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Mechanisms of Lactone Hydrolysis in Neutral and Alkaline Conditions

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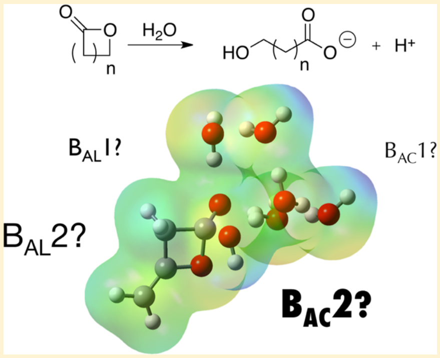
Supporting Information

ABSTRACT: The neutral and base-catalyzed hydrolysis of nine carboxylic acid esters was studied using a hybrid supermolecule-PCM approach including six explicit water molecules. The molecules studied included two linear esters, four *β*-lactones, two *γ*-lactones, and one *δ*-lactone: ethyl acetate and methyl formate, *β*-propiolactone, *β*-butyrolactone, *β*-isovalerolactone, diketene (4-methyleneoxetan-2-one), *γ*-butyrolactone, 2(5*H*)-furanone, and *δ*-valerolactone. DFT and *ab initio* methods were used to analyze the features of the various possible hydrolysis mechanisms. For all compounds, reasonable to very good qualitative and quantitative agreement with experimental work was found, and evidence is provided to support long-standing hypotheses regarding the role of solvent molecule as a base catalyst. In addition, novel evidence is presented for the existence of an elimination−addition mechanism in the basic hydrolysis of diketene. A parallel work addresses the acid-catalyzed hydrolysis of lactones.



1. INTRODUCTION

The hydrolysis of carboxylic acid esters is one of the best-studied reactions in chemistry. It is very often encountered both in the laboratory and in biological systems and is frequently used as a model reaction upon which general principles, such as free energy relationships, have been developed.

The hydrolysis of numerous ester substrates in a myriad of solvents and reaction conditions has been the subject of vast numbers of publications during a period extending over a century. An excellent review by Kirby summarizes most kinetic and mechanistic results obtained before the advent of computational chemistry methods.[1]

Nevertheless, in comparison with the wide availability of empirical works, relatively few computational approaches have addressed the hydrolysis of esters.[2−12] In the case of lactone hydrolysis, the disproportion is even larger, computational works being especially scarce.

Esters hydrolyze through a variety of mechanisms, depending on their substitution pattern and the reaction conditions. Ingold proposed a widely used classification of ester hydrolysis mechanisms that consists of a combination of three letters and a number:[13] the A or B initials if the mechanism is acid- or base-catalyzed, followed by either the $_{AC}$ or $_{AL}$ subindexes if acyl- or alkyl-oxygen cleavage takes place, and 1 and 2 for uni- and bimolecular mechanisms, respectively. The initial B is also used for the uncatalyzed attack of water on the unprotonated ester. Unimolecular $B_{AL}1$ and $B_{AC}1$ are both uncatalyzed, despite the B initial. The latter is the only mechanism never to have been observed.

Because of their ring-strained nature, lactones feature all the possible hydrolysis mechanisms within a few simple molecules and hence small structural variations can have large effects on their reactivity, especially in *β*-lactones.[14] This makes lactones ideal candidates for both the experimental and theoretical study of the mechanisms of ester hydrolysis.

The compounds chosen in this study (1) encompass four *β*-lactones (*β*-propiolactone, BPL; *β*-butyrolactone, BBL; *β*-isovalerolactone, BIVL; diketene, DIK), two *γ*-lactones (*γ*-butyrolactone, GBL; 2-furanone, FUR) and one *δ*-lactone (*δ*-valerolactone, DVL). For use as a reference for the lack of ring strain, and more importantly as a general model of linear ester reactivity, two linear esters whose hydrolysis has been widely studied were also included: the rather unreactive ethyl acetate (AcOEt) and the more labile methyl formate (COOMe).

In addition to the strictly mechanistic discussion, ester hydrolysis pathways are of relevance to chemical carcinogenesis, because of their relationship to DNA-alkylation mechanisms. Since the early studies on chemical carcinogenesis it has been clear that genotoxic lactones exert their effects through ring-opening reactions, in which covalent adducts with DNA are formed.[15,16]

In general, only those lactones that are reactive enough to undergo hydrolysis in neutral medium are also able to react with biological nucleophiles *in vivo*. In addition, whether the reactions occur through alkyl or acyl cleavage is of great importance, since the evidence suggests that only those

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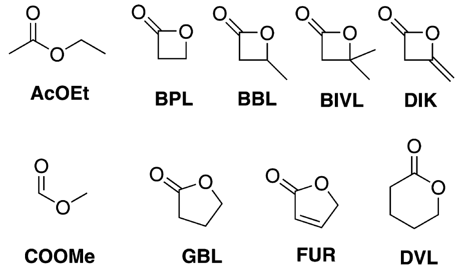
lactones that undergo alkyl-oxygen bond cleavage (β-lactones such as BPL, BBL) afford stable DNA adducts,[17] and are therefore effective carcinogens, whereas those that follow acyl cleavage mechanisms (β-lactone diketene) afford short-lived amide adducts, which are themselves rapidly hydrolyzed.[18]

Within the compounds studied (Scheme 1), COOMe (as is the case of formates in general) and DIK follow the $B_{AC}2$ mechanism, BPL and BBL are two of the rare instances of the neutral $B_{AL}2$ hydrolysis, and BIVL follows the $B_{AL}1$ mechanism. Linear unactivated alkyl esters (as AcOEt) and medium-sized or large lactones (as GBL, FUR and DVL) do not hydrolyze in neutral medium. Regarding the base-catalyzed mechanisms, $B_{AC}2$ is exceedingly common and all the compounds studied hydrolyze through this mechanism in alkaline medium. $B_{AL}2$ is very rare, to the point that its very existence is disputed.[19,20]

Scheme 1. Compounds Studied



Since water is both the solvent and one of the reactants, the role of water molecules in the solvation shell is of paramount importance, and thus the first solvation shell was modeled explicitly using a hybrid supermolecule-PCM approach. Up to six water molecules were included to study the specific role of solvent molecules.

2. METHODOLOGY

2.1. Experimental Study. Since no experimental data were available for the hydrolyisis of FUR, an experimental study was performed. See the electronic Supporting Information (SI) for the methodology and experimental results.

2.2. Computational Details. *2.2.1. Reaction Paths.* Geometries were optimized at the DFT B3LYP/6-31++G(d,p) level of theory, using the default PCM solvent model with default parameters followed by harmonic analysis of the structures (zero imaginary vibration modes for minima and one for transition states). This level of theory has been used for similar systems such the hydration reaction of the carbonyl group[12] and produces results within less than 1 kcal of the larger 6-311++G(2df,2p) basis set. Different correlation-exchange functionals were also found to produce equal or worse results.

For species attracting most interest (e.g., those corresponding to the transition states of the rate-limiting steps and the corresponding minima), optimizations were refined at the DFT/6-311++G(2df,pd) level and were also followed by single-point energy calculations at the MP2/6-31++G(d,p), MP4/6-31++G(d,p) and QCISD/6-31++G(d,p) levels of theory.

Thermochemical values were computed at 298 K using uncorrected DFT B3LYP/6-31++G(d,p) frequencies. Intrinsic Reaction Coordinate (IRC) paths were computed to link transition states with the corresponding reactants and products. Atomic Polar Tensor (APT) charges were computed when necessary. All calculations were performed using G09 on a Mountain workstation.

2.2.2. ΔH in Solution. Whereas PCM calculations include the contribution of solvation free energy to the total energy, and thus afford ΔG with appropriate statistical thermodynamics and solvation terms, enthalpy values as reported by the software in PCM calculations include the statistical thermodynamics enthalpic term plus the solvation free energy contribution. Therefore, unlike G_{PCM}, H_{PCM} needs to be corrected for the difference between solvation enthalpies and free energies ($T\Delta S_{solv} = \Delta H_{solv} - \Delta G_{solv}$).

