Bioorganic Chemistry 37 (2009) 11–25

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

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

Rafik Karaman *

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

ARTICLE INFO

Article history:
Received 11 July 2008
Available online 25 October 2008

Keywords:
Tri-methyl effect
Stereopopulation control
Hydroxy-acids
Lactonization
Proximity orientation
Steric effects

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

* Fax: +972 2 2790413.
E-mail address: dr_karaman@yahoo.com

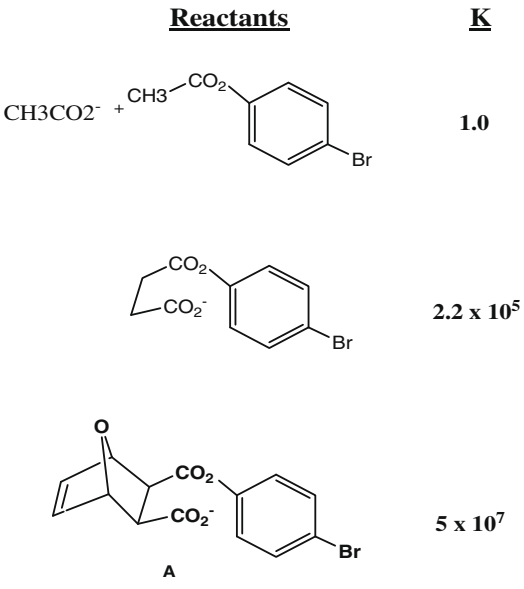
0045-2068/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bioorg.2008.08.006

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].

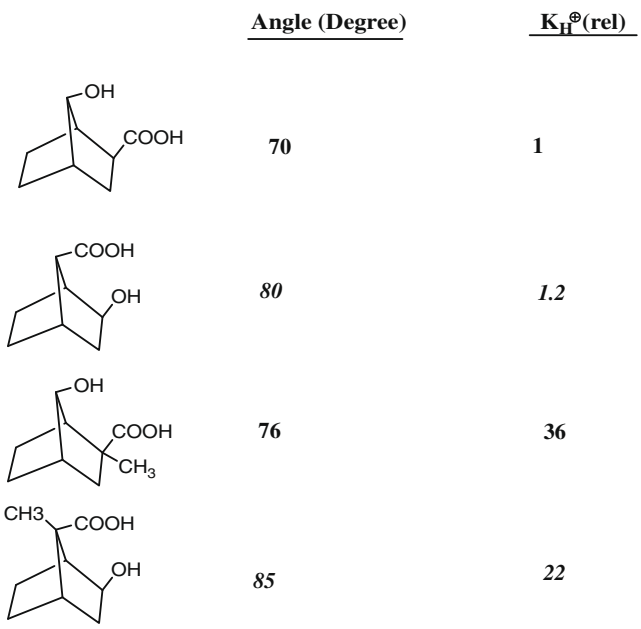
In 1970, Cohen studied the lactonization of a series of hydroxyhydrocinnamic acids and found rates in the range of 10^{15}. He attributed this large enhancement to what he called "stereopopulation control" [11]. Cohen's proposal was attacked by various researches who claimed that the high rate of enhancement 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).

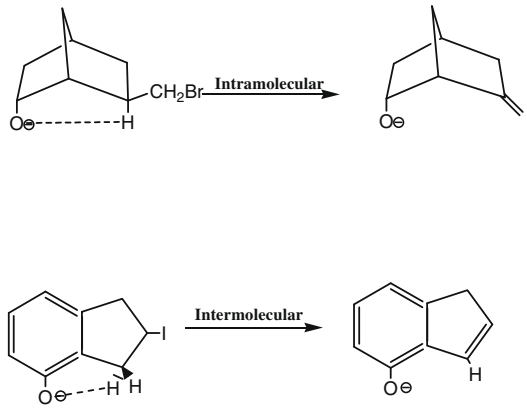
In the past ten years some prodrugs based on hydroxyhydrocinnamic acid derivatives have been introduced, [16]. For example, Borchardt et al. reported the use of the 3-(2'-acetoxy-4', 6'-dimethyl)-phenyl-3, 3-dimethylpropionamide derivative (pro–prodrug) that is capable of releasing the biologically active 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.

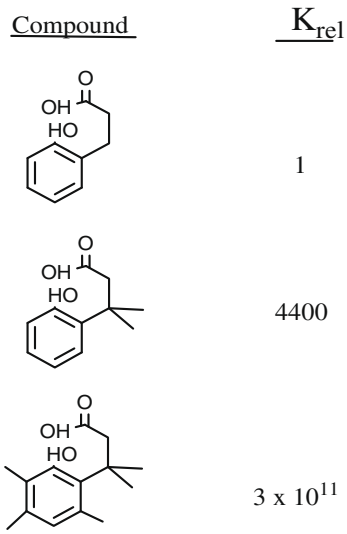


Scheme 3. The effect of the distance between O and H on the nature of the elimination reaction.

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



Scheme 4. Relative reactivity of a lactonization of some hydroxyhydrocinnamic acids.

computer in the Al-Quds University computer center. The MM2 molecular mechanics strain energy calculations were executed using Allinger's MM2 program installed in Chem 3D Ultra 8.0. [20]. The starting geometries of all compounds calculated in this study were obtained from ArgusLab program, [21]. The theoretical calculations were carried out by the standard programs based on the Restricted Hartree–Fock (RHF) method, [22] with full optimization of all geometrical variables (bond lengths, bond angles, and dihedral angles). The geometry optimization in all calculations was done with estimations of second derivatives (Hessian matrix) for each of the $3n - 6$ parameters in each species ($2n - 3$ for planar structures), [23]. DEP analytical gradients were used throughout the optimization. Geometries were optimized in internal coordinates and were terminated when Herberts test was satisfied in the Broyden-Fletcher-Goldfarb-Shanno method (BFGS). All optimizations were terminated when the change in energy on successive iterations was less than 0.00001 kcal/mol and the change in density matrix elements on two successive iterations was less than 0.001 kcal/mol. Because the energy of an organic molecule is strongly dependent on its conformation, we were concerned with the identification of the most stable conformation of the hydroxyhydrocinnamic acid derivatives studied herein. This was accomplished by rotation of the substituent (OH) about the bond leading to the phenyl ring. This rotation is crucial for derivatives that have a phenolic OH that can hydrogen bond with the carbonylic oxygen of the carboxylic acid moiety. 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 one and only one negative vibrational force constant [24]. The "reaction coordinate method" [25], was used to calculate the activation energy for each step in the lactonization process, and the step with the highest activation energy value was chosen to be the rate-limiting step for the cyclization process for each of the hydroxy acid series. In this method, a value of one bond is limited for the appropriate degree of freedom while all other variables are optimized. The activation energy of ring cyclization in the lactonization process of the hydroxy acid derivatives was calculated from the difference in the energies of the optimized structure of a hydroxy acid and the corresponding transition state. The transition state structure was calculated by a gradual decrease in the distance between the hydroxylic oxygen and the carboxylic carbon of the acid, which was followed by a proton transfer from the etheric oxygen to the hydroxylic oxygen of the cyclic tetrahedral intermediate. Similarly, the free energy of activation for the acid-catalyzed cyclization was calculated by subtracting the energy of the global minimum structure of a protonated acid from that of the corresponding transition state. This transition state was formed via the approach of the phenolic oxygen onto the protonated carboxylic carbon, followed by a proton transfer from the etheric oxygen of the protonated tetrahedral intermediate to one of its two hydroxylic groups. It should be emphasized that calculations of activation energy of one process occupy a personal computer for many days when using the "reaction coordinate" in HF/6-31G method. Hence, it is not feasible to use higher levels of ab initio method for achieving more accurate results.

3. Results and discussion

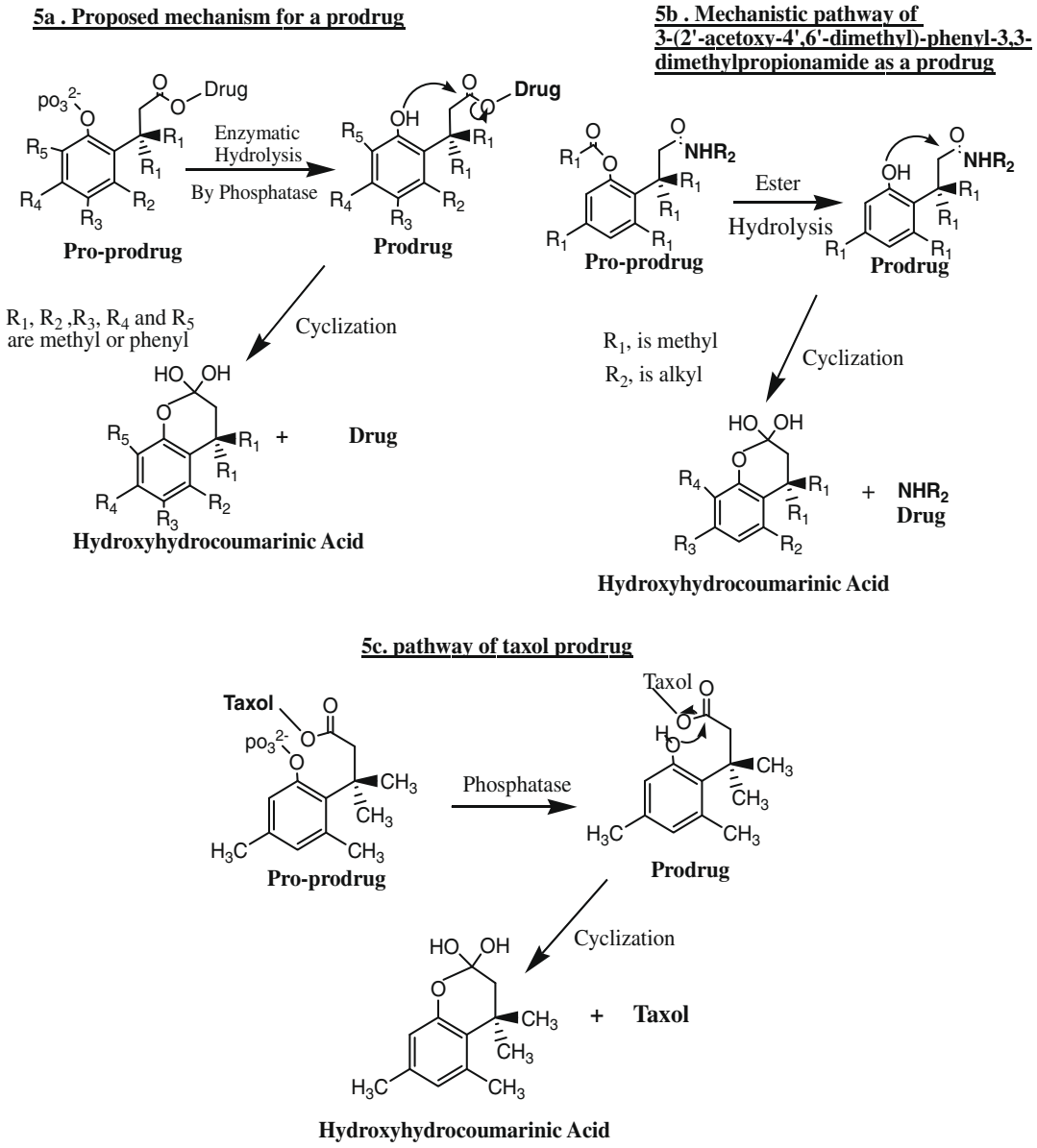
General consideration: Because the energy of an organic molecule is strongly dependent on its conformation, we were concerned with the identification of the most stable conformation (global minimum) for each of the derivatives of the hydroxyhydrocinnamic acid calculated in this study. This was accomplished by rotation of the carboxylic acid group (COOH) about the bond leading to the phenolic ring (i.e. variation of the dihedral angle β defined by atoms 1–4, (see Chart 1) and calculation of the conformational energies.

