# **Spontaneous Hydrolysis of Ethyl Formate: Isobaric Activation Parameters**

J. F. MATA-SEGREDA

School of Chemistry, University of Costa Rica, 2060 Costa Rica Received 3 May 1999; accepted 17 September 1999

ABSTRACT: Ethyl formate undergoes spontaneous autocatalytic hydrolysis via water catalyzed (neutral), as well as hydrogen-ion catalyzed mechanisms. The activation parameters for the neutral reaction are  $\Delta H^{\ddagger} = 91 \pm 8$  kJ/mol and  $\Delta S^{\ddagger} = -48 \pm 8$  J K<sup>-1</sup>/mol. This result is in contrast to the values reported in the hydrolyses of the more polar activated haloesters. The specific rate of neutral hydrolysis of ethyl acetate can also be predicted. © 2000 John Wiley & Sons, Inc. Int J Chem Kinet 32: 67–71, 2000

# INTRODUCTION

Esters with electron-withdrawing substituents in either the acyl or alkyl moieties undergo hydrolysis in the absence of added acid or base. This is a special case of general base catalysis by water itself, the so-called *neutral* or *water-catalyzed* hydrolysis of esters [1-3].

The neutral hydrolyses of carboxylic anhydrides and activated amides and esters take place with: (i) high solvent deuterium kinetic isotope effects in the range from 2 to 4, (ii) large rate-decreasing salt effects, (iii) very negative entropies of activation in the range from -0.05 to -0.2 kJ K<sup>-1</sup>/mol, and (iv) large negative volumes of activation from -9 to -22 cm<sup>3</sup>/mol.

The low entropies are counterbalanced by low enthalpies of activation (from 25 kJ/mol to 80 kJ/mol), these latter being the result of the high electrophilic character of the carboxyl carbon atom bound to electron-withdrawing substituents.

These kinetic features suggest transition state (TS) structures in which many solvent molecules are immobilized and subjected to electrostriction associated with the solvation of developing charges and the transfer of protons. The commonly accepted minimal structure for the TS complex is the following:



in which a second  $H_2O$  molecule acts as the general base, abstracting a proton from the nucleophilic  $H_2O$ . There is experimental [16,18] and theoretical [21,22] basis to consider a cyclic atomic array made of one RCO-X molecule and three water molecules, as a more complete picture of the TS complex.

Esters of formic acid also undergo neutral hydrolysis, at faster rates compared with the corresponding acetates. The reason for this rate differential is doubtlessly the result of decreased steric retardation and electron release. Furthermore, hyperconjugation exerted by the methyl group in acetate esters is absent in formates. Thus, the electrophilic character of the carboxyl carbon atom in formates is greater, resulting in their increased hydrolytic fragility.

Ethyl formate undergoes this spontaneous process through two parallel mechanistic pathways: water catalysis and specific hydrogenion catalysis. The second

Correspondence to: J. F. Mata-Segreda

<sup>© 2000</sup> John Wiley & Sons, Inc. CCC 0538-8066/00/010067-05

process arises from the accumulation of hydrogen ion in the medium, derived from the ionization of the relatively strong formic acid ( $pK_a = 3.751$  at 25°C) formed as one of the reaction products. (See equations that follow.)

$$HCO_{2}Et + H_{2}O \longrightarrow HCO_{2}H + EtOH$$
$$HCO_{2}H = H^{+} + HCO_{2}^{-}$$
$$HCO_{2}Et + H_{2}O \xrightarrow{H^{+}} HCO_{2}H + EtOH$$
$$d[HCO_{2}H]/dt = k_{1} [HCO_{2}Et]$$
$$+ k_{2} [H^{+}] [HCO_{2}Et]$$
(1)

During the early stages of the reaction, the slower water-catalyzed hydrolysis route is the main kinetic contributor. As H<sup>+</sup> accumulates, the second mechanism becomes more significant. The reaction progress curve of this process is thus expected to be of sigmoidal shape. This kinetic scheme is similar to the autocatalyzed reduction of aqueous toluidine blue by phenyl hydrazine reported by Jonnalagadda and Nattar [23].

It can be safely hypothesized that the water-catalyzed hydrolysis of alkyl formates should involve a much higher  $\Delta H^{\ddagger}$  and a less negative  $\Delta S^{\ddagger}$  than the values observed for haloesters and anhydrides, due to the absence of polar substituents.

This account presents the isobaric activation parameters, at normal pressure, for the water-catalyzed hydrolysis of ethyl formate and a discussion of the kinetic features of this autocatalytic reaction.

