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Isergonic relationship in the acid-catalyzed hydrolysis of carboxylic esters with hydrogen-bonding capability†

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ABSTRACT: The average value of the enthalpies of activation for the acid-catalyzed hydrolyses of ethyl 2-hydroxypropanoate and five acetate esters with hydrogen bonding capability is $57 \pm 7\,\mathrm{kJ\,mol^{-1}}$ ($p = 0.05$). This value is $11\,\mathrm{kJ\,mol^{-1}}$ lower than the mean observed for primary and secondary alkyl acetates and ethyl alkanoates, measured in water and in mixtures of water with organic solvent with high water content. The difference is attributed to tighter transition-state complex hydration via hydrogen bonding, relative to reactant ester species. Enthalpy–entropy compensation with an isokinetic temperature of 346 K was found to be valid at $p < 0.05$, a value typical for solvent-mediated kinetic effects. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: acid-catalyzed ester hydrolysis; hydrophilic esters; hydrogen bonding; activation parameters; enthalpy–entropy compensation

INTRODUCTION

Enzymes function by lowering transition-state (TS) energies[1] and energetic intermediates[2] and also, apparently by raising reactant-state energy.[3] Stabilization of TS complexes through atomic contacts remote from the reaction center is known to occur in enzyme catalysis.[4] This mechanism affects not only catalysis *per se*, but also enzyme selectivity. One such kind of interaction is the hydrogen bond.[5] The pre-organized nature of active sites is often indicated as the reason for the catalytic efficacy of these atomic contacts because rate enhancement results from bringing the reacting species together at the active site, thus increasing their effective local concentration. Certain molecular orientations and rotamer distributions are also favored, that result in reactive positions that resemble the TS complex. As a net result, there is a reduction in the entropy cost of these concentration and orientation effects for TS complex formation. In this way, any resulting favorable effect on $\Delta H^{\ddagger}$ contributes to a greater extent to the reduction of $\Delta G^{\ddagger}$.

Site-mutagenesis experiments have given a clear picture of the effect of hydrogen bonding to TS complexes,[6] ranging from weak bonds to sites remote from the reaction center, up to much stronger interactions with the atoms whose bonds undergo either scission or formation.[7] Hence it is useful to establish the minimal amount of rate acceleration expected from this kind of interaction in simple systems with thermal freedom, as opposed to the pre-organized nature of enzyme catalytic sites.

Hydrogen bonding to sites other than the reaction center also seems to play a role in simpler non-enzyme systems, such as the acid-catalyzed hydrolysis of carboxylic esters. Ethyl 2-hydroxypropanoate undergoes hydrolysis five times faster than ethyl 2-methylpropanoate at 25 °C,[8] despite the fact that the van der Waals volume of the 2-propyl group ($34.12\,\mathrm{cm^3\,mol^{-1}}$)[9] is similar to the same molecular parameter for the 1-hydroxyethyl group ($28.49\,\mathrm{cm^3\,mol^{-1}}$).[9] An analogous result is that of ethyl hydroxyacetate ($18.27\,\mathrm{cm^3\,mol^{-1}}$)[9] and ethyl chloroacetate ($21.85\,\mathrm{cm^3\,mol^{-1}}$);[9] the first ester being three times more reactive under the same conditions.[8]

Hydrogen-bonding capability in the alkyl moiety also shows the same trend, although to a lesser extent. 2-Hydroxyethyl acetate and 3-oxabutyl acetate undergo acid hydrolysis 30% faster than propyl acetate at 25 °C,[8] despite the similarity in the van der Waals volumes of the chains: 28.50, 39.33 and $34.13\,\mathrm{cm^3\,mol^{-1}}$, respectively (van der Waals volumes calculated from data in Ref. 9).

It is well known that the magnitude of steric hindrance is associated with solvation processes.[10] Therefore, it is important to address to this basic issue to help understand quantitative aspects of enzyme selectivity and catalytic efficiency.

In order to achieve this goal, it was decided to compare the kinetic behavior of the acid-catalyzed hydrolysis of esters with hydrogen-bonding capability vs. unfunctionalized alkyl analogs. This experimental model leads to a straightforward hypothesis: there are stabilizing distant solvation interactions in the non-enzyme hydrolysis of

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esters capable of hydrogen bonding, despite the thermal freedom in homogeneous aqueous solution.