In the AM1 and ab initio calculations for the hydroxyhydrocinnamic acid derivatives **1a–1d** and **2a–2d**, two types of conformations in particular were considered: one in which the phenolic proton is coplanar to the phenyl ring and *syn* to a substituent (the aliphatic carboxylic acid chain) and another in which it is coplanar to the phenyl ring and *anti* to the substituent. It was found that for hydroxy acid **1a** the global minimum structure is with the conformation where the aliphatic chain is extended and the phenolic hydroxyl group has an *anti* orientation to the carboxylic acid moiety (no hydrogen bonding exists between the phenolic proton and the carboxylic acid oxygens). For hydroxy acids **1b–1d** and **2a–2d**, the conformations with minimum energies were those with hydrogen bonds between the phenolic proton and the carboxylic oxygen (*syn* orientation) (see Fig. 1).

The dispute over the question whether the model studied by Cohen et al. really reflects the catalysis of enzymes through stereopopulation control [11] or strain relief [14a–c], as suggested by others, led us to investigate the thermodynamic and kinetic factors that play a role in the reaction of this model system. The selection of the hydroxyhydrocinnamic acid derivatives computed in this study was made because of the availability of their experimental data (kinetics [11] and crystal structures [26,27]).

3.1. Conformational analysis of hydroxyhydrocinnamic acid derivatives

Lactones: The structures of lactones **4a–4d** are shown in Fig. 1 (for the numbering of atoms, see Scheme 6, structure **4**). Comparison of the values of the bond distances for the calculated lactones to that of known aryl substituted lactones show close similarity. On the other hand, the picture is quiet different when comparing the bond angles. The calculated bond angles in the aromatic rings of lactones **4a–4d** differ significantly from the ideal value for a bond angle in un-substituted phenyl ring (120°). For lactone **4c**, the values are in the range of 117.2–123.2° and for **4a**, **4b**, and **4d**, the values are 118.5–121.5°, 117.9–122.2°, and 116.8–120.7°, respectively. The relatively large range values obtained for **4c** is perhaps due to the accommodation of the methyl groups in positions 3, 5, 7 and 8. Furthermore, the effect of the accommodation is seen in the increase of the bond angles C3–C4–C5 and C4–C5–C14 (124.25° and 123.54°, respectively). Consequently, the distance between C13 and C14 is narrowed to 2.91 Å. It should be



Scheme 5. Mechanistic pathways for different pro–prodrugs using a hydroxyhydrocinnamic acid as a drug carrier moiety.

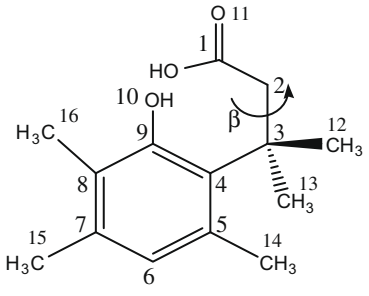


Chart 1. Angle of attack α (nucleophilic-oxygen/carbonyl-carbon/αλπηα-carbon) in the lactonization process of hydroxy acids. β is the dihedral angle $C_1C_2C_3C_4$.

pointed out that this distance is equal to the distance between C15 and C16 which are separated by only two carbons, whereas, the distance between C13 and C14 is separated by three carbons. This is in accordance with the crystal structure analysis of lactone **4c**. [26,28] Inspection of the conformations of the lactones reveals, unexpectedly, that the lactone ring is not coplanar with the phenyl ring, showing the extent of deviation in the structures of lactones **4a**. Lactones **4b** and **4c** have bond angles around 26–28° as judged by the value of the dihedral angle C2–C3–C4–C5. The lactone ring in lactone **4d** exhibits a boat conformation that resulted in a drastic deviation of the bond angles C2–C1–O10 (111°) and C3–C4–C9 (116.8°) from the idealized values of about 120°. Moreover, the C2–O10 distance is enlarged in lactone **4d** (1.44 Å) when compared to lactones **4a**–**4c** (an average value of 1.38 Å). The gem-dimethyl effect is significant in the structures of lactones **4c** and **4d**, where the bond angles of the carbons that are attached to the dimethyl groups are decreased and those for the neighboring un-substituted carbons are increased [29].

Hydroxy acids: Fig. 1 shows the calculated global minima for hydroxy-acids **1a–1d**. Comparison of the structures of the different four acid molecules indicates that except for acid **1a** all the others, 1b–**1d**, have similar conformational shapes, in which the aliphatic side chain extends approximately perpendicular to the plane of the aromatic ring and a hydrogen bonding net exists between the phenolic proton and the carboxylic moiety. In molecule **1a**, the

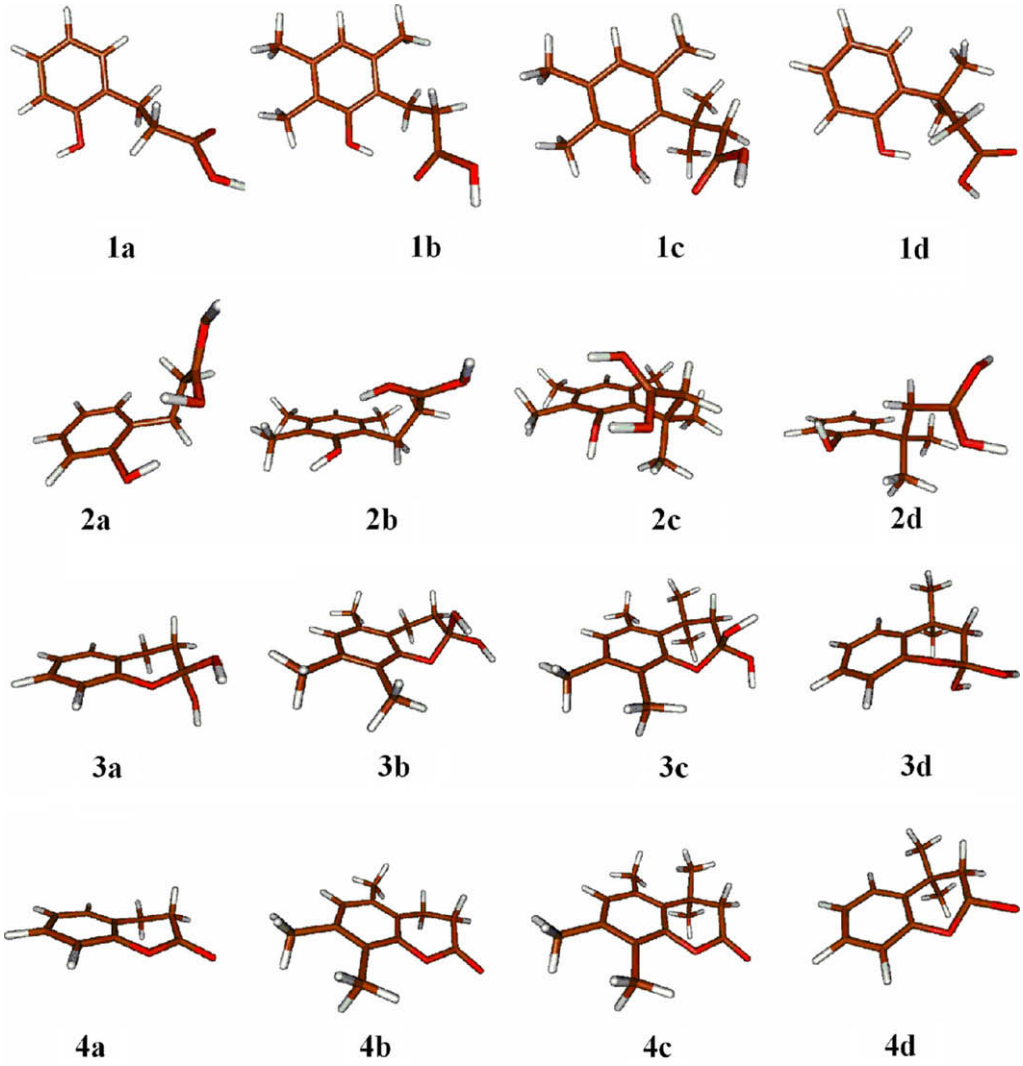
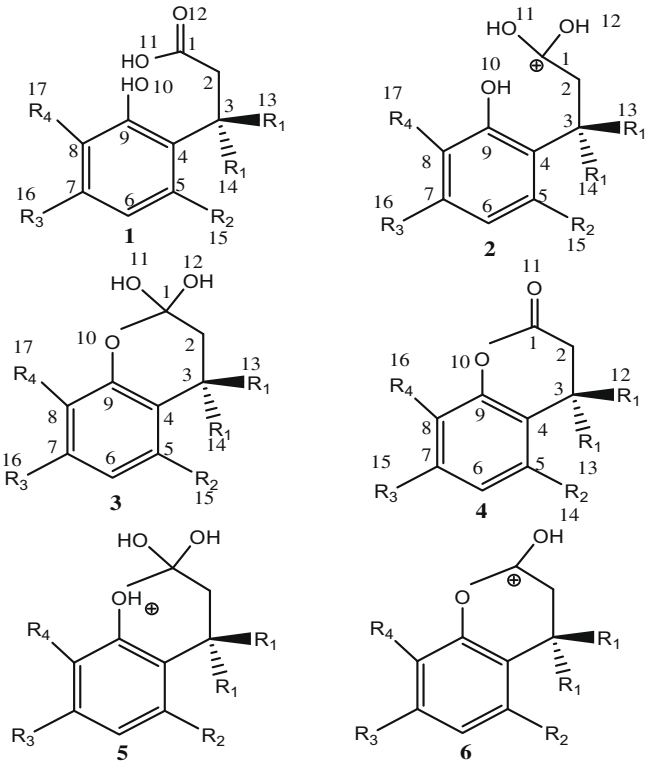


Fig. 1. The global minimum structures of hydroxyhydrocinnamic acids **1a**–**1d**, the corresponding protonated hydroxyhydrocinnamic acids **2a**–**2d**, the corresponding tetrahedral intermediates **3a**–**3d** and the corresponding lactones **4a**–**4d**.

aliphatic chain is perpendicular to the phenylic ring, but it is extended in such a way that the phenolic proton is far away from the carboxylic group that prevents intramolecular hydrogen bonding. [28] Careful inspection of the data suggests that the phenyl ring in the four molecules preserves its planarity despite the deviation in the bond angles from 120°. The extent of the deviation is dependent on the structure of the acid molecule, for molecules **1b** and **1c**, the deviation is as great as 7°, whereas in **1a** and **1d**, the deviation is less than 3°. This is similar to the deviation seen for the structures of lactones **4a–4d**. The larger values of deviation seen in **1b–1c** and **4b–4c** are attributed to the distortion effect of the three methyl groups attached to the phenyl ring. When comparing the structures of acids **1c** and **1d** to that of lactones **4c** and **4d** (see Fig. 1), the same phenomenon of the gem-dimethyl effect which is reflected in the enlargement of the bond angle C1C2C3 and shrinking of the bond angle C2C3C4 is evident. Further, the distance between the two methyl groups on C3 and C5 is decreased when compared to the methyl groups between C7 and C8. This is probably occurs in order to overcome the conformational restriction caused by the accommodation of the methyl groups on C3.