As Pliego and Riveros have discussed,[21] one can estimate absolute solvation enthalpies (and entropies) for ionic species from cluster-continuum calculations ($\Delta H^{*}_{solv}(\text{ion})$), by combining the clustering enthalpy (or entropy) of the supermolecule, obtained through statistical mechanics ($\Delta H^{\circ}_{clust}(\text{supermol})$), the vaporization enthalpy (or entropy) of the solvent ($\Delta H_{vap}(\text{solvent})$) and the solvation enthalpy (or entropy) of the supermolecule $\Delta H^{*}_{solv}(\text{supermol})$ as shown in eqs 1 and 2 (the star and circle superscripts refer to 1 atm and 1 mol dm^{-3} standard states, respectively).

$$\Delta H^{*}_{solv}(\text{ion}) = \Delta H^{\circ}_{clust}(\text{supermol}) + n\Delta H_{vap}(\text{solvent}) + \Delta H^{*}_{solv}(\text{supermol}) \quad (1)$$

$$\Delta S^{*}_{solv}(\text{ion}) = \Delta S^{\circ}_{clust}(\text{supermol}) + n\Delta S_{vap}(\text{solvent}) + \Delta S^{*}_{solv}(\text{supermol}) \quad (2)$$

Of these three contributions, the third term is unavailable from PCM calculations, but it can be estimated according to the Born model from the PCM solvation free energy and the temperature dependence of the solvent relative permittivity, ε.[21]

$$\Delta H^{*}_{solv}(\text{supermol}) = \Delta G^{*}_{solv}(\text{supermol})\left(1 - \frac{T}{\varepsilon - 1}\frac{\partial \ln \varepsilon}{\partial T}\right) \quad (3)$$

$$\Delta S^{*}_{solv}(\text{supermol}) = -\Delta G^{*}_{solv}(\text{supermol})\left(\frac{1}{\varepsilon - 1}\frac{\partial \ln \varepsilon}{\partial T}\right) \quad (4)$$

It should be noted that when modeling reaction pathways, we are interested in variations of G, H and S along the path within solution

Scheme 2. (a)$B_{AC}1$, (b) $B_{AL}1$, (c) $B_{AL}2$ and (d) Simplified $B_{AC}2$ Mechanisms of Neutral Hydrolysis

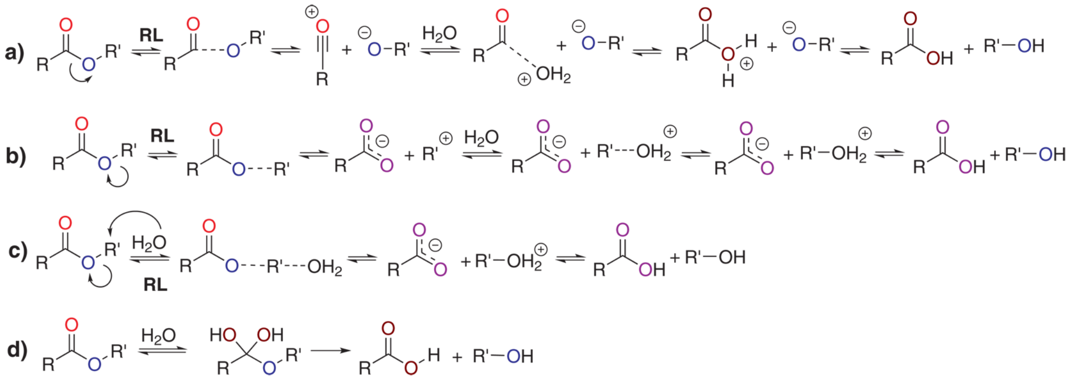


Table 1. Energy Barriers Calculated for the Neutral Hydrolysis of Lactones (B3LYP 6-31++G(d,p))

	$\Delta^{\ddagger}H$ (kJ mol^{-1})				$\Delta^{\ddagger}G$ (25 °C) (kJ mol^{-1})				
	TS_{BAL2}	TS_{BAL1}	TS_{BAC1}	TS_{BAC2}	TS_{BAL2}	TS_{BAL1}	TS_{BAC1}	TS_{BAC2}	lowest
COOMe	159.0	288.5	287.5	70.0	142.2	270.1	295.2	109.1	$B_{AC}2$
AcOEt	181.0	223.3	265.9	89.9	151.4	235.5	271.1	128.8	$B_{AC}2$
BPL	84.0	145.7	221.3	81.6	91.8	146.2	201.0	111.3	$B_{AL}2$
BBL	98.8	107.3	189.4	84.7	95.9	109.1	203.5	110.4	$B_{AL}2$
BIVL	N/A	75.0	239.9	88.6	N/A	79.7	226.0	118.7	$B_{AL}1$
DIK	N/A	139.5	158.3	57.2	N/A	148.1	152.5	90.9	$B_{AC}2$
GBL	144.2	230.4	198.3	100.3	138.8	215.1	216.6	134.4	$B_{AC}2$
FUR	181.9	236.0	210.0	115.5	166.1	212.5	227.2	147.	$B_{AC}28$
DVL	182.1	229.5	198.5	93.2	198.1	234.5	216.0	135.3	$B_{AC}2$

rather than absolute changes from gas-phase to solution, and thus only $\Delta\Delta H^{*}_{solv}$ and $\Delta\Delta S^{*}_{solv}$ along the path are required.

$$\Delta\Delta H^{*}_{solv}(\text{ion}) = \Delta\Delta H^{\circ}_{clust}(\text{supermol}) + \Delta\Delta H^{*}_{solv}(\text{supermol}) \quad (5)$$

$$\Delta\Delta S^{*}_{solv}(\text{ion}) = \Delta\Delta S^{\circ}_{clust}(\text{supermol}) + \Delta\Delta S^{*}_{solv}(\text{supermol}) \quad (6)$$

$\Delta\Delta G^{\circ}_{clust}$, $\Delta\Delta H^{\circ}_{clust}$ and $\Delta\Delta S^{\circ}_{clust}$ contributions are fully taken into account in supermolecule-PCM calculations through the statistical thermodynamics terms, and hence the only term we need to correct for is the difference $T\Delta\Delta S^{*}_{solv}(\text{supermol}) = \Delta\Delta H^{*}_{solv}(\text{supermol}) - \Delta\Delta G^{*}_{solv}(\text{supermol})$, which is unaccounted in PCM calculations. Activation enthalpies, ΔH, (eq 7) were thus computed using the thermal enthalpies at 298 K as reported by the software in PCM calculations and were corrected by adding the $T\Delta\Delta S^{*}_{solv}(\text{supermol})$ from eq 4. ΔG^{*}_{solv} values were estimated as the difference in single point energy between gas-phase and PCM calculations, using using the IEFPCM solvation model in the SMD parametrization.[22] We have used $(\partial \ln \varepsilon)/(\partial T) = -4.57 \times 10^{-3}$ and $\varepsilon = 78.4$ at 298 K.[23]

$$\Delta H = \Delta H_{PCM} + T\Delta\Delta S^{*}_{solv}(\text{supermol}) \quad (7)$$

3. RESULTS AND DISCUSSION

3.1. Neutral Hydrolysis. We modeled the reaction pathways for all four possible neutral hydrolysis mechanisms. Three of them ($B_{AC}1$, $B_{AL}1$ and $B_{AL}2$) are rather simple and take place in a single rate-limiting step (labeled **RL**), followed by rapid addition of water to carbocations (or elimination) and proton transfers. Scheme 2a−c shows the generally accepted reaction pathways for these three neutral hydrolysis mechanisms.[24]

The $B_{AC}2$ hydrolysis mechanism is more complex and occurs in two steps (Scheme 2d). In the first one, a water molecule attacks the carbonyl carbon in an addition reaction that yields a tetrahedral intermediate. This intermediate is unstable and decomposes in the second step.

Table 1 shows the activation parameters calculated for each of the compounds studied in the neutral hydrolysis mechanisms. Since the addition step in the $B_{AC}2$ mechanism precludes any further reaction, a high barrier blocks the entire pathway, and thus only this step was included in this comparison.

The calculated free energies suggest that β-lactones are the ones most susceptible to neutral hydrolysis: BPL (Figure 1) and BBL show very low barriers in the $B_{AL}2$ pathways; tertiary BIVL follows the $B_{AL}1$ pathway, and the $B_{AC}2$ addition transition state is the lowest energy path for DIK. Since formates are quite reactive, COOMe is also prone to neutral hydrolysis through the $B_{AC}2$ mechanism. The steps in the $B_{AC}2$ pathway following the nucleophilic attack are discussed below.

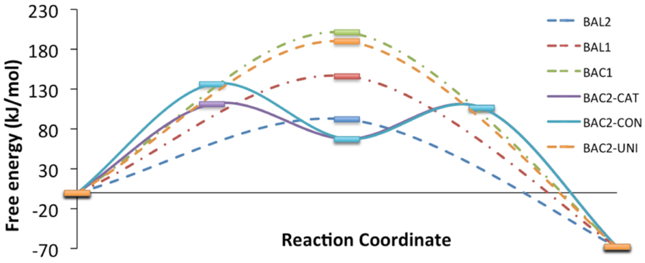


Figure 1. Variation in the free energy (25 °C) along the various reaction paths for the neutral hydrolysis of BPL.

The larger γ and δ-lactones and AcOEt show very high energy barriers for all mechanisms and would not be expected to hydrolyze in neutral aqueous solution.

The $B_{AC}1$ barriers are extremely high in energy for all the compounds, and each of them has more favored hydrolysis pathways. This is not unexpected, since this mechanism has never been observed experimentally.

3.1.1. The $B_{AL}2$ and $B_{AL}1$ Mechanisms. No transition states could be located for the $B_{AL}2$ hydrolysis of BIVL and DIK, since the steric hindrance in the case of BIVL and a combination of steric repulsion and the sp^2 hybridization of the alkyl-oxygen carbon in DIK blocked this mechanism. BPL and BBL do favor this pathway: the barrier was low, and also much lower than that for the $B_{AC}2$ standard hydrolysis mechanism. The rest of the esters showed very high barriers for bimolecular alkyl cleavage.

