

Measurement of Equilibrium Constants for the Formation of Esters from Aliphatic Carboxylic Acids and Alcohols

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A method for assessing the magnitude of esterification equilibrium constants for a series of alkyl acetates is described. The constants are quite sensitive to electronic effects, with the largest values being obtained for those in which the alkyl groups are electron donating.

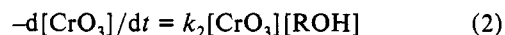
A knowledge of ester equilibria (eq 1) is important to a proper understanding of many processes in organic and bioorganic chemistry. In particular, a number of biological reactions include esters as reactants, intermediates, or final products, and a thorough understanding of these systems therefore requires a quantitative knowledge of the equilibrium constants.



Previous work in this area has often involved the use of aromatic compounds that contain chromophores which can be used to monitor the concentration of one or more of the compounds participating in the equilibrium.¹ The corresponding reactions of aliphatic compounds, which are more directly applicable to biochemical processes but lack suitable chromophores, have been less well studied.

Although there is a substantial amount of information available on the rates of hydrolysis of esters (under both basic² and acidic³ conditions), the corresponding equilibrium constants are not generally available.⁴ A leading textbook,⁵ for example, describes methods that can be used to shift equilibrium 1 to the right and thereby obtain a good yield of ester, but it presents no data related to the magnitude of the equilibrium constants themselves. This paucity of data may be related to the lack of a methodology that can be used to nonevasively assess the concentrations of the reactants and products without altering the equilibrium.

We have recently shown that it is possible to obtain the concentration of an alcohol present in an acidic solution by determining the rate of reduction of chromic acid added (in very small concentrations) to the solution (eq 2).⁶ If k_2 can



be determined independently for the specific reaction conditions, and the rate and chromic acid concentration can be

measured spectrophotometrically, the concentration of the alcohol can be estimated with good accuracy.

Using this approach, the equilibrium constant for each reaction can be measured by two different methods. In the first, the ester is dissolved in an acidic solution and, after equilibrium has been established, the concentration of alcohol present determined by adding a small amount of chromic acid to an aliquot and measuring its rate of reduction spectrophotometrically. In the second method