Intermediates: The structures of the calculated tetrahedral intermediates **3a–d** obtained from the intramolecular cyclization of the corresponding hydroxy-acids are depicted in Fig. 1. The calculations results indicate that the phenyl ring in these molecules is planar and that the deviation in the bond angles from the ideal value of 120° is significantly decreased when compared to the values calculated for the corresponding acids and lactones (2° vs. 6°). This is because of strain relief from the more flexible conformation of the intermediate compared to that of the acid and the lactone. It is worth noting that vast discrepancies are seen in the calculated values of the bond angle C2C1O10 for the different intermediates (for the numbering see Scheme 6). Values of 118° are calculated for **3a** and **3b**, whereas values of 111.2° and 105.7° are calculated for **3c** and **3d**. This indicates that the presence of the methyl groups on C3 in both **3c** and **3d** contributes to stabilization of the tetrahedral intermediates and relief in strain energy upon the lactonization, as indicated by the closeness of these values to the ideal value of 109°. Furthermore, the data shows that the calculated bond distances C1–O11 and C1–O12 for **3a** and **3b** are shorter than that of C1–C10 (1.39 vs. 1.42 Å); whereas the values for these bonds in **3c** and **3d** are relatively close (1.42 Å). The similarity between the bond distances C1–O11 and C1–O12, on one hand, and C1–C10 on the other hand, suggests that the bond breaking that furnishes an acyclic product (breaking of C1–C10) and the bond cleavage that forms a cyclic lactone (by breaking either C1–O11 or C1–O12) is likely to happen indiscriminately. In the cases of intermediates **3a** and **3b**, opening of the cyclic ring to reform the hydroxy-acid



a : R_1, R_2, R_3, R_4 = -H
b : R_1 = H; R_2 ,R_3 ,R_4 = - CH_3
c : R_1, R_2, R_3, R_4 = $-CH_3$
d : R_1 = CH_3; R_2, R_3, R_4 = - H
e : R_1, R_4= CH_3; R_2, R_3 = - H
f : R_1, R_2= CH_3; R_3, R_4 = - H
g: R_1 ,R_2 ,R_3 = CH_3 R_4 = - H

Scheme 6. Hydroxyhydrocinnamic acid derivatives.

is much more likely to be dominant over the formation of the corresponding cyclic lactone. Moreover, inspection of the calculated data reveals that intermediates **3c** and **3d** exhibit a gem di-methyl effect similar to that seen in both the corresponding hydroxy-acids and lactones.

Protonated hydroxy-acids: Since the lactonization of hydroxy-acids **1a–1d** is catalyzed by acid, we calculated the geometries and the energies for the corresponding protonated hydroxy-acids in order to compare their reaction processes to that of the un-catalyzed ones. The AM1 calculated global minimum structures for the protonated hydroxy-acids **2a–2d** are shown in Fig. 1. Inspections of the calculated geometries of these molecules indicate that all of them exhibit a conformation by which the aliphatic carboxylic chain is engaged in a hydrogen bonding net with the neighboring phenolic proton. This engagement results in the formation of an eight-member ring by which the phenolic proton plays a dominant role in the nature and scope of its shape (see Fig. 1). It should be emphasized that the global minimum structures for the neutral hydroxy-acids **1a–1d** have similar shapes to that of the corresponding protonated hydroxy-acids **2a–2d**, except for that of **1a** in which the aliphatic carboxylic group resides in an extended chain and the corresponding protonated acid **2a** exhibits a folded conformation. Comparison of the calculated data indicates similarity in the calculated parameters of the two systems (**1** vs. **2**) except for that of **1a** and **2a** due to the change in the conformation of the aliphatic chain.

3.2. Energy calculations

The controversy concerning the main reason behind the driving force for the unique acceleration of the intramolecular reaction of hydroxyhydrocinnamic acids **1** has continued for several decades. In order to verify whether stereopopulation control, suggested by Cohen et al. [11] or the conventional steric effect by means of strain energy relief, as proposed by Wilcox and Winans [14a] and supported by a theoretical study by Houk et al. [14b], is in fact the dominant player in the execution of this kind of reaction, the following points were addressed: (1) calculations of ground state energies of all the species involved in the reaction (ΔG, ΔH and ΔS), (2) calculation of the barriers for rotation of the side chain in **1** in order to establish whether the conformational restriction is an important factor in the enhancement of the lactone formation, (3) calculations of activation energy values of ring cyclization.

3.2.1. Ground state properties (thermodynamic parameters, ΔG, ΔH, and ΔS)

Since the theoretical study by Wilcox et al. [14a] was based on the assumption that the mechanism for the formation of lactone **4** during the intramolecular cyclization of hydroxyhydrocinnamic acid **1** (with or without the catalysis of acid) is via the formation of the tetrahedral intermediate **3**, we have calculated all the entities involved in the suggested mechanism. The heat of formation for seven different hydroxyhydrocinnamic acids **1a–1g**, and their corresponding protonated acids **2a–2g**, tetrahedral intermediates **3a–3g**, lactones **4a–4g**, protonated tetrahedral intermediates **5a–5g**, and carbocations **6a–6g**, were calculated by AM1 semi-empirical calculations (see structures in Scheme 6). The differences in the heat of formation of **3** and **1** ($\Delta H_{3,1}$), **5** and **2** ($\Delta H_{5,2}$), **6** and **1** ($\Delta H_{6,1}$), **4** and **2**($\Delta H_{4,2)}$, and the differences in MM2 strain energies of **3** and **1** ($\Delta E_{s\ 3,1)}$, were calculated. The calculated data was examined for linear relationships with log k_{exp}. The results obtained are shown in Eqs. (1–4) (see Table 1), where C is a constant (intercept) and A is the slope. Eq. (1) is represented graphically in Fig. 2a. It is worth noting that a correlation of steric energies $\Delta E_{s3,\ 1}$ (MM2 molecular mechanics) with the differences of AM1 heat of formation was established in order to gain credibility to use AM1 for estimating strain energies of this type of molecule. Eq. (5) and Fig. 2b illustrate the correlation between $\Delta E_{s1,3}$ and AM1 $\Delta\Delta H_{f1,3}$. Examination of the results described in Eq. (1–4) indicates a moderately strong correlation between log k_{exp} and the heat of formation dif-

Table 1
Correlation equations for AM1 and MM2 calculated properties of hydroxy-acids with their experimental lactonization rates

No.	Equation $\Delta\Delta H_f = A \log K_{exp}$	R
1	$\Delta\Delta H_{f1,3} = 0.6501 \log K_{exp} + 0.1450$	0.98
2	$\Delta\Delta H_{f4,1} = 0.4470 \log K_{exp} + 1.2630$	0.91
3	$\Delta\Delta H_{f2,5} = 0.8855 \log K_{exp} + 3.3972$	0.89
4	$\Delta\Delta H_{f6,1} = 0.8678 \log K_{exp} - 0.3429$	0.99
5	$\Delta Es_{\ 1,3} = 1.0037\ \Delta\Delta H_{f1,3} + 0.7565$	0.97
13	$E = 1.2165\ \alpha/r - 48.933$	0.99 (for **1a**)
14	$E = 1.0648\ \alpha/r - 43.257$	0.99 (for **1d**)
15	$E = 0.8636\ \alpha/r - 32.159$	0.99 (for **1c**)
18	$E = 1.0142\ \alpha/r - 38.584$	0.99 (for **1h**)
19	$E = 1.227\ \alpha/r - 51.441$	0.99 (for **1i**)
20	$E = 1.1997\ \alpha/r - 43.619$	0.99 (for **1j**)
21	$E = 1.2493\ \alpha/r - 36.049$	0.99 (for **1k**)
22	$E = 1.3504\ \alpha/r - 56.118$	0.99 (for **1l**)
23	$E = 0.1934\ \alpha/r - 8.7507$	0.98 (for protonated **1a**)
24	$E = 0.1531\ \alpha/r - 6.7426$	0.98 (for protonated **1d**)
25	$E = 0.1548\ \alpha/r - 2.7455$	0.98 (for protonated **1h**)
26	$E = 0.1567\ \alpha/r - 7.7239$	0.96 (for protonated **1i**)
27	$E = 0.1655\ \alpha/r - 5.7645$	0.99 (for protonated **1j**)
28	$E = 0.2287\ \alpha/r - 8.0677$	0.99 (for protonated **1k**)

ferences ($\Delta\Delta H$), especially for the change in energies from the hydroxyhydrocinnamic acid **1** to the corresponding tetrahedral intermediate **3**. Similarly, a strong correlation exists between $\Delta E_{s1,3}$ and $\Delta\Delta H_{f1,3}$. This result justifies the use of AM1 method for predicting strain energies for this kind of molecule.

However, when calculating the value of the difference between $\Delta\Delta H_{f1,3}$ of **1c** and $\Delta\Delta H_{f1,3}$ of **1a** and comparing it to the value of the experimental rate reaction ratio k_{exp} (**1c**)/k_{exp} (**1a**) (see Eq. (1) and Fig. 2a) we find that the change in energies between **1c** and **1a** ($\Delta\Delta H_{f1,3}$ **1c** and $\Delta\Delta H_{f1,3}$ **1a**) gives a steric acceleration of 10^6 which is much less than the experimentally determined rate value (k_{exp} **1c**/k_{exp} **1a** = 10^{11}[11]).

