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Hydrolysis and retro-aldol cleavage of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate: competing reactions

Bishwajit Ganguly[a]*, Manoj K. Kesharwani[a†], Marija Matković[b], Nikola Basarić[b], Ajeet Singh[a†] and Kata Mlinarić-Majerski[b]**

The hydrolysis of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (1) and the parent ester ethyl 3-hydroxybutyrate (4) has been studied experimentally and computationally. In the hydrolysis of *threo*-ester 1 with 2 M NaOH, predominantly retro-aldol product was observed, whereas the hydrolyzed product was present in a minor amount. When the reaction is carried out under the same conditions with the parent ester ethyl 3-hydroxybutyrate (4), hydrolyzed product is exclusively observed. The competitive pathways, namely hydrolysis and the retro-aldol reaction for 1 and 4 were investigated using DFT calculations in the both gas and solvent phase. The calculated results in the solvent phase at B3LYP/6–31 + G* level revealed that the formation of retro-aldol products is kinetically preferred over the hydrolysis of *threo*-ester 1 in the presence of a base. However, the parent ester 4 showed that the retro-aldol process is less favored than the hydrolysis process under similar conditions. The steric effect imposed by the bulky adamantyl group to enhance the activation barriers for the hydrolysis of the ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (1) was further supported by the calculations performed with *tert*-butyl group at the α-carbon atom of ethyl 3-hydroxybutyrate (7).

Supporting information may be found in the online version of this paper.

Keywords: ester hydrolysis; retro-aldol; DFT; solvent effect; adamantane

INTRODUCTION

The hydrolysis of carboxylic acid esters (RCOOR′) is one of the most fundamental and thoroughly studied chemical reactions.[1–9] A variety of experimental and theoretical studies[10–55] on ester hydrolysis have provided critical insights into the fundamental reaction mechanism. Besides extensive interests within chemistry, the mechanism of base-catalyzed hydrolysis of esters figures prominently in many biological processes,[6–9,56,57] such as the metabolism of the neurotransmitter acetylcholine and the degradation of cocaine. Applications include the design of transition-state analogs that inhibit acetylcholinesterase[58,59] and that elicit anti-cocaine catalytic antibodies.[60–63] The rate of hydrolysis can have major impact on the metabolism of many drugs and prodrugs.[64] It is known that the hydrolysis rate can be controlled by steric effect[65] which is clearly demonstrated in the metabolism of some particular drugs.[66,67] Ester hydrolysis ($RCOOR' + H_2O \rightarrow RCOOH + R'OH$) involves cleavage of either the acyl-oxygen or alkyl-oxygen bond.[6–9] The mode of cleavage may be determined by isotopic labeling and by stereochemical studies. Both types of cleavage are observed with acid or base catalysis and the result is a rich array of possible mechanisms. The base catalyzed hydrolysis of the majority of common alkyl esters occurs by the attack of the hydroxide ion at the carbonyl carbon. This mode of hydrolysis has been designated by $B_{AC}2$ (base catalyzed, acyl oxygen cleavage, bimolecular),[6–9] and is believed to occur by a two-step mechanism.[6–9] Generally, this is the accepted mechanism that consists of the formation of a tetrahedral intermediate (first step), followed by a decomposition of the tetrahedral intermediate to produce $RCOO^- + R'OH$ (second step).[68,69] Another less common mode of ester hydrolysis, $B_{AL}2$ (base-catalyzed, alkyl-oxygen cleavage, bimolecular) competes with the $B_{AC}2$ mode.[6–9] The $B_{AL}2$ mode, which leads to the same products as the $B_{AC}2$ process, is essentially an S_N2 substitution with a carboxylate leaving group (Scheme 1).[6–9] Reaction pathways and energy barriers for the both $B_{AC}2$ and $B_{AL}2$ modes of hydrolysis of representative alkyl esters have been studied in the gas phase and the highest energy barrier

* *Correspondence to: B. Ganguly, Analytical Science Discipline, Central Salt and Marine Chemicals Research Institute (Council of Scientific and Industrial Research), Bhavnagar, Gujarat 364 002, India.*
E-mail: ganguly@csmcri.org

** *Correspondence to: K. Mlinarić-Majerski, Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, P.O. Box 180, Zagreb 10 002, Croatia.*
E-mail: majerski@irb.hr

a *B. Ganguly, M. K. Kesharwani, A. Singh*
Analytical Science Discipline, Central Salt and Marine Chemicals Research Institute (Council of Scientific and Industrial Research), Bhavnagar, Gujarat, 364 002, India

b *M. Matković, N. Basarić, K. Mlinarić-Majerski*
Department of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička cesta 54, Zagreb 10 002, Croatia

† *These authors have contributed equally in this paper.*

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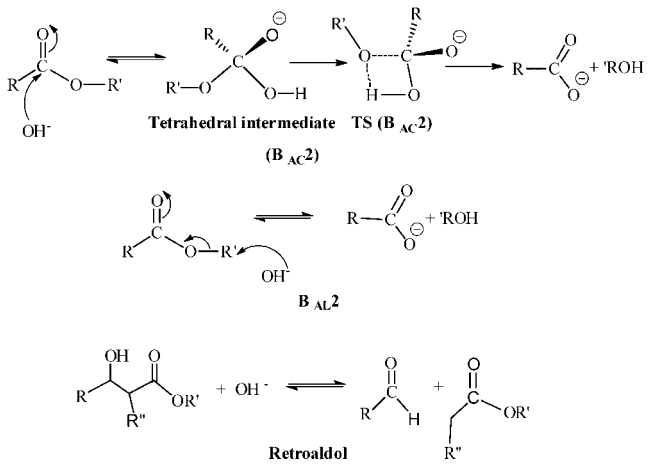
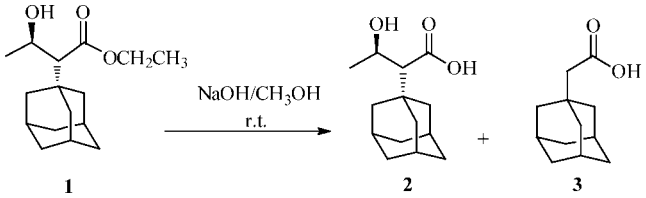
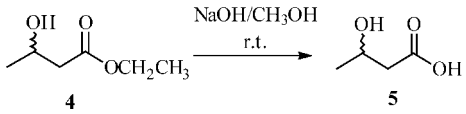