Owing to its particular structure, BIVL was the only one among the compounds studied to clearly favor the $B_{AL}1$ mechanism. Although the $B_{AL}1$ hydrolysis of linear esters affords a short-lived tertiary carbocation as a product (Scheme 2), in the located transition state for lactones, both alkyl- and acyl-oxygen cleavage take place almost simultaneously (Figure 2), and hence rather than hydrolysis a decarboxylation reaction can be said to take place. Since the reaction is concerted, the zwitterion does not develop fully. Nevertheless, C−O bond cleavage is much more advanced at the transition state geometry than C−C cleavage (bond lengths are 2.19 vs 1.60 Å) and a large partial positive charge concentrates in the alkyl carbon, even if it is not a fully developed cation (the Mulliken and APT atomic charges are 0.773 and 1.225, respectively).

These results are in excellent agreement with the early kinetic work of Liang and Bartlett, who reached a similar conclusion based on the evidence that (i) the reaction products are CO_2 and isobutene, (ii) BIVL is only decarboxylated in polar solvents such as water, which suggests a highly charged transition state; (iii) water does not participate in the reaction

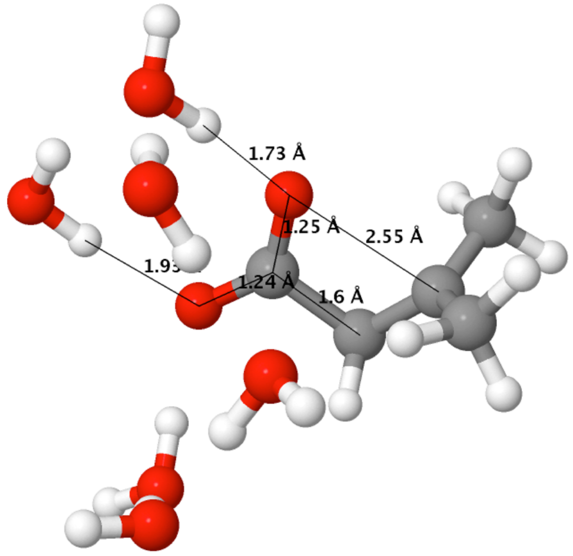


Figure 2. Structure of the transition state of BIVL in the $B_{AL}1$ mechanism.

directly; (iv) the transient cation cannot be trapped with powerful nucleophiles.[25]

IRC calculations suggested that the reaction products for all cases of $B_{AL}1$ hydrolysis in lactones are carbon dioxide and the elimination product, although these products have only been observed experimentally in the decomposition of BIVL since $B_{AL}1$ is nonexistent for the other lactones. The $B_{AL}1$ hydrolysis of linear esters AcOEt or COOMe is not decarboxylative and would yield the secondary carbocation from a σ-rearrangement.

Close inspection of the reported values shows that for both $B_{AL}2$ and $B_{AL}1$ the activation enthalpies and free energies are very similar, which implies that the activation entropies are null, or in some cases slightly positive. This is the expected result for an unimolecular ring-opening reaction. However, in the case of the bimolecular reaction, a negative value would be expected. This suggests that the entropic contributions are somewhat overestimated in the $B_{AL}2$ mechanism.

3.1.2. The $B_{AC}2$ Mechanism.

Among the compounds studied, only DIK and COOMe have low barriers for the $B_{AC}2$ addition and lack an alternative preferred hydrolysis mechanism. However, the $B_{AC}2$ mechanism is the most common pathway of neutral hydroylsis for activated linear esters, and both its alkaline and acid counterparts ($B_{AC}2$ and $A_{AC}2$) are the usual mechanisms of catalyzed hydrolysis (see below). Thus, it is interesting to study the full two-step reaction pathway in detail.

The calculated differences in free energy and enthalpy for the full mechanism are reported in Table 2. Since several different transition states were found for the addition step (catalyzed and concerted, see below), these were labeled $TS_{AD}CAT$ and $TS_{AD}CON$; we labeled the tetrahedral intermediate DIOL, and the cleavage transition state TS_{CLV}.

Also, a fully concerted single-step mechanism exists (TS_{UNI}), in which the leaving group is expelled synchronically with the attack of water on the carbonyl group, thus bypassing the intermediate.

Reactant Complex. Finding global minimum structures for solvated structures using a cluster-continuum approach is always a complex task, since an exceedingly large number of possible solvent configuration exists. The ability of water molecules to form hydrogen bonds with each other, and also with the solute, further complicates this task, since a unbalanced description of solvent−solvent interactions along the reaction path may result in spuriously (de)stabilized stationary points.

Since the reaction paths studied in this work are very different in nature, we have compared the reactant geometries connected to each transition state by means of IRC calculations and also tested additional solvent arrangements by manually redistributing the hydrogen-bond patterns in the minima from IRC. From these we have chosen the one showing the lowest free energy (Figure 3). Whereas the free energy differences among the minima considered were small (5 kJ mol^{-1}), this choice has some effect in the absolute $\Delta^{\ddagger}G$ predictions (see below), but a very limited one in the mechanistic diagnosis.

Addition. The addition reaction in the neutral $B_{AC}2$ mechanism pathway has been proposed to occur not by direct addition (Scheme 3a) but rather in a base-catalyzed fashion, which affords a negatively charged intermediate and a hydronium ion (Scheme 3c - $TS_{AD}CAT$), which then undergo proton transfer to afford a neutral intermediate.

Some authors have suggested that proton transfers are concerted with the attack rather than taking place sequentially, and thus that no transient ions are formed (Scheme 3b - $TS_{AD}CON$). Several theoretical pathways have been described, which involve different numbers of water molecules mediating the simultaneous proton transfers. The availability of this reaction mechanism has been attributed to the lack of sufficient explicit solvent molecules in the modeling of the system, and when a large explicit solvation shell is present, it reverts to catalyzed addition.[12]

Table 2. Energy Barriers Calculated for the Neutral $B_{AC}2$ Hydrolysis of the Esters Studied at the B3LYP/6-31++G(d,p) Level of Theory

	$\Delta^{\ddagger}H$ (kJ mol^{-1})					$\Delta^{\ddagger}G$ (25 °C) (kJ mol^{-1})				
	$TS_{AD}CAT$	$TS_{AD}CON$	DIOL	TS_{CLV}	TS_{UNI}	$TS_{AD}CAT$	$TS_{AD}CON$	DIOL	TS_{CLV}	TS_{UNI}
COOMe	70.0	108.1	53.1	62.9	145.3	109.1	130.6	71.3	99.2	162.4
AcOEt	89.9	125.1	52.8	88.4	195.9	128.8	138.4	80.5	129.0	221.3
BPL	81.6	123.4	79.1	68.3	170.2	111.3	136.3	67.4	106.4	189.6
BBL	84.7	129.5	82.1	66.1	180.5	110.4	140.6	73.3	100.8	190.9
BIVL	90.7	126.3	84.3	73.3	181.4	118.7	147.5	78.3	107.6	191.1
DIK	57.2	87.5	51.6	41.5	124.9	90.9	106.1	49.9	79.1	123.0
GBL	100.3	134.0	71.2	86.6	190.9	134.4	143.5	84.9	126.4	207.2
FUR	111.5	144.6	85.2	101.1	204.6	147.8	150.9	92.4	131.8	214.2
DVL	93.2	147.5	72.9	76.4	185.0	135.3	154.9	83.3	117.4	211.9

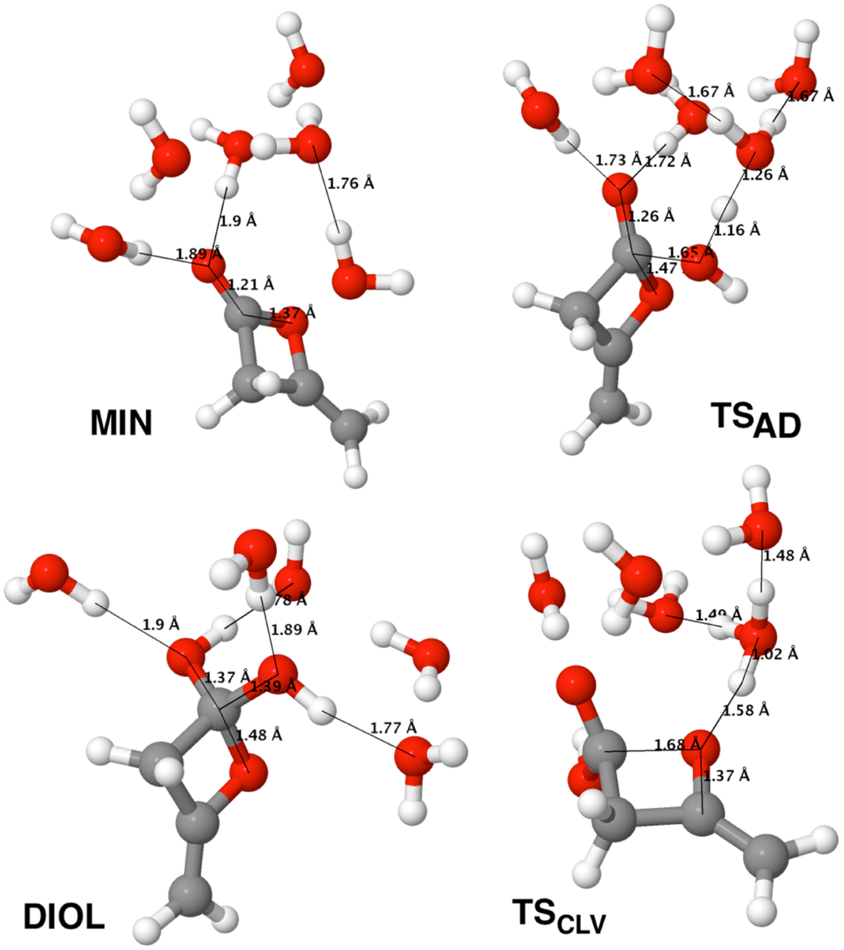
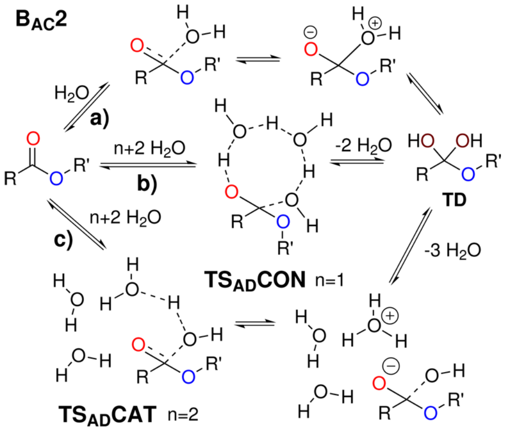