In order to shed light on the real differences in energies between **1a** and **1c**, calculations of molecular vibration frequencies and entropic and zero point energy contributions have been conducted. The AM1 calculations of the heat of formation for structures **1**, **2**, **3**, **4**, **5** and **6** (see Scheme 6) enable us to compare enthalpic energies (ΔH_f). This comparison still gives a crude estimate of the expected rate acceleration since ΔH_f is only a potential energy component. Real reactions are governed by free energy changes between the starting materials, the transition states, the intermediates and the products. Eq. (6) describes the free energy changes in hydroxyhydrocinnamic acid system.

$$\Delta\Delta G_{1,3} = \Delta\Delta H_{f1,3} - T\Delta S_{1,3} \quad (6)$$

where $\Delta\Delta G_{1,3}$ is ΔG of the hydroxy acid **1** − ΔG of the corresponding intermediate **3**

$\Delta\Delta H_{f1,3}$ is ΔH_f of **1** − ΔH_f of **3**, and $\Delta S_{1,3}$ is S of **1** − S of **3**

The change in free energy values of **1a–1d** and **3a–3d** were calculated using Eq. (6), and the resulting $\Delta\Delta G_{1,3}$ values were plotted against the rate experimental values ($k_{exp.}$) with the resulting curve shown in Fig. 2c.

Examination of Fig. 2c indicates a strong correlation (see Eq. (7)) between $\Delta\Delta G_{3,1}$ and the rate ratio of the unimolecular cyclization/bimolecular cyclization log k_X−log k_{PAA}, where k_X and k_{PAA} are the rates cyclization of the intramolecular reaction of hydroxyhydrocinnamic acid **1** and the intermolecular reaction of phenol and acetic acid, respectively.

$$\Delta\Delta G_{3,1} = 0.8602(\log k_X - \log k_{PAA}) + 0.9946 \; R = 0.962 \quad (7)$$

Using Eq. (7), we calculated the difference between the free energy ($\Delta\Delta G_{3,\ 1}$) of hydroxy acids **1a** and **1c** and obtained a value of 9.92 kcal/mol. Based on this value, the predicted rate enhancement of the lactonization of **1c** compared to that of **1a** should be 1.8×10^7, which is10^4-fold less than the experimentally determined value. This result excludes the notion that the remarkable rate enhancement seen in the lactonization of **1c** is solely accommodated by conventional steric effects [14a–d].

3.2.2. A barrier for rotation of the side chain in hydroxy-acids 1

In order to see whether the conformational restriction plays an important role in the rate acceleration of the lactonization process of hydroxyhydrocinnamic acids **1a–1d**, calculations of the rotation barriers in the aliphatic carboxylic acid side chain around the C2C3 bond were executed and the results are depicted in Fig. 3.

When comparing the values of the rotation barriers for hydroxy-acids **1a–1d**, we find that **1a** has the highest barrier and **1c** has the lowest barrier with a 3 kcal/mol difference between them. Furthermore, the C1–O10 distance in hydroxyhydrocinnamic acid **1a–1d** is largely affected by the dihedral angle C1C2C3C4; accordingly, the change in the latter leads to change in the heat of formation of the resulting conformation. It should be emphasized that C1–O10 distance should be crucial for the enhancement of the lactonization rate according to the stereopopulation control (conformational locking) suggested by Cohen [11]., When plotting the C1–O10 distance in **1a** and **1c** against the H_f of the resulting conformational structure, an important result emerges. In **1c**, the shortest C1–O10 distance value occurs in the most stable conformation and

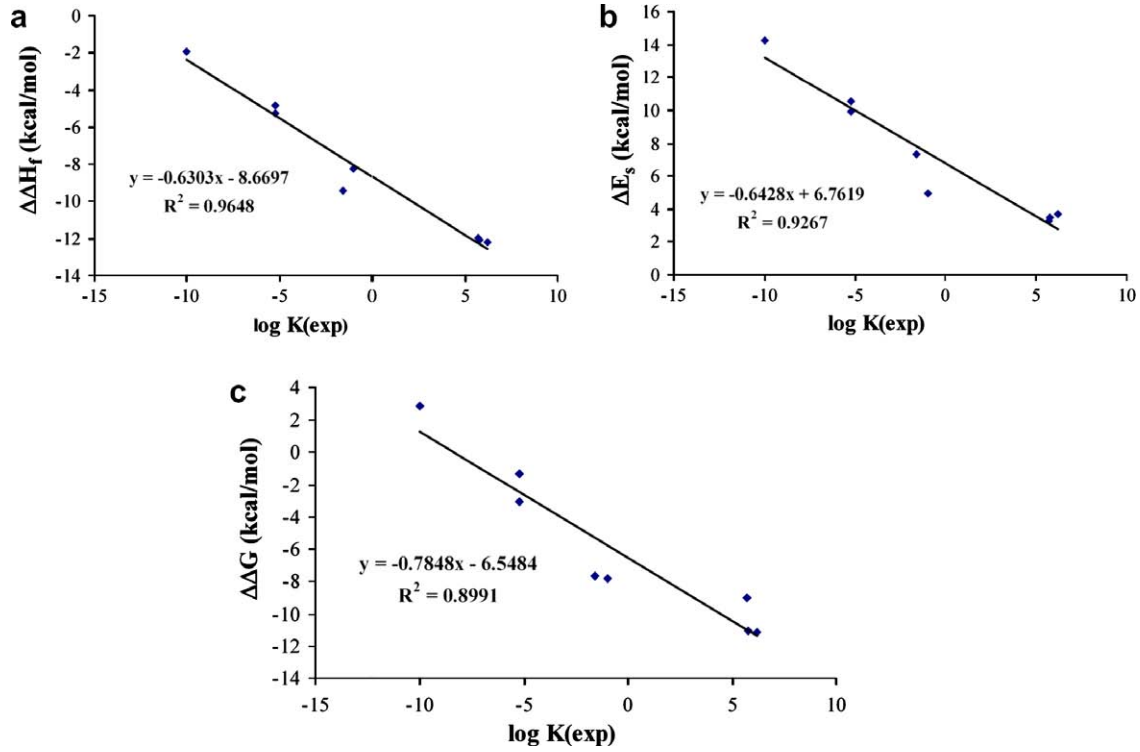


Fig. 2. (a): Plot of $\Delta\Delta H_{f1,3}$ vs. log k_{exp} (see text) for the lactonization processes of hydroxyhydrocinnamic acids **1a–1d**. (b) Plot of $\Delta E_{s3,1}$ vs. $\Delta\Delta H_{f1,3}$ (see text) for the lactonization processes of hydroxyhydrocinnamic acids **1a–1d**. (c) Plot of $\Delta\Delta G_{3,1}$ vs. log k_{exp} (see text) for the lactonization processes of hydroxyhydrocinnamic acids **1a–1d**.

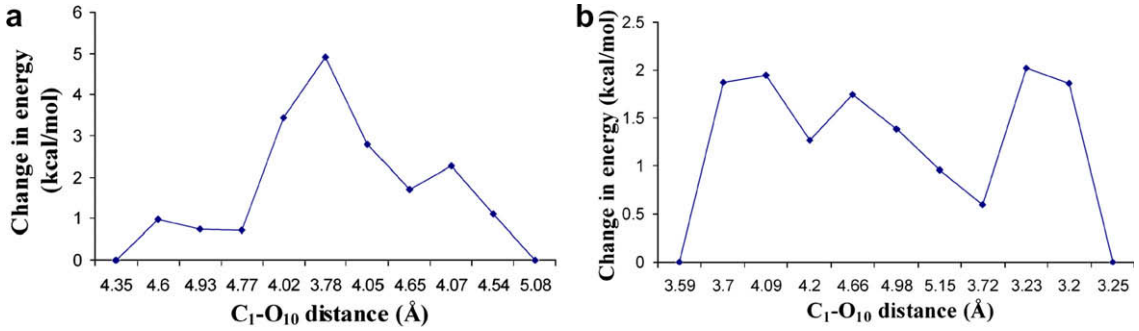


Fig. 3. Plot of change in energy vs. C2–C3 (a) bond distance and dihedral angle C1C2C3C4 (b) value obtained from the rotation of the carboxylic moiety around C2–C3 bond in hydroxyhydrocinnamic acids **1a** and **1c**.

for **1a**, the shortest distance value occurs in the highest energy conformation as shown in Fig. 3.

The immediate question arising is: what is the contribution of the conformational locking that was suggested by Cohen, to the rate acceleration seen with **1c** compared to that seen in **1a**. In order to answer this question, AM1 calculations of the thermodynamic parameters ΔG, ΔH, and S were conducted for each of the energetically most stable conformers in **1a–1d**, and for the conformers with the shortest C1–O10 distance values. The data obtained is summarized in Table 2. Examination of the table reveals that for **1a** to be in an appropriate position to intra-molecularly react and furnish the corresponding lactone (O10 in close proximity to C1), the energy (ΔG) needed is 10.73 kcal/mol. This energy is composed of 4.91 kcal/mol as ΔH and 5.82 kcal/mol as $-T\Delta S$, while only 3.93 kcal/mol (1.85 kcal/mol as ΔH and 2.08 kcal/mol as $-T\Delta S$) is required for **1c** to fulfill the same task. The approximate 7 kcal/mol difference between the paths of **1a** and **1c** corresponds to about 1.4×10^6 in the rate enhancement of **1c** over **1a**. Again, the calculations of the thermodynamic parameters in regard to the conformational restrictions imposed on these molecules clearly shows that conformational locking is not the main ruling factor in the rate acceleration of acid **1c** (10^6 calculated value vs. 10^{11} experimentally determined value). Never less, some contribution of the conformation locking to the rate enhancement is indeed worth considering.

3.2.3. The kinetic parameters (activation energy, ($\Delta\Delta G^{\ddagger}$)

Since predicting rates of lactonization based on potential energies has failed to give results that are similar to experimental rates, we sought a solution by using another approach from that of calculating thermodynamic parameters. Our approach is based on calculating the activation energies of the lactonization processes for each of hydroxyhydrocinnamic acids **1**. In order to accomplish this task, it is necessary to investigate the lactonization mechanism. Kinetic studies conducted by Cohen's group on the lactonization of these acids in a wide range of pH values did not reveal a strong conclusion about the mechanism [11a]. However, he proposed two different mechanisms to explain his experimental findings (see Chart 2). The drawings **a** and **b** in the chart describe the two different mechanisms for the acid catalyzed lactonization, and drawings **c** and **d** are the proposed mechanisms for the base-catalyzed lactonization. In both the acid and the base-catalyzed reactions, two different mechanisms were considered. The first mechanism involves a rate-determining attack of the hydroxyl moiety on the protonated carboxylic acid to form the transient tetrahedral intermediate (**a** for the acid-catalyzed reaction and **c** for the base-catalyzed reaction), and the second alternative mechanism, is the one by which a collapse of the tetrahedral intermediate is rate limiting (**b** for the acid catalyzed and **d** for the base catalyzed reactions). In light of the fact that the overall rate enhancement factor found by Cohen et al. [11a] is not independent on the type of catalyst involved and that general acid catalysis is more effective than a general base catalysis by a factor of 10^3, we agree with the authors that it is unfeasible to determine which one of the two mechanisms is in fact the one that can explain the remarkable acceleration rates in this kind of system. This conclusion is also supported by (1) the fact that bimolecular esterification reactions are generally follow the mechanism by which the formation of the tetrahedral intermediate is rate limiting [30], and until now there is no convincing argument that an intramolecular esterification has a different mechanism, (2) variation in physical properties such as pK_a values of the hydroxyhydrocinnamic acids or other hydroxy acids would be predicted to have similar effects on rate by either mechanism.