### **Materials**

Ethyl formate (Eastman) was distilled from CaO to eliminate both free EtOH and  $HCO_2H$  formed on standing on the shelf.

### **Kinetic Measurements and Data Treatment**

The experiments were done by titration of  $HCO_2H$  formed with NaOH/bromocresol green (pH range 3.8–5.4), in runs made by mixing 0.10 dm<sup>3</sup> of distilled water with 3.0 cm<sup>3</sup> of the ester. The amount of sampling was always 3.00 cm<sup>3</sup> aliquots, titrated against 0.1 mol/dm<sup>3</sup> NaOH. This procedure ensures a maximum error of 1% in the early titrations. In all experiments, more than ten data points were collected (90% or more of the total extent of reaction).

The raw data were fitted to the integrated form of Eq. (1):

$$\ln\{[\text{HCO}_{2}\text{H}]_{\infty}/([\text{HCO}_{2}\text{H}]_{\infty} - [\text{HCO}_{2}\text{H}])\} = k_{1}t + k_{2} \int_{0}^{t} [\text{H}^{+}]dt \quad (2)$$

From the point of view of statistical analysis, Eq. (2) is a multilinear regression equation, where time and the cumulative hydrogenion concentration ( $\int [H^+] dt$ ) are the independent variables. Yamasaki et al. have published a method for the calculation of rate constants from "linear" rate equations similar to the case at hand [4]. However, the much lower number of measurements allowed by the experimental procedure and the uncertainty associated with the cumulative hydrogenion concentration restrict the quality of the regression coefficients from this numerical method (see later).

Thus, the following "chemical" approach was taken. In separate runs, the values of  $k_2$  were determined in the presence of dilute HCl ( $0.05 - 0.10 \text{ mol}/\text{dm}^3$ ). The second-order rate constants were calculated by dividing the observed pseudo-first-order specific rates by the corresponding values of [HCl].

The  $k_1$  values were determined as the slopes in Eq. (3b):

$$g(t) = \ln[\text{HCO}_2\text{H}]_{\infty} - ([\text{HCO}_2\text{H}]_{\infty} - [\text{HCO}_2\text{H}]) - k_2 \int_0^t [\text{H}^+]dt \quad (3a)$$

$$g(t) = k_1 t \tag{3b}$$

The cumulative hydrogenion concentration was obtained by fitting the  $[H^+]$  – time data pairs to a cubic polynomion and subsequent analytical integration. The cubic fit was empirically found to provide the smallest variance, in all cases. The  $[H^+]$  values were calculated from the pK<sub>a</sub> of formic acid, which is almost temperature independent in the thermal range (e.g., 30–50°C) of this study [1 and tables in *CRC Handbook of Chemistry and Physics*].

## **RESULTS AND DISCUSSION**

#### **Activation Parameters**

The acid-catalyzed hydrolysis of HCO<sub>2</sub>Et shows no extraordinary features. The second-order specific rates in Table I yield the values of  $60 \pm 2$  kJ/mol for the enthalpy barrier and an entropy of activation of  $-89 \pm 7$  J K<sup>-1</sup>/mol. This result agrees with the results from the literature [2]: 60.5 kJ/mol and -86 J K<sup>-1</sup>/mol.

Figure 1 shows the reaction progress curves for the spontaneous hydrolysis of HCO<sub>2</sub>Et at different temperatures. The sigmoidal curves tend to become more hyperbolical as the temperature increases. This behav-



Spontaneous hydrolysis of HCOOEt

Figure 1 Reaction progress curves for the spontaneous hydrolysis of ethyl formate in water solvent.

ior agrees qualitatively with the expectation that the water-catalyzed reaction must proceed with a high enthalpy of activation, as stated in the hypothesis. Reactions with high-energy barriers are greatly accelerated by temperature, compared with reactions of lower  $\Delta$ H<sup>‡</sup>. At higher temperatures, faster reaction via the water-catalyzed mechanism results in earlier accumulation of H<sup>+</sup> in the medium and the earlier predominance of the faster H<sup>+</sup>-catalyzed reaction.