Scheme 1. The $B_{AC}2$, $B_{AL}2$ of ester hydrolysis and retro-aldol mechanism



Scheme 2. Reactions of **1** with NaOH



Scheme 3.

calculated for the $B_{AC}2$ process is always lower than the barrier for the $B_{AL}2$ process.[54]

threo-2-(1-Adamantyl)-3-hydroxybutyric acid (**2**) is an adamantyl analog[70] of the well known 3-hydroxybutyric acid[71,72] and generally one of novel artificial hydrophobic β-hydroxy acids.[73,74] Hydrophobic properties make it interesting as a building block in depsipeptide synthesis. Depsipeptides are heterodetic peptides in which at least one amide bond has been replaced with an ester bond. These peptide derivatives are promising lead compounds for drug discovery.[75] The ester bond in depsipeptides can be formed by incorporating hydroxy acid into the peptide backbone[76] which makes hydroxy acid crucial building block for depsipeptide synthesis. Therefore, the development of methods for synthesis and isolation of novel hydroxy acids is an interesting field in peptide chemistry.[77,78] To incorporate hydroxy acids into more complex peptides and peptidomimetics, it is important to understand their reactivity. The reactivity of amino or hydroxy acids in peptide chemistry, especially considers the possibility of protecting the functional groups,[79] the facility of protective groups cleavage[79] and the possibility of making amide[79,80] or ester bond.[81] Not all building blocks in peptide chemistry posses the same reactivity toward introduction of protective group or the formation of peptide bond.[82,83] To avoid the formation of by-products, building blocks in peptide chemistry are used in their protective forms. Because of the attractively simple methodology for the esterification of amino acids, this method of carboxyl protection remains in the practice of peptide synthesis.[79] Ester group is very often the choice of protection for carboxylic group[84] which gives importance to the hydrolysis as a method for the deprotection of carboxylic groups.[79,84,85]

Ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**) was successfully used in the preparation of small depsipeptide fragments.[86] Herein, we report experimental and computational study of the hydrolysis of ethyl esters **1** in presence of a base. During the preliminary investigation, we were intrigued by the finding that the ester **1** yields retro-aldol product **3** predominantly and hydrolysis was a side reaction (Scheme 2). However, the parent ester ethyl 3-hydroxybutyrate (**4**) yields hydrolysis product **5** only (Scheme 3). These experimental results prompted us to examine the competitive reaction pathways for esters **1** and **4** with the hydroxide ion computationally. It is worthy to note that the hydrolysis of esters has been extensively studied, however, to the best of our knowledge, computational studies on base catalyzed retro-aldol reactions are scarce in the literature. It is known that aldol and retro aldol reactions are catalyzed by either acid or base. The reversibility of the aldol reaction, i.e., an equilibrium between aldol and carbonyl compounds is one of the most important characteristics of the aldol reaction. Conversion of aldol to retro aldol products is catalyzed by a base to deprotonate the hydroxy group followed by the breaking of C—C bond. There are a few reports on theoretical modeling of thermal retro-aldol reactions of β-hydroxy esters.[87,88] Recently *de novo* computational design of breaking of a carbon–carbon bond with retro-aldolases was reported, where four different catalytic motifs were used in a non-natural substrate.[89]

EXPERIMENTAL

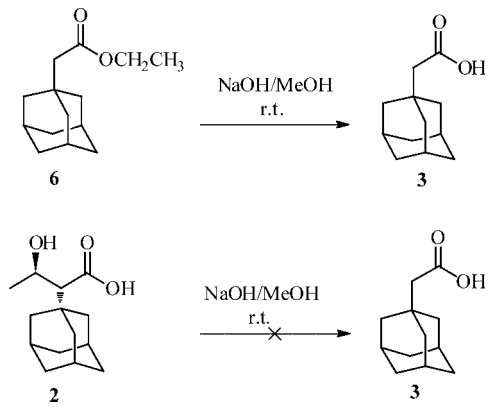
Hydrolysis of ethyl *threo*-3-hydroxy-2-(1-adamantyl)butyrate (*1*)

The corresponding ester **1**[86] (266 mg, 1 mmol) was dissolved in MeOH (5 ml) and 2 M NaOH (5 ml) was added. The reaction was stirred at room temperature. At the appropriate time aliquots of 2 ml were taken (Table 1.) and the solvent evaporated. The crude residue was suspended in CH_2Cl_2 (35 ml) and washed with water

Table 1. Reactions of **1** with 2 M NaOH in MeOH

Entry	Time (h)	Conversion (%)[a]	Product ratio (%)[b]	
			3	**2**
1	1	41	74	26
2	4	55	79	21
3	24	69	81	19
4	120	100	83	17

[a] The conversion was determined from the mass of recovered **1** and isolated products **2** and **3**.
[b] The product ratio was determined from ^{1}H NMR spectra of isolated mixture of **2** and **3**.



Scheme 4.

(2 × 10 ml). The organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated and the starting compound **1** recovered. The water phase was acidified with 1 M HCl (pH ~ 3), precipitate extracted with diethyl ether (2 × 25 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the mixture of products **2** and **3** obtained. The recovered starting compound **1** and products **2** and **3** were identified by ^{1}H NMR. The ratio of products **2** and **3** was determined by ^{1}H NMR and the conversion of the reaction was determined from the mass balance of isolated products. The reaction was repeated with NaOD/D_2O in NMR tube. However, due to low resolution and complexity of NMR spectra, the conversion could be described only qualitatively, confirming slow hydrolysis of starting compound to the mixture of products.

