

The transition-state acidity and carbonyl stretching frequency in ester hydrolysis. A substituent-effect approach

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Dedicated to Prof. Roberto Rossi and Prof. Edmundo Rúveda

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Abstract

The acidity of the transition-state complex in the acid-catalysed hydrolysis of esters increases by the effect of electron-withdrawing groups in either the acyl or alkyl moieties. From the pK_a of 13 transition-state complexes, the vibrational frequency of the carbonyl oscillator in the transition state was found equal to $1300 \pm 100 \text{ cm}^{-1}$, the same as in the cases of saponification of methyl formate and the methoxide-catalysed methanolysis of *p*-bromophenyl benzoate. This suggests that the transition-state complexes of both lyonium and lyate catalysed reactions share similar structural features.

Keywords: Transition-state carbonyl stretching frequency, transition-state acidity, ester hydrolysis

Introduction

The conversion of reactant molecules into transition-state (TS) complexes involves changes in their inertial features (translation and geometry) and the force constants associated with the different internal modes. Reactant-molecule force constants are in principle obtainable from the vibrational frequencies determined from spectroscopic measurements.

Kinetic isotope effects constitute a useful experimental approach for the structural elucidation of TS complexes,¹ as well as substituent-effect studies.² Reasonable atom connectivities, geometry and force field are the goals to achieve for the description of these transient molecular entities. The first two features are based on chemical intuition or isotopic labelling experiments, whereas the third comes from the molecular analysis of kinetic measurements or from theoretical calculations. In many cases, the force constants of modes perpendicular to the reaction coordinate are similar to their initial-state counterparts or at least, are assumed from analogy with the reactants.¹

This type of information finds utility not only as intrinsic knowledge of reaction mechanisms but also for the rational design of drugs by molecular mechanics.³ Thus, it is useful to have reasonable values of force constants for TS complexes, as numerical data *per se*, or to be used as reference values.

I report here that no significant effect from structure was observed on the carbonyl stretching frequency in the TS of the acid-catalysed hydrolysis of esters.

Model

Esters with poor leaving groups are likely to be subjected to general-base catalysis by H₂O, both in the water-catalysed pathway,⁴ as well as in the acid-catalysed route.⁵⁻⁸ This occurs by rate determining removal of a proton from the nucleophilic water molecule, by a second water molecule acting as a base.

A partial molecular-orbital description of the process is a collision in which there is flow of charge density from a non-bonding orbital in the nucleophilic H₂O (HOMO) to the π^* molecular orbital of the carbonyl group (LUMO). As the new O-C bond forms, there is a decrease in the C=O bond order.

A rather intuitive approach can be used for the calculation of the TS vibrational frequency of the carbonyl moiety, in the acid-catalysed hydrolysis of esters. One could calculate the stretching force constant, if data were available for an *ad hoc* Badger's rule,⁹ relating force constant (f_v^\ddagger) and bond order (n_{CO}^\ddagger):

$$f_v^\ddagger = a + b n_{CO}^\ddagger \quad (1)$$

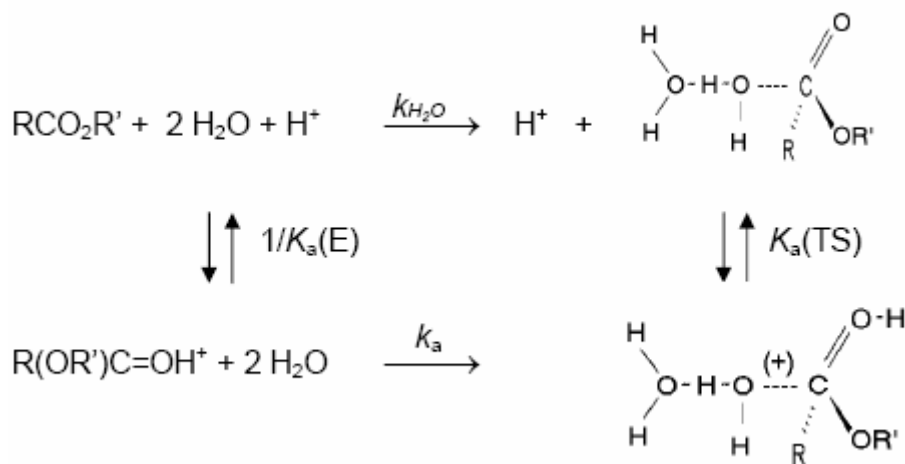
A working hypothesis will be the assumption that TS complexes follow the same relation, obeyed by their reactant-state counterparts. Thus, the two parameters in equation 1 can be calculated from known force constants in the literature.⁹ The mean value for C-O is 5.4 mdyne Å⁻¹, 12.6 mdyne Å⁻¹ for >C=O and 19.06 mdyne Å⁻¹ for C≡O. Thus, equation 1 results as $f_v^\ddagger = 6.83 n_{CO}^\ddagger - 1.31$.