Figure 3. $B_{AC}2$ minima and transition states for DIK.

Scheme 3. Addition Reaction in the $B_{AC}2$ Mechanisms of Neutral Hydrolysis



All addition pathways may also involve a variable number of solvent molecules beyond those strictly involved as reactants (n, in Scheme 3), which help stabilize the transient charges through hydrogen bonds.

Gunaydin and Houk[10] have proposed an addition mechanism catalyzed simultaneously by a hydroxide and a hydronium ion. These would be formed in the autoionization of water, which would be the limiting step at $\Delta^{\ddagger}G = 99$ kJ mol^{-1}. Whereas such a mechanism can hardly explain the observed dependence of the hydrolysis rate on the nature of the ester, its study in a cluster-continuum approach would require significantly more explicit water molecules and is beyond the reach of this work. Da Silva et al. have recently reported a detailed study of this mechanism in the neutral hydrolysis of activated and non-activated esters.[26]

We have located several transition states for the addition step (Figure 4 reports the ones found for AcOEt), all of which feature increasingly larger cyclic arrays of hydrogen-bonded water molecules connecting the nucleophilic water molecule and the carbonyl oxygen (alkyl oxygen in the case of TS_{UNI}).

The transition state geometries can be characterized according to the number of water molecules within the cycle: TS_{UNI} and $TS_{AD}CON_b$ have two, $TS_{AD}CON$ and $TS_{AD}CAT_b$ have three ($n = 1$) and $TS_{AD}CAT$ has four ($n = 2$), as shown in Figure 4.

TS_{UNI} corresponds to the single-step hydrolysis reaction, in which nucleophilic attack, acyl cleavage and hydrogen transfer from water to alkyl oxygen all occur simultaneously, and has the highest free energy in the set (221 kJ mol^{-1} for AcOEt). $TS_{AD}CON_b$ and $TS_{AD}CON$ correspond to concerted pathways, as evidenced by the oxygen−hydrogen bond distances in the cyclic array, and have intermediate free energies (175 and 139 kJ mol^{-1}, respectively, for AcOEt). $TS_{AD}CAT_b$ and $TS_{AD}CAT$ correspond to a base-catalyzed mechanisms with water acting as a catalyst, since only one proton transfer takes place simultaneously within the solvation shell. The catalyzed pathways show the lowest free energy (136 and 129 kJ mol^{-1}

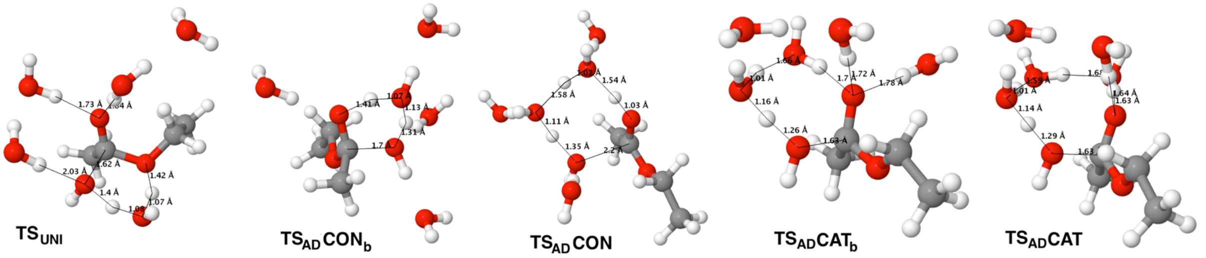


Figure 4. B$_{\mathrm{AC}}$2 addition transition states for AcOEt.

for TS$_{\mathrm{AD}}$CAT$_{\mathrm{b}}$ and TS$_{\mathrm{AD}}$CAT, respectively), which suggests that this is indeed the preferred mechanism.

In order to confirm that the stepwise nature of the TS$_{\mathrm{AD}}$CAT mechanism is not a consequence of having all the water molecules within the cyclic array, we have extended the calculations to nine and eleven explicit water molecules and still the proton transfers are found to be stepwise after the initial catalyzed addition.

Our calculations agree with those of Wang and Cao,[12] who performed a detailed study of the base-catalyzed addition of water onto linear carbonyl compounds. The present results suggest that the base-catalyzed multistep mechanism also takes place in lactones (Scheme 3c). In this mechanism, the base-catalyzed water-ester encounter is the limiting step (TS$_{\mathrm{AD}}$CAT); subsequent proton transfers within the solvation shell are, as shown in the aforementioned work, "almost isoenergetic" and non rate-limiting and finally lead to a stabilized neutral gem-diol intermediate.

We have identified intermediate local minima and transition states that lie along the stepwise proton transfer pathway from the hydronium cation to the acyl oxygen anion, and thus connect the initial addition product with the neutral tetrahedral intermediate (DIOL) (see SI). Excluding the β-lactones, the ring strain seems be of little importance in the addition step, the effect being mainly entropic.

Intermediate. In general, the tetrahedral intermediates were found to be quite high in energy, in keeping with the elusive nature of tetrahedral carbonyl addition intermediates, which have seldom been isolated.[27] The more reactive COOMe and β-lactones showed more stable intermediates, whereas in the case of the larger lactones and AcOEt the diol was higher in energy. Within β-lactones, the order of free energy was DIK < BPL < BBL < BIVL, because of the electron-donating nature of the methyl substituents.

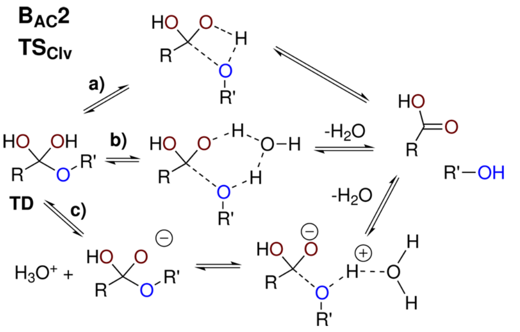
Interestingly, the tetrahedral intermediates of β-lactones were entropically favored, unlike those of the other compounds studied. This can be understood in terms of the increased flexibility of a sp^3 hybridized carbon within the rigid tetragonal structure of β-lactones.

The tetrahedral intermediate of DIK is exceptionally stable when compared to other β-lactones (also in the base- and acid-catalyzed mechanisms, see below), since it combines favorable enthalpic and thermoentropic contributions. This is probably due to the effect of the methylene group: the square structure of β-lactones enforces 90° angles, and DIK has two sp^2 carbons, whose preferred geometry is 120°. Transition of the sp^2 carbonyl carbon to sp^3 hybridization is thus especially favored in DIK.

The transition states for the reverse addition reaction were around 40−50 kJ mol^{-1} higher than the intermediates, and the breakdown reactions had similar or even lower barriers (see below). This suggests that the intermediates are short-lived, with predicted half-lives well below microseconds.

Cleavage. The ester breakdown step involves both cleavage of the ester bond and transfer of a proton from the acyl to the alkyl oxygen as shown in Scheme 2. We have located several transition states for this step (Scheme 4): (a) Cleavage of the acyl-oxygen bond and direct concerted proton transfer from the carbonyl oxygen to the leaving group; (b) a water-assisted concerted mechanism, symmetrical to the concerted addition mechanism, in which water-assisted proton transfer and bond cleavage occur simultaneously; and (c) acid-catalyzed cleavage, a transition state symmetrical to the favored addition reaction; after the dissociation of the intermediate in a fast proton transfer to the surrounding solvation shell, the hydronium ion formed catalyzes the cleavage step.

Scheme 4. Acyl Oxygen Bond Cleavage Reaction in B$_{\mathrm{AC}}$2 Mechanisms of Neutral Hydrolysis



Among the breakdown pathways, the acid-catalyzed pathway—symmetrical to the favored addition—was the most favored (Scheme 4c). Since the addition step was base-catalyzed by a water molecule, the symmetrical cleavage was catalyzed by a hydronium ion, which arises from the dissociation of the intermediate. This behavior has been observed experimentally in the hydrolysis of activated esters with poor leaving groups, whose rate-limiting breakdown is catalyzed in acidic media.[1] Thus, the results reported in Table 2 correspond to the hydronium-catalyzed cleavage of the dissociated intermediate.

