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Computationally Designed Enzyme Models to Replace Natural Enzymes in Prodrug Approaches

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Introduction

The striking efficiency of enzyme catalysis has inspired many organic chemists to explore enzyme mechanisms by studying certain intra molecular processes such as enzyme models which proceed faster than their intermolecular counterparts. This research brings about the important question of whether enzyme models will replace natural enzymes in the conversion of prodrugs to their parental drugs.

Enzymes are mandatory for the inter conversion of many prodrugs to their parental drugs. Among the most important enzymes in the bioconversion of prodrugs are amides (ex. trypsin, chymotrypsin, elastase, carboxypeptidase, and aminopeptidase) and ester-based prodrugs (ex. paraoxonase, carboxylesterase, acetylcholinesterase and cholinesterase). Most of these enzymes are hydrolytic enzymes, however, non-hydrolytic enzymes, including all cytochrome P450 enzymes, are also capable of catalyzing the bioconversion of ester and amide-based prodrugs [1].

Today, the consensus is that the catalytic activity of an enzyme is based on the combined effects of catalysis by functional groups and the ability to reroute intermolecular reactions through alternative pathways by which substrates bind to preorganized active sites. Rate acceleration by enzymes can be due to (a) covalently enforced proximity, as in chymotrypsin, [2] (b) non-covalently enforced proximity, as in the catalytic activity of metallo-enzymes, [3] (c) covalently enforced strain, and [4] (d) non-covalently enforced strain, which has been heavily studied in models that mimic the enzyme lysozyme [5].

The rate constants for a large majority of enzymatic reactions exceed 10^{10} to 10^{18} fold the non-enzymatic bimolecular counterparts. For example, reactions catalyzed by cyclophilin are enhanced by 10^5 and those by orotidine monophosphatedecarboxylase are enhanced by 10^{17} [6]. The significant rate of acceleration achieved by enzymes is brought about by the binding of the substrate within the confines of the enzyme pocket called the active site. The binding energy of the resulting enzyme-substrate complex is the dominant driving force and the major contributor to catalysis. It is believed that in all enzymatic reactions, binding energy is used to overcome prominent physical and thermodynamic factors that create barriers for the reaction [7] (ΔG). The striking efficiency of enzyme catalysis has inspired many organic chemists to explore enzyme mechanism(s) by studying certain intra molecular processes (enzyme models) which proceed faster than their intermolecular counterparts. Both, enzymes and intra molecular processes are similar in that the reacting centers are held together (covalently with intra molecular systems, and non-covalently with enzymes) [8].

During the last six decades, reaction models for mimicking enzyme catalysis has been advocated by a variety of chemists. Among enzyme models based on enthalpic driving forces are: (1) near attack proximity orientation model proposed by Bruice's group [9,10]; (2) orbital steering theory proposed by Koshland's group [11]; (3) spatiotemporal hypothesis devised by Menger et al. [12,13-18]; and (4) stereo population control suggested by Cohen's group [19-21]. Mechanistic studies based on these models have played an important role in elucidating the chemistry of the groups involved in enzyme catalysis as well as in unraveling the mechanisms available for particular processes. Based on these studies, it seems reasonable to assume that an understanding of efficiency depends on the structure in intramolecular catalysis, which draws the basis for utilizing these enzyme models as linkers to certain drugs for synthesizing prodrugs with higher bioavailability than their corresponding parental drugs. In addition, it was found that slight changes in the structural features of the enzyme model could provide a broad range of reaction rates ranging from 1 to 10^{15} [22]. With such a broad range, prodrugs will be designed so that they will undergo non-enzymatic (chemical) conversion to their parental drugs in a fast or slow manner according to the required goal.

Prodrugs are bio reversible derivatives of drug molecules designed to overcome pharmaceutical, pharmacokinetic or pharmacodynamic barriers, such as low oral absorption, lack of site specificity, insufficient chemical stability, poor solubility, toxicity, and unacceptable taste/odor. The prodrug approach is becoming more popular and successful, as prodrugs comprise around 10% of the world's marketed medications and 20% of all small molecular medications approved between 2000 and 2008 [23,24].

An ideal drug candidate needs to have specific properties, including chemical and enzymatic stability, solubility, low clearance by the liver or kidney, permeation across biological membranes, potency, and safety.

