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Computationally Designed Prodrugs Based On Enzyme Models

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Abstract: The striking efficiency of enzyme catalysis has inspired many organic chemists to explore enzyme mechanism(s) by studying certain intramolecular processes (enzyme models) which proceed faster than their intermolecular counterparts. This editorial describes the use of computational methods such as quantum mechanics and molecular mechanics to explore the mechanisms of various enzyme models for assigning the factors affecting the rate-limiting step and determining the mode and action of the reaction. Among the enzyme models discussed herein are: (a) proton transfer between two oxygen atoms and proton transfer between nitrogen and oxygen in Kirby's enzyme model; (b) intramolecular acid-catalyzed hydrolysis in some of Kirby's N-alkylmaleamic acids; (c) proton transfer between two oxygen atoms in Menger's rigid system; (d) acid-catalyzed lactonization of hydroxy-acids as studied by Cohen and (e) SN2-based cyclization as studied by Bruice. These enzyme models were utilized as linkers to be covalently attached to commonly used drugs having poor bioavailability or/and bitter sensation. The conversion rate of the prodrug to its active form is solely determined on the structural features of the linker.

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Pioneering studies over the past sixty years, have vastly contributed in understanding how enzymes catalyze biochemical transformations. Today, a consensus has been reached by the scientific community which states that enzyme catalysis is based on the combined effects of the catalysis by functional groups and the ability to reroute intermolecular reactions through alternative pathways by which substrates can bind to pre organized active sites.

Generally, enzymatic reaction rates are 10^{10} to 10^{18} fold more than their non-enzymatic bimolecular counterparts. The tremendous rate acceleration manifested by enzymes is as a result of the substrate binding within the confines of the enzyme active site. The binding energy of the resulting enzyme substrate complex is the main driving force and contributor to catalysis. It is assumed that in all bio-transformations catalyzed by enzymes, binding energy is used to overcome the physical and thermodynamic factors that make barriers to the reaction (free energy) [1-5].

The high rates of intramolecular reactions are fascinating for chemists because they are reminiscent of the efficiency of enzyme catalysis and it is widely believed that a common source is, at least for a significant part, responsible for both

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enthalpic and entropic effects [6-8]. The similarity between intramolecularity and enzymes has prompted a number of chemists and biochemists to design chemical models based on intramolecular reactions consisting of two reacting centers in order to understand the mode and the mechanism by which enzymes exert their high catalytic activities [6-8]. Over the past 50 years, suggestions have been put forward in attempts to interpret changes in reactivity versus structural variations in intra molecular systems.

Nowadays, the use of computational chemistry for calculating geometries and energies of ground and transition states has become a common tool for organic, bioorganic and medicinal chemists alike. Computer science principles are utilized by computational chemists to aid in solving chemical problems by incorporating theoretical chemistry results into efficient computer programs to calculate the geometries and physical and chemical properties of molecules. Kinetics and thermodynamics calculations for biological systems having pharmaceutical and medicinal interests are considered an important challenge to the health community. Computational calculations utilizing Quantum Mechanics (QM) such as *ab initio*, semi-empirical and Density Functional Theory (DFT) methods, and Molecular Mechanics (MM) methods are increasingly being used and broadly accepted as reliable tools for the prediction of potential drugs and prodrugs alike [9].

In this editorial, the mechanisms of some enzyme models (mimicking enzyme catalysis) that have been advocated to understand how enzymes work were computationally explored. The tool used in the study is computational approach consisting of calculations using a variety of different molecular orbital and molecular mechanics methods and correlations between experimental and calculated reaction rate values (activation energies).