Table I gives the  $k_1$  and activation parameters for the water-catalyzed hydrolysis of HCO<sub>2</sub>Et. The uncertainty limits in  $k_1$  are in the range from 3% up to 13%, higher than what is customary for solution kinetics. The algorithm used involves the unavoidable build up and spread of errors in the data trios: time, [HCO<sub>2</sub>H] and  $\int [H^+] dt$ . Nevertheless, the plot  $\ln(k_1/t)$ 

**Table I**Isobaric Activation Parameters at NormalPressure for the Spontaneous Hydrolysis of EthylFormate in Water Solvent

Temperature/K	$10^5 k_1/s^{-1}$	$10^3 k_2/s^{-1} \text{ mol}^{-1} \text{ dm}^3$
303.2	$0.78 \pm 0.06$	$5.01 \pm 0.03$
310.2	$2.1 \pm 0.1$	$5.23\pm0.05$
312.8	$3.1 \pm 0.4$	$9.9 \pm 0.1$
318.4	$5.8 \pm 0.2$	$17 \pm 1$
323.0	$6.7 \pm 0.3$	_
$\Delta H^{\ddagger}/kJ \ mol^{-1}$	91 ± 8	$60 \pm 3$
$\Delta S^{\ddagger}/J K^{-1} mol^{-1}$	$-48 \pm 8$	$-89 \pm 7$

T) vs. 1/T gives an acceptable linear correlation  $y = (18 \pm 3) - (11 \pm 1) \times 10^3 x$ , with r = 0.98, p < 0.005.

Quantum mechanical calculations carried out by Wolfe et al. [22] yielded a value of 66 kJ/mol for the water-catalyzed hydration of formaldehyde in water solvent. This substrate has a more electrophilic carbonyl carbon atom than the ester carbonyl. As it should be expected, this enthalpy barrier is lower than the experimental value of  $\Delta H^{\ddagger} = 91 \pm 8$  kJ/mol for the water catalyzed hydrolysis of HCO<sub>2</sub>Et.

In contrast, the entropies of activation for these two reactions must be similar; a value of -51 J K<sup>-1</sup>/mol for the hydration of CH<sub>2</sub>O and  $-48 \pm 8$  J K<sup>-1</sup>/mol for the hydrolysis of HCO<sub>2</sub>Et.

Multiple simultaneous fitting of the data to Eq. (2) gives regression coefficients that agree with the specific rates in Table I, but only within an order of magnitude. Nevertheless, analysis of variance (ANOVA) indicates that both "independent variables" in Eq. (2) are statistically significant at p = 0.01. The correlation equation for the *multifit rates* (*x*) and the *chem* rates (*y*) obtained from Eq. (3 b) is  $y = (1.2 \pm 0.7) + (0.8 \pm 0.2) x$ , r = 0.91, and p = 0.95 (*multifit* values not shown).

The failure in the attempt to produce rate constants from the linear treatment of Eq. (2) is due to the relative scarcity of data points (10–15 points) and the higher uncertainty of the  $\int [H^+] dt$  values, compared with time alone. Both variables are weighted equally,



**Figure 2** Isergonic plot for the water-catalyzed hydrolyses of haloesters, carboxylic anhydrides and amides in water solvent.

though their degrees of accuracy are not the same. No further discussion is devoted to this calculation method, because it produced unreliable results.

As noted earlier, an enthalpy-entropy correlation can be observed for the neutral hydrolysis of esters, amides, and carboxylic anhydrides. There is experimental evidence indicating that for all these substrates, solvent and TS complexes interact essentially by only a single physical mechanism. Figure 2 shows activation figures for a group of haloesters, amides, and carboxylic anhydrides [2,3,14–17]; the data pair found for ethyl formate in this work fits well within the set of data. The isokinetic temperature observed is  $276 \pm$ 30 K (r = 0.89, p < 0.005). This value is in the range associated with solvation effects in aqueous media (isokinetic temperatures around 300 K), which arise from both electronic as well as steric interactions [19].

It is interesting to note that the isokinetic temperature for the acid-catalyzed hydrolysis of alkyl acetates and thioacetates is 330 K, in 62% aqueous acetone [19]. The similarity between the isokinetic temperatures for the neutral and acid-catalyzed reactions is somewhat to be expected because in the words of Kirby [2]: "Since a protonated ester may be regarded as a reactive ester bearing a strongly electron-withdrawing substituent on the carbonyl oxygen atom it is not unreasonable to suppose that they will react with water similarly to esters with strongly electron-withdrawing substituents in the other two positions."

The water-catalyzed hydrolysis of ethyl formate was studied, among other aryl and alkyl formates, by Stefanidis and Jencks [5]. These authors reported  $k_1 = 2.1 \times 10^{-7} \text{ s}^{-1}$  for HCO<sub>2</sub>Et at 25°C in 1.0 mol/dm<sup>3</sup> KCl. This value agrees (within a factor of 2) with  $4.2 \times 10^{-7} \text{ s}^{-1}$ , found by Sawyer and Kirsch [6] for the hydrolysis of HCO<sub>2</sub>Me under the same conditions. The  $k_1$ 's obtained in this work seem much higher, at first glance, than what would be expected from the results of these authors.

