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A new mathematical equation relating activation energy to bond angle and distance: A key for understanding the role of acceleration in lactonization of the trimethyl lock system

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ABSTRACT

AM1 semi-empirical molecular orbital and ab initio HF at the 6-31G level calculations for the lactonization processes of 12 different hydroxy acids (**1a–1l**) which differ in their structural features have been conducted. The calculations obtained reveal the following: (1) The rate-limiting step in the lactonization process is formation of a tetrahedral intermediate and not its collapse as was previously reported. (2) The rate-limiting step in both the acid-catalyzed and uncatalyzed lactonization is composed of two successive steps: approach of the hydroxyl toward the carbonyl carbon until it reaches a distance of 1.4 –1.5 Å, followed by proton transfer from the ether-type oxygen to one of the hydroxyls in the tetrahedral intermediate. Calculations of the activation energies for formation of the tetrahedral intermediate in the 12 hydroxy acids studied indicate: (1) A linear relationship exists between the change in enthalpic energy (E) and the ratio of the attack angle (nucleophilic-oxygen/carbonyl-carbon/αλπηα-carbon) to the distance (nucleophilic-oxygen/carbonyl-carbon) termed α/r; (2) The slope (S) of E vs. α/r plots depend on the nature of the hydroxy acids. Furthermore, plots of S values against the experimental rate values ($\log k_{exp}$) show a linear correlation with a high correlation coefficient. The combined results suggest that hydroxy acids with low S values have high k_{exp} values due to enthalpic proximity effects.

1. Introduction

Studies of enzyme mechanisms by Bruice and Benkovic, [1] Jencks, [2] and Bender, [3] over the past four decades, have contributed in understanding the mode and scope of enzyme catalysis. Today, the consensus is that the catalytic activity of an enzyme 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 bind to pre organized active sites. Rate acceleration by enzymes can be attributed to (a) covalently enforced proximity, such as in the case of chymotrypsin, [4] (b) non-covalently enforced proximity, which is represented in the catalytic activity of metallo-enzymes, [5] (c) covalently enforced strain, [6], and (d) non-covalently enforced strain, which has been heavily studied on models that mimic the lysozyme enzyme which is most closely associated with rate acceleration due to this kind of strain [7].

The estimated 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 accelerated by10^{5} and those by orotidine monophosphate decarboxylase are accelerated by 10^{17} [8]. The significant rate enhancement manifested 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 make barriers to the reaction ($\Delta G^{\ddagger}$). These factors are: (1) the change in entropy ($\Delta S^{\ddagger}$), in the form of the freedom of motions of the reactants in solution; (2) the hydrogen bonding net around bio-molecules in aqueous solution; (3) a proper alignment of catalytic functional groups on the enzyme; and (4) the distortion of a substrate that must occur before the reaction takes place [9].

In the last 40 years, scholarly studies have been done by Bruice, [10] Cohen, [11] Menger, [12] and others to find chemical model systems that are capable of achieving rates comparable to these seen with enzyme catalyzed reactions. Important examples of such models are those based on rate acceleration due to covalently enforced proximity. The most frequently cited example of such acceleration is the model presented by Bruice et al. on the intramolecular cyclization of dicarboxylic semi esters to furnish the corresponding anhydrides [10]. Using this model, Bruice et al. shows that a relative rate of anhydride formation can reach

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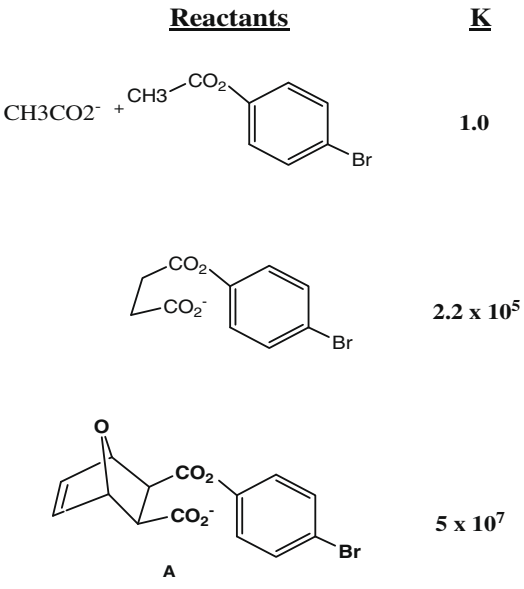
5×10^7 upon the intramolecular cyclization of dicarboxylic semi ester **A** when compared to an intermolecular reaction of the counterpart reactants (Scheme 1). Other examples of rate acceleration as a consequence of proximity include: (1) reactants such as those described in Scheme 2 which obey the principles of "orbital steering" theory suggested by Koshland [13]. The examples depicted in the scheme indicate a vast importance to the angle of attack value of the hydroxyl on the rate of the intramolecular lactonization reaction; (2) the "spatiotemporal hypothesis" presented by Menger 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 centers involved in the lactonization reaction (as shown in Scheme 3 and [12]) (3) the gem-trimethyl lock (stereopopulation control) proposed by Cohen to explain the relatively high acceleration rates in the acid catalyzed lactonization reactions of hydroxyhydrocinnamic acids containing two methyl groups on the β position of their carboxylic moieties (Scheme 4) and [11].