The reasons for the symmetry between the addition and cleavage steps lie in the similarity between the nucleophile and the leaving group. Notwithstanding ring strain, the leaving groups in all the compounds are (mostly primary) alkyl alcohols, which behave similarly to water in terms of their nucleophilicity and acid−base behavior.

The breakdown transition states were 25−50 kJ mol^{-1} higher in free energy than the tetrahedral intermediates, and ring strain seems to play a minor role in this energy difference. For AcOEt, the energy barriers for the addition and cleavage step were very

Table 3. Comparison of the Experimental and Theoretical Activation Parameters for the Neutral Hydrolysis of the Compounds Studied at the B3LYP/6-31++G(d,p) Level of Theory

	$\Delta^{‡}H°$ (kJ mol^{-1})		$\Delta^{‡}S°$ (J mol^{-1}K^{-1})		$\Delta^{‡}G°$ (25 °C)(kJ mol^{-1})		mechanism	
	exp	calcd	exp	calcd	exp	calcd	exp	calcd
COOMe[28]	76 ± 2	70	−115 ± 7	−131	110	109	$B_{AC}2$	$B_{AC}2$
AcOEt[1]		90		−131	~128	129	$B_{AC}2$	$B_{AC}2$
BPL[29]	83 ± 2	84	−46 ± 8	−27	97	92	$B_{AL}2$	$B_{AL}2$
BBL[29]	88 ± 3	99	−44 ± 9	+10	101	96	$B_{AL}2$	$B_{AL}2$
BIVL[25]		75		−17	~87	80	$B_{AL}1$	$B_{AL}1$
DIK[30]	56 ± 2	57	−126 ± 6	−114	94	91	$B_{AC}2$	$B_{AC}2$

similar, which is in keeping with the usual assumption that for unactivated esters neither the addition nor the breakdown step is, by itself, rate-limiting in the $B_{AC}2$ mechanism.

Concerted Reaction. Regarding the concerted mechanism found (TS_{UNI}), the energy barrier was higher than that of the addition-breakdown mechanism, due mostly to an enthalpic effect (Table 2).

3.1.3. Comparison with Empirical Data. Table 3 compares the calculated and experimental activation parameters (when available) of the neutral hydrolysis of the compounds studied. Although the activation parameters for the hydrolysis/decomposition of BIVL are not known, the neutral reaction rate constant is 2.7×10^{-4} min^{-1} (298 K), which allows its $\Delta^{‡}G°$ to be estimated. The case of AcOEt is similar, since the reaction is very slow (half-life is ~75 years), and hence the $\Delta^{‡}G°$ value is a rough estimation.

Favored Pathway. The theoretical free energy differences are in excellent qualitative agreement with the experimental observations and the pathways predicted to be favored are in agreement with those deduced from experimental work.

BPL and BBL, which are indeed the two only known examples of neutral $B_{AL}2$ hydrolysis, are correctly predicted to follow the bimolecular alkyl cleavage mechanism. The least energetic pathways for COOMe and DIK are $B_{AC}2$, whereas the only tertiary alkyl lactone studied, BIVL, favors the $B_{AL}1$ mechanism, in keeping with the experimental work reported in the literature. In the cases of those esters that do not to hydrolyze to a significant extent in neutral medium (GBL, FUR, DVL and AcOEt) very high theoretical energy barriers were found for all pathways.

The reaction products found in the $B_{AL}1$ mechanism by IRC calculations are consistent with the experimental observation that the major decomposition products of BIVL in water are CO_2 and isobutene. In these experiments, the corresponding addition product is minor, even in the presence of strong nucleophiles that should be able to scavenge the putative carbocation.[25]

Accuracy. The activation parameters are generally in good accordance with the empirical results (see Table 3). Errors for those compounds favoring the $B_{AC}2$ mechanism (COOMe, AcOEt and DIK) are of only a few kJ mol^{-1} and the activation free energies of BPL and BBL are understimated by about 5 kJ mol^{-1}. The mean unsigned error (mue) is 3.9 kJ mol^{-1}, whereas the mean deviation is −3.6 kJ mol^{-1}, indicative of systematic underestimation.

A possible cause for the larger deviation from experimental results in the $B_{AL}2$ mechanism could be the decreased rigidity of the hydration shell. Since the atoms on which partial charge develops (the attacking water molecule and the carboxylate leaving group) are quite distant from each other, the two solvation subshells are less tightly connected than in the reactants. The loss of intersolvent hydrogen bonds would be expected to produce an increase in the activation enthalpy and also an increase in activation entropy, since the molecules are less tightly bound and hence freer.

Corrections have been carried out to take into account the role of solvation entropies of the supermolecule and improve PCM estimations of ΔH by adding a thermoentropic contribution $T\Delta\Delta S^{*}_{\mathrm{solv}}$(supermol). Since most entropic effects arise within the first solvation shell ($\Delta\Delta S°_{\mathrm{clust}}$(supermol)) and are well modeled with the statistical thermodynamic terms from the quantum chemistry calculations, $\Delta S^{*}_{\mathrm{solv}}$(supermol) is fairly constant for all reactant and transition state assemblies, and the thermoentropic corrections to ΔH are very small with values within ±2 kJ mol^{-1} (see Supporting Information).

Qualitatively, the trends in the activation entropies are fairly correct: the $B_{AC}2$ additions show more negative $\Delta^{‡}S$ than the $B_{AL}2$ reactions. This is coherent with the fact that in the $B_{AC}2$ mechanism bond cleavage is delayed, whereas in $B_{AL}2$ the positive contribution of bond-breaking to entropy is simultaneous to the nucleophilic attack. Experimentally, the neutral hydrolysis of linear alkyl haloesters is enthalpy-controlled, and the activation entropies for most linear compounds are within a narrow range ($-\Delta^{‡}S° \approx 160$ J mol^{-1} K^{-1}), in good agreement with the values of around −130 J mol^{-1} K^{-1} that we found for the linear esters and the larger lactones.

As regards the activation entropies for the $B_{AL}2$ mechanism, the experimental values for the few known cases of bimolecular alkyl cleavage are negative and low: ~−50 J mol^{-1} K^{-1}, as shown in Table 3. This variation possibly derives from the aforementioned error due to the solvation shell and could probably be improved if several more explicit water molecules were introduced into the cluster.

We also computed the solvent kinetic isotope effect (SKIE) when hydrogen atoms in the water cluster were substituted by heavier deuterium isotopes. For the $B_{AC}2$ mechanism, normal SKIE ($k_H > k_D$) is reported in the literature with values of $k_H/k_D \approx 2$ for the rather labile ethyl dichloro- and difluoroacetate,[31] 2,2-dichlorovinyl chloroacetate,[32] or methyl-2,6-dicarboxybenzoates.[33] Our results afforded a k_H/k_D of 4.7 for COOMe and of 4.0 for DIK, in semiquantitative agreement with the experimental values.

Other Methods. The energy barriers calculated at other levels of theory are reported in the Supporting Information file. Use of the B3LYP functional with the larger basis set 6-311++G(2df,2dp) did not afford significant improvement: the error in $\Delta^{‡}G°$ was increased (mue is 11 kJ mol^{-1}), the results being overestimated (the average deviation is +8 kJ mol^{-1}). Whereas the activation energies at the DFT-B3LYP level were in reasonably good agreement with the experimental values, the results at the post-HF levels of theory used were strongly overestimated.

Scheme 5. $B_{AL}2$ Mechanism of Alkaline Hydrolysis and the $B_{AC}2$ Addition Step

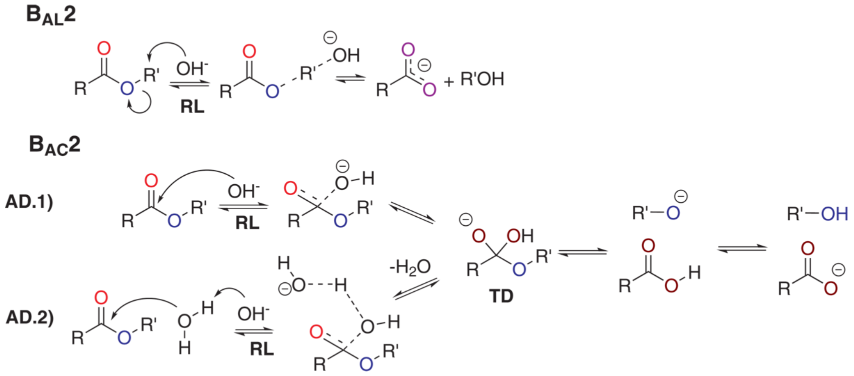


Table 4. Energy Barriers Calculated for the Alkaline Hydrolysis of Some Lactones

	$\Delta^{\ddagger}H$ (kJ mol^{-1})				$\Delta^{\ddagger}G$ (25 °C) (kJ mol^{-1})			
		$B_{AC}2$				$B_{AC}2$		
	$B_{AL}2$	TS_{AD}	TD	TS_{clv}	$B_{AL}2$	TS_{AD}	TD	TS_{clv}
COOMe	135.6	36.1	27.1	27.9	132.5	67.2	46.6	59.2
AcOEt	160.1	51.6	47.8	55.2	144.6	85.9	72.9	89.1
BPL	88.0	47.3	24.3	29.2	88.1	78.8	49.8	56.9
BBL	102.1	50.0	30.1	30.8	102.1	81.6	54.0	61.6
BIVL	138.4	56.4	33.8	32.8	141.4	87.7	58.7	63.6
DIK	N/A	28.1	−14.1	−17.0	N/A	60.8	10.5	20.3
GBL	135.5	57.0	39.2	41.9	130.9	86.8	60.1	73.2
FUR	140.1	64.6	52.3	55.8	133.5	95.3	74.1	89.7
DVL	150.8	45.8	34.7	31.1	141.8	80.4	51.7	68.2

