Supramolecular Reactivity and Catalysis

Supramolecular reactivity and catalysis thus involve two main steps:

(i) **Binding***:* which selects the substrate, and

(ii) **Transformation**: of the bound species into products within the supermolecule formed. Both steps take part in the molecular *recognition* of the *productive* substrate and require the correct molecular information in the reactive receptor. Compared to molecular reactivity, a binding step is involved that precedes the reaction itself. **Catalysis additionally comprises a third step**, the **release of the substrate**. *The selection of the substrate is not the only function of the binding step*.

In order to promote a given reaction, the binding should strain the substrate so as to bring it toward the transition state of the reaction; thus, *efficient catalysts should bind the transition state more strongly than the free state of the substrate in order to lower the free energy of activation.*

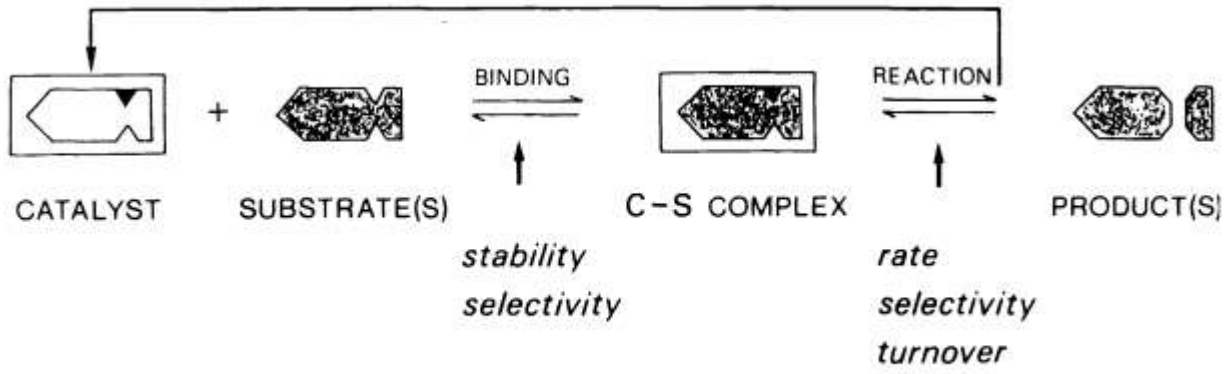


Fig. 6. Schematic representation of the supramolecular catalysis process.

However, the design of catalysts capable of optimal transition state stabilization does not consist in searching for strongest binding of strict transition state analogues (**TSA**) of the substrate, but rather of (TSA-X), i.e., of TSA minus X, where X represents the atom(s) of the functional group(s) in the catalyst that react(s) with the bound substrate.

The existence of strong interactions between the substrate and the receptor site of the catalyst may be used to facilitate the reaction in several ways, such as: a thermodynamic effect, strong binding forcing the substrate into contact with the reactive groups; a steric effect, fixation of the substrate being able to distort it towards its transition state geometry; an electrostatic (electronic, protonic, ionic) effect, consisting of a possible activation of the functional groups of the catalyst

(and possibly of the substrate also) by modification of their physico-chemical properties (pK_a, polarity, etc.) as a consequence of substrate fixation, which may perturb charge distributions in both the substrate and the catalyst with respect to their free, unbound state; such an activation of the catalyst by the substrate itself is a sort of *suicidal* behavior, the substrate facilitating its own consumption.

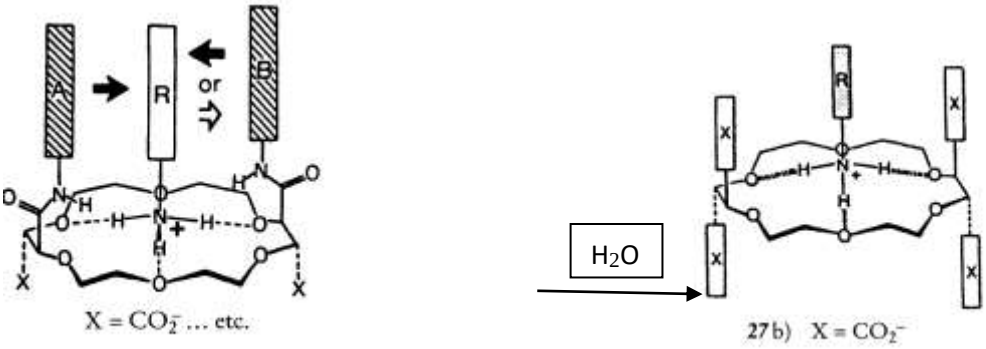
So 3 steps;

(i) Recognition (selectivity); (ii) Complex (between catalyst and substrate); and (iii) Product

<u>Catalysis by Reactive Macrocyclic Cation Receptor Molecules</u>: The ability of [18]-O_6 macrocyclic polyethers to bind primary ammonium ions opens the possibility to induce chemical transformations on such substrates.