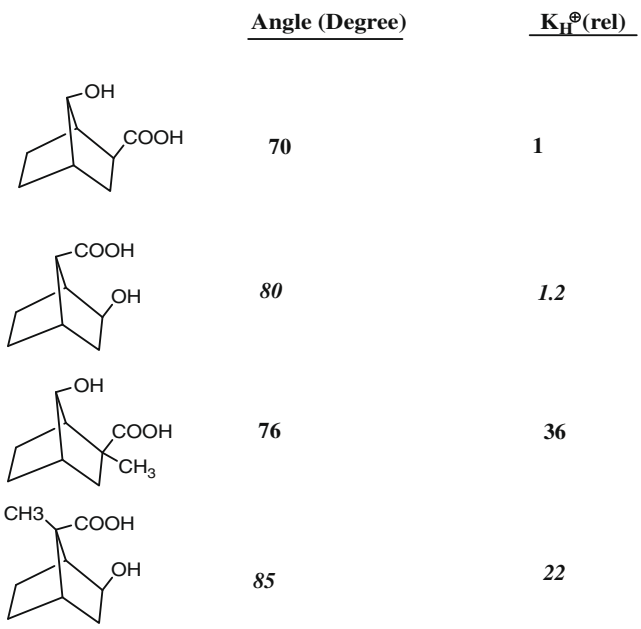
In 1970, Cohen studied the lactonization of a series of hydroxyhydrocinnamic acids and found rates in the range of 10^{15}. He attributed this large enhancement to what he called "stereopopulation control" [11]. Cohen's proposal was attacked by various researches who claimed that the high rate of enhancement obtained in Cohen's laboratory was due to a relief in strain energy that occurs upon the lactonization of hydroxyhydrocinnamic acid and that is was not due to stereopopulation control driven by the trimethyl lock system [14].

Our interest in examining Cohen's model stems from the need to make a chemical device that is composed of a drug and an entity that binds to the drug and can undergo a rapid reaction upon administration to the human body to furnish the drug and the pharmacologically inactive moiety [15]. This device is known as a chemically driven pro–prodrug (Scheme 5a). There is a pressing need for such devices since a significant number of drugs have low solubility in water so that their use in intravenous injection (I.V.) dosage forms is not feasible. Linking these drugs to an entity such as hydroxyhydrocinnamic acid system enables them to be used intravenously due to the higher water solubility of the drug–hydroxyhydrocinnamic acid complex (pro–prodrug).

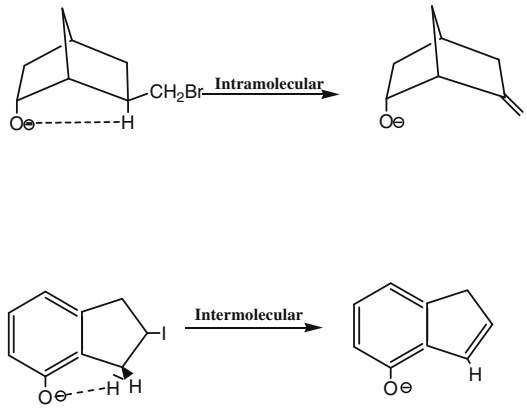
In the past ten years some prodrugs based on hydroxyhydrocinnamic acid derivatives have been introduced, [16]. For example, Borchardt et al. reported the use of the 3-(2'-acetoxy-4', 6'-dimethyl)-phenyl-3, 3-dimethylpropionamide derivative (pro–prodrug) that is capable of releasing the biologically active amine (drug) upon acetate hydrolysis by enzyme triggering, [17] (Scheme 5b). Another successful example of the pharmaceutical applications for a stereopopulation control model is the prodrug Taxol which enables the drug to be water soluble and thus to be administered to the human body via intravenous (I.V.) injection (Scheme 5c). Taxol is the brand name for paclitaxel, a natural diterpene, approved in the USA for use as anti-cancer agent, [18].



Scheme 1. Relative reactivity of lactonization of some dicarboxylic semiesters.



Scheme 2. Relative reactivity of lactonization of some hydroxy acids.



Scheme 3. The effect of the distance between O and H on the nature of the elimination reaction.

In this paper, we describe the AM1 semi-empirical as well as the ab initio HF/6-31G calculations results (thermodynamic and kinetic data) for the acid-catalyzed and un-catalyzed lactonization reactions of a series of hydroxyhydrocinnamic acids as well as for a variety of different hydroxy acids that until now were believed to have high acceleration lactonization rates due to steric effects.

2. Methods

The AM1 semi-empirical and the HF/6-31G ab initio calculations were done using Gaussian 98 version 3.0 [19], running on a