The hydrolysis of HCO<sub>2</sub>Et at 30°C was studied in the presence of 1.0 mol/dm<sup>3</sup> KCl to assess the salt effect. The result was 10<sup>6</sup>  $k_1 = 6.0 \pm 0.7 \text{ s}^{-1}$  and 10<sup>3</sup>  $k_2 = 5.56 \pm 0.07 \text{ s}^{-1} \text{ mol}^{-1} \text{ dm}^3$ . The effect of 1.0 mol/dm<sup>3</sup> ionic strength is a 30% depression in  $k_1$ . The magnitude of the effect is similar to that observed in the neutral hydrolyses of CHF<sub>2</sub>CO<sub>2</sub>Et [7], CF<sub>3</sub>COSEt [8], and acetic anhydride [9]. Thus, the  $k_1$  value of Stefanidis and Jencks corrected for the inhibitory salt effect should be  $2.7 \times 10^{-7} \text{ s}^{-1}$ .

According to the result of this work, the  $k_1$  extrapolated down to 25°C is  $1.9 \times 10^{-6}$  s<sup>-1</sup>, a value that is seven times larger than the one observed by the authors cited. The mismatch is equivalent to a deviation of 4% in  $\Delta G^{\ddagger}$ , an amount lower than the experimental uncertainty associated to the activation parameters.

It is then concluded that, in spite of the degree of uncertainty in the  $k_1$  values and the corresponding activation parameters, the experiment supports the stated hypothesis.

#### **Extrapolation to Ethyl Acetate**

The dynamic features of TS complexes contribute an important aspect of mechanistic chemistry, not only for the study of simple reactions, but also for the understanding of enzymic reactions, be it aimed at basic bioorganic studies or design of drugs. Simple models, such as the present, are useful in setting limits to the intrinsic stereodynamic features of chemical reactions in solution.

The quantitative features of the neutral hydrolysis of  $HCO_2Et$  indicate that protonation of the *neutral* TS complex decreases the enthalpy of activation by about 30 kJ/mol, and that the higher degree of solvent electrostriction associated to the protonated complex is evidenced by a  $\Delta S^{\ddagger}$  value 40 J K<sup>-1</sup>/mol more negative than the value for the neutral hydrolytic reaction.

The thermodynamic activation requirements should be much more stringent for the water-catalyzed hydrolyses of alkyl carboxylates other than for formates or esters bearing electron-withdrawing substituents vicinal to the carboxyl moiety. One obvious case is ethyl acetate. A half-life of 89 years was estimated by Skrabal and Zahorka in 1929 [cited in reference 2] for this reaction at 25°C in water solvent ( $k_1 = 10^{-9.6} \text{ s}^{-1}$ ).

The  $\Delta H^{\ddagger}$  for the hydrogen-ion catalyzed hydrolysis of CH<sub>3</sub>CO<sub>2</sub>Et is equal to 68 kJ/mol [10]. For the neutral reaction, the corresponding  $\Delta H^{\ddagger}$  can be expected to be just around 0.10 MJ/mol.

 $\Delta S^{\ddagger}$  can be estimated by following this rationale. The entropies of the TS complexes in the alkaline hydrolyses of acetates are more negative than for formate hydrolysis by about 21 J K<sup>-1</sup>/mol [11]. This result has been interpreted in terms of freezing of the rotational degree of freedom of the methyl group in acetates. This rigidity may be due to a greater degree of solvent immobilization for acetate TS as compared with formate TS. Basically, the same result is observed when comparing the saponification of ethyl acetate and  $\gamma$ -butyrolactone [12], because there is no rotating methyl group in the lactone ring.

Use of Eyring's equation with  $\Delta H^{\ddagger} = 105 \pm 5 \text{ kJ/}$ mol and  $\Delta S^{\ddagger} = -69 \text{ J K}^{-1}/\text{mol} (-48 \text{ J K}^{-1}/\text{mol} - 21 \text{ J K}^{-1}/\text{mol})$  yields  $k_1 = 10^{-9.2 \pm 0.8} \text{ s}^{-1}$ , a number in agreement with the estimate of Skrabal.