Hydrolysis of ethyl 3-hydroxybutyrate (*4*)

The ester **4** (26.4 mg, 0.2 mmol) was dissolved in MeOH (1 ml) and 2 M NaOH (1 ml) was added. The reaction was stirred at room temperature and monitored by TLC (the used eluent was 5% MeOH in CH_2Cl_2, and spots were visualized by mixture of $KMnO_4$: K_2CO_3:aq.5%NaOH:H_2O = 2 g:20 g:5 ml:300 ml. After 5 min the reaction was completed. The reaction was repeated with NaOD/D_2O in NMR tube and reaction product **5** identified *in situ* by ^{1}H NMR spectra.

Hydrolysis of ethyl (1-adamantyl)acetate (*6*)

The ester compound **6** (44.9 mg, 0.2 mmol) was dissolved in MeOH (1 ml) and 2 M NaOH (1 ml) was added. The reaction was stirred at room temperature. After 1 h the solvent was removed, crude residue suspended in CH_2Cl_2 (35 ml) and washed with water (2 × 10 ml). The organic phase was dried over anhydrous $MgSO_4$. After solvent evaporation the unreacted compound **6** was recovered. The water phase was acidified with 1 M HCl (pH ~ 3), precipitate extracted with diethyl ether (2 × 25 ml) and dried over anhydrous $MgSO_4$. After solvent evaporation compound **3** was isolated (86%). Unreacted ester **6** and product **3** were identified by ^{1}H NMR.

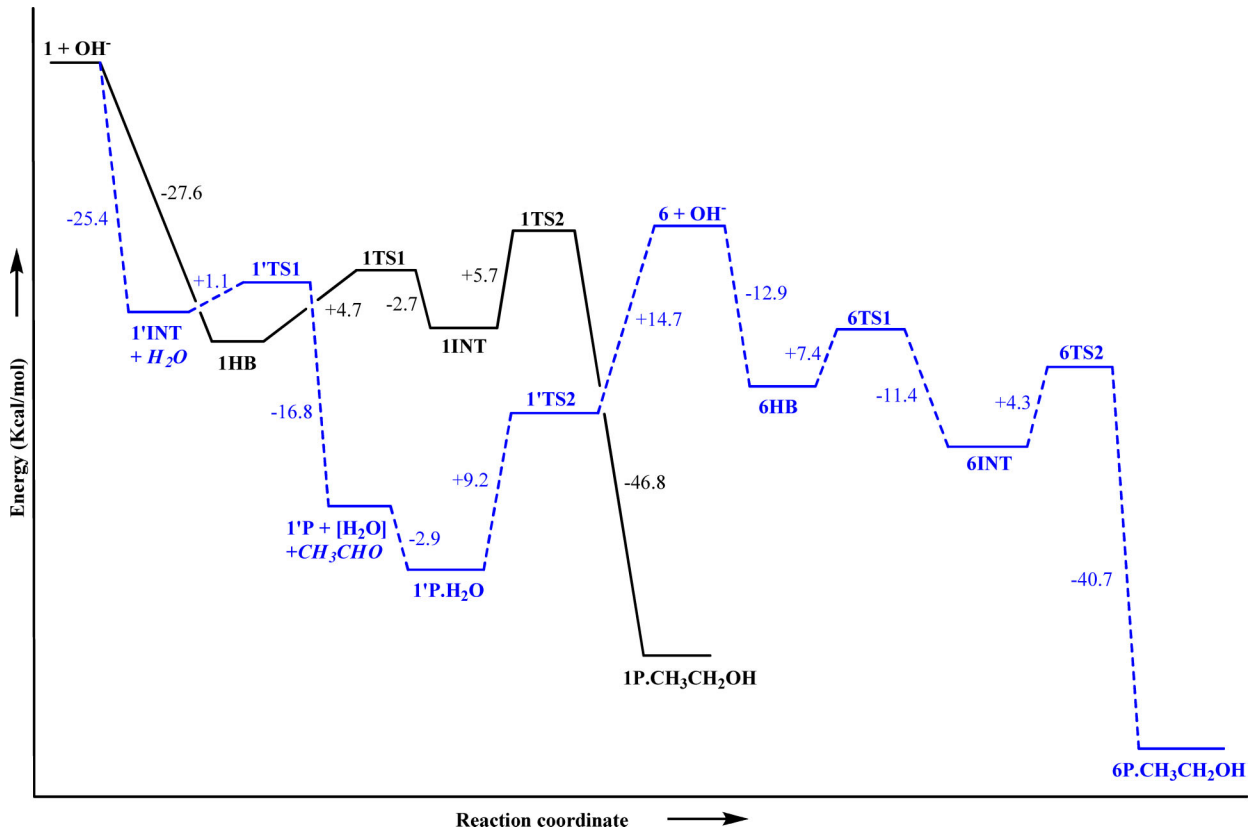


Figure 1. B3LYP/6–31 + G* calculated relative to gas phase free energies in kcal/mol for $B_{AC}2$ hydrolysis (solid line) and retro-aldol process (doted line) of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**). The liberated side products during the formation of intermediate steps are given in italics and the addition of new species for further process is given in []

Attempts of retro-aldol reaction of *threo*-3-hydroxy-2-(1-adamantyl)butyric acid (*2*)

The hydroxy acid **2**[70] (23.9 mg, 0.1 mmol) was dissolved in MeOH (0.5 ml) and 2 M NaOH (0.5 ml) added. The reaction was stirred at room temperature. After 1 h the solvent was removed and the crude residue suspended in CH_2Cl_2 (20 ml) and washed with water (2 × 5 ml). The water phase was acidified with 1 M HCl (pH ~ 3), precipitate extracted with diethyl ether (2 × 15 ml) and dried over anhydrous $MgSO_4$. After solvent evaporation the acid **2** was recovered and identified by ^{1}H NMR.

