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Effects of substitution on the effective molarity (EM) for five membered ring-closure reactions – A computational approach

Rafik Karaman *

Faculty of Pharmacy, Al-Quds University, P.O. Box 20002, Jerusalem, Occupied Palestinian Territory

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ABSTRACT

DFT molecular orbital calculations of kinetic parameters for ring closing reactions of substituted 4-bromobutyl alcohols 1–5 and 4-bromobutyl amines 6–10 (Brown's system) indicate that accelerations in ring closing rate in both systems are largely the result of strain effects as opposed to the currently advanced proximity orientation. Furthermore, the calculated effective molarity (EM) values derived from the DFT data reveal that replacing the nitrogen (6–10, Brown's system) with an oxygen (1–5, alcoholic analog) results in a decrease in demands on directional flexibility to form 5-membered ring, thus enhancing the rate of the cyclization reaction. In the absence of experimental data the DFT approach could be utilized to predict effective molarities (EM) for intramolecular processes.

1. Introduction

During the second half of the past century a respected number of research groups were engaged in invoking enzyme models that operate via intramolecular processes [1]. The purpose of their studies was to unravel the mechanism by which enzymes exert their extraordinary catalysis. The list of enzyme models includes: (a) "near attack conformations, NACs, model proposed by Bruice and Pandit to explain the significant accelerations in rate for intramolecular ring closing reactions of dicarboxylic semi esters [2]. (b) Menger's "spatiotemporal hypothesis" suggesting the importance of the time by which two reactive centers are in a close proximity to yield a productive proton transfer reaction [3]. (c) Koshland "orbital steering" theory devised to explain the remarkable enhancements in rate for bicyclic lactone formation from hydroxy acids [4]. (d) Cohen's "stereopopulation control" hypothesis to rationalize the high accelerations in rate for lactonization process of the gem-trimethyl lock system [5].

The above mentioned enzyme models are mainly based on two types of intramolecular reactions: (1) proton transfer process by which a proton (an electrophile) is transferred to a nucleophilic center and this step is considered as the rate limiting step. (2) S_N2 type reactions that involve ring closing as a result of an attack of a nucleophile on an electrophilic center within the molecule. The rate of an intramolecular S_N2 reaction is determined on both factors, the size of the ring being formed and the nature of the nucleophile (heteroatom) [6].

Ring closing reactions to form five membered and six membered rings are highly favored over the formation of rings of other sizes. This is because of Ruzicka's two competing factors: (i) unfavorable interactions that hinder the formation of small rings. (ii) Low probability of ends meeting for closing large sized rings [7].

Other structural parameter that affects an intramolecular reaction rate is the "gem-dialkyl effect". It was concluded that substitution of gem-dialkyl group on certain positions resulted in a significant rate enhancements, especially in ring closing reactions yielding to five and six membered ring cyclic products [1,8].

Recently, we have been studying the driving force(s) behind accelerations in rate of a variety of intramolecular processes that have been exploited as enzyme models [9]. Using molecular mechanics, DFT and *ab initio* levels of theory, we investigated the thermodynamic and kinetic properties of (a) acid-catalyzed lactonization of hydroxy acids as studied by Cohen [5] and Menger [3]; (b) intramolecular proton-transfer in rigid systems as studied by Menger [3] and (c) S_N2-based cyclization as studied by Bruice and Mandolini [2,7] arriving at the following findings: (1) Both, strain and unstrained proximity effects play important role in determining the closeness of an electrophile to a nucleophile and consequently enhancing or inhibiting the reaction rate. (2) The nature of the reaction being intermolecular or intramolecular is determined on the distance between a nucleophile and an electrophile. (3) Rate enhancements in S_N2 intramolecular reactions are entirely due to strain effects. (4) Both, enthalpic and entropic effects are

* Tel./fax: +972 2 2790413.
E-mail address: dr_karaman@yahoo.com

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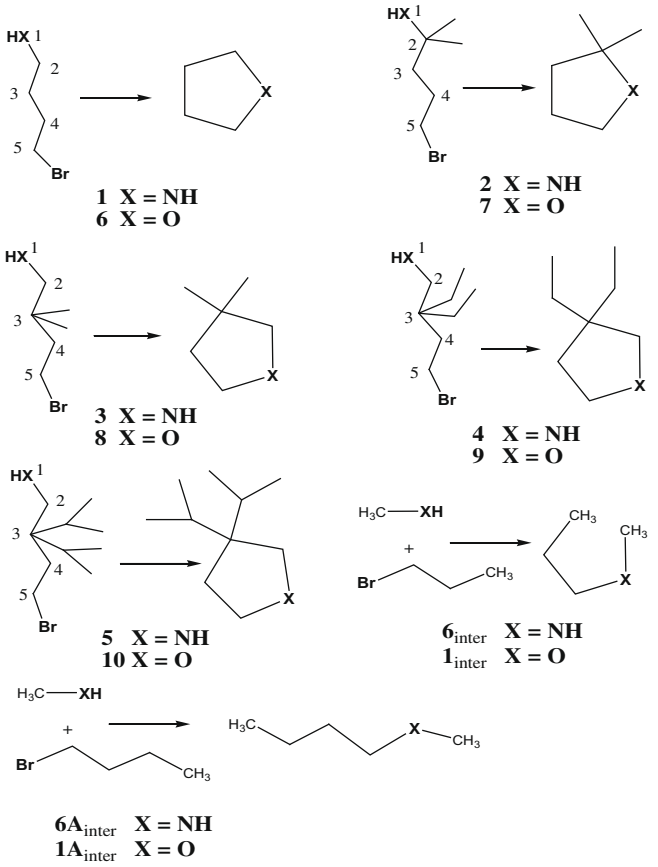

Chart 1. Ring closing reactions for **1**–**10**, $\mathbf{1}_{inter}$, $\mathbf{1A}_{inter}$, $\mathbf{6}_{inter}$, and $\mathbf{6A}_{inter}$.

important factors for rate enhancements in intramolecular processes.

Continuing our investigations on the mode and action by which the gem-dialkyl effect enhances the reactivity of S_N2 closing reaction, we have computed the DFT at B3LYP/6-31G (d,p) kinetic properties for ring closing reactions of 4-bromobutyl alcohols **1**–**5** and compare it to our previous calculations on the cyclization reactions of 4-bromobutyl amines **6**–**10** (Brown's system) (see Chart 1) [9]. Our goal was to investigate the source of the accelerations in rate of intramolecular reactions posses the *gem*-dialkyl effect, to explore the role of a nucleophile (heteroatom) in these types of reactions as well as to establish a computational method for prediction effective molarities (EM) values for intramolecular processes that are difficult to be experimentally determined.

2. Calculation methods

The DFT calculations were carried out using the quantum chemical package Gaussian-98 [11]. The MM2 molecular mechanics strain energy calculations were performed using Allinger's MM2 program [12] installed in Chem 3D Ultra 8.0 [13]. The starting geometries of all molecules presented in this study were obtained using the Argus Lab program [14] and were initially optimized by AM1 level of theory [11]. The calculations were carried out based on the restricted Hartree–Fock (RHF) method with full optimization of all geometrical variables [15]. The global minimum structures of the starting materials in **1**–**10** were found by conducting rotation of the amino or the hydroxyl groups around the adjacent C–C bond. To avoid results with local minima optimization, frequency calculation were carried out for these systems. An energy minimum (a stable compound or a reactive intermediate) has no negative vibrational force constant. A transition state is a saddle point which has only one negative vibrational force constant [16]. The "reaction coordinate method" [17] was used to calculate the activation energy in systems **1**–**10**. In this method, one bond length is constrained for the appropriate degree of freedom while all other variables are freely optimized. The activation energy values for ring closing reactions **1**–**5** were calculated from the difference in energies of the global minimum structures and the higher derived transition state (TS) of the cyclization reaction, obtained by a decrease in the distance between the hydroxy group (–OH) and the carbon attached to the bromine (–C5) in increments of 0.1 Å. The activation energy values for ring closing of **6–10** were calculated from the difference in energies of the global minimum structures and the higher derived transition state (TS) of the cyclization process, obtained by a decrease in the distance between the amine nitrogen (–NH2) and the carbon attached to the bromine (–C5) in increments of 0.1 Å. Verification of the desired reactants and products was accomplished using the "intrinsic coordinate method" [15]. The transition state structures were verified by their only one negative frequency. Full optimization of the transition states was accomplished after removing all constrains imposed while executing the energy profile. The activation energies obtained from DFT level of theory for **1**–**10** were calculated with and without the inclusion of solvent (water). The calculations with the incorporation of a solvent were performed using the integral equation formalism model of the Polarizable Continuum Model (PCM) [18].

3. Results and discussion

We have calculated the DFT at B3LYP/6-31G (d,p) thermodynamic and kinetic properties for ring closing reactions of 4-bromobutyl alcohols **1**–**5** to the corresponding tetrahydrofuran derivatives (Chart 1). The calculated DFT enthalpic and entropic energies for the global minimum (GM) and the derived higher transition state (TS) structures for systems **1**–**5** in the gas phase and in water are summarized in Table 1. The calculated DFT optimized GM and TS structures for processes **2**, **3** and **5** are illustrated in Figs. 1a and 1b, respectively. Also included in Figs. 1a and 1b the DFT calculated structures for the optimum GM and TS structures for the reactions of the corresponding substituted 4-butyllamines **7**, **8** and **10**.

Inspection of Fig. 1a reveals that the gas phase calculated global optimum structures in both **1**–**5** and **6**–**10** derivatives (**1**GM–**10**GM) have similar conformational pattern such that the carbon (C5) attached to bromine (–Br6) is in a syn orientation with the nucleophile (–OH or –NH2). It should be noted that the same picture was obtained when the same calculations were carried out in the presence of one molecule of water. This result excludes the notion that strained derivatives such as **5**GM and **10**GM prefer to be engaged in a coiled conformation while the unstrained derivatives such as **1**GM and **6**GM reside in an extended form [2,10]. Further, Fig. 1b shows that the optimized TS structures have the nucleophile (OH in **1**–**5** and NH2 in **6**–**10**), the carbon attached to bromine (C5) and bromine (–Br6) in a co linearity complying with Baldwin rules.

Using the calculated DFT enthalpies and entropies for the GM and TS structures for **1**–**5**, we have calculated the enthalpic activation energies ($\Delta H^{\ddagger}$), the entropic activation energies ($T\Delta S^{\ddagger}$), and the activation free energies in the gas phase ($\Delta G^{\ddagger}$) and in water ($\Delta Gs^{\ddagger}$) for the corresponding ring closing reactions. The calculation results are summarized in Table 2. Also included in the table are Allinger's MM2 strain energy difference of the reactant and the product (ΔE_s) and the calculated DFT properties for ring closing reactions of the corresponding substituted 4-bromobutyl amines **6**–**10**.

Since the DFT calculations for processes **6**–**10** have shown linear relationship between $\Delta G^{\ddagger}$s and $\Delta G^{\ddagger}$ with ΔE_s (Fig. 2a) we have conducted similar correlation ship for ring closing reactions of **1**–**5**.