This paper reports the isobaric activation parameters in the acid-catalyzed hydrolyses of ethyl 2-hydroxypropanoate, 2,3-dihydroxypropyl acetate,[11] 1,2,3-propyl triacetate,[11] 1,2-ethyl diacetate, 3-oxapentyl acetate and 3,6-dioxaoctyl acetate in water solvent, catalyzed by aqueous H^+ under normal pressure.

RESULTS AND DISCUSSION

Kinetics

The reactions followed the well-established pseudo-second-order rate law:

$$\text{ester} + H_2O \xrightarrow{HCl} \text{alcohol} + RCO_2H \qquad d[RCO_2H]/dt = k_2[H^+][\text{ester}] \tag{1}$$

The observed second-order rate coefficients are listed in Table 1. They have an average standard deviation of 3%.

Structure exerts no strong effect on the magnitude of the k_2 values, in contrast to alkyl acetates, where the steric bulk of the alkyl moieties results in a decrease in k_2. This feature had already been reported for the acid-catalyzed hydrolyses (aqueous H_2SO_4) of 3-oxaalkyl acetates,[12] the mono-, bi- and triacetates of glycerol[11] and 1,2-propyl diacetate.[11]

Table 1. Second-order specific rates for the hydrolysis of the esters by aqueous HCl, in water solvent

Ester	Temperature (°C)	$10^4 k_2$ ($s^{-1}\,mol^{-1}\,dm^3$)
Ethyl 2-hydroxypropanoate	25.0[a]	1.28
	30.0	1.62 ± 0.02
	35.0	2.55 ± 0.02
	40.2	3.2 ± 0.1
	45.0	4.2 ± 0.2
	49.8	5.8 ± 0.1
1,2 Ethyl diacetate	25.0[a]	0.809
	30.0	1.26 ± 0.02
	35.0	1.87 ± 0.02
	40.2	2.76 ± 0.07
	45.0	3.98 ± 0.09
	49.8	5.96 ± 0.08
3-Oxapentyl acetate	27.5	0.82 ± 0.06
	30.7	1.22 ± 0.03
	34.8	1.6 ± 0.1
	39.4	2.8 ± 0.1
	43.1	3.6 ± 0.2
	48.5	5.1 ± 0.1
3,6-Dioxaoctyl acetate	30.0	1.44 ± 0.03
	35.0	2.17 ± 0.01
	40.2	3.2 ± 0.2
	45.0	4.4 ± 0.1
	49.8	6.68 ± 0.08

[a] From Ref. 8.

Esters with hydrogen-bonding capability undergo acid hydrolysis at moderately faster rates than their alkyl analogs. For example, 3-oxabutyl acetate reacts twice as fast as butyl acetate at 37.0 °C.[11,12] One could point to differences in leaving-group pK_a (BuOH, $pK_a = 16.0$; $MeOCH_2CH_2OH$, $pK_a = 14.84$) as a sufficient explanation for this observation, rather than a solvent effect on TS complex stability. This rationale is overruled when other polar esters are also compared with 3-oxabutyl acetate. At 37.0 °C, the relative rates of hydrolysis of 3-oxapentyl acetate ($pK_a = 15.1$), 1,2-ethyl diacetate ($pK_a = 15.3$), 2-chloroethyl acetate ($pK_a = 14.31$) and acetylcholine ($pK_a = 13.9$) are 1.00 ± 0.02,[12] 0.98 ± 0.05,[12] 0.97[8] and 0.91 ± 0.02,[14] respectively. This shows that a $\Delta pK_a \approx 2$ yields <10% variation in k_2. Hence the pK_a of the leaving group or TS complex polarity seems not as explanation for the observation, either.

Activation parameters

Table 2 gives the isobaric activation parameters. The activation enthalpies for the acid hydrolyses of unfunctionalized alkyl acetates and ethyl alkanoates have been found to be fairly constant,[8,15] between 65 and 70 kJ mol^{-1}. The mean value found in the present study for esters with hydrogen-bonding capability was 57 ± 7 kJ mol^{-1} ($p = 0.05$). This 11 kJ mol^{-1} difference is statistically significant at $p < 0.01$.