A similar result is obtained on consideration of the effect of replacing a hydrogen atom by a methyl group in the hydration of H<sub>2</sub>CO and CH<sub>3</sub>CHO, and of HCO<sub>2</sub>Me and CH<sub>3</sub>CO<sub>2</sub>Me to give the corresponding tetrahedral *gem*-diols. This structural effect has been estimated to be  $\delta\Delta G^{\circ} \approx \delta\Delta G^{\ddagger} = 20$  kJ/mol [13,20–22]. The specific rate for the neutral hydrolysis of CH<sub>3</sub>CO<sub>2</sub>Et at 25°C can then be calculated by correcting the value for HCO<sub>2</sub>Et by the magnitude of the stereoelectronic effect due to the H/CH<sub>3</sub> replacement:

$$k_1(CH_3CO_2Et) = 1.9 \times 10^{-6} \text{ s}^{-1} \times \exp(-20 \times 10^3/RT)$$
  
 $k_1(CH_3CO_2Et) = 10^{-9.2} \text{ s}^{-1}$ 

The results obtained for the spontaneous catalyzed hydrolysis of  $HCO_2Et$  are consistent with the behavior of the much less reactive acetate analogue. This consistency is an indirect way to check on the validity of the rate constants and activation parameters determined in this study.

The author wishes to express his gratitude to Prof. William P. Jencks and to Dr. Dimitros Stefanidis for their collegial assistance, concerning the magnitude of the rate constants in this work.

#### BIBLIOGRAPHY

 Laughton, P. M.; Robertson, R. E. In: Solvent-Solute Interactions; Coetzee, J. F.; Ritchie, C. D. Eds.; Marcel Dekker: New York, 1969.

- Kirby, J. In: Comprehensive Chemical Kinetics, Vol. 10; Bamford, C. H.; Tipper, C. F. H. Eds.; Elsevier: Amsterdam, 1972.
- Jencks, W. P. Catalysis in Chemistry and Enzymology; Dover: New York, 1987.
- 4. Yamasaki, Y.; Watanabe, A.; Kakuda, T.; Tokue, I. Int J Chem Kinet 1998, 30, 47.
- Stefanidis, D.; Jencks, W. P. J Am Chem Soc 1993, 115, 6045.
- Sawyer, C. B.; Kirsch, J. F. J Am Chem Soc 1973, 95, 7375.
- 7. Jencks, W. P.; Carriuolo, J. J Am Chem Soc 1961, 83, 1743.
- Fedor, L. R.; Bruice, T. C. J Am Chem Soc 1965, 87, 4138.
- Bunton, C. A.; Fuller, N. A.; Perry, S. G.; Pitman, I. H. J Chem Soc 1962, 4478.
- 10. The  $\Delta H^{\ddagger}$  for the acid-catalyzed hydrolysis of ethyl acetate was checked in this laboratory, and a value of 68 kJ/mol resulted, in good agreement with the value of 66 kJ/mol in the NBS Tables for Chemical Kinetics.
- Thornton, E. K.; Thornton, E. R. In: Transition States of Biochemical Processes; Gandour, R. D.; Schowen, R. L. Eds.; Plenum Press: New York, 1978; p 34.
- Frost, A. A.; Pearson, R. G. Kinetics and Mechanism, 2nd ed.; John Wiley & Sons: New York, 1963; pp 327– 334.
- 13. Guthrie, J. P. J Am Chem Soc 1973, 95, 6999.
- Bunton, C. A. Fendler, J. H. J Am Chem Soc 1965, 30, 1365.
- Talbot, R. J. E. In: Comprehensive Chemical Kinetics, Vol. 10; Bamford, C. H.; Tipper, C. F. H. Eds.; Elsevier: Amsterdam, 1972.
- Davis, K. R.; Hogg, J. L. J Org Chem 1983, 48, 1041;
  Gopalakrishnan, G.; Hogg, J. L. J Org Chem 1984, 49, 3161.
- Haak, J. R.; Engberts, J. B. F. N. J Am Chem Soc 1986, 108, 1705.
- Venkatasubban, K. S.; Bush, M.; Ross, E.; Schultz, M.; Garza, O. J Org Chem 1998, 63, 6115.
- 19a. Leffler, J. E.; Grunwald, E. Rates and Equilibria of Organic Reactions; John Wiley & Sons: New York, 1963; 19b. Schowen, R. L. J Pharm Sci 1967, 56, 931.
- 20. Critchlow J. E. J Chem Soc Faraday Trans 1 1972, 68, 1774.
- Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. J Am Chem Soc 1983, 105, 31.
- 22. Wolfe, S.; Kim, C. K.; Yang, K.; Weinberg, N.; Shi, Z. J Am Chem Soc 1995, 117, 4240.
- 23. Jonnalagadda, S. B.; Nattar, K. Int J Chem Kinet 1999, 31, 83.