Kurz¹⁰ showed the usefulness of the virtual acidity of TS complexes, as a diagnostic tool for the study of their molecular features. The $pK_a(\text{TS})$ should be between that of protonated ester and the value for the tetrahedral adduct. Protonated acetate esters show $pK_a = -4.61$ ¹¹ ($n_{CO} \sim 1.5$ ¹²) and a value of $pK_a = 12.5$ is estimated for the tetrahedral adduct ($n_{CO} = 1.0$).¹³ This rationale leads to the empirical relation:

$$pK_a = 47 - 34 n_{CO} \quad (2)$$

Calculation of $pK_a(\text{TS})$ should allow the estimation of n_{CO}^\ddagger , which in turn leads to the calculation of f_v^\ddagger , or the corresponding value for the stretching frequency of the carbonyl oscillator in the transition state.

The virtual pK_a 's of the TS complexes in the acid-catalysed hydrolyses of carboxylic esters can be determined from the specific rates of the water (neutral) and acid reactions, as indicated in Scheme 1:



where $k_{\text{H}^+} = k_a K_a(\text{E})$.

Scheme 1

Consideration of the above cycle ($\oint d\Delta G^0 = 0$) affords:

$$pK_a(\text{TS}) = \log (k_{\text{H}^+} / k_{\text{H}_2\text{O}}) \quad (3)$$

Results and Discussion

Table 1 gives the $pK_a(\text{TS})$ for the TS complexes in the acid-catalysed hydrolysis of 13 esters at 25 °C. They were calculated from rate data in the literature.

Effect of structure on $pK_a(\text{TS})$

The TS acidities of the five RCO_2Et vary according to expectance. The more acidic TS complexes are the ones with the electron-withdrawing groups ($^+\text{H}_3\text{NCH}_2-$, $\text{CH}_3\text{CH}(\text{OH})-$ and ClCH_2-), followed by formate and acetate.

The $pK_a(\text{TS})$ of the acetates also shows a clear electronic effect from the alkyl or aryl moieties. As expected, TS complexes become more acidic as the electron-withdrawing ability of OR' increases. A positive correlation is thus expected between $pK_a(\text{TS})$ and $pK_a(\text{R}'\text{OH})$. Figure 1 shows the prediction to be borne out by experiment:

$$pK_a(\text{TS}) = - (1.4 \pm 0.2) + (0.44 \pm 0.02) pK_a(\text{R}'\text{OH}) \quad (4)$$

The relationship holds well ($r^2 = 0.98$, $p < 0.005$) over a range of almost 9 $pK_a(\text{R}'\text{OH})$ units for all acetates but the glyceryl ester (*vide infra*).

Table 1. Virtual acidities of the TS complexes in the acid-catalysed hydrolysis of a series of carboxylic esters

Ester	$pK_a(\text{TS})$
Ethyl formate (30 °C) ¹⁴	2.5 ± 0.2
Ethyl acetate ^{7, 15}	5.7
Ethyl chloroacetate ⁷	2.6
Glycine ethyl ester hydrochloride ⁷	0.29
Ethyl lactate (30 °C) ¹⁶	26 ± 0.1
Vinyl acetate ¹⁵	3.1
Acetylcholine chloride ¹⁷	4.5
Glyceryl monoacetate (30 °C) ¹⁶	3.4 ± 0.1
Phenyl acetate ^{7, 15}	3.0
<i>p</i> -Methylphenyl acetate ⁷	3.2
<i>p</i> -Chlorophenyl acetate ⁷	2.9
<i>m</i> -Nitrophenyl acetate ⁷	2.1
<i>p</i> -Nitrophenyl acetate ⁷	1.7

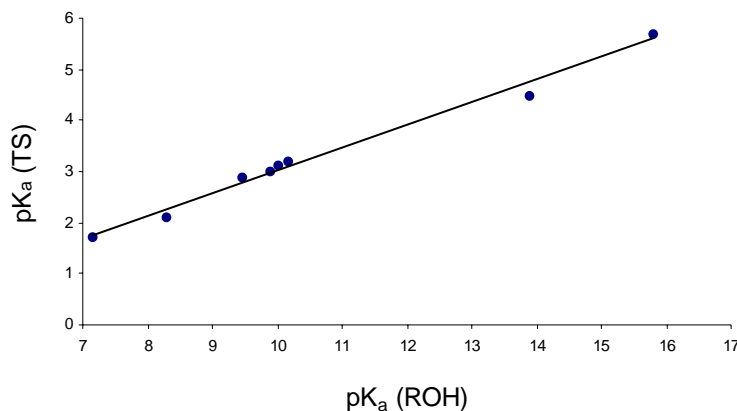


Figure 1. Influence of the electronic effect of substituent R' in the acidity of the TS complex, in the acid-catalysed hydrolysis of acetate esters.

