Symmetry control in reactions in molecular cavities

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The multistep reaction processes which occur in molecular cavities, like those involved in host–guest inclusion compounds, have been found to depend on the fulfilment of certain symmetry requirements; similarly, a symmetry control is observed whenever molecular cavities are formed by the active sites of specific enzyme–substrate complexes. It seems reasonable to suggest that, if the enzymatic structures are known, a careful use of these simple symmetry considerations may contribute to a better interpretation of the reactivity–structure correlations obtained by computer aided molecular graphic models of these enzymatic complexes.

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Considerable interest has been shown in the possibility of using host–guest inclusion compounds to generate asymmetric syntheses; in particular, they can be used to obtain unequal amounts of enantiomeric or diastereomeric stereoisomers starting from prochiral guest molecules inside chiral host cavities[1,2].

Before it is possible to obtain reliable results using this technique, knowledge must be gained of the structure of the host–guest inclusion compound, and also certain symmetry requirements must be fulfilled[3–6].

The reactions that take place in molecular cavities are the subject of a much broader range of research than host–guest type inclusion compounds; a certain number of enzymatic processes are intriguing as they can be correlated to catalytic reactions in inclusion compounds (e.g. in cyclodextrins and paracyclophanes[1]. A set of highly sophisticated interrelated cavities in compounds such as kinases (which determine the overall catalytic activity) correspond to the single cavities or channels expected in host–guest inclusion compounds[7].

The simplest case of a reaction process involving a host–guest inclusion compound is a multistep reaction process:

$$H + G \rightarrow [G]_H \xrightarrow[\Delta]{h\nu} [Exc]_H \rightarrow [P]_H \rightarrow H + P$$

where H, G and P represent the host, guest and product, respectively, and $[G]_H$, $[Exc]_H$ and $[P]_H$, the guest, the intermediate or transition state, and the product inside the host cavity, respectively.

SYMMETRY REQUIREMENTS

The following symmetry requirements may be suggested for the occurrence of any single step of this process:

- the intersection set of the symmetry groups of the species involved should contain at least, as a common element, the identity element of the included species. The occurrence of this condition only determines the formation of an inclusion compound; it usually generates a disordered structure for the complex with consequent low efficiency of the reaction step.
- Whenever additional symmetry elements exist in common between the reaction species, an ordered complex structure results with higher efficiency of the reaction step.
- All the symmetry elements present in the lower symmetric structures should be present in the higher symmetric structures, i.e. they should be in a group–subgroup relation; whenever more than one subgroup is possible, the larger one determines which reaction pathway is more probable.

Any reaction step which involves an inclusion compound and complies with the previously suggested symmetry requirements can be said to be 'symmetry allowed under cavity control', and denoted by 'S'; analogously, the lack of these requirements gives rise to a reaction step which can be said to be 'symmetry forbidden under cavity control' and denoted by 'A'; these symmetry requirements include the cases when the species involved are chiral.

In particular, if H and G denote the symmetry groups for an empty host cavity and a guest respectively and no common symmetry element exists except the guest identity E_g, then:

$$H \cap G = \{E_g, 0\} \quad (1)$$

However, if additional symmetry elements m_i exist in common, then:

$$H \cap G = \{E_g, m_i\} \quad (2)$$

Analogously, if A, B and C represent the symmetry groups of a host–guest complex and two different possible host–product complexes P_1 and P_2, so that:

$$A = H \cap G;\ B = H \cap P_1;\ C = H \cap P_2 \quad (3)$$

Then, the group–subgroup relation states:

$$A \subseteq H;\ B \subseteq H;\ C \subseteq H \quad (4)$$

The larger subgroup between B and C determines the most probable reaction pathway of the reaction step.

These symmetry relations have been applied to specific reactions which involve inclusion compounds[8,9].

