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The Future of Prodrugs Designed by Computational Chemistry

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When knowledge fails to provide answers to important questions such as how to improve the bioavailability of vital medications, "Imagination is more important than knowledge," as Albert Einstein once said. Ingenuity in the design of effective prodrugs has been lacking in quantity and quality. The reasons behind the low quality of ingenuity could be related to the fact that medicinal chemists have expertise in organic and organometalic chemistry not in biochemistry and biology. On the other hand, pharmaceutical chemists, biologists, and biochemists do not have the expertise to make sophisticated chemical devices. Therefore, in order for a prodrug strategy to work, a team consisting of all this expertise is necessary.

A prodrug is a pharmacologically inactive chemical derivative that can be utilized to temporarily alter the physicochemical properties of a specific drug to increase its usefulness and minimize its toxicity. Prodrugs have gained attention as an approach for improving drug therapy since the early seventies. Examples of prodrugs include the antirheumatic agent oxindole succinicate, the anticonvulsant agent progabide, the anti-inflammatory drugs valdecoxib, prednisolone and fluocinolone acetonide, and the anti-glaucoma agent (dipivefrin) [1].

Ideally, the prodrug should be cleaved to the parental drug as soon as its purpose is achieved, followed by rapid elimination of the released linker moiety [2,3]. Prodrugs are designed so that they undergo cleavage in physiologic environments via enzyme catalysis and/or via in vivo chemical reactions. In both cases, the rate of prodrug cleavage from its parental drug is not controlled by the chemist but by the dosage route environment and the abundance of certain enzymes in the route.

The modern approach to be discussed in this editorial implies the design of prodrugs based on intramolecular processes utilizing molecular orbital methods and correlations between experimental and calculated values. No enzyme is needed for the catalysis of the conversion of a prodrug to the corresponding drug. The rate of drug release is dependent only on the rate limiting step for the conversion of its corresponding prodrug. Knowledge gained from enzyme catalysis and intramolecularity was used in the design.

The chemistry of intramolecular processes has been important in modeling the extraordinary efficiency of enzymes. In the last five decades, scholarly studies have been done by Bruice, Jencks, Bender, Menger, Kirby and others to assemble enzyme model systems that are capable of achieving rates comparable to those seen in processes catalyzed by enzymes. Important examples of such models are those based on rate enhancement due to covalently enforced proximity [4,5]. The most frequently cited example of such acceleration is the model presented by Bruice and Pandit [6,7] on the intramolecular cyclization of dicarboxylic semi esters. Other examples of rate acceleration as a consequence of proximity include: (1) reactants obey the principles "orbital steering" suggested by Dafforn and Koshland [8]; (2) the "spatiotemporal hypothesis" presented by Menger et al. [9-16] which suggests that a type of a reaction, in proton transfer processes, whether intermolecular or intramolecular, is largely determined by the distance between the two reacting centers; (3) the gem-trimethyl lock (stereopopulation control) proposed by Milstien and Cohen [17-19] which explains the relatively high acceleration rates in the acid catalyzed lactonization reactions of hydroxyhydrocinnamic acids; (4) Proton transfer between two oxygen's and between nitrogen and oxygen in Kirby's enzyme models [4,5].

The use of theoretical methods for computing physicochemical and molecular properties has been a progressive goal of organic, organometallic, inorganic, and pharmaceutical chemists alike. Thermodynamic and kinetic energy-based calculations for biological moieties that have pharmaceutical/medicinal interest are a great challenge. Nowadays, quantum mechanics such as ab initio, a semi-empirical and density functional theory, and molecular mechanics are widely accepted as tools that provide structure-energy calculations for the prediction of potential drugs and prodrugs [20].