Ethyl 2-hydroxypropanoate has the lowest $\Delta H^{\ddagger}$ value in the group. Deletion of this value affords an average enthalpy of activation of 59 ± 5 kJ mol^{-1} ($p = 0.05$). Hence the finding is not an artifact produced by the

Table 2. Isobaric activation parameters for the acid-catalyzed hydrolysis of the esters studied, in water solvent

Ester	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (kJ K^{-1} mol^{-1})
AcOR/HCl ($N = 14$[a])	66 ± 2	Variable
AcOEt/Dowex ($N = 6$[b])	67 ± 4	Variable
AcOEt/HCl	68 ± 9	−0.092 ± 0.006
AcOEt/Dowex	72 ± 3	−0.077 ± 0.006
$\langle \Delta H^{\ddagger} \rangle$[c] = 68 ± 2 kJ mol^{-1} ($p = 0.05$)		
2,3-Dihydroxypropyl acetate/H_2SO_4[d]	59 ± 3	−0.13 ± 0.01
1,2,3-Propyl triacetate/H_2SO_4[d]	54 ± 1	−0.15 ± 0.05
3-Oxapentyl acetate/HCl	66 ± 2	−0.105 ± 0.008
Ethyl 2-hydroxypropanoate/HCl	46 ± 2	−0.16 ± 0.02
1,2-Ethyl diacetate/HCl	58 ± 4	−0.13 ± 0.03
3,6-Dioxaoctyl acetate/HCl	59 ± 2	−0.124 ± 0.007
$\langle \Delta H^{\ddagger} \rangle$[c] = 57 ± 7 kJ mol^{-1} ($p = 0.05$)		

[a] From Refs. 8 and 15.
[b] From Ref. 28.
[c] $\langle \Delta H^{\ddagger} \rangle$ are given as average values with 95% confidence limits.
[d] From Ref. 11.

contribution of that ester, because the difference is still statistically significant at $p < 0.01$.

Considerable TS electrostriction is built up in the acid-catalyzed hydrolysis of unfunctionalized carboxylic esters, as indicated by negative volumes of activation of around $-9\,cm^3\,mol^{-1}$,[16] and entropies of activation in the range from $-0.08\,kJ\,K^{-1}\,mol^{-1}$ to $-0.12\,kJ\,K^{-1}\,mol^{-1}$.[15]

Various pieces of evidence have been adduced to establish that the acid-catalyzed hydrolysis of esters involves a tetrahedral addition intermediate. The convincing evidence comes from studies using ^{18}O as a tracer.[15,17] Oxygen exchange with the solvent and hydrolysis occur at comparable rates. This observation suggests that the intermediate has a lifetime long enough for the proton transfers required for such isotopic exchange to take place.

Kirby offers an excellent discussion on the kinetic effect of water.[15] Plots of $\log(k_{obs}/[esterH^+])$ against $\log a_{H_2O}$ have slopes close to 2 for ester hydrolyses and for ^{18}O exchange. This is taken as evidence that two molecules of water are involved in the TS for each reaction.

The protons of a molecule of water undergoing addition to the carbonyl group become acidic as bond formation develops. The role of a second molecule of water must be to bind one proton from the nucleophile. Hence an acceptable mechanism involves a molecule of water acting as a general base to assist the nucleophilic addition of the other molecule of water to the protonated ester carbonyl group.

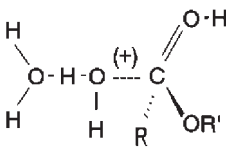
The commonly accepted TS complex core structure can be represented as shown in Scheme 1. Qualitatively, this TS complex must be regarded as a hydrophilic solute that requires a tighter aqueous solvation cavity, relative to initial ester molecules. Hence esters with hydrogen-bonding capability (and their TS complexes) should interact much more strongly with the surrounding aqueous medium than their more hydrophobic alkyl analogs. This qualitative argument is supported by consideration of the hydration enthalpies for a few solutes such as methanol ($-84\,kJ\,mol^{-1}$) or formaldehyde ($-64\,kJ\,mol^{-1}$) as compared with ethylene ($-16\,kJ\,mol^{-1}$). This structural feature, and the $\Delta S^{\ddagger}$ and $\Delta V^{\ddagger}$ values mentioned above lead to the expectation of lower activation enthalpies for the case of esters with hydrogen bonding capability, a claim supported by experiment.