A similar multistep reaction process may be suggested in case of an enzyme–substrate complex:

$$E + Sub \rightarrow [Sub]_E \rightarrow [Exc]_E \rightarrow [Prod]_E \rightarrow E + Prod$$

where E, Sub and Prod represent the enzyme, substrate and product, respectively; $[Sub]_E$, $[Exc]_E$, and $[Prod]_E$, represent the guest, intermediate and product formed inside a specific enzymatic 'active site' which has been assumed to be an enzymatic 'set' of cavities[10–14].

ENZYMATIC CAVITIES

Both NMR and X-ray structures of certain enzyme–substrate complexes have shown the existence of 'clefts' which may be mimicked by cavities. If the active sites for a specific enzyme–substrate reaction step are taken into account, the previously described symmetry considerations can be extended to this type of biological process.

As previously stated, the suggested symmetry requirements account for the case when both the enzymatic set of cavities forming the 'active site' and the substrate are chiral. In particular, they require the matching of their chiralities as happens, for instance, when right hand fingers (i.e. the various flexible molecular parts of a substrate) enter a right handed glove (i.e. the enzymatic flexible set of cavities).

Also for this multistep reaction process any single reaction step, such as the formation of the enzyme–substrate complex, may be said to be symmetry permissable under cavity control and denoted 'S' or it may be said to be symmetry forbidden and denoted 'A' (with reference to the stated symmetry requirements). Hence, a reaction process denoted by an 'S,S' sequence represents a two step reaction process with a sequence of two allowed or 'S' steps.

Based on the structural analysis of known 'active sites', as in the case of indoleacryloyl-α-chymotrypsin, and with the help of models which account for symmetry requirements, it is possible to mimick single reaction steps for a specific substrate and correlate these models with the experimental behaviour of the same enzyme–substrate.

For instance, α-chymotrypsin and methyl-L-*N*-acetylphenylalaninate give rise to the formation of an enzymatic complex which complies with the symmetry requirements, i.e. it is an 'S' reaction step. Analogously, the structure of the hydrolytic product corresponds to an 'S' reaction step. The overall catalytic reaction process may be denoted as an S,S sequence of steps. This symmetry behaviour correlates with a high reaction specificity[5] as shown by a value of 6.2×10^4 $M^{-1}s^{-1}$ for the constant k_{cat}/K_m, (where k_{cat} is the reaction catalytic rate constant and K_m is the complex dissociation constant) and by the steric L specificity of the overall process. It is worth noting that the step involving the formation of the reaction intermediate has not been reported for the difficulty of creating a reasonable model of its structure[15].

An A,A sequence occurs during the hydrolysis of D and L-β-phenyl-α-chloropropionates in α-chymotrypsin: it may be shown that both steps involving the enzyme substrate and the enzyme-product comply with the 'no symmetry' requirement: this A,A sequence matches an observed loss of stereospecificity, i.e. both D and L enantiomeric products are formed, with a low reaction specificity constant k_{cat}/K_m of 35 $M^{-1}s^{-1}$ for both enantiomers[7].

An A,S sequence occurs during the hydrolysis of D and L enantiomers of 3-methoxy-carbonyl-3,4-dihydroisocarbostyril in α-chymotrypsin; in this case a disordered first step is followed by an ordered one involving the hydrolysis product: the overall process has been observed[16] to give rise to a reversed D steric specificity constant of 4.3×10^4 $M^{-1}s^{-1}$.

The significant aspect displayed by these examples concerning α-chymotrypsin and various substrates is that only in the case of an S,S or A,S sequence does the overall enzymatic process show stereospecificity.

Whenever the structure of a particular enzyme–substrate complex is known, it is possible to employ powerful tools such as computer aided graphic techniques to unveil new aspects of the fundamental correlation between reactivity and structure. It seems reasonable to the author to assume that a major contribution to these studies might come from an accurate use of the symmetry considerations discussed in this paper: they were developed and tested for inclusion compounds but show significant compatibility for many enzymatic systems.

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