In the past few years, we have been researching the origin and nature of the factors affecting the rate-limiting step and responsible for the extraordinary enhancements in rate of a number of intramolecular processes (enzyme models). Using quantum mechanics methods including ab initio and DFT at different levels, AM1 semi-empirical molecular orbital method and MM2 molecular mechanics method, we have computed the kinetic and thermodynamic parameters for the acid-catalyzed lactonization of hydroxy-acids as investigated by the two groups of Milstein [10] and Menger [11-15], Bruice's SN2-based-cyclization reactions of di-carboxylic semi-esters to anhydrides [16-17], proton transfer between two oxygens in Kirby's acetals, proton transfer between nitrogen and oxygen in Kirby's enzyme models, and proton transfer from oxygen to carbon in some of Kirby's enol ethers [18-26]. The conclusions emerged from these studies are: (i) Rate accelerations in the intramolecular processes studied are due to proximity orientation of the two reacting centers. This proximity can stem from strain effects or can be due to enthalpic effects not related to strain imposed on a starting material and/or the corresponding transition state. For instance, the calculations of Bruice's di-carboxylic semi-esters cyclization demonstrated that the reaction's rate is dependent on the strain energy of the transition state and the reactant, and not to the so called ''reactive rotamer effect". In addition, they revealed that the reactivity of the semi-ester is linearly correlated with the strain energy difference between the transition state and the corresponding reactant and no correlation was found between the reaction rate and the distance between the two reacting centers. On the other hand, the calculations on Cohen's acid-catalyzed lactonization and Menger's hydroxy-acids demonstrated that driving force for the acceleration in rates in these two processes is proximity with un-enforced strain origin and the rate of the reaction is solely dependent on the ratio between the attack angle of the nucleophile and the distance between the two reacting centers.

This result is in accordance with Menger's ''spatiotemporal hypothesis" that relates rate of a reaction to the distance between the two reacting centers. (ii) Both, entropy and enthalpy effects are important factors in determining the rate accelerations in intramolecular processes studied. (iii) The nature of the reaction (inter- or intra-molecular) is determined on the distance between the two reacting centers. For instance,

the calculations on Menger's rigid cycloalkanes revealed that intramolecular processes are favored over the corresponding intermolecular reactions when the distance between the two reactive centers is less than 2.4 Å, whereas, when the distance is more than 3 Å, the reaction prefers intermolecular engagement [27-43]

New prodrugs based on the above discussed enzyme models

The computational studies on intramolecularity have proven that there is a crucial need to further explore mechanisms for other intramolecular processes to be exploited in the design for efficient prodrugs. Exploration of the reaction mechanism would provide an accurate design of an efficient chemical device to be used as a prodrug linker that can be covalently linked to a drug which can chemically convert into the active parent drug. For example, the calculations study on Kirby's acetals mechanism led to a design of aza-nucleoside (to treat myelodysplastic syndromes) [44], phenylephrine (decongestant) [45]. Atovaquone [46-48] and statins (to treat high cholesterol levels in the blood) [49] prodrugs. In these examples, the acetal moiety was linked to the hydroxyl group of the active drug such that the prodrug has the potential to convert to its parent active form upon its exposure to physiological environment with rates that are solely determined on the structural features of the linker (Kirby's acetal). Other different prodrugs linkers such as Kirby's N-alkylmaleamic acids were also studied and exploited for the design of some prodrugs such as tranexamic acid (to treat bleeding conditions) [50], cefuroxime (antibacterial) [51] and acyclovir (anti-viral drug to treat Herpes Simplex) prodrugs [52]. Additionally, exploring the mechanism of Menger's Kemp acid enzyme model has led to the design of dopamine prodrugs for the treatment of Parkinson's disease [53]. Dimethyl fumarate prodrugs to treat psoriasis were also designed, synthesized and are under *in vitro* and *in vivo* kinetic studies [54]. Similarly, prodrugs for masking the bitter taste of antibacterial drugs such as cefuroxime, amoxicillin and cephalexin [55-60], atenolol (anti-hypertensive) [61-62] and paracetamol (pain killer) were designed, synthesized and their kinetics were studied [63]. The role of the prodrug linker in these prodrugs is to block the free amine (antibacterial drug or atenolol) or the hydroxyl group (paracetamol) which is responsible for the drug's bitter taste, and to enable the release of the drug in a programmable manner. Replacing the amine group with an amide or the hydroxyl group with ester eliminates the capability of the molecule to hydrogen bond with the bitter taste receptor, thus masking the bitter taste of the parent drug.

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