One suggestion was to explore the possibility that these esters and their TS complexes could be more basic than their unfunctionalized alkyl analogs, owing to intramolecular hydrogen bonding between the protonated carbonyl and any of the oxygen acceptors in the alkyl moiety. The energy of the solvent–solute interactions would be about the same in both the initial and transition states. Thus, as a result of this intramolecular stabilizing interaction, the greater fraction of protonated ester would be a less complicated explanation for the $11\,kJ\,mol^{-1}$ decrease in the value of $\Delta H^{\ddagger}$. For the case at hand, intramolecular hydrogen bonding is a proposal difficult to consider in 55 M water medium for small solute molecules with no special structural features, such as the constrained geometries of substituted maleate monoanions. It is reasonable that hydrogen bonding by water decreases the strength of intramolecular bonds.[18] Hence solvent–solute hydrogen bonding is a more probable interaction. Moreover, if any intramolecular hydrogen bonding led to increased basicity, ethanolamine would be a stronger base than ethylamine, and the same would be expected for the pairs diethanolamine–diethylamine, triethanolamine–triethylamine and tris(hydroxymethyl) aminomethane–*tert*-butylamine. Thermodynamic data in the literature for the dissociation of these protonated amines in aqueous solution at 25 °C point in the opposite direction (ΔpK_a values calculated from ΔG° for the dissociation of the ammonium ions in aqueous solution at 25 °C[19]). The alkylamines are more basic than their hydroxy analogs by ΔpK_a ranging from 1.13 to 2.96.

The above qualitative considerations permit the following argument to be constructed: for this kind of stabilization mechanism between TS complexes and solvent molecules, the maximal reduction in energy for the system is achieved when certain requirements of intermolecular configuration are met. The geometric conditions clearly imply a constraint for which the decrease in energy content will be accompanied by some degree of entropy loss. Thus, enthalpy–entropy compensation must exist in the acid-catalyzed hydrolysis of esters with hydrogen-bonding capability.

The validity of isokinetic (isergonic) relationships has been an ongoing issue for the past four decades. The strongest critic is, perhaps, Exner.[20] He has pointed to the fact that since both activation entropies and enthalpies are derived from the same data set, then the two quantities are statistically dependent. This situation creates the problem of propagation of uncertainty due to covariance. Exner further indicated that if an enthalpy–entropy correlation truly exists, the Arrhenius plots of the homologous reactions under study should mutually intersect at the isokinetic temperature β. Figure 1 shows that these four esters comply with Exner's criterion at a temperature around 3.2×10^2 K.

Since $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are statistically correlated, the direct linear fitting must be carried out accounting for the uncertainties in both variables (double-weighted least-squares fitting). All data pairs have different degrees of precision (a heteroscedastic data set). As expected from the result of the first test, the activation



Scheme 1

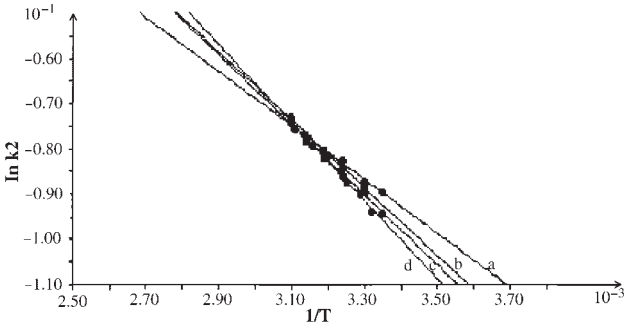


Figure 1. Exner's test for isokinetic relationship. (a) Ethyl 2-hydroxypropanoate; (b) ethyl 1,2-diacetate; (c) 3,6-dioxaoctyl acetate; (d) 3-oxapentyl acetate

parameters were found to correlate. The regression equation with 95% confidence limits is $\Delta H^{\ddagger}$ (kJ mol^{-1}) $= (104 \pm 5) + (363 \pm 43)\Delta S^{\ddagger}$ (kJ K^{-1} mol^{-1}) ($r^2 = 0.998$). Inclusion of the previously determined parameters for 2,3-dihydroxypropyl acetate and 1,2,3-propyl triacetate[11] yields essentially the same result for 95% confidence limits ($r^2 = 0.97$):

$$\Delta H^{\ddagger}\ (\text{kJ mol}^{-1}) = (103 \pm 10) + (346 \pm 80)\Delta S^{\ddagger}(\text{kJ K}^{-1}\text{ mol}^{-1}) \quad (2)$$

This isokinetic temperature $\beta = 346$ K is in the range frequently associated with solvation effects.[21]