The ab initio molecular orbital method (quantum mechanics) is based on rigorous utilization of the Schrodinger equation with a number of approximations. Use of the ab initio method is restricted to small systems that do not have more than thirty atoms due to the length of computation time [21-23]. MINDO, MNDO, MINDO/3, AM1, PM3 and SAM1, are semi-empirical methods based on the Schrodinger equation with the addition of terms and parameters to fit experimental data and have afforded vast information for practical application [24-26]. Density functional theory (DFT) is a semi-empirical method used to calculate structures and energies for medium-sized systems of biological and pharmaceutical interest and is not restricted to the second row of the periodic table [27]. Unlike quantum mechanics, molecular mechanics is a mathematical approach used for the calculation of structures, energy, dipole moment, and other physical properties, and is capable of handling many diverse biological and chemical systems such as proteins, large crystal structures, and relatively large solvated systems. However, this method is limited by the determination of parameters such as the large number of unique torsion angles present in structurally diverse moieties [28].

Recently, DFT and ab initio methods were used to assign the factors affecting the rate-determining step and thus the reaction rate in numerous intramolecular reactions. Among these processes are: (1) cyclization reactions of di-carboxylic semi-esters by Bruice and Pandit [6,7] lactonization of hydroxy-acids by Cohen and Milstein [17-19] and Menger [9-16]; (3) intramolecular SN2-based cyclization reactions by Brown's group [29] and Mandolini's group [31]; (4) proton transfer between two oxygen's in Kirby's acetals [4,5] and proton transfer between nitrogen and oxygen in Kirby's carboxylic amines [4,5]; (5) proton transfer between two oxygens in rigid carboxylic amides by Menger et al. [9-16]; (6) proton transfer from oxygen to carbon in Kirby's enol

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ethers [4,5]; (7) proton transfer between two oxygens in N-alkylmaleamic acids by Kirby [4,5]. The results from these studies revealed: (a) rate enhancement in intramolecular processes is due to both entropy and enthalpy effects. In the cases by which enthalpic effects were predominant, such as in cyclization reactions, steric effects were the cause for the accelerations, whereas proximity orientation was the dominant factor in the cases of proton transfer reactions. (b) The reaction type being intermolecular or intramolecular is determined by the distance between the two reacting centers. A distance of less than 3 Å between the two reacting centers promoted an intramolecular engagement. (c) The efficiency of proton transfer between two oxygens and between nitrogen and oxygen in Kirby's acetal systems is due to a strong hydrogen bond in the products and the corresponding transition states leading to them [31-42].

From these studies on intramolecularity, it was concluded that the reaction mechanism must be investigated in order to assign the factors determining the reaction rate. This information is then used to design an efficient chemical device to be used as a prodrug linker capable of liberating the parental drug in a programmable manner (slow or fast release) [31-42]. For example, exploring the mechanism for the proton transfer in Kirby's acetals [4,5] has led to the design of prodrugs of azanucleosides for the treatment of myelodysplastic syndromes, where the prodrug linker is attached to the hydroxyl group of the nucleoside [31-42]. In addition, prodrugs of paracetamol capable of masking the bitter taste of the parental drug were also designed such that the linker is covalently linked to the phenolic group of paracetamol, which is believed to be responsible for the bitterness of the drug [31-42]. The prodrugs were designed to undergo cleavage reactions in physiological environments such as the stomach at pH 1.5, intestine at pH 6.5, and blood circulation at pH 7.4, with rates that are solely dependent on the structural features of the pharmacologically inactive linker.

Different linkers were also investigated for the design of large numbers of prodrugs that might be efficient in releasing the parental drugs in various rates that are dependent on the nature or the structural features of the linkers. Examples of these prodrugs include the anti-Parkinson's agent dopamine [31-42], the anti-viral agent acyclovir [31-42], and anti-malarial agent atovaquone [31-42]. This research can provide novel prodrugs that may have the potential to have enhanced dissolution, membrane penetration, and thus better bioavailability.

In the past, the prodrug approach was viewed as a last resort after all other ways were exhausted. Nowadays, the prodrug approach is being considered in the very early stages of the drug development process. While the classic prodrug approach was focused on altering various physiochemical parameters, the modern computational approach considers using a design of linkers with drugs that have poor bioavailability to release the parental drugs in programmable manner and improve their bioavailability. With the possibility of designing prodrugs with different linkers, the rate of release of the parental drugs will be controlled.

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