These deviations can be understood in terms of the loose hydrogen bonds that connect the water molecules with one another and with the esters. The energy and the bond distance of these weak bonds are highly dependent on the method used, and hence geometries frozen at DFT-B3LYP are quite distant from the equilibrium geometries at the MP-n or QCISD levels of theory in terms of both energy and distance. Deviations of this kind and size have been reported in very similar systems.[12]

3.2. Alkaline Hydrolysis.

Since the unimolecular $B_{AC}1$ and $B_{AL}1$ mechanisms are uncatalyzed, only two base-catalyzed mechanisms of ester hydrolysis exist (Scheme 5): the almost universal $B_{AC}2$ and the exceedingly rare $B_{AL}2$, of which very few instances are known,[20] the clearest one being 2,4,6-tritert-butylbenzoate.[19] In addition, well-known examples of $B_{AL}2$ methanolysis of methyl esters in methanolic methoxide exist.[34]

The theoretical $B_{AL}2$ and $B_{AC}2$ energy barriers for the compounds studied are summarized in Table 4 and show that acyl-oxygen cleavage is favored over the alkyl-oxygen cleavage in all cases, including the β-lactones, which are known to react in neutral medium with water and alcohols with alkyl-oxygen cleavage. For BPL, the less hindered β-lactone and the one most prone to alkyl cleavage, the $B_{AL}2$ transition state is only 10 kJ mol^{-1} higher in energy than the $B_{AC}2$ addition, which would mean about 1% of alkyl-cleavage products in the basic hydrolysis of BPL. Such a minor contribution could have gone undetected in the experiments, from which it was concluded that BPL undergoes acyl-oxygen cleavage.

3.2.1. The $B_{AC}2$ Mechanism.

The $B_{AC}2$ mechanism has been proposed to occur through several pathways, depending on the nature of the leaving group: concerted or featuring a tetrahedral intermediate. There is also doubt about whether the hydroxide ion acts as a nucleophile or as a base catalyst in the addition step. In this work, a two-step pathway was found for all compounds. Figure 5 shows the equilibrium geometries for the reactant complex, the addition transition state, the intermediate, and the cleavage transition state for GBL.

3.2.2. Reactant Complex.

Finding global minimum structures for solvated systems using a cluster-continuum approach is a challenging task, especially in the case of ions. Since all the molecules under study are known to hydrolyze via the $B_{AC}2$ mechanism, we have used IRC calculations starting from the $B_{AC}2$ addition encounter complex to locate the reactant complex which was then chosen as free energy minimum. The hydrogen-bond pattern was also manipulated in search of other possible minima, but none were found to be lower in energy.

Addition. Some authors have proposed that the hydroxide-catalyzed hydrolysis of esters does not involve the attack of the hydroxide ion on the carbonyl (Scheme 5AD.1), but rather that the hydroxide catalyzes the addition of neutral water (Scheme 5AD.2).[35−37] However, this mechanism involving the hydroxide-catalyzed addition of neutral water has only been observed in computational studies that included very few explicit water molecules.[35−37] Thus, the limited number of hydrogen bonds may have resulted in a poorly solvated negative charge, and hence in an unrealistic stabilization of the proton-transfer mechanism.

In the present work, direct nucleophilic attacks (Scheme 5AD.1) were observed for all of the molecules studied. In addition, transition states were exhaustively sought using initial guesses featuring hydroxide acting as a general base catalyst. These initial geometries systematically converged to the transition state corresponding to the direct nucleophilic addition of the anion.

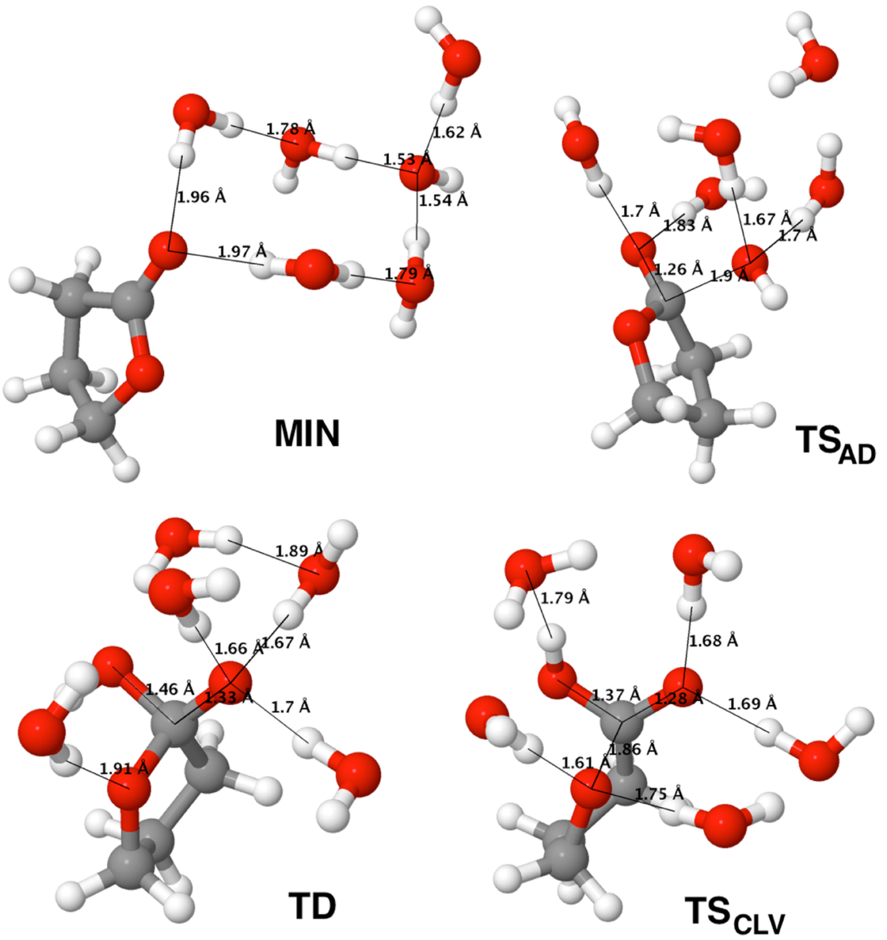


Figure 5. Structure of the addition and cleavage transition states of GBL in the alkaline $B_{AC}2$ mechanism.

The structure of the addition transition states showed two water molecules hydrogen-bonded to the nucleophile, and two solvating the incipient charge in the carbonyl group; the fifth one was bound to those solvating the hydroxyde ion.

The high reactivity of COOMe and DVL is due to steric factors: COOMe lacks acyl and alkyl substituents, and thus the addition of the hydroxide is unhindered. As regards DVL, the chair conformation and the fact that the hydrogen atom facing hydroxide is in equatorial position favor the attack.

Interestingly, the double bond in FUR has a significant effect on the addition barrier with respect to GBL, about 8 kJ mol^{-1} on $\Delta^{\ddagger}G$ (in experiments, FUR reacts about hundred-fold slower than GBL). This effect is a consequence of the ring geometry, since the alkaline hydrolysis rate constants of their open-chain counterparts (ethyl propanoate and ethyl propenoate) are only 20% different (less than 0.5 kJ mol^{-1} in $\Delta^{\ddagger}G$).

Intermediate. The intermediates lay quite high in energy, with free energies around 40−50 kJ mol^{-1} above those of the reactants, and thus their equilibrium ratio with respect to the reactants would be around 10^{-7}−10^{-10} to 1. A single exception exists: the tetrahedral intermediate of DIK was found to be exceptionally stable, possibly for the reasons given in the discussion of the neutral reaction. Within the β-lactones, the order of free energy of the intermediates was DIK < BPL < BBL < BIVL, as in the addition reaction, because of the electron-donating nature of the methyl substituents.

The transition states for the reverse addition reaction were around 20 kJ mol^{-1} higher than the intermediates, and the breakdown reactions had similar or even lower barriers (see below), in keeping with the very short life of these intermediates.