Up to this stage, no discussion has been devoted to neighboring-group participation by the hydrogen-bonding oxygen atoms as a mechanistic possibility. In the case of ethyl 2-hydroxypropanoate, a nucleophilic interaction could be conceived between the 2-hydroxy group and the protonated carboxyl, to yield an epoxide-like intermediate. After departure of the ethoxy-leaving group, the resulting α-lactone would rapidly undergo hydrolysis. A similar effect might also be considered with the oxaalkyl esters or the esters of glycerol. Acyl compounds certainly undergo intramolecular transfer to adjacent hydroxyl groups but at rates faster than either hydrolysis or intermolecular alcoholysis.[22,23] The entropies of activation for the cases where neighboring groups assist in the formation of the TS are not as negative as the values measured in this work. For example: (a) The reported value of $\Delta S^{\ddagger}$ for the hydrolysis of 2-bromopropanoate at neutral pH to yield 2-hydroxypropanoate is $+37$ J K^{-1} mol^{-1};[24] (b) the aminolysis of phenyl 4-(*N*,*N*-dimethylamino)butanoate proceeds with a $\Delta S^{\ddagger}$ 52 J K^{-1} mol^{-1} less negative than the value for the similar intermolecular reaction between trimethylamine and phenyl acetate;[22] (c) for the acetolysis of *trans*-2-methoxycyclohexyl 4-bromobenzenesulfonate $\Delta S^{\ddagger}$ is -14 J K^{-1} mol^{-1};[25] (d) the saponification of *cis*-2-hydroxycyclopentyl acetate proceeds with $\Delta S^{\ddagger} = -32$ J K^{-1} mol^{-1}, which is 96 J K^{-1} mol^{-1} less negative than the measured value for cyclopentyl acetate.[26]

The average value of $\Delta S^{\ddagger}$ for the acid-catalyzed hydrolysis of the group of esters with hydrogen-bonding capability studied in this work is -0.13 ± 0.02 kJ K^{-1} mol^{-1}. It is more negative than the values for the unfunctionalized analogs ethyl acetate (-0.092 kJ K^{-1} mol^{-1}), propyl acetate (-0.102 kJ K^{-1} mol^{-1}), 2-propyl acetate (-0.106 kJ K^{-1} mol^{-1}) or butyl acetate (-0.109 kJ K^{-1} mol^{-1}). Hence any kind of assistance from neighboring groups seems unlikely in the acid-catalyzed hydrolysis of esters with hydrogen-bonding capability.

A last point must be added with regard to the $\Delta H^{\ddagger}$ values. The activation enthalpies for the acid-catalyzed hydrolyses of the highly polar (but non-hydrogen-bonding) 2,2,2-trichloroethyl acetate,[8] ethyl chloroacetate,[8] acetylcholine[14] and ethyl 3-(trimethylammonium)propanoate[15] are 66, 66, 67 and 67 kJ mol^{-1}, values identical with those observed for the less polar unfunctionalized alkyl esters. This further observation agrees with our hypothesis that polarity of the TS complex is not the general feature that explains the lower $\Delta H^{\ddagger}$ of the hydrolysis of esters with hydrogen-bonding capability.

CONCLUSION

The results of this work support the hypothesis that hydrogen bonding to atoms remote from the reaction center contributes to the stabilization of the TS complex in the acid hydrolysis of esters in aqueous medium. An 11 kJ mol^{-1} decrease in $\Delta H^{\ddagger}$ was observed relative to alkyl-unfunctionalized analogs. The effect is attributed to stronger TS hydration, relative to reactant ester species. This $\delta\Delta H^{\ddagger} = -11$ kJ mol^{-1} corresponds to $\delta\Delta S^{\ddagger} = -32$ J K^{-1} mol^{-1}, necessary to meet the solvent configuration requirements needed to increase the degree of TS complex solvation in the presence of thermal freedom.

EXPERIMENTAL

All esters were common chemicals from different commercial sources. The reaction mixtures were made by dissolving 3 cm^3 of the ester in 100 cm^3 of 0.2 M HCl. The rates were measured by titration of free acid at suitable reaction times with NaOH–phenolphthalein in 3.00 cm^3 aliquot portions withdrawn from the reaction flask, immersed in a constant-temperature water-bath. In all experiments, >15 data points were collected (>95% of the total extent of reaction).

The data were fitted to the first-order kinetic scheme [NaOH] (cm^3) $= A - B\exp(-k_1 t)$, by using a non-linear least-squares computer program in the package ENZFITTER.[27] Error limits are standard deviations from the means obtained from at least three experiments. Second-order specific rates were obtained by dividing the observed k_1 by the corresponding value of [HCl].

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