Considering the failure of the kinetic and isotopic effects and the activation entropy results obtained by Cohen et al. to distinguish between rate-limiting formation or breakdown of a tetrahedral intermediate in the lactonization of hydrohydrocinnamic acids [11a], we found that appropriate theoretical calculations would provide an excellent tool for resolving the dilemma behind the nature of the mechanism for the lactonization of hydroxy acids.

Chart 3 describes all possible routes for intramolecular lactonization reactions of hydroxyhydrocinnamic acids which are believed to be applicable to other hydroxy acids as well. We have calculated all the entities involved in the reaction processes as well as the activation energies of the appropriate steps drawn in Chart 3.

Table 2
AM1 calculated thermodynamic properties of the low and high energy conformations in **1a–1d** and **1h**

	Low energy conformation (**I**)			High energy conformation (**II**)					$\Delta\Delta G_{II-I}$	$T\Delta S_{II-I}$	$\Delta H_{f\ II-I}$
	H_f	$C_1C_2C_3C_4$	C–O bond	S	H_f	$C_1C_2C_3C_4$	C–O bond	S			
1a	−126.64	−171.58	4.345	111.30	−121.72	8.41	3.780	91.97	10.68	−5.76	4.92
1b	−142.57	100.97	3.809	128.03	−147.14	352.97	3.494	114.56	8.59	−4.01	4.58
1c	−140.66	53.22	3.591	134.47	−138.64	341.22	3.230	127.47	4.01	−2.08	2.02
1d	−127.60	138.78	3.665	116.48	−124.29	354.78	2.389	101.86	7.67	−4.36	3.31
1h	−97.58	181.36	4.007	112.00	−90.32	−13.63	1.981	105.51	9.19	−1.93	7.26

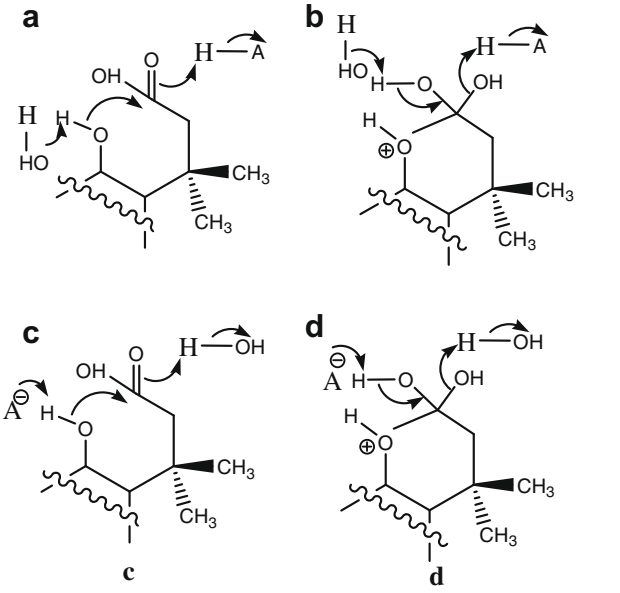


Chart 2. Mechanisms of acid- (**a** and **b**) and base- (**c** and **d**) catalyzed lactonization of hydroxyhydrocinnamic acids.

This was accomplished by the following: (1) finding the global minimum structure of each of the hydroxyhydrocinnamic acids and then calculating the energy needed for the formation of the tetrahedral intermediate by using Eq. (8).

$$E_{act}(\Delta\Delta G^{\ddagger}) = \Delta\Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad (8)$$

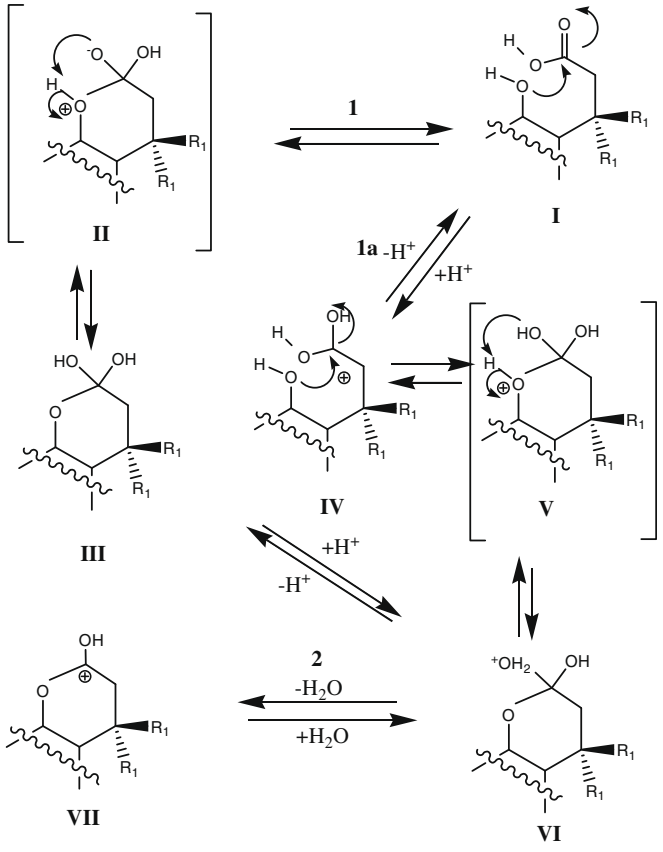


Chart 3. All possible routes for uncatalyzed and acid-catalyzed lactonization of hydroxy acids.

where

$$\Delta\Delta H^{\ddagger} = \Delta H\,(\text{transition state}) - \Delta H_f\,(\text{hydroxy} - \text{acid } \mathbf{1})$$

$$\Delta S^{\ddagger} = \mathbf{S}\,(\mathbf{transition\ state}) - \mathbf{S}\,(\mathbf{hydroxy} - \mathbf{acid\ 1});\ \mathbf{T} = \mathbf{298\ K}.$$

(2) Calculating the activation energy needed for the collapse of the tetrahedral intermediate **VI**, by stretching the bond C–$OH2^+$ in **VI** until the transition state is reached (step **2**).

*Calculation of the activation energies for the formation of the tetrahedral intermediates (steps **1** and **1a** in Chart 3).* Using AM1 and HF (31-G) methods we calculated the activation energies of the lactonization processes for each of acids **1a–1d**, acid-catalyzed and un-catalyzed. The *ab initio* HF/6-31G and the AM1 activation energy values were calculated with and without the inclusion of solvent (water) and the results obtained indicate that the effect of water on the relative rate values is negligible. This is in accordance with previously reported studies of Houk et al., on lactonization of hydroxy-acids, that indicate that the solvation effect is more-or-less cancel out when comparing reactivities of species having the same structural features (even though the absolute rate constants cannot be evaluated) [14b].

The activation energy results of both lactonization processes are summarized in Table 2. Using Eq. (9) we calculated the rates of the lactonization in the two processes (**1** and **1a**, Chart 3) and the calculated values obtained are depicted in Table 2.

$$\Delta\Delta G^{\ddagger} = -RT\ln k_{\mathbf{calc}} \quad (9)$$

where $\Delta\Delta G^{\ddagger}$ is the free energy of activation, k_{calc} is the calculated rate, T is the temperature in kelvin and R is a constant.

The calculated rate values were examined for a linear relationship with the experimentally determined rate values. They were found to agree with the expressions shown in Eqs. (10)–(12).

$$\log(k_{\mathbf{1x}}/k_{\mathbf{1a}})_{\mathrm{calc\ I\ to\ III}} = 0.9911\log k_{\mathbf{exp}} - 0.1238\ R = 0.99 \quad (10)$$

where k_{1x} is the rate cyclization of hydroxy acid **1b–1d**, and k_{1a} is the rate cyclization of hydroxy acid **1a**. **I–III** are the process from structure **I** to structure **III**.

$$\Delta\Delta G^{\ddagger}(\mathrm{HF}) = -1.1666\log k_{\mathbf{exp}} + 64.248\ R = 0.99 \quad (11)$$

where $\Delta\Delta G^{\ddagger}$ (HF) is the calculated activation energy by HF/6-31G

$$\log(k_{\mathbf{2x}}/k_{\mathbf{2a}})_{\mathrm{calc\ IV\ to\ VI}} = 0.9768\log k_{\mathbf{exp}} - 0.6725\ R = 0.99 \quad (12)$$

where k_{2x} is the rate cyclization of protonated hydroxy acid **2b–2d**, and k_{2a} is the rate cyclization of hydroxy acid **2a**. **IV–VI** is the process from structure **IV** to structure **VI**.

The calculated rate values of the lactonization processes of **1a** and **1c** using Eqs. (10) and (12) are 10^4 and $10^{14.5}$, respectively. This gives a predicted rate enhancement of $10^{10.5}$ which is in striking agreement with the experimentally determined value (10^{11}). In order to investigate the effect of the acid catalyst on the relative activation energies of the lactonization of hydroxy-acids **1c** and **1a**, the rate values of the acid catalyzed lactonization ($\log k_{\mathrm{calc\ IV\ to\ VI}}$) were plotted against these of the uncatalyzed lactonization processes ($\log k_{\mathrm{calc\ I\ to\ III}}$). The correlation obtained is described in Eq. (13).

$$\log(k_{\mathbf{2x}}/k_{\mathbf{2a}})_{\mathrm{calc\ IV\ to\ VI}} = 0.9891\log(k_{\mathbf{1x}}/k_{\mathbf{1a}})_{\mathrm{calc\ I\ to\ III}} + 0.6388\ R = 0.98 \quad (13)$$

The closeness of the equation slop to the value of 1 and of the intercept to the value of less than 1 indicates clearly that the relative activation energies of the lactonization of **1a–1d** in the acid catalyzed and in the un-catalyzed processes are similar. Thus, it is safe to conclude that the differences in the entropic and enthalpic energies of the transition states and the ground states of the molecules involved in these two processes are not affected by the presence of the catalyst.