COMPUTATIONAL DETAILS

Geometries were fully optimized without any symmetry constraints at B3LYP/6–31 + G* level,[90–92] with the Jaguar program package.[93] Harmonic force constants were computed at the optimized geometries to characterize the stationary points as minima. The calculated number of imaginary frequency (Imag) at the same level of theory i.e.; energy minimum structures without imaginary frequencies (NImag = 0), and transition states with only one imaginary frequency (NImag = 1). The gas phase energies discussed are computed free energy values. Intrinsic reaction coordinate (IRC)[94,95] calculations were performed on TSs in order to confirm that TSs did, indeed, lead to the formation of complex and intermediates of the hydrolysis and retro-aldol reactions. Solvent calculations were performed using Polarized Continuum Solvation Model (PCM)[96-100] and methanol ($\varepsilon = 32.63$) as a solvent at same level of theory. Our computed single-point PCM bulk solvent simulations used the B3LYP/6–31 + G* optimized equilibrium geometries. For solvent calculations Gaussian 03 program was used.[101]

RESULTS AND DISCUSSION

Ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**) was prepared by reduction of adamantane substituted ethyl β-ketoester.[86] In order to obtain *threo*-2-(1-adamantyl)-3-hydroxybutyric acid (**2**) the ethyl ester derivative *threo*-**1** was submitted to the base hydrolysis (Scheme 2) and the conversion was monitored by ^{1}H NMR spectroscopy of isolated products (refer Experimental section). The conversion of **1** was completed in five days (Table 1), and **2** and **3** were isolated as minor and major product, respectively.

To examine the influence of adamantyl group on hydrolysis of adamantyl-substituted ethyl 3-hydroxybutyrate, such as **1**, parent compound, ethyl 3-hydroxybutyrate (**4**) was hydrolyzed under the same conditions (Scheme 3). In the presence of a base, ethyl 3-hydroxybutyrate (**4**) was completely hydrolyzed in 5 min, yielding the hydroxy acid **5** as the sole product. Comparing the hydrolysis process of **1** and **4**, it appears that the adamantyl group facilitates retro-aldol reaction for **1** and suppresses the formation of acid **2** via hydrolysis. However, it is not clear whether retro-aldol reaction takes place on hydrolyzed product **2** or on starting ester **1**, leading first to intermediate ethyl (1-adamantyl) acetate (**6**) which then hydrolyzes to **3**. To gain more insight into the processes, two additional experiments were performed (Scheme 4). The hydrolysis of **6** was very efficient, with conversion of more than 86% in 1 h. However, when acid **2** was submitted to the same conditions, retro-aldol reaction did not take place. These observed results suggest that the retro-aldol reaction takes place initially for **1**, which subsequently hydrolyzes to the corresponding acid **3**, while the hydrolysis of **1** and formation of acid **2**, as a minor product is a parallel process.

To gain a better insight on the competing reactions described herein, density functional calculations (B3LYP/6–31 + G*)[90–92] have been employed to examine the potential energy surface (PES) for the hydrolysis and retro-aldol processes of **1** and **4**. The potential energy profiles for the hydrolysis and retro-aldol process of **1** in the gas phase are given in Fig. 1. The choice of B3LYP method in this study is two fold: (i) to compute the results with reasonable accuracy;[68,69] (ii) can be applied to the bulky systems in hands like adamantyl groups within the reasonable computational expenses. B3LYP/6–31 + G* optimized geometries involved in hydrolysis of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**) are given in Fig. 2. The PES of **1** with OH^- ion showed that the first transition state **1TS1** is 22.9 kcal/mol lower than isolated reactants (Fig. 1). It has been reported that a first order saddle point must connect with two local minima associated with a 'reactant' (or an intermediate) and a 'product' (or an intermediate). Hence, a plausible calculated energy barrier can never be negative. For bimolecular reaction, if the energy of a transition state is lower than the total energy of the separated

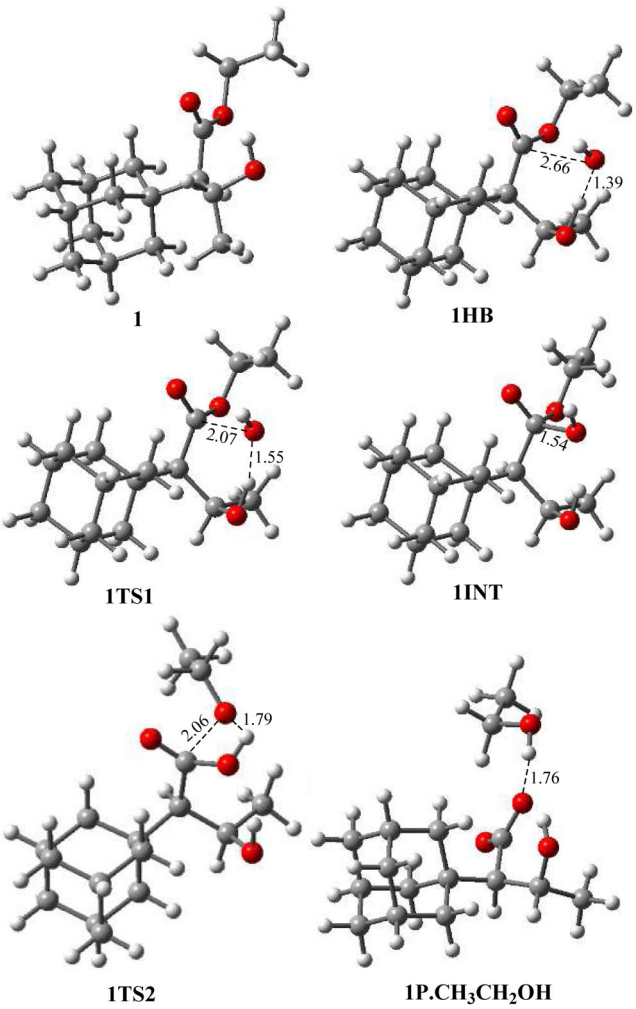


Figure 2. B3LYP/6–31 + G* optimized geometries with important distances (Å) involved in $B_{AC}2$ hydrolysis of ethyl *threo*-2-(1-adamantyl) -3-hydroxybutyrate (**1**). (Gray: carbon; red: oxygen; white: hydrogen)

