

Hydroxide as General Base in the Saponification of Ethyl Acetate

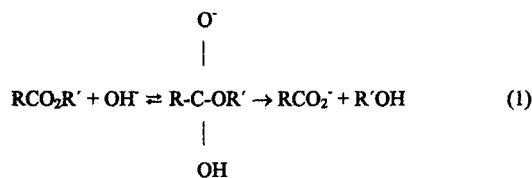
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Abstract: The second-order rate constant for the saponification of ethyl acetate at 30.0 °C in H₂O/D₂O mixtures of deuterium atom fraction *n* (a *proton inventory* experiment) obeys the relation $k_2(n) = 0.122 \text{ s}^{-1} \text{ M}^{-1} (1 - n + 1.2n) (1 - n + 0.48n)/(1 - n + 1.4n) (1 - n + 0.68n)^3$. This result is interpreted as a process where formation of the tetrahedral intermediate is the rate-determining step and the transition-state complex is formed via nucleophilic interaction of a water molecule with general-base assistance from hydroxide ion, opposite to the direct nucleophilic collision commonly accepted. This mechanistic picture agrees with previous heavy-atom kinetic isotope effect data of Marlier on the alkaline hydrolysis of methyl formate (Marlier, J. F. *J. Am. Chem. Soc.* **1993**, *115*, 5953).

The alkaline hydrolysis of carboxylic esters in solution is commonly accepted to take place by a two-step mechanism, where formation of the tetrahedral intermediate is strongly rate-determining¹ and occurs through direct nucleophilic collisions between hydroxide ions and ester molecules (eq 1, the B_{AC}2 mechanism).



Marlier² challenged this commonly held view in 1993 on the basis of heavy-atom kinetic isotope effect experiments. The author measured carbonyl carbon and oxygen as well as nucleophilic oxygen kinetic isotope effects for the alkaline hydrolysis of methyl formate in water solvent at 25 °C. Carbonyl oxygen $k_{16}/k_{18} = 0.999$, carbonyl carbon $k_{12}/k_{13} = 1.038$, and oxygen nucleophile $k_{16}/k_{18} = 1.023$ were interpreted as consistent with a stepwise mechanism with rate-limiting formation of the tetrahedral intermediate. The isotope effect on the oxygen nucleophile was interpreted as a molecular event where the attacking nucleophile in aqueous alkali is water, with general base assistance from hydroxide.

Hydroxide ion is strongly solvated in aqueous environment, as can be inferred from its high enthalpy of hydration of -423.4 kJ/mol .³ A direct ester/OH⁻ nucleophilic collision must involve a great amount of desolvation energy. Esters of carboxylic

acids undergo alkaline hydrolysis with relatively low enthalpies of activation, e.g., 40 kJ/mol for ethyl formate, 43 kJ/mol for ethyl acetate, 44 kJ/mol for ethyl isobutyrate, and 52 kJ/mol for ethyl pivalate,¹ too low a value to account for extensive desolvation.

Kinetic data on the saponification of ethyl acetate in mixtures of water and organic solvents show that one water molecule is involved in the formation of the transition-state (TS) complex. These cases include acetone–H₂O mixtures in the range from pure water to a water concentration of 22 M,⁴ dioxane–H₂O mixtures over the water concentration range from 24 to 53 M,⁴ and DMSO–H₂O mixtures with water concentrations from 5 to 25 M.⁵ This idea of general-base catalysis also fits well with the intuitive picture of a moving negatively charged “OH” atomic configuration, randomly diffusing in aqueous media via a Grotthuss mechanism,⁶ until it becomes attached to the aqueous solvation sphere of the ester. Once in place, the TS complex for ester alkaline hydrolysis may be formed through the intermediacy of a bridging water molecule. Thus, considerations other than Marlier’s kinetic isotope effects also suggest the direct nucleophilic collision as a less likely mechanism for the saponification of carboxylic esters.

A *proton inventory* experiment⁷ for the saponification of a common carboxylic ester will clearly discriminate the direct nucleophilic collision from the general-base-catalyzed mechanism, since this kind of probe allows the determination of the minimal structure of the TS complex. A minimal structure includes all the reacting molecules and ions involved in the formation of the TS complex, without details about the configuration of loosely bound solvent molecules.

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Table 1. Second-Order Specific Rates for the Saponification of Ethyl Acetate at 30.0 °C in Mixtures of H₂O/D₂O of Deuterium Atom Fraction *n*

<i>n</i>	<i>k₂(n)</i> /s ⁻¹ M ⁻¹
0.000	0.122 ± 0.007
0.190	0.128 ± 0.007
0.237	0.13 ± 0.01
0.438	0.138 ± 0.003
0.609	0.144 ± 0.002
0.998	0.160 ± 0.001

This paper presents the proton inventory for the saponification of ethyl acetate at 30.0 °C. The results agree with the mechanism proposed by Marlier.