*Calculations of the activation energies for the collapse of the tetrahedral intermediate (steps **2** in* Chart 3*):* The activation energy for the collapse of intermediate **VI** can be theoretically determined by stretching the C–OH2$^+$ bond in **VI** and calculating the resulting energy as a function of the bond distance. We have conducted a reaction coordinate method to calculate the activation energy for the collapse of the tetrahedral intermediate **VI** in the un-catalyzed and acid-catalyzed lactonization reactions of **1a–1d**. Surprisingly, the AM1 results obtained clearly indicate that in all cases an elimination of water from intermediate **VI** occurs without activation. Additionally, in some cases, an elimination of a water molecule has occurred during the proton transfer in the approach processes (**1** and **1a** Chart 3). This indicates, in contrast to what was reported by Houk et al. [14b], that step **2** is not a rate-limiting step and the rate of the lactonization process is dependent only on the energy needed for the formation of intermediate **III**. AM1 calculations of the reverse reaction, where one of the oxygen atoms of a water molecule is forced to approach the cationic carbon of **VII**, reveals that the energy needed for the formation of **VI** is 17.09 kcal/mol for **1a**, 16.23 kcal/mol for **1d**, and 15.38 kcal/mol for **1c**. Further, the energy profile for this approach does not show a maximum energy that indicates the reach of a transition state, and when the system is fully optimized (by removing the constrains imposed on a bond distance C–OH2$^+$), the resulting global minimum structure is actually the carbocation **VII** which is surrounded by a water molecule that is in a remote distance from its center.

The driving force for the acceleration in the lactonization process of 1c: The importance of ground state conformations and the lack of translational entropy in intramolecular and enzymatic reactions have drawn attention from Bruice [1] and Menger [12]. Both have suggested that the unique acceleration in rates found in some systems involving intramolecular cyclization is mainly driven by the proximity of the nucleophile to the electrophile of the ground state molecules. On the other hand, Jencks [2] and Page [5] have offered a different explanation to the acceleration based on entropic driving forces that are caused from freezing out motions and dampening of vibrational frequencies in the transition state.

The following discussion examines each of the proposals and the related phenomenal explanations that have been introduced concerning the effects that dominate the scope of intramolecular reactions of hydroxy-acids and similar systems. The forces that play a role in the lactonization of the hydroxyhydrocinnamic acid system stem from direct interaction and there are no remote effects, thus they are covalently enforced. First, we have examined the feasibility of a covalently enforced strain being the driving force for such rate enhancement.

The term strain usually describes steric effects that might cause acceleration or an inhibition of a reaction rate. For intermolecular reactions, a reaction between A and B may be faster in A – B than in A + B if A – B is significantly strained and relieves strain when achieving a transition state. The same principle is applied for intramolecular reactions, where the reactant has two reactive centers which resemble the two reactants A and B in the intermolecular process. Generally there are two opposite situations in which a reaction can be driven by strain: (i) when the reaction rate is inhibited and the interaction between the reacting centers is impeded as a result of a steric hindrance, as in the case of S_N2 substitution of cyclohexyl halides, and (ii) when the reaction is enhanced due to a relief in strain of the ground state while approaching a transition state, as in the case of S_N2 of epoxides [31].

Strain-accelerated reactions occur for compounds that, by necessity, are rigid with high bond rotation barriers. Further, such compounds have distorted bond distances and/or bond angles when compared to strain-free compounds [32]. Our calculations indeed predict distortion of bond angles and bond distances in the phenylic ring of hydrohydroxycinnamic acid **1c**, supported by the X-ray crystal structure of the corresponding alcohol,[26]. The same distortion with the same magnitude is observed in hydrohydroxycinnamic acid **1b** and to some extent in the corresponding tetrahedral intermediates **3c** and **3b**. If the acceleration is due to strain relief, comparable rates for **1c** and **1b** should be seen. However, the lactonization rate of **1c** is 10^{10} times faster than that of **1b**. In addition, the distortion in bond angles and bond distances for the aliphatic carboxylic acid moiety and the lactone ring found, in the X-ray structures and in the AM1 calculations of the calculated geometries of **1a–1d**, **3a–3d**, and **4a–4d**, suggests that there is no significant strain relief upon the lactonization processes of hydrohydroxycinnamic acids **1** (structures **1** to **3** to **4**, see Scheme 6).

The second point that supports the exclusion of strain as a driving force for rate acceleration is that in hydroxy-acid **1c**, the rotation barrier around C2–C3 is found to be much smaller than that of **1a**. If Wilcox's assumption is correct, the C2–C3 bond in **1a** should be more favorable to rotation than that of **1c**, based on the assumption that the acceleration is driven by strain. Furthermore, if strain-accelerated reactions occur for compounds that, by necessity, are rigid with high bond rotation barriers, this will lead us to conclude that the lactonization of hydroxyhydrocinnamic acid **1c** is not due to steric effects.

Since we have excluded the notion that strain is the main driving force for the enhancement of the lactonization of **1**, we have examined the second possible driving force, the proximity effect. The term proximity effect was first used by Bruice et al. many years ago when they reported a significant acceleration in the rates for anhydride formation in a series of dicarboxylic semiesters. This acceleration reaches 5×10^7 for dicarboxylic semiester **A** compared to that of a corresponding bimolecular counterpart (see Scheme 1) [1].

Bruice's hypothesis to explain the remarkable enhancement in the reaction rates for his system is, the two reacting centers, the nucleophile (COO–) and the electrophile (–C(O)–O–) are covalently linked and are in a close proximity to each other, enabling them to interact more efficiently compared to a reaction between two reactants that are separate entities. In this intramolecular model system, the carboxylate anion and the carbonylic ester are in a productive orientation, such that the complex is strain-free and the rate acceleration is due to a loss in translational and vibrational degrees of freedom prior to a transition state. Generally, this process is accompanied by a decrease in the negative value of ΔS.

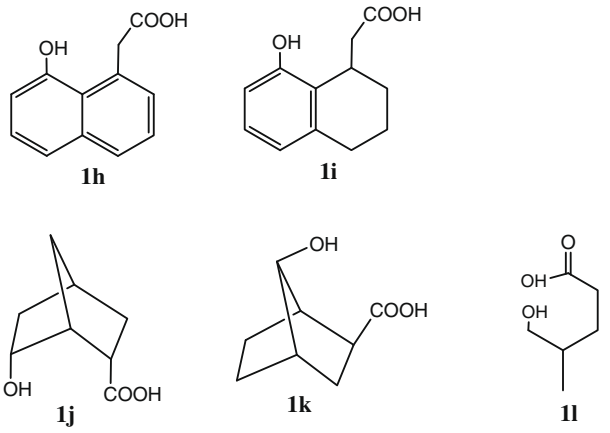
To examine if the rules of close proximity are applied to the lactonization process of hydrohydroxycinnamic acid system, we have considered the following aspects: (1) ground state conformations (distance between the two reacting centers), (2) ground state energies (ΔH, ΔS, and ΔG), (3) barriers to rotation around C2C3 bond and the conformations and the energies of the resulting geometries, (4) transition state conformations and energies. Examination of the data presented in this section reveals: (I) among all the conformations that are obtained from a rotation around C2–C3 bond in hydroxyhydrocinnamic acid **1c**, the global minimum conformation was found to have the shortest distance, between the two reacting centers (C1 and O10) (II) in contrast to **1c**, hydroxyhydrocinnamic acid **1a** was found to have a global minimum conformation with the longest C1–O10 bond distance among all other possible conformations that can be created from the rotation around C2–C3 bond, (III) for **1a** to be in a conformation by which the distance C1–O10 is comparable with that of **1c** (pre-organized conformation) a rotation of 180° around the C2–C3 bond should be applied with an energy expense of 4.9 kcal/mol. Furthermore, the change in entropy (ΔS_{GSGS_P}) upon the transfer from the global minimum conformation (GS) to the pre-organized conformation (GS_P) is 19.5 cal/mol which is equal to −5.82 kcal/mol. Simple calculations for the difference in the free energies ($\Delta\Delta G_{GSGS_P}$)

of **1c** and **1a** upon pre-organization to form productive complexes is about 7 kcal/mol (3.93 kcal/mol for **1c** and 10.73 kcal/mol for **1a**). ΔS_{GSGSp} and $\Delta\Delta G_{GSGSp}$ refer to changes in free energies from the ground state global minima to the pre-organized ground state complexes (**IV**). The difference in the activation energies ($\Delta\Delta G^{\ddagger}$) between **1a** and **c** is 14 kcal/mol (see Table 2), where $\Delta\Delta G^{\ddagger}$ corresponds to the difference in energies between the global minima ground states and the corresponding transition states (TS). It is now clear that the 14 kcal/mol difference between the activation free energy values of **1a** and **c** is composed of two fractions of 7 kcal/mol each. One fraction is accounted for by the energy needed for the pre-organization in the ground state, and the other fraction is accounted for by enthalpic changes through the reaction pathway until the transition state is reached. It should be noted that careful examination of the entropic and enthalpic changes during the energy pathway of the second fraction indicates that the energy is completely composed of enthalpic changes (ΔH) and that the change in entropy (ΔS) from the pre-organized to the transition states is almost zero [33].

Therefore, we conclude that the first fraction of the 14 kcal/mol needed for a pre-organization of the ground state relates to proximity effects. The second fraction difference of the 7 kcal/mol between the free energies of **1a** and **c** also may be due to proximity effects. In order to provide strong evidence for this, we calculated the change in the value of the angle of attack (**a**) as a function of a change in the distance between the two reacting centers (C1 and O10). The results obtained were examined for a linear correlation, and a strong correlation was observed between the energy E and α/r, which is the ratio between the angle of attack value (α) (see Chart 1) and the distance C1–O10 (r) as shown in Eqs. (14–16). Further, it was found that the order of the slope value (S) is:

$$S(\mathbf{1a}) > S(\mathbf{1d}) > S(\mathbf{1c}).$$

Menger has advocated abandoning thermodynamic models involving entropy in favor of distance effects on rate, and he has also derived an equation relating rate and distance [12]. This interesting finding (relationship between energy, distance, and angle of attack) led us to expand our theoretical study on other hydroxy acids that undergo intramolecular lactonization. We have chosen five different hydroxy acids (**1h–1l**, see Scheme 7) that have been experimentally studied and their experimental rates were measured [14b,d]. Since the activation energy values for the lactonization reactions of **1a–1d** when calculated by AM1 were comparable to that calculated by HF (6-31G), we decided to study the lactonization of **1h–1l** only by AM1 semi-empirical method since the HF (6-31G) is a relatively time consuming program. Using calculated heat of formation (ΔH_f), entropies (S) of **1h–1l**, and their corresponding protonated species **2h–2l**, and the energies of their calculated transition states ($\Delta H^{\ddagger}$ and $S^{\ddagger}$), we calculated the free energy changes for the lactonization processes of the hydroxy-acids ($\Delta\Delta G^{\ddagger}$) summarized in Table 3. The geometries of the calculated transition states for **1a–1d** as well as **1h–1l** and that of their corresponding protonated species are illustrated in Fig. 4. In a similar method to that used for **1a–1d**, we calculated the α/r values for **1h–1l** and that for **2h–2l**. The calculated properties of hydroxy acids **1h–1l** were examined for linear correlation with the experimental rate values. The correlation results indicate a moderately strong correlation between $\Delta\Delta G^{\ddagger}$ and log k_{exp} (see Fig. 5a and Eq. (17) for the un-catalyzed processes and Fig. 5b and Eq. (18) for the acid-catalyzed processes). Similar correlation results as well were obtained when plotting the ***E*** values against the α/r values that were calculated from the approaching processes of the hydroxy acids (see Eqs. (19–23) for the un-catalyzed processes and Eqs. (23–28) for the acid-catalyzed reactions). The slope (S) values obtained from the correlations of E vs. α/r for **1a–1l** were plotted against the logarithmic values of k_{exp} and the result of this correlation is depicted in Fig. 5c and d, and Eqs. (30) and (31), where Fig. 5c and Eq. (30) represent the un-catalyzed lactonization processes and Fig. 5d and Eq. (31) represent the acid-catalyzed ones.