reactants, it implies that at least one other stable structure exists between the separated reactants and the transition state.[68,69] Therefore, we have located the possible complex **1HB** between the reactant and the transition state (**1TS1**) (Figs 1 and 2). Transition state **1TS1** further goes to the tetrahedral intermediate **1INT** with the formation of C—O bond between OH^- ion and the carbonyl carbon atom. The intermediate **1INT** is below 2.7 kcal/mol with respect to the first transition state **1TS1** (Fig. 1). Further, four-membered cyclic transition state **1TS2** is formed for the expulsion of ethoxide ion from the tetrahedral intermediate **1INT**. The calculated free energy of activation is 5.7 kcal/mol from the tetrahedral intermediate **1INT**. The overall potential energy surface suggests that the second step is the rate-determining step for the hydrolysis of **1**, which is in accord with previous reports of ester hydrolysis.[68,69] The formation of products is exergonic in nature.

The competing retro-aldol process for adamantyl-substituted ester **1** with hydroxide ion has also been computed at the same level of theory and is shown in Fig. 1 and the stationary points located for the retro-aldol process are shown in Fig. 3. The

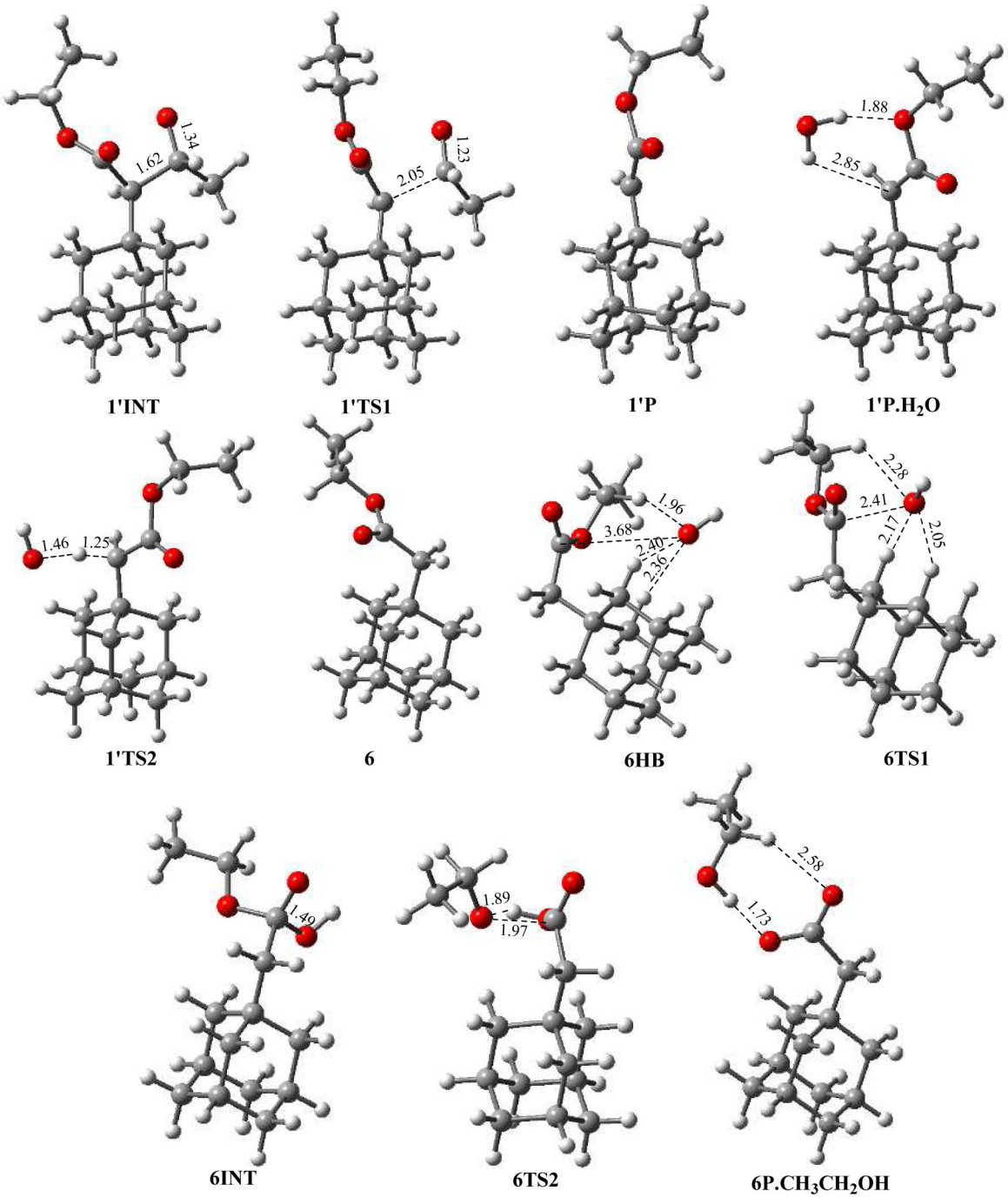


Figure 3. B3LYP/6–31 + G* optimized geometries with important distances (Å) for retro-aldol process of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**). (Gray: carbon; red: oxygen; white: hydrogen)

