 mL), c_0(**5**) = 0.6 M, CO/H_2 (1:1, 20 bar), 20 h, 40 °C. Substrate conversion and yields were determined by GC. [b] The reaction was carried out under H_2 (20 bar), without CO. [c] The reaction was carried out without CF_3SO_3H. acac = acetylacetonate.

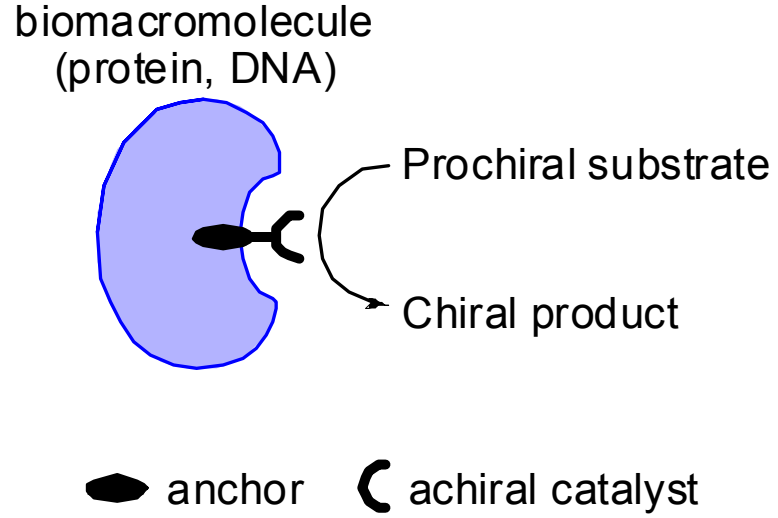
K_{ass} ~ 10 M^{-1}

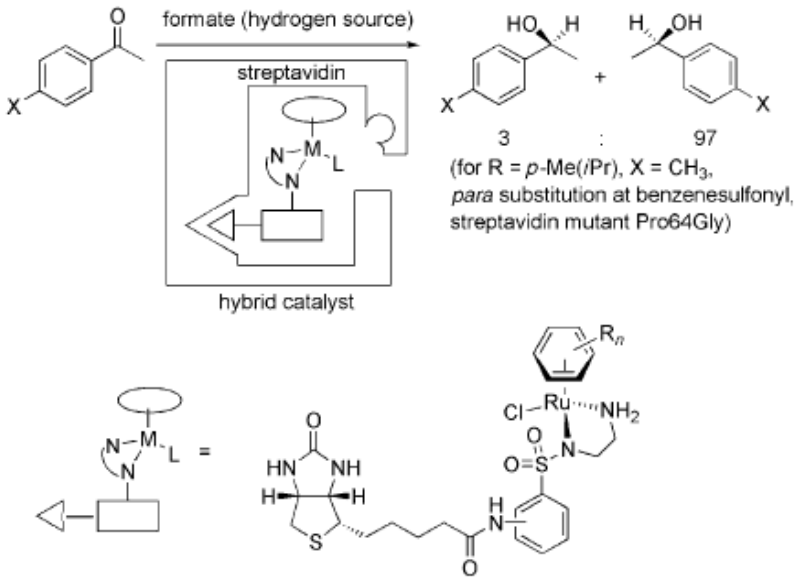




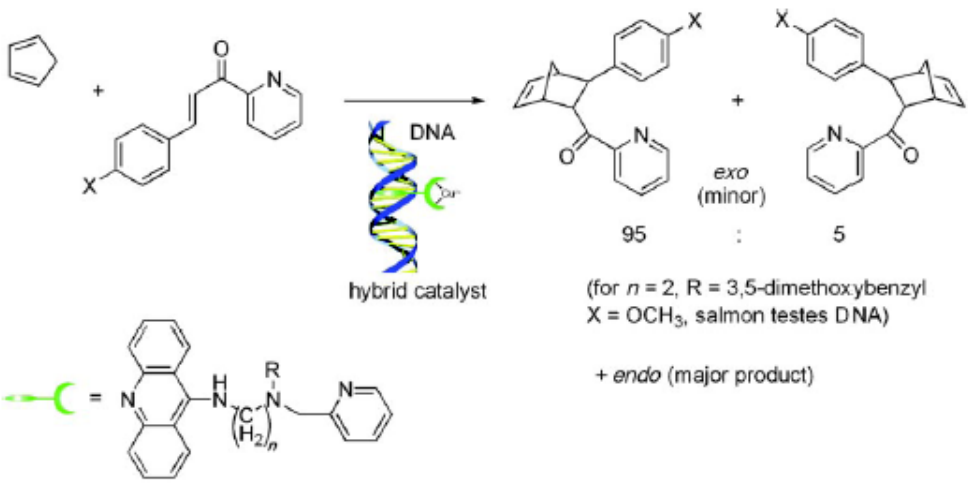
B. Breit et al., *Angew. Chem. Int. Ed.* **2009**, 48, 8022 –8026

Taking advantage form nature





T. R. Ward et al. *Proc. Natl. Acad. Sci. USA* **2005**, 102, 4683



G. Roelfes, B. L. Feringa, *Angew. Chem.* **2005**, 117, 3294