The molecular explanation of this finding is as follows. The strength of neutral acids in aqueous medium is mainly an entropy-driven process.¹⁸ The average value of ΔH° for the ionisation of alkanolic and benzoic acids is -1.5 kJ/mol, whereas the corresponding value for ΔS° is -24 kJ/mol at 25 °C. Electron-withdrawing substituents in neutral acids are effective for charge delocalisation in the anionic conjugate bases. This effect implies a lower degree of

orientation of the neighbouring water molecules around anions, thus making $T\Delta S^\circ$ less unfavourable.

Protonated amino acids (cationic state) may be taken as ground-state models for the TS complexes in the acid catalysed hydrolysis of esters. The average values are $\Delta H^\circ = +2.5$ kJ/mol and $T\Delta S^\circ = -11$ kJ/mol at 25 °C.¹⁸ The magnitude of the entropy term is now less negative than for neutral RCO_2H because the cost of hydration of H^+ is partly offset by the desolvation of the conjugate cationic acid. The same predominance of entropy over enthalpy is observed in protonated organic weak oxygen bases such as ethanol, diethyl ether or acetone in water solvent: $\Delta H^\circ = +2.6$ kJ/mol and $T\Delta S^\circ = +16$ kJ/mol at 25 °C.¹¹

The five aryl-acetate $\text{p}K_a(\text{TS})$ values produce a Hammett $\rho = 1.5 \pm 0.2$. This value indicates that the effect of substituent in the aromatic ring is quite significant, even across the bridging oxygen atom. Major electronic effects are expected to operate through the relatively weak and polarisable bonds of the TS complex, which are significantly being perturbed during the course of the reaction.² The strong bonds in reactant molecules and those “non-reacting” bonds in the TS complex are less likely to be perturbed by the action of substituents. As a way of comparison, this Hammett ρ parameter is certainly larger than $\rho = 0.47$, for the ionisation of $\text{ArCH}_2\text{-CO}_2\text{H}$ in water solvent at 25 °C.¹⁹

Linear free-energy relationships such as equation 4 exist when substituents and reaction centre interact by only a single physical mechanism.¹⁹ Thus, it can be expected the glyceryl ester not to obey equation 4, because its TS complex interacts with solvent molecules mainly through hydrogen bonding, whereas the main interaction mechanism for the alkyl and aryl homologues with solvent water is of electrostatic nature.

TS carbonyl vibrational stretching frequency

Equation 2 allows the calculation of $n_{\text{CO}^\ddagger} = 1.3 \pm 0.1$ for the group of esters. This result leads to a value of $f_v^\ddagger = 7.6 \pm 0.1$ mdyne \AA^{-1} .

The vibrational frequency of the carbonyl C-O bond in the TS of the acid-catalysed hydrolysis of esters is now obtainable from the carbonyl stretching frequency of esters of 1730 cm^{-1} :

$$\omega_{\text{C=O}^\ddagger} / \omega_{\text{C=O}}^{\text{Ester}} = (f_v^\ddagger / 12.6 \text{ mdyne } \text{\AA}^{-1})^{1/2}$$

$$\omega_{\text{C=O}^\ddagger} = 1730 \text{ cm}^{-1} (7.6/12.6)^{1/2} \approx 1300 \text{ cm}^{-1}$$

The precision of $\omega_{\text{C=O}^\ddagger}$ is $\pm 100 \text{ cm}^{-1}$. It is very interesting to point out that Mitton and Schowen²⁰ reported a value of $1300 \pm 200 \text{ cm}^{-1}$ for the carbonyl stretching mode in the TS complex of the methoxide-catalysed methanolysis of 4-bromophenyl benzoate. Their result was derived from a carbonyl $^{18}\text{O}/^{16}\text{O}$ kinetic isotope effect. A similar value results from the carbonyl $^{12}\text{C}/^{13}\text{C}$ kinetic isotope effect in the saponification of methyl formate, measured by Marlier.²¹

These results suggest that similar TS structural features occur in the lyonium and lyate catalysed solvolyses of carboxylic esters.

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