Experimental Section

Materials. Ethyl acetate (BDH) was distilled under normal pressure. Deuterium oxide (99.8%) was from Aldrich.

Preparation of Solutions. The mixtures were prepared gravimetrically in 100 or 50-mL volumetric flasks. A predetermined amount of aqueous 0.1 M NaOH was used in their preparation to yield final NaOL (L = H, D) concentrations of about 10 mM, except the case of 99.8% D₂O, where metallic sodium was used to make NaOD.

Kinetic Runs and Data Treatment. The reaction temperature was 30.0 °C. The reactions were started by addition of enough ethyl acetate to the NaOL/L₂O solution, so that equimolar initial quantities of both reagents were present. Sampling was done every five minutes. Titration of the remaining amount of NaOL with 0.0100 M HCl/neutral red in 2000-μL aliquot portions was done by means of a Gilmore microburet. Each run was followed to at least 75% of completion. The rate determinations in the L₂O mixtures were carried out in duplicate, the D₂O experiment was done in triplicate, and the H₂O experiment was run five times.

Second-order rate constants were obtained as the slopes of 1/[NaOL] vs reaction time plots by linear least-squares fitting.

Results and Discussion

Specific-Rate Values. The saponification of ethyl acetate with NaOH in water solvent obeys the rate law

$$-d[\text{NaOH}]/dt = k_2[\text{NaOH}][\text{AcOEt}]$$

Table 1 gives the second-order rate constants in different H₂O/D₂O mixtures of deuterium atom fraction *n*. The inverse overall kinetic solvent isotope effect $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 0.76 \pm 0.01$ agrees quite well with the reported value of 0.75 for this reaction.⁸ The rate data have standard errors ranging from 0.3% up to 8% (average 3% standard error). Thus, there is no need to analyze this set of data at statistical certainties greater than 95% (vide infra).

Proton Inventory. The purpose of a proton inventory experiment is to determine how many exchangeable hydrogenic sites contribute to the observed overall solvent kinetic hydrogen isotope effect. In this kind of study, one relates the observed $k_2(n)$ and *n* data pairs through the Gross–Butler equation⁷

$$k_2(n) = k_2(n=0) \frac{\text{TS}}{\prod (1-n+n\phi_{\text{TS}})} \frac{\text{R}}{\prod (1-n+n\phi_{\text{R}})} \quad (2)$$

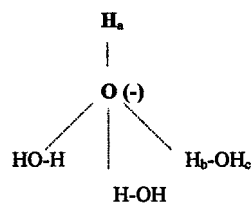
where the ϕ values are the isotopic fractionation factors for all exchangeable hydrogenic sites in the TS complex and reactant

species (R). Each ϕ value gives the ratio of the preference for deuterium over protium relative to the similar preference in bulk solvent molecules.

For the system under study, one has

$$k_2(n) = k_2(n=0) \frac{\text{TS}}{\prod (1-n+n\phi_{\text{TS}})} / \text{reactant-state contribution} \quad (3)$$

The structural model of Gold and Grist for aqueous hydroxide is the most appropriate for the interpretation of proton inventory data⁹ because it takes into account the strong specific solute–solvent interactions inherent to the structure of aqueous hydroxide. The ion is considered as being tightly solvated by three water molecules, as shown in the following structure:



The Gold–Grist model gives the values $\phi_a = 1.2–1.5$, $\phi_b = 0.65–0.70$, and $\phi_c = 1$. The mean values 1.4, 0.68, and 1.0 will be used, respectively. Thus

$$\text{reactant-state contribution, RSC}(n) = (1-n+1.4n)(1-n+0.68n)^3 \quad (4)$$

and

$$\text{transition-state contribution, TSC}(n) = \frac{\text{TS}}{\prod (1-n+\phi_{\text{TS}}n)} \quad (5)$$

Inserting eqs 4 and 5 into eq 3 and solving for TSC(*n*) gives:

$$\text{TSC}(n) = k_2(n)(1-n+1.4n)(1-n+0.68n)^3/k_2(n=0) \quad (6)$$

Once the contributions from all reactant species are stated from known experimental or calculated fractionation factors,⁷ the next step in the interpretation of the data is carrying out a polynomial analysis of TSC(*n*). This analysis determines the number of hydrogenic sites that, in the transition state, make the greatest contributions to the overall kinetic isotope effect. The mathematical description of the TSC(*n*) data as a function of *n* should lead to the minimal structure of the TS complex.

Figure 1 shows the rate data as a curve increasing with *n*. The qualitative meaning of the positive slope is that TSC(*n*) > RSC(*n*) and the curvature suggests a multiproton mechanism.