The conversion of a prodrug to the parental drug at the target site is crucial for the prodrug approach to be successful. Generally, activation involves metabolism by enzymes that are distributed throughout the body. Many prodrugs contain ester or amide bonds, which are formed by derivatizing a hydroxyl, carboxyl, or amine group present in the parental drug. When the ester or amide bond of the prodrug is cleaved, the active parental drug is released. In vivo cleavage of ester and amide bonds generally occurs through hydrolysis or oxidation. Many ester and amide-based prodrugs have been developed after being designed to improve the oral bioavailability of drugs [25-27]. The major problem with these prodrugs is the difficulty in predicting their bioconversion rates, and thus their pharmacological or toxicological effects. Moreover, the rate of hydrolysis is not always predictable, and bioconversion can

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be affected by various factors such as age, health conditions and gender [28–30].

Modern computational methods can be used for the design of innovative prodrugs for drugs that contain hydroxyl, phenol, or amine groups. For example, mechanisms of some enzyme models that have been used to gain a better understanding of enzyme catalysis have been recently investigated and utilized for the design of novel prodrug linkers [31-37]. Using computational methods such as DFT, molecular mechanics and ab initio, various enzyme models were investigated for assigning the factors affecting the rate-determining step and playing dominant roles in governing the reaction rate. Among these enzyme models are: (a) proton transfer between two oxygens in Kirby's acetals [38-47] and proton transfer between nitrogen and oxygen in [38-47]; (b) intramolecular acid-catalyzed hydrolysis in some of Kirby's maleamic acid amide derivatives [38-47]; (c) proton transfer between two oxygens in rigid systems as investigated by Menger [12-18]; (d) the acid-catalyzed lactonization of hydroxy-acids as studied by Cohen et al. [19] and Menger [12]; and (e) the SN2-based cyclization as studied by Brown [48], Bruice and Mandolini [9,49].

These studies have revealed the following conclusions: (i) rate enhancement in intramolecular processes is a result of both entropy and enthalpy effects. In intramolecular cyclization processes where enthalpic effects were predominant, steric effects were the determining factor for the acceleration, whereas proximity orientation was the determining factor in proton-transfer reactions. (ii) The distance between the two reacting centers is the main factor in determining whether the reaction type is intermolecular or intramolecular. When the distance exceeded 3 Å, an intermolecular engagement was preferred because of the involvement of a water molecule (solvent). When the distance between the electrophile and nucleophile was <3 Å, an intramolecular engagement was preferred. (iii) The efficiency of proton transfer between two oxygens and between nitrogen and oxygen in Kirby's enzyme models is attributed to a relatively strong hydrogen bonding in the products and the transition states leading to them [31-37].

It was concluded from the studies on intramolecularity that there is a need to further investigate the reaction mechanism for assigning the factors determining the reaction rate. This would allow for better design of an efficient chemical device that can be used as a prodrug linker and that will have the potential to chemically and not enzymatically liberate the active drug in a programmable and controlled manner. For example, the mechanism for proton transfer in Kirby's acetals were explored and directed the synthesis of novel prodrugs of aza-nucleosides for the treatment of myelodysplastic syndromes where the prodrug linker is attached to the hydroxyl group of the nucleoside [50]. The prodrugs were designed such that they undergo cleavage reactions in physiological environments such as stomach, intestine, and/or blood circulation, with rates that are solely dependent on the structural features of the pharmacologically inactive linker. Different linkers were also investigated for the design of a large number of prodrugs such as anti-Parkinson (dopamine), [51] anti-viral (acyclovir), and [52] anti-malarial (atovaquone) with enhanced dissolution, membrane penetration, and bioavailability [53]. In addition, prodrugs for masking the bitter taste of atenolol, dopamine, pseudoephedrine, amoxicillin, cephalexin, cefaclor, and paracetamol were also designed and synthesized [54,55]. The role of the linkers in these prodrugs is to block the free amine or phenol group, which is responsible for the bitter taste of the drug, in the corresponding parental drugs and to enable the release of the drug in a programmable manner [50-55].

These examples highlight the great potential and impact of modern computational approaches for prodrug design. Furthermore, with the possibility of designing prodrugs that have different linkers, the rate of release of the parental drugs can be controlled without the presence of an enzyme.

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