abstraction of β-hydroxyl proton of **1** with hydroxide ion leads to an intermediate **1'INT** and the formation of a water molecule. This process seems to be instantaneous on the potential energy surface as it lacks the formation of any complex or transition state while going from reactants to the anionic intermediate **1'INT**. The intermediate **1'INT** is 25.4 kcal/mol below the separated reactants (Fig. 1). The C—C bond cleavage for the expulsion of acetaldehyde takes place via **1'TS1** with a small free energy of activation 1.1 kcal/mol yields **1'P** and acetaldehyde (Fig. 1). As mentioned in the experimental studies, the hydrolysis to **3** occurs after the retro-aldol process (Scheme 4). Hence, it is important to examine the conversion of **1** via the formation of retro-aldol product **6**. In the potential energy surface, we have computed the transfer of a proton from water to **1'P**, which in turn forms another intermediate **6**. This process proceeds via transition state **1'TS2** with free energy of activation 9.2 kcal/mol with respect to the complex **1'P.H$_2$O** (Fig. 1). Water was used as a proton donor instead of methanol due to its higher deprotonation ability.[102] The formation of **6** with hydroxide ion is relatively higher in energy presumably due to the instability associated with OH^- ion in absence of solvent medium. First step involves the transition state **6TS1** with free energy of activation of 7.4 kcal/mol, showing the attack of hydroxide ion on carbonyl carbon of **6,** which in turn leads to another intermediate **6INT**. The C—O distance in **6TS1** and **6INT** is 2.41 and 1.49 Å, respectively. Second step involves the breaking of another C—O bond with free energy of activation 4.3 kcal/mol (**6TS2**). The final product is more exergonic than the hydrolysis process of **1**. The stationary points located on the PES for the hydrolysis and retro-aldol processes of **1** with OH^- ion seem to favor the formation of the later products.

Contrary to **1**, the parent ester ethyl 3-hydroxybutyrate (**4**) hydrolyzed completely in presence of a base. The reaction pathways for hydrolysis and retro-aldol reactions of **4** with hydroxide ion examined in gas phase with B3LYP/6–31 + G* level of theory are given in Fig. 4. The calculated stationary points on the potential energy surface for **4** with OH^- ion are shown in Fig. 5. The PES for the hydrolysis of ethyl 3-hydroxybutyrate (**4**) with hydroxide is similar to that of **1** (Fig. 4). The calculated free energy of activation for the first transition state **4TS1** with respect to **4HB** is 1.6 kcal/mol, whereas, the free energy of activation calculated for the expulsion of ethoxide ion is 6.1 kcal/mol with respect to **4INT** (Fig. 4).[68,69]

The retro-aldol process of parent ester **4** with hydroxide ion is similar to that of ester **1** (Figs 1 and 4). The gas phase optimized geometries involved in retro-aldol process of **4** are given in Fig. 6. The formation of anionic intermediate **4'INT** after abstraction of β-hydroxy proton with OH^- ion is 21.9 kcal/mol lower than reactants. The C—C bond cleavage of β-hydroxy ester leads to the expulsion of acetaldehyde through a small free energy of activation 1.3 kcal/mol. The proton transfer process has also been calculated for **4** (Fig. 4). The PES for the hydrolysis and retro-aldol processes of **4** with OH^- ion seems to suggest that both processes are kinetically comparable. Hence, both hydrolysis and retro-aldol products should be observed, which is not in agreement with the experimental observation. To note that the

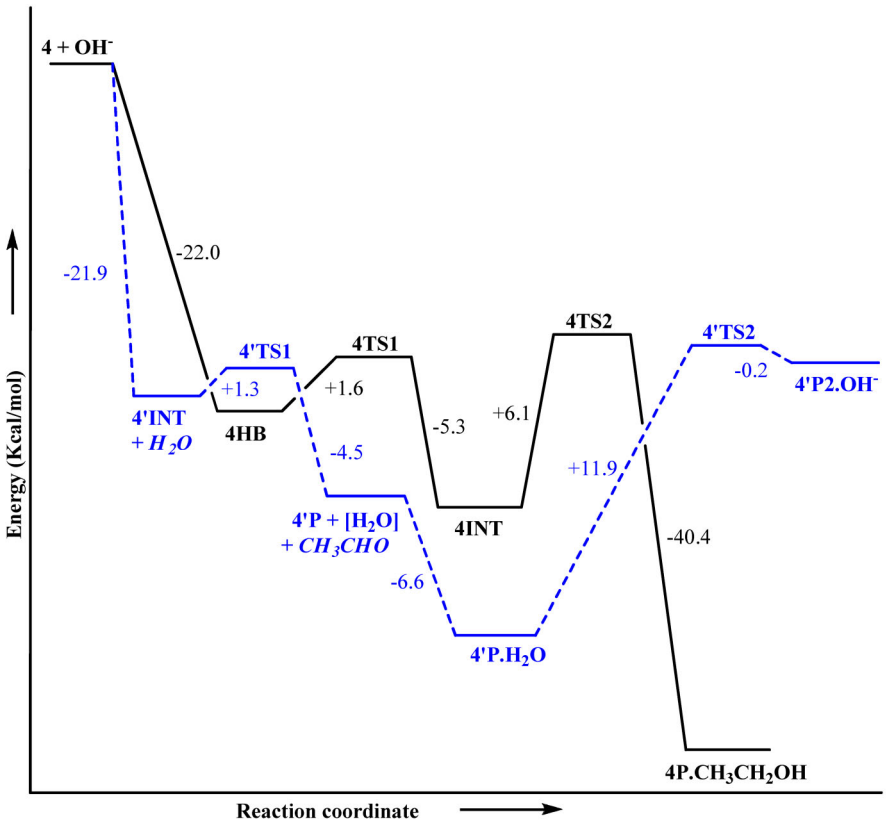


Figure 4. B3LYP/6–31 + G* calculated relative to gas phase free energies in kcal/mol for $B_{AC}2$ hydrolysis (solid line) and retro aldol process (doted line) of ethyl 3-hydroxybutyrate (**4**). The liberated side products during the formation of intermediate steps are given in italics and the addition of new species for further process is given in []