Polynomial fitting was performed on the TSC(*n*) data. The values of total standard deviation are 0.0138 for linear fit, 0.00269 for quadratic, and 0.00308 for the cubic function. Intuition calls for quadratic fit, since no reasonable mechanism can be envisioned for a process involving three protons undergoing bonding changes in the TS, while it is easy to visualize a two-proton process.

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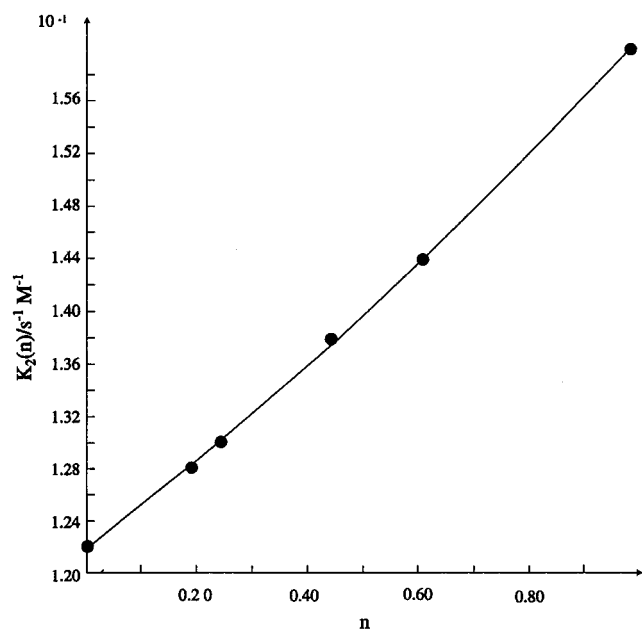


Figure 1. Proton inventory of the saponification of ethyl acetate at 30.0 °C. Data points are fitted to eq 8.

The analysis of variance allows us to make the final choice. Two analyses of variance were carried out. Since the precision of the $k_2(n)$ values was fair but far from optimal, the analyses were run separately with the six TSC(n) values (from the nominal six rate values) and with the 18 data pairs calculated from the six $k_2(n)$'s plus the 12 values corresponding to $k_2(n) \pm$ one standard error.

The first calculation rendered the quadratic term to be statistically significant at the 99% certainty level. This result was doubtlessly due to a fortunate cancellation of errors, but speaks in favor of the validity of the quadratic term in TSC(n). The second calculation took into account the actual quality of the data. In this case, for the quadratic term, Fisher $F = 4.17$, $p = 0.06$.¹⁰

The best quadratic fit to the data resulted as

$$\text{TSC}(n) = 1 - 0.32n - 0.093n^2 \quad (7)$$

Thus, the relationship between $k_2(n)$ and n for the saponification of ethyl acetate at 30.0 °C is given by

$$k_2(n) = (0.122 \text{ s}^{-1} \text{ M}^{-1})(1 - 0.32n - 0.093n^2)/(1 - n + 1.4n)(1 - n + 0.68n)^3 \quad (8)$$

Mechanism for the Saponification of Carboxylic Esters.

The basic hydrolysis of esters has been extensively studied in the liquid phase¹ as well as experimentally¹¹ and theoretically¹² in the gas phase.

Riveros and Takashima observed that the methyl esters of formic, pivalic, and benzoic acids react with OH^- in the gas phase via the $\text{B}_{\text{AC}2}$ hydrolytic pathway and $\text{S}_{\text{N}2}$ at the methyl group. The $\text{B}_{\text{AC}2}/\text{S}_{\text{N}2}$ product ratios were found to be 2.7, 9.0, and 12, respectively.^{11a} This result indicates that, unlike in the solution process, there is negligible steric effect for the $\text{B}_{\text{AC}2}$ process in the gas phase. This observation led Takashima and Riveros to state that the salient dynamic feature of the $\text{B}_{\text{AC}2}$ mechanism in the gas phase was "the ease with which the tetrahedral intermediate evolves into the products". The data

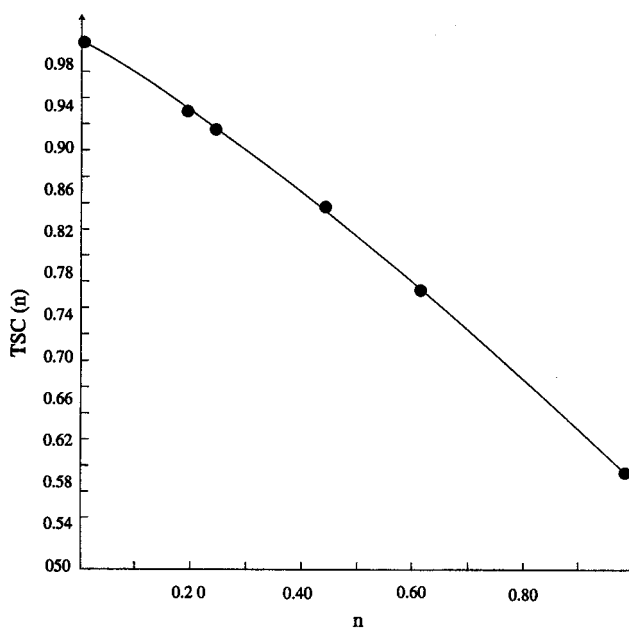


Figure 2. TSC (n) data fitted to $(1 - n + 1.2n)(1 - n + 0.48n)$.