Scheme 7. Hydroxy acids (**1h – 1l**).

$$\Delta\Delta G^{\ddagger} = -2.0165 \log k_{exp} + 53.818 \; R = 0.96 \quad (17)$$

$$\Delta\Delta G^{\ddagger} = -1.6788 \log k_{exp} + 45.512 \; R = 0.98 \quad (18)$$

$$S = -0.0564 \log k_{exp}(\text{corrected}) + 1.3295 \; R = 0.98 \quad (30)$$

$$S = -0.0111 \log k_{exp}(\text{corrected}) + 0.1997 \; R = 0.98 \quad (31)$$

Table 3
AM1 calculated properties for acid-catalyzed and uncatalyzed lactonization processes of hydroxy acids

Compound (X)	Log $_{exp}$ (K_{1x}/K_{1a})	Log K_{exp} corrected	$\Delta\Delta G^{\ddagger}_{x-1a}$ **I − III**	Log$_{Calc}$ (K_{1x}/K_{1a}) I–III	$\Delta G^{\ddagger}$	S	Compound (HX)	$\Delta\Delta G^{\ddagger}_{x-2a}$ **IV − VI**	Log$_{Calc}$ (K_{2x}/K_{2a}) **IV–VI**	$\Delta G^{\ddagger}$	S
1a	0.000000	1.653213	0.00	0.00000	48.07	1.2165	**2a**	0.00	0.00000	41.24	0.1934
1b	NC	NC	−0.51	0.37039	47.56	–NC–	**2b**	−0.35	0.25419	40.89	–NC–
1c	9.346787	8.89000	−14.65	10.6395	33.42	0.8636	**2c**	−14.27	10.36361	26.97	0.1032
1d	3.647817	3.69453	−5.45	3.95803	42.62	1.0648	**2d**	−2.66	1.93183	38.58	0.1531
1h	2.727000	4.53421	−4.88	3.57999	43.19	1.0142	**2h**	−3.06	2.24483	38.18	0.1548
1i	1.522878	3.022032	−2.97	2.17881	45.1	1.227	**2i**	−2.22	1.62860	39.02	0.1567
1j	1.425968	2.543701	2.32	−1.70190	50.39	1.1997	**2j**	−1.27	0.93168	39.97	0.1655
1k	−3.65321	−2.53548	13.47	9.88167	61.54	1.4922	**2k**	8.77	6.43372	50.01	0.2287
1l	−2.53927	−0.40187	6.31	4.62905	54.38	1.3504					

Exp refers to experimental and Calc refers to calculated.
$\Delta\Delta G^{\ddagger}_{\mathbf{1x-1a}}$ is the activation energy difference of hydroxy acid (**X**) and hydroxy acid **1a**.
$\Delta\Delta G^{\ddagger}_{\mathbf{2x-2a}}$ is the activation energy difference of protonated hydroxy acid (HX) and hydroxy acid **1a**.
$K_{\mathbf{1x}}/K_{\mathbf{1a}}$ is the relative rates of hydroxy acid (**X**) and hydroxy acid **1a**.
$K_{\mathbf{2x}}/K_{\mathbf{2a}}$ is the relative rates of protonated hydroxy acid (HX) and hydroxy acid **2a**.
S is the slop of the curve obtained from plotting the values of E (energy) vs. a/r (the ratio of the angle of attack a and C_1–O_{10} distance).

log k_{exp} (corrected) is calculated from the following equation:

$$\log k_{exp}(\text{corrected}) - \log k_{exp}(\text{observed}) + \log(e^{-T\Delta S/RT})$$

Comparing the un-catalyzed and the acid catalyzed processes reveals (1) the activation energy ($\Delta\Delta G^{\ddagger}$) values needed for the lactonization of hydroxy acids are much higher in the un-catalyzed reactions, and when plotting the values of $\Delta\Delta G^{\ddagger}$ for the un-catalyzed lactonization reactions against the $\Delta\Delta G^{\ddagger}$ values for the acid-catalyzed ones, a slope of 1.2197 is obtained (Eq. (32)). (2) In both cases, the value of the angle of attack (α) is dependent on the distance between the two reacting centers (r), and the ratio α/r is increased upon the increase in the enthalpic energy (E) during the approach processes. Further, when the values of S (obtained from the slopes of E vs. α/r curves for the un-catalyzed lactonization reactions, *k equation)* were plotted against these for the acid-catalyzed processes, a slope of 4.7975 is obtained (Eq. (33)). This indicates that the energy needed for changing the α/r value is about 4.8-folds higher in the un-catalyzed reactions compared to that in the acid-catalyzed reactions.

$$\Delta\Delta G^{\ddagger}\text{uncatalyzed} = 1.2197\Delta\Delta G^{\ddagger}\text{catalyzed} - 1.0749 \quad R = 0.97 \quad (32)$$

$$S\ \text{uncatalyzed} = 4.7975\ S\ \text{catalyzed} + 0.3621 \quad R = 0.94 \quad (33)$$

The effect of the α/r values on the activation energy for the formation of the tetrahedral intermediate: Examination of the correlation Eqs. (30) and (31) indicates that the energy needed to increase the value of angle α to reach the optimal value for the formation of a stable transition state is less for **1c** than for **1a**. This indicates that the approach of the hydroxyl group to the carbonylic carbon in the case of **1c** is much easier than in the case of **1a**. This conclusion is also supported by the results obtained from the reaction coordinate method that show that the aliphatic side chain in **1c** is more rigid than that of **1a** [34]. The degree of flexibility of the side chain was evaluated by the resulting energies upon rotating the carboxylic moiety around the C2–C3 while the distance C1–O10 was kept constant. The combined results suggest that the driving force in the second stage of the approach is also due to a proximity effect. Hydroxy acids that are rigid in the organized state (C1–O10 = 1.5–2.5 Å) have a lower activation energy (such as **1c**) than these with a less rigidity (such as **1a**).

4. Summary and conclusion

We have reported a systematic theoretical study on the uncatalyzed and acid-catalyzed lactonization of a variety of hydroxy acids. This study includes AM1 and HF/6-31G calculations of the entropic and enthalpic energies of ground states, intermediates, and products involved in these reactions. Moreover, a reaction coordinate method was used to verify the rate-limiting step for the lactonization process by calculating the activation energies of all steps involved and finding the true transition states. The combined theoretical results reveal the following: (1) in contrast to what was suggested by Houk et al. [14b], the rate-limiting step for the lactonization of hydroxy acids studied herein is the formation and not the collapse of the tetrahedral intermediate.

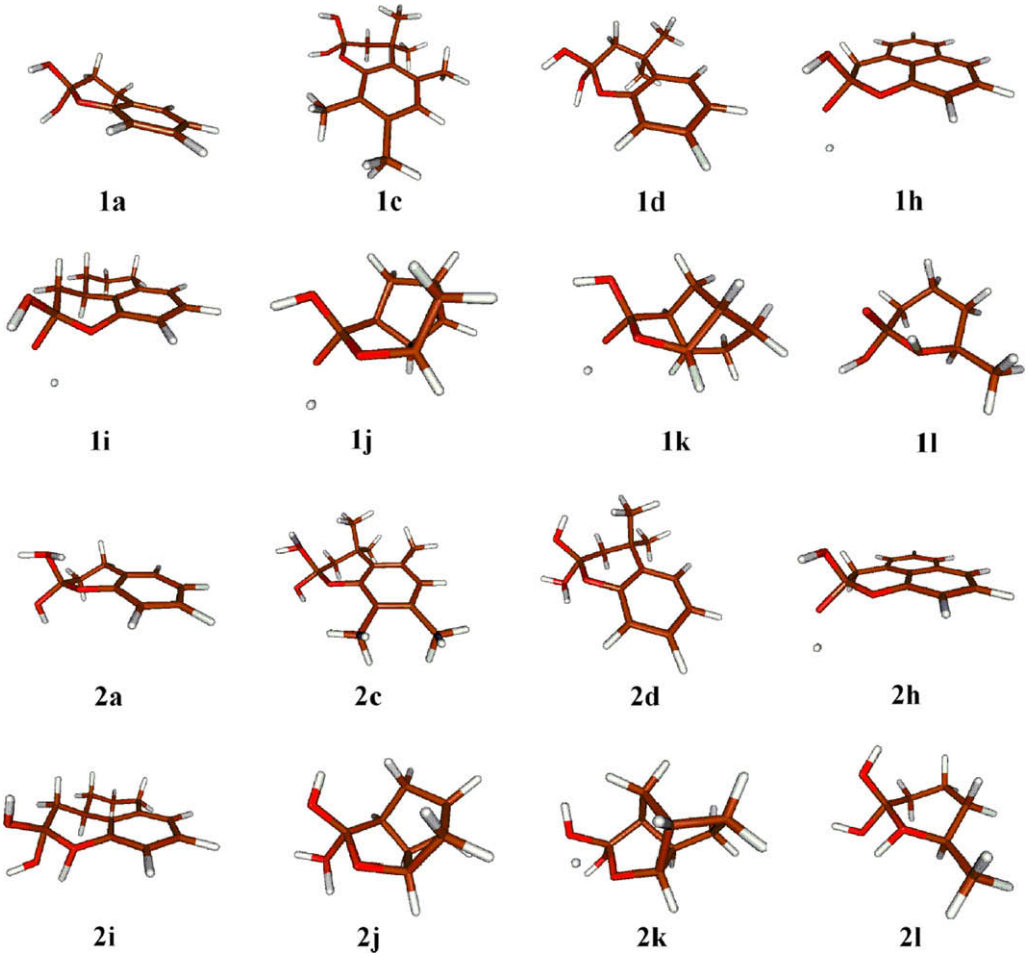


Fig. 4. Structures of the transition state of the lactonization of hydroxy-acids **1a**–**1d**, **1h**–**1l**, **2a**–**2d** and **2h**–**2l**.