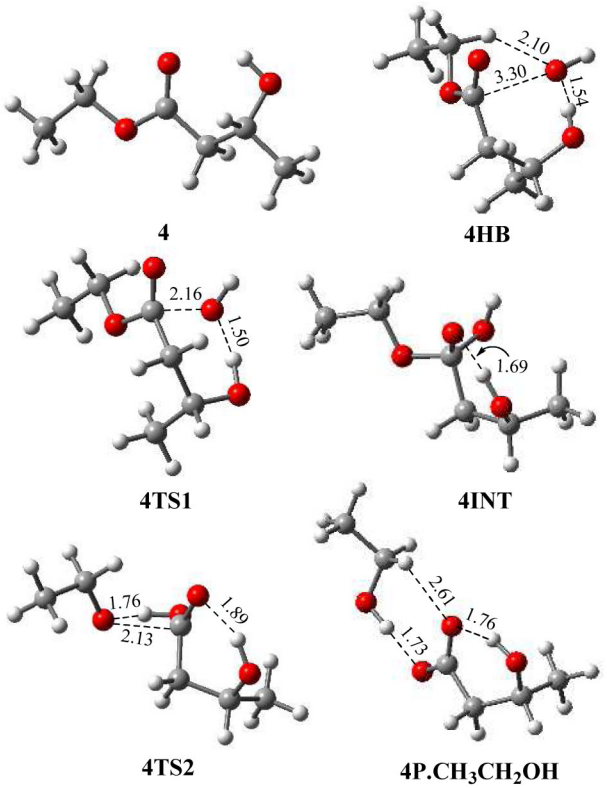


Figure 5. B3LYP/6–31 + G* optimize geometries with important distances (Å) involved in $B_{AC}2$ hydrolysis of ethyl 3-hydroxybutyrate (**4**).

reactions were carried out in a polar solvent medium and solvent does play an important role in many reactions. Therefore, the influence of solvent (methanol in this case) on the potential energy surfaces of **1** and **4** should also be considered in this study.

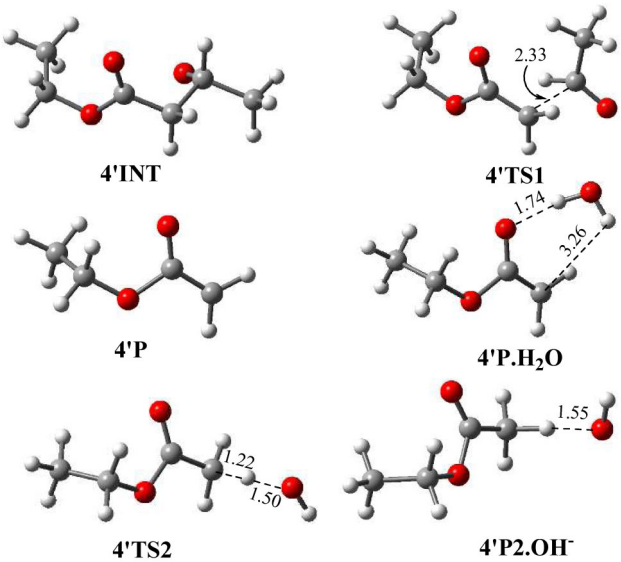


Figure 6. B3LYP/6–31 + G* optimize geometries with important distances (Å) for retro-aldol process of ethyl 3-hydroxybutyrate (**4**).

The hydrolysis and retro-aldol processes of **1** with hydroxide ion were calculated in methanol using polarized continuum model (PCM).[96–100] Single-point calculations were performed using gas phase optimized geometries for each stationary point at same level of theory. In the case of $B_{AC}2$ hydrolysis of **1**, the activation barrier for the formation of transition state **1TS1** was found to be 8.1 kcal/mol. The complex **1HB** in methanol was found to be higher in energy than the reactants,[68,69] which suggest that the reaction kinetics of the hydrolysis process is not expected to be influenced by the complex **1HB**.[103] The calculated activation barriers show that the formation of **1TS2** is the rate determining step for the hydrolysis process. The transition state **1TS2** lies 16.1 kcal/mol above separated reactants (Fig. 7). The calculated reaction energies show that the hydrolysis is exothermic in nature (Fig. 7). The retro-aldol reaction for **1** with OH^- ion shows that the formation of intermediate **1'INT** is 5.0 kcal/mol higher in energy than separated reactants (Fig. 7).[104] The transition state **1'TS1** for the C—C bond breaking is 12.9 kcal/mol higher in energy compared to separated reactants. Subsequently, the activation barrier for the proton transfer process through the transition state **1'TS2** is 8.0 kcal/mol from separated reactants (Fig. 7). The retro-aldol product **6** further undergoes the hydrolysis reaction via two transition states **6TS1** and **6TS2**. The formation of **6HB** in methanol was found to be higher in energy than **6** and not considered in this PES. Overall, the PES for the retro-aldol followed by the hydrolysis process of **1** show that **6TS1** is the rate determining step in the whole process, which is 1.4 kcal/mol lower than the rate determining step for the hydrolysis of **1** (Fig. 7). Therefore, the calculated results suggest that the retro-aldol process is kinetically favored over the hydrolysis reaction of **1** with OH^- ion. It is known that retro-aldol reactions are reversible in nature.[105,106] However, in this case the subsequent hydrolysis process followed by the retro-aldol makes it irreversible, which was observed in the experimental product ratios with time (Table 1).

The calculated results showed a different trend for the reaction of **4** with hydroxide ion in methanol (Fig. 8). The hydrolysis process was found to be kinetically and thermodynamically preferred than that of retro-aldol process (Fig. 8). The calculated activation barrier for the hydrolysis process of **4** with OH^- ion is 3.3 kcal/mol lower in energy than the corresponding retro-aldol reaction. The intermediate product formed due to the expulsion of acetaldehyde in the initial stage of the retro-aldol process shows that the preceding transition state **4'TS1** is 0.1 kcal/mol lower in energy. It might be possible that the complex formation can take place instead of isolated intermediate products. The associated complexed form is 3.6 kcal/mol lower in energy than **4'TS1**, which, subsequently would go to **4'P.H_2O** (Supporting information, Figure S1).