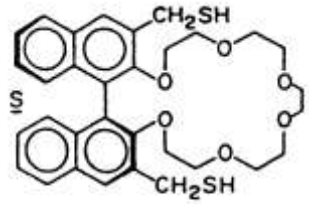
Activation and *orientation* by binding was observed for the hydrolysis of *O*-acetyl hydroxylamine, which forms such a stable complex **27b** (R = CH_3COO) with the macrocyclic tetracarboxylate receptor that it remains protonated and bound even at neutral pH, despite the low pK_a of the free species. As a consequence, **its hydrolysis is accelerated and exclusively gives acetate ($RCOO^-$) and hydroxylamine (NH_2OH)**, whereas in the presence **of K^+ ions, which displace the substrate, it yields also acetyl hydroxamic acid, CH_3CONH-OH**. Thus, strong binding may be sufficient for markedly accelerating a reaction and affecting its course, a result that also bears on enzyme-catalyzed reactions.

Chemical transformations may be induced by reaction between a bound substrate and functional groups borne by the macrocyclic receptor unit, as illustrated in structure **74**.



Ester cleavage processes have been most frequently investigated in enzyme model studies. Macrocyclic polyethers fitted with side chains bearing thiol groups cleave activated esters with

marked rate enhancements and chiral discrimination between optically active substrates. The optically active binaphthyl reagent **75** performs thiolysis of activated esters of amino acids with pronounced acceleration and chiral recognition (see **76**)



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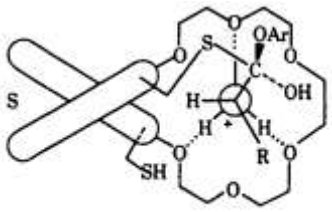

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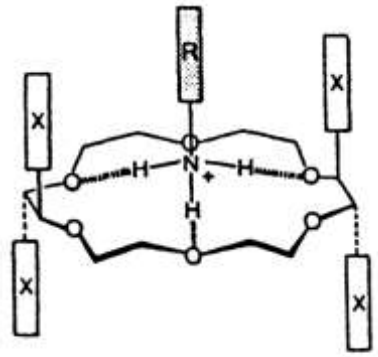
The tetra-L-cysteinyl macrocycle **27d** binds p-nitrophenyl (PNP) esters of amino acids and peptides, and reacts with the bound species, releasing p-nitrophenol as shown in **77.**

The reaction displays

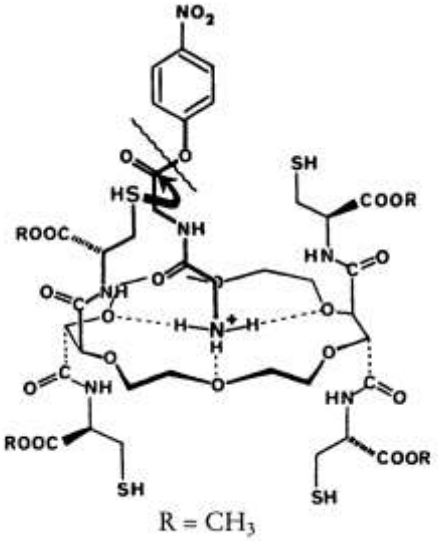
(1) Substrate selectivity in favour of dipeptide ester substrates, with; (2) marked rate enhancements, (3) Inhibition by complexable metal cations that displace the bound substrate,

(4) High chiral recognition between enantiomeric dipeptide esters, and (5) Slow but definite catalytic turnover.

Binding of the substrate probably activates the thiol groups by increasing their acidity that may also be of importance in enzymatic reactions.



27d) X = (L)–CH(CH2SH)–CO2Me



R = CH_3

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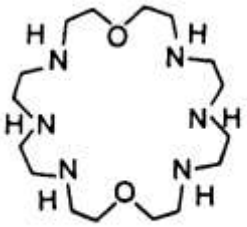
Catalysis by Reactive Anion Receptor Molecules: The catalysis *of phosphoryl transfer* is of particular interest, namely in view of the crucial role of such processes in biology and of the numerous enzymes that catalyse them. *ATP hydrolysis* was found to be catalyzed by a number of protonated macrocyclic polyamines. In particular, [24]-N_6O_2 **38**, strongly binds ATP and markedly accelerates its hydrolysis to ADP and inorganic phosphate over a wide pH range. The reaction presents first-order kinetics and is catalytic with turnover. It proceeds *via* initial formation of a complex between ATP and protonated **38**, followed by an intracomplex reaction that may involve a combination of acid, electrostatic, and nucleophilic catalysis. Structure **80** represents a possible binding mode in the ATP-X complex and indicates how cleavage of the terminal phosphoryl groups might take place. A transient intermediate, identified as phosphoramidate **81**, is formed by phosphorylation of the macrocycle by ATP and is subsequently hydrolyzed. In this process, catalyst **38** presents ATPase type activity.

38 + ATP ⟶ ATP Hydrolysis of **80** ⟶ **ADP** + phosphoramidate **(81)**



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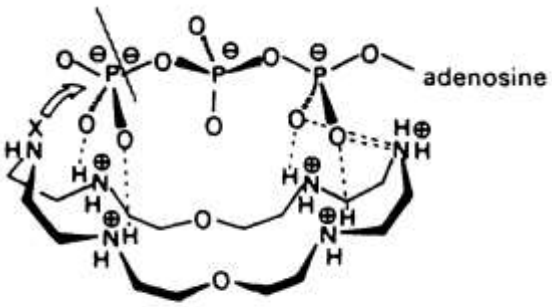

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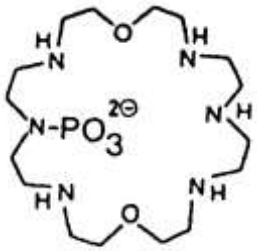

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