Breakdown. In close analogy to the transition states found for the neutral $B_{AC}2$ hydrolysis, several types of transition states were found for the cleavage step, which, as before, included acyl-bond cleavage and a proton transfer from the acyl to the alkyl oxygen. One-step cleavage pathways were observed, which corresponded to the breakdown of the intermediate and concerted proton transfer, either direct or mediated by a water molecule (see Table S17 in Supporting Information for detailed energies and structures). Two-step breakdown reactions were also observed, in which the cleavage and the proton transfer occurred sequentially. Two possibilities were found, the symmetrical counterpart of the addition reaction, with the alkoxide (instead of hydroxide) as a leaving group (or nucleophile in the reverse reaction), and a cleavage reaction with water acting as an acid catalyst, which yielded hydroxide and the hydroxyacid as products and would be the symmetrical counterpart of the unobserved hydroxide-catalyzed addition of water.

The two-step cleavage mechanisms were found to be favored for all compounds over concerted pathways. Since they afforded the alkoxide and the undissociated neutral carboxylic acid, subsequent fast proton transfers must occur before the final products are formed. Whereas β-lactones showed largely similar barriers for catalyzed and uncatalyzed cleavage, larger lactones and linear esters clearly favor the noncatalyzed path, which is symmetrical to the only observed addition step. This pathway was preferred over the acid-catalyzed alternatives because the negative charge rested mostly on the unprotonated acyl oxygen (the APT atomic charges are −1.56 and −1.20 for the acyl and alkyl oxygen atoms, respectively, in the alkaline tetrahedral intermediate, compared to −1.15 and −1.10 for the neutral diol), and thus the basicity of the alkyl oxygen is not much increased, nor its susceptibility to acid catalysis. Thus, water is too poor an acid catalyst to assist the reaction, except in the case of the highly strained *β*-lactone intermediates.

The lowest breakdown transition states (reported in Table 4) were about ∼15 kJ mol^{-1} higher in free energy than the tetrahedral intermediates for the less strained compounds and between 5 and 10 kJ mol^{-1} in the case of lactones. For the least reactive species, AcOEt, the breakdown reaction had a similar activation free energy to that of the addition step, which suggests that the cleavage step is not rapid enough to be neglected, as also occurred in the neutral $B_{AC}2$ cleavage. In contrast, COOMe and lactones showed much lower energy barriers for their cleavage reactions, and the addition step can be considered to be fully rate-limiting. Thus, ethoxide in acetyl acetate can be seen as a worse leaving group than methoxide in methyl formate.

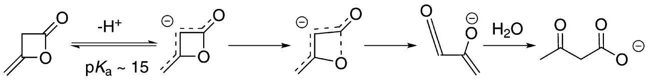
Activation enthalpy for the alkaline $B_{AC}2$ cleavage reaction (with the respective reactant, the tetrahedral intermediate, as a reference) is very low, and even negative in some cases, as is also the case with the breakdown of the tetrahedral intermediate in the neutral $B_{AC}2$ hydrolysis of the *β*-lactones and GBL (Table 2). This, together with the activation free energies discussed above, implies that breakdown activation entropies are of the order of −50 J K^{-1} mol^{-1} with respect to the intermediate. This negative value is rather large for what is essentially a unimolecular cleavage reaction, but is well within the range of values we have encountered in the study of $B_{AC}1$ and $B_{AL}1$ unimolecular neutral hydrolysis (see above). If parameters were to be calculated with respect to the initial reactant complex, strikingly large negative activation entropies around −150 J K^{-1} mol^{-1} would be obtained. However, these are mostly due to the large endoentropic effect of going from the reactant cluster to tetrahedral intermediate.

3.2.3. A Rare Case of Elimination−Addition Hydrolysis: Diketene. Whereas the theoretical and experimental activation free energies for the $B_{AC}2$ hydrolysis of DIK are in reasonable agreement, the calculated activation enthalpy for diketene is very low when compared to any other ester, especially the *β*-lactones, and also very different from the experimental values (Table 5).

The *α* hydrogen in diketene is known to be highly acidic, with an experimental pK_a value of 15, a result that has also been replicated theoretically.[38] In the experimental study of the alkaline hydrolysis of DIK, it was assumed that the dissociated form was unreactive as regards hydrolysis and constituted a kinetic dead alley.[30] However, the strong deviation between the experimental and theoretical activation enthalpies, within a series of compounds with reasonably good agreement, motivated us to search for an additional parallel reaction: an elimination-addition pathway (Scheme 6).

This reaction has been observed in the hydrolysis of esters[39−41] and amides[14] carrying very labile *α* hydrogens. Since the addition−elimination ($B_{AC}2$) and the elimination-addition pathways are kinetically indistinguishable, the preference for one or the other must be based on additional evidence, such as SKIE[42] or substitution of the labile H atoms by other side groups. Experimental evidence such as SKIE or Brönsted *β* parameter suggests that the rare elimination-addition mechanism does not to take place in the case of lactones such as the very acidic 5-nitrocoumaran-2-one[42] or 3-phenyl-2-coumaranones,[43] which follow the more common $B_{AC}2$ pathway. However, diketene is intrinsically more strained than the five-membered cycle in coumaranones and could perhaps react through this mechanism. The equilibrium geometry for the corresponding transition state is shown in Figure 6.

Scheme 6. Elimination−Addition Hydrolysis Mechanism of DIK



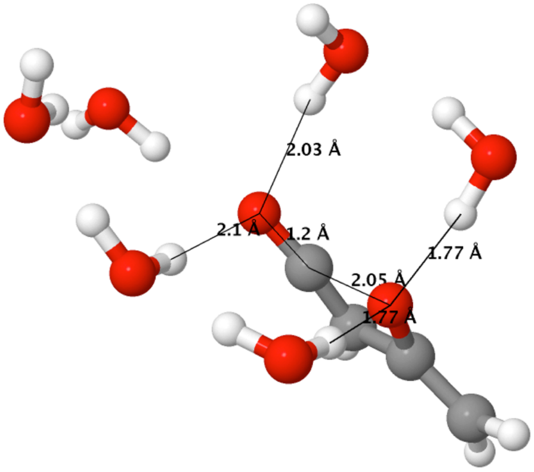


Figure 6. Transition state for the unimolecular ring-opening reaction of dissociated DIK.

The theoretical barrier for the unimolecular acyl cleavage of dissociated diketene was $\Delta^{\ddagger}H° = 40.3$ kJ mol^{-1} and $\Delta^{\ddagger}G° = 61.6$ kJ mol^{-1}, with respect to the lactone+OH^-+$5H_2O$ cluster. The higher activation enthalpy and entropy are in keeping with a unimolecular reaction.

The addition−elimination and the elimination−addition pathways have very similar activation free energies (see Table 4), and thus the reaction could be expected to proceed through a mixture of both, in which case the measured rate coefficient and the experimental activation parameters would correspond to a combination of the two processes.

3.2.4. Comparison with the Experimental Data. The experimental activation parameters for the alkaline hydrolysis reaction of the compounds studied are given in Table 5.

Preferred Pathway. The results are in good qualitative agreement with the experimental values: all molecules clearly favor the $B_{AC}2$ mechanism over the alkyl alternative.

Owing to the symmetry of the hydroxide nucleophile and the alkoxide leaving group, it has been proposed that neither the addition nor the breakdown reactions is fully rate-limiting except for esters with very good leaving groups, for which the addition is indeed a kinetic bottleneck. This is in excellent agreement with our results: as ring-strain increases, so does the difference between the addition and cleavage activation free energies. The obvious example are the *β*-lactones, whose high

Table 5. Experimental Activation Parameters for the Alkaline Hydrolysis of Some Lactones in Water

	$\Delta^{\ddagger}H^{\circ}$ (kJ mol^{-1})		$\Delta^{\ddagger}S^{\circ}$ (J mol^{-1} K^{-1})		$\Delta^{\ddagger}G^{\circ}$ (25 °C) (kJ mol^{-1})		mechanism	
	exp	calcd	exp	calcd	exp	calcd	exp	calcd
COOMe[44]	38.7 ± 2.5	36.1	−83 ± 8	−105	63.4 ± 4.9	67.2	$B_{AC}2$	$B_{AC}2$
AcOEt[45]	45.3 ± 0.9	51.6	−111 ± 1.9	−115	78.4 ± 1.6	85.9	$B_{AC}2$	$B_{AC}2$
BPL[44]	50.1 ± 0.9	47.3	−71 ± 3	−105	71.3 ± 1.3	78.8	$B_{AC}2$	$B_{AC}2$
BBL[46]	51.3 ± 2.1	50.0	−74 ± 6	−106	73.4 ± 2.7	81.6	$B_{AC}2$	$B_{AC}2$
BIVL		56.4		−105	~77	87.7	$B_{AC}2$	$B_{AC}2$
DIK[30]	47.4 ± 0.6	28.1/40.3	−63 ± 2	−110/−71	66.1 ± 0.8	60.8/61.6	$B_{AC}2$	$B_{AC}2$/$B_{AC}1$
GBL[44]	44.6 ± 1.3	57.0	−94 ± 5	−100	72.6 ± 2.0	86.8	$B_{AC}2$	$B_{AC}2$
FUR	49.8 ± 0.8	64.6	−104 ± 3	−103	80.8 ± 1.8	95.3	$B_{AC}2$	$B_{AC}2$
DVL[44]	30.1 ± 1.7	45.8	−117 ± 6	−116	65.0 ± 2.5	80.4	$B_{AC}2$	$B_{AC}2$

ring strain lowers the energetic barrier for the cleavage step by almost 20 kJ mol^{-1}.