It appears that the bulky adamantyl group enhances the activation barrier for the hydrolysis of the ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**) through deleterious steric interaction with the nucleophile compared to parent ester ethyl 3-hydroxybutyrate (**4**). To corroborate this observation, we have further calculated the hydrolysis of the parent ester ethyl 3-hydroxybutyrate substituted with *tert*-butyl group (**7**) at α-carbon atom (Supporting information, Figure S2). The calculated activation barrier for the hydrolysis of **7** was found to be 15.9 kcal/mol, which is much higher than the parent ester **4** (10.6 kcal/mol). It is clear that the bulkiness of substituents influence the activation barrier for the hydrolysis of esters.

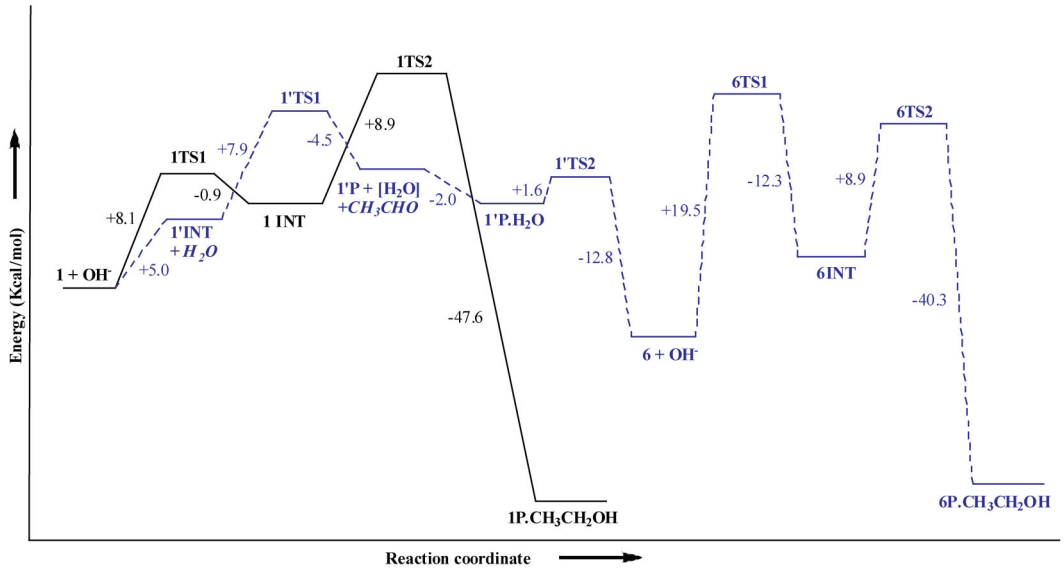


Figure 7. B3LYP/6–31 + G* calculated relative electronic energies in kcal/mol for $B_{AC}2$ hydrolysis (solid line) and retro aldol process (doted line) of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**) in methanol. The liberated side products during the formation of intermediate steps are given in italics and the addition of new species for further process is given in []

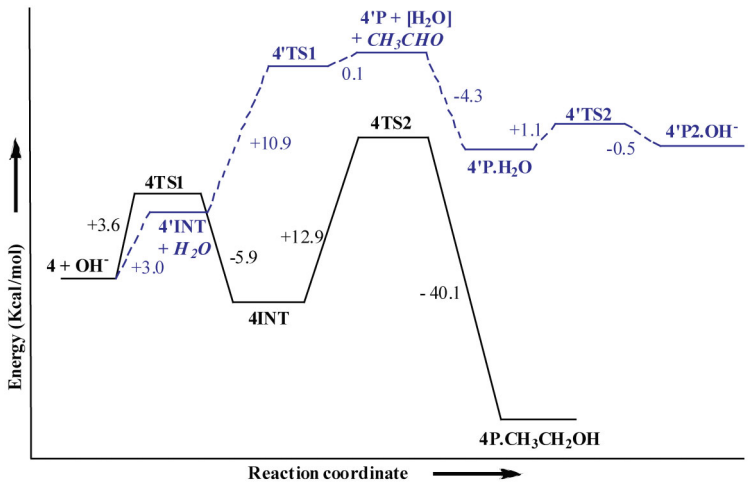


Figure 8. B3LYP/6–31 + G* calculated relative electronic energies in kcal/mol for $B_{AC}2$ hydrolysis (solid line) and retro-aldol process (doted line) of ethyl 3-hydroxybutyrate (**4**) in methanol. The liberated side products during the formation of intermediate steps are given in italics and the addition of new species for further process is given in []

CONCLUSIONS

In the present work, we have showed that the course of a reaction can be changed with appropriate substituent on the substrate. The reaction of ethyl *threo*-2-(1-adamantyl)-3-hydroxybutyrate (**1**) with a base leads toward the formation of retro-aldol as major products. However, under similar conditions, parent ethyl 3-hydroxybutyrate (**4**) formed hydrolysis product. The computed B3LYP/6–31 + G* results shed the light on the dramatic change in the course of reaction of **1** and **4** in alkaline medium. The large activation barrier for the hydrolysis of adamantyl-substituted esters **1** in methanol leads to **2** as the minor product. The bulky adamantyl group enhances the steric strain in the system and increases the barrier for the hydrolysis process, so the reaction pathway is redirected to energetically more feasible process of retro-aldol reaction. It is reasonable to presume that other groups of similar bulkiness can cause the same effect on the reaction pathway which is a presumption yet to be investigated. Retro-aldol process is kinetically and thermodynamically unfavored in the case of parent ester **4** with hydroxide ion. The role of solvent is profound to rationalize the experimentally observed results.

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