available for the saponification of methyl formate in the gas phase suggest that it proceeds with little or no activation energy.^{11a} Quantum mechanical calculations of Ornstein et al.¹² have yielded results that indicate the breakdown of the tetrahedral intermediate as rate determining in the gas-phase alkaline hydrolysis of methyl, ethyl, and isopropyl acetates. This theoretical result agrees with those of Riveros and contrasts with experience in solution.

Fink and Hadad^{11b} studied the gas-phase reaction of the simple esters HCO_2Me , HCO_2Et , $\text{CH}_3\text{CO}_2\text{Me}$, and $\text{CH}_3\text{CO}_2\text{Et}$ with different nucleophiles. The authors found the hard NH_2^- to react faster than the soft $\text{N}\equiv\text{CCH}_2^-$ anion via the $\text{B}_{\text{AC}2}$ mechanism, followed by a proton transfer within the ion-molecule complex, to yield the corresponding alcohols and RCNH^- and $\text{RC}(\text{O}^-)=\text{CH}_2\text{CN}$, respectively. However, the extent of $\text{B}_{\text{AC}2}$ reaction among the possible reaction channels (proton-transfer, $\text{S}_{\text{N}2}$, E_2 , and $\text{B}_{\text{AC}2}$) was larger for the bulkier nucleophile. Carbonyl groups are considered hard centers, responsive, to the basicity of the nucleophile.¹³ The observed kinetic trends suggest that formation of the nucleophile-carbonyl bond is not rate determining in the gas phase, a result in agreement with the early proposal of Riveros.^{11a}

Solvent plays a fundamental role in the saponification of carboxylic esters, much beyond the naïve consideration as only a material medium, that has an effect on both the frequency of molecular collisions and long-range chemical interactions with reactants and TS complexes. This assertion is based on experimental results that point to the formation of the tetrahedral intermediate as rate-determining step in solution¹ and the existence of steric hindrance to its formation. An appropriate mechanistic picture for this system must take into account the solvent molecules that should be included in the minimal TS structure.

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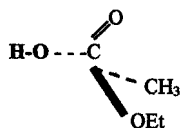
The $TSC(n)$ data were fitted to eq 9 with the computer program package ENZFITTER.¹⁴ The *best* fractionation factors for the quadratic polynomial were

$$TSC(n) = (1 - n + \phi_1 n)(1 - n + \phi_2 n) \quad (9)$$

$$\phi_1 = (1.20 \pm 0.01)\phi_2 = 0.482 \pm 0.006$$

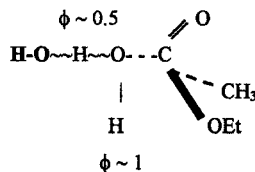
Figure 2 shows the result. These numerical values can be translated into a TS structure.

A TS complex resulting from the direct nucleophilic collision could be depicted as follows:



Such a structure requires a linear $TSC(n)$ function because of the involvement of only one hydrogen, a situation in disagreement with experiment.

The mechanism of Marlier implies the following minimal TS structure:



The values of ϕ can be predicted from independent mechanistic and structural studies. The type of *in-flight* bridging protons is known to have a fractionation factor of the order of

0.5. The proton attached to the nucleophile oxygen atom resembles those in *gem*-diols and hemiketals, for which a ϕ value of 1.2 was reported,¹⁵ though Wolfenden¹⁶ showed this value to have been overestimated by about 10%. Therefore, its magnitude can be taken as close to 1.0. The third proton in the “HO” configuration must have a fractionation factor between 1.4 (as in hydroxide) and the value 1.0, as in a fully formed water molecule. *Formyl* hydrogen kinetic isotope effect for the alkaline hydrolysis of methyl formate allowed Kirsch et al.¹⁷ to estimate that the TS is located at about 40% along the reaction coordinate toward the tetrahedral intermediate. This means the hydroxide character has been reduced to about 60% in the TS. Thus, $\phi = 1.4^{0.6} = 1.2$ in fine agreement with experiment.

The results of this work support the predictions derived from the mechanism of Marlier for the alkaline hydrolysis of carboxylic esters.

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