GBL has not been observed to undergo any ^{18}O isotopic exchange during alkaline hydrolysis, which suggests that cleavage of the intermediate (k_{clv}) is much faster than the inverse addition reaction (k_{exch}). In this work, based on the activation free energies, a k_{clv}/k_{exch} ratio of about one hundred would be expected, and thus negligible O-exchange.

Accuracy. Reasonable quantitative agreement was also obtained, although the activation free energies were overestimated for all compounds (mue 8.5 kJ mol^{-1}), the linear esters and the *β*-lactones showing less deviation than the larger lactones. In addition, the reactant configuration used as a free energy reference corresponds to an encounter complex between a hydroxide ion, the ester and five water molecules and is in all likelihood higher in energy than the standard states of 1 mol dm^{-3} concentration for hydroxide and ester and unit activity for water. Thus, all the reported results are expected to somewhat underestimate the theoretical activation free energy. Quantifying the free energy cost of forming the reactant complex from the ester and OH^{-} at 1 mol dm^{-3} concentration is not a straightforward calculation.

The use of the larger basis set 6-311++G(2df,2pd), as in the neutral mechanisms, resulted in increased excess error (mue 13.8 kJ mol^{-1}). The especially large divergence between the experimental and theoretical $B_{AC}2$ activation enthalpy for DIK has been discussed on the basis of the base-catalyzed elimination-addition mechanism. Since corrections have been carried out to take into account the role of solvation entropies of the supermolecule and improve PCM estimations of ΔH, the source of the general error in activation enthalpies is not clear.

As occurred in the neutral mechanisms and for the same reasons, the activation energy at the post-HF levels of theory shows large deviations from the experimental values, when available, and from the DFT-B3LYP results. Both free energy differences for the transition states and the tetrahedral intermediates were underestimated, to the point that for some lactones the intermediate was more stable than the reactants.

4. CONCLUSIONS

A comprehensive study on the hydrolysis of nine carboxylic acid esters in neutral and alkaline conditions was performed, and the various possible mechanisms are evaluated and discussed.

While much of the knowledge about ester hydrolysis reactions comes from mechanistic interpretations of empirical kinetic results, this work has made the connection in the opposite direction: theoretical conclusions, themselves supported by the agreement with the available kinetic results, reinforce certain hypotheses and weaken others, regarding features of the hydrolysis mechanisms such as:

1. The assignment of hydrolysis pathways to each particular compound.
2. The second-order base-catalyzed nature of neutral $B_{AC}2$.
3. The fact that lactone $B_{AL}1$ are decarboxylation reactions rather than hydrolysis.
4. The role of hydroxide as a nucleophile rather than a general base in alkaline.
5. The rate-limiting nature of the breakdown step of the tetrahedral intermediate.

Some conclusions have been obtained that should help guide future experiments, such as the evidence supporting the novel elimination-addition $B_{AC}1$ hydrolysis pathway for diketene in alkaline medium, or the possible contribution of $B_{AL}2$ to the alkaline hydrolysis of *β*-propiolactone.

■ ASSOCIATED CONTENT

Supporting Information

Equilibrium geometries and energies for all computed structures. Energy barriers for the additional addition and cleavage pathways of the neutral $B_{AC}2$ reaction. Results at the MP2/6-31++G(d,p), MP4/6-31++G(d,p) and QCISD/6-31++G(d,p) levels of theory on B3LYP/6-31++G(d,p) geometries, and also at the B3LYP/6-311++G(2df,pd) level of theory. A detailed description of the experimental study of FUR hydrolysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kirby, A. J. In *Ester formation and hydrolysis and related reactions*; Bamford, C. H., Tipper, C. F. H., Eds.; Comprehensive Chemical Kinetics; Elsevier, Amsterdam The Netherlands, 1972; Vol. *10*; pp 57−201.
(2) Kallies, B.; Mitzner, R. *J. Mol. Model.* **1998**, *4*, 183−196.
(3) Janoschek, R.; Fabian, W. M. F. *J. Org. Chem.* **1999**, *64*, 3271−3277.
(4) Schmeer, G.; Sturm, P. *Phys. Chem. Chem. Phys.* **1999**, *1*, 1025−1030.
(5) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Phys. Chem. A* **2000**, *104*, 7672−7678.
(6) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Am. Chem. Soc.* **2000**, *122*, 1522−1530.
(7) Zhan, C.-G.; Landry, D. W.; Ornstein, R. L. *J. Am. Chem. Soc.* **2000**, *122*, 2621−2627.
(8) Pliego, J. R.; Riveros, J. M. *J. Phys. Chem. A* **2004**, *108*, 2520−2526.
(9) Yamabe, S.; Tsuchida, N.; Hayashida, Y. *J. Phys. Chem. A* **2005**, *109*, 7216−7224.
(10) Gunaydin, H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 15232−15233.
(11) Shi, Z.; Hsieh, Y.-h.; Weinberg, N.; Wolfe, S. *Can. J. Chem.* **2009**, *87*, 544−555.
(12) Wang, B.; Cao, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 3266−3270.
(13) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press, 1969; pp 457−463.
(14) Kaiser, E. T.; Kézdy, F. J. *Prog. Bioorg. Chem.* **1976**, *4*, 239−267.
(15) Dickens, F.; Jones, H. E. H. *Br. J. Cancer* **1961**, *15*, 85−100.
(16) Dickens, F.; Jones, H. E. H. *Br. J. Cancer* **1963**, *17*, 100−108.
(17) Manso, J. A.; Pérez-Prior, M. T.; García-Santos, M. P.; Calle, E.; Casado, J. *Chem. Res. Toxicol.* **2005**, *18*, 1161−1166.
(18) Gómez-Bombarelli, R.; González-Pérez, M.; Pérez-Prior, M. T.; Manso, J. A.; Calle, E.; Casado, J. *Chem. Res. Toxicol.* **2008**, *21*, 1964−1969.
(19) Barclay, L. R. C.; Hall, N. D.; Cooke, G. A. *Can. J. Chem.* **1962**, *40*, 1981−1985.
(20) Douglas, J. E.; Campbell, G.; Wigfield, D. C. *Can. J. Chem.* **1993**, 1841−1844.
(21) Pliego, J. R.; Riveros, J. M. *J. Phys. Chem. A* **2001**, *105*, 7241−7247.
(22) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378−6396.
(23) Fernández, D. P.; Goodwin, A. R. H.; Sengers, J. M. H. L. *Int. J. Thermophys.* **1995**, *16*, 929−955.
(24) March, J. *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 4th ed.; John Wiley: New York, 1992.
(25) Liang, H. T.; Bartlett, P. D. *J. Am. Chem. Soc.* **1958**, *80*, 3585−3590.
(26) da Silva, P. L.; Guimarães, L.; Pliego, J. R. *J. Phys. Chem. B* **2013**, *117*, 6487−6497.
(27) Adler, M.; Adler, S.; Boche, G. *J. Phys. Org. Chem.* **2005**, *18*, 193−209.
(28) Begum, S.; Zeb, M. A.; Pirzada, N. *J. Chem. Soc. Pak.* **2000**, *22*, 255−259.
(29) Pérez-Prior, M. T.; Manso, J. A.; García-Santos, M. P.; Calle, E.; Casado, J. *J. Org. Chem.* **2005**, *70*, 420−426.
(30) Gómez-Bombarelli, R.; González-Pérez, M.; Pérez-Prior, M. T.; Manso, J. A.; Calle, E.; Casado, J. *J. Phys. Org. Chem.* **2009**, *22*, 438−442.
(31) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743−1750.
(32) Euranto, E. *Pure Appl. Chem.* **1977**, *49*, 1009−1020.
(33) Hurst, G. H.; Bender, M. L. *J. A* **1971**, *93*, 704−711.
(34) Bunnett, J. F.; Robison, M. M.; Pennington, F. C. *J. Am. Chem. Soc.* **1950**, *72*, 2378−2381.
(35) Marlier, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 5953−5956.
(36) Mata-Segreda, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 2259−2262.
(37) Pliego, J.; Riveros, J. *Chem.—Eur. J.* **2002**, *8*, 1945−1953.
(38) Gómez-Bombarelli, R.; González-Pérez, M.; Pérez-Prior, M. T.; Calle, E.; Casado, J. *J. Org. Chem.* **2009**, *74*, 4943−4948.
(39) Bender, M. L.; Homer, R. B. *J. Org. Chem.* **1965**, *30*, 3975−3978.
(40) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993−3002.
(41) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 3003−3009.
(42) Tobias, P. S.; Kezdy, F. J. *J. Am. Chem. Soc.* **1969**, *91*, 5171−5173.
(43) Heathcote, D. M.; ad John H. Atherton, G. A. D. B.; Page, M. I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 535−540.
(44) Blackburn, G. M.; Dodds, H. L. H. *J. Chem. Soc., Perkin Trans. 2* **1974**, 377−382.
(45) Tommila, E.; Murto, M. *Acta Chem. Scand.* **1963**, *17*, 1947−1956.
(46) Olson, A. R.; Youle, P. V. *J. Am. Chem. Soc.* **1951**, *73*, 2468−2471.