The rate-limiting step in these reactions is composed of two successive steps: (a) an approach of the hydroxyl group towards the carbonylic carbon of the hydroxy acid, (b) a proton transfer from the etheric oxygen onto the anionic oxygen of the carboxylic moiety. In step (a), the energy needed for the approach is dependent on the nature of the hydroxy acid and its value is composed of two components, the change in entropy and the change in enthalpy. The change in entropy is dominant in the first stage of the approach (C1–O10 distance is 4–2.5 Å), while the change in enthalpy is dominant in the second stage of the approach (C1–O10 distance is 2.5–1.5 Å). In hydroxy acids such as **1c** and **1d**, the change in entropy from the ground state (C1–O10 distance is around 3A°) to the organized ground state (C1–O10 distance is around 2.5 Å) is much smaller than that in **1a** and **1b** due to proximity effects. Similarly, in the second stage, the change in enthalpy for **1c** and **1d** is less than that in **1a** and **1b** due to proximity effects that exist in the tri-methyl lock system. In step (b), the energy needed for the transfer of a proton is independent of the nature of the hydroxy acid and its value is almost constant, for more details concerning the suggested mechanism, see cartoon depicted in Chart 4, (2) the AM1 and the HF calculations provide a rationale for predicting the value of the activation energy once the angle of the attack and the distance between the two reacting centers are known. Using the resulted correlation equation we can predict new potential hydroxy acids that are capable of lactonizing at high rates comparable to those catalyzed by enzymes, (3) to our knowledge, this is the first time that a correlation between activation energy and angle of attack has been shown, (4) in contrast to that suggested by Wilcox et al. [14a] thermodynamic properties are not a good tool in estimating kinetic rates, and it is necessary to verify a transition state and calculate the free energy of activation.

In the body of this text, we pointed out that there are two different proposals for acceleration in reactions and enzymes: the proximity effects of Menger [12] and Bruice [1] and the entropic driven force suggested by Jencks [3]. Based on our results, we found that Jencks' proposal does not fit to our case of study, since we found that there is no change in entropy from the GSp to the TS and that all the entropic changes occur during the pre-organization step. Further, our calculated frequency results indicate that the ratio of the number of frequencies below 1000 cm^{-1} to the total number of frequencies did not change along the reaction coordinate from the GSp to the TS (C1–O10 distance between 2.5 and 1.5A). On the other hand, we found that the proximity effect proposal is very well applied to the system we have studied. Our ground state energy calculations show that **1c** possesses a near attack conformation (NAC), while **1a** requires about 7 kcal/mol in order to reach the NAC which provides the proper overlapping of van der Waals surfaces to create the transition state. This difference in energy is equal to 10^6-fold in the rate ratio of **1c**/**1a**. Moreover, we have shown that in the second stage of the approach (from the pre-organized state to the transition state) the energy needed for **1a** to reach the transition state is about 7 kcal/mol more than that needed for **1c** to reach its transition state (10^6-folds in **1c**/**1a** ratio rate). This is again because the pre-organized structure of **1c** is in a more favorable conformation to allow effective overlapping of the van der Waals surfaces than the pre-organized conformation of **1a**, which was theoretically proven to undergo conformational changes during the second stage of the approach due to a relatively high flexibility when compared to **1c**.

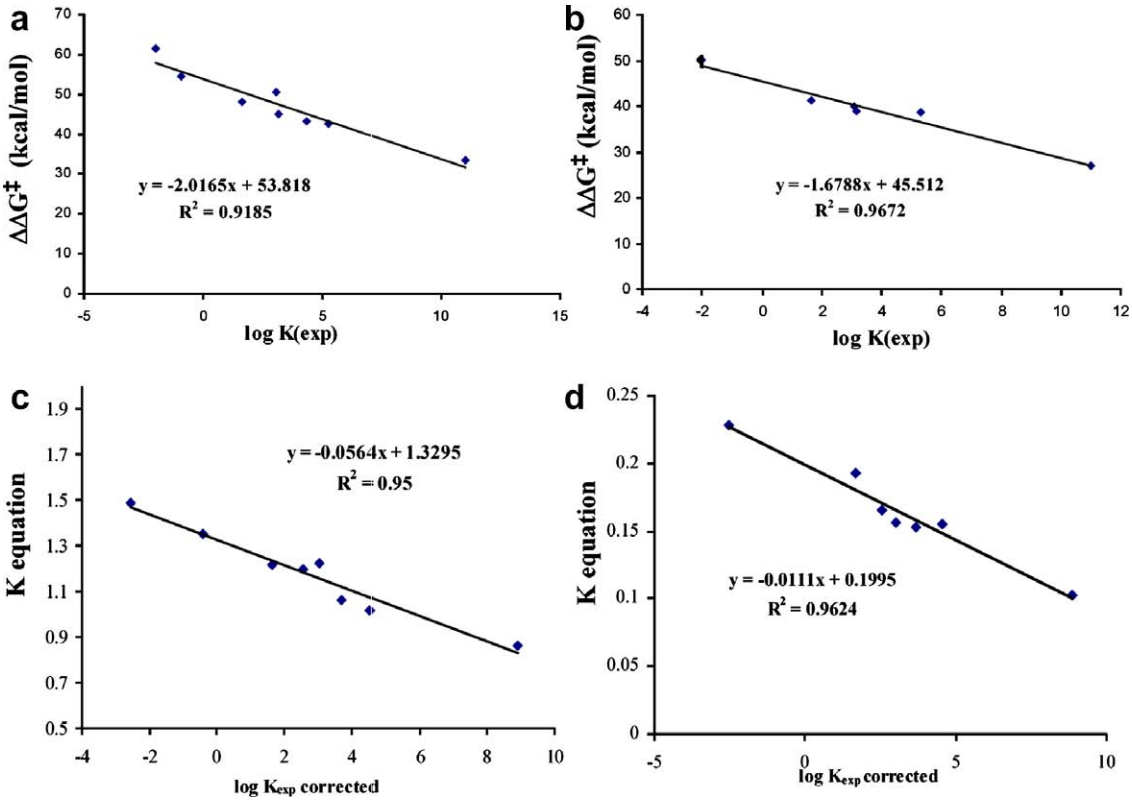


Fig. 5. (a) Plot of $\Delta\Delta G^{\ddagger}$ vs. log k_{exp} (see text) for the lactonization processes of hydroxyhydrocinnamic acids **1a**–**1d** and **1h**–**1l**. (b) Plot of $\Delta\Delta G^{\ddagger}$ vs. log k_{exp} (see text) for the lactonization processes of hydroxyhydrocinnamic acids **2a**–**2d** and **2h**–**2l**. (c) Plot of k_{eq} (*S*) vs. log k_{exp} (corrected) for the lactonization processes of hydroxyhydrocinnamic acids **1a**–**1d** and **1h**–**1l** (see text). (d) Plot of k_{eq} (*S*) vs. log k_{exp} (corrected) for the lactonization processes of hydroxyhydrocinnamic acids **2a**–**2d** and **2h**–**2l** (see text).

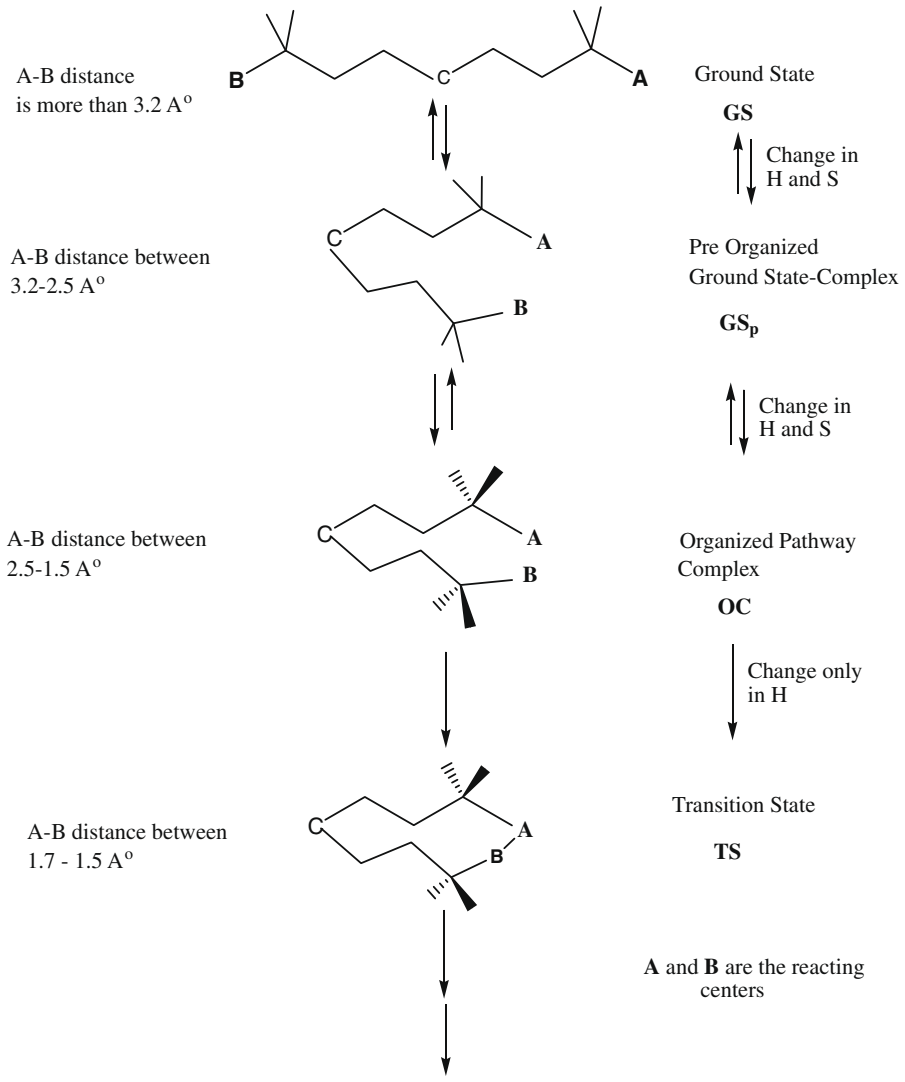


Chart 4. Proposed mechanism for the approach of O_{10} to C_1 in the lactonization of hydroxy acids. A and B are the reactive centers.

Acknowledgments

We thank the Karamans Co. and the German–Palestinian–Israeli fund agency for support of our hardware computational facilities. We also give a special thanks to Dr. Omar Deeb and Sherin Alfalah for computational software support and technical assistance. Many thanks are given to Nardene Karaman and the referees for general assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bioorg.2008.08.006.

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[34] A rotation of the carboxylic moiety around C2–C3 bond in **1a** and **1c** was conducted using a reaction coordinate method. This was accomplished by changing the dihedral angle O10C1C2C3 in increments of 36° while keeping the C1–O10 distance constant (2.0, 1.9 or 1.8 Å). The calculations indicate a higher barrier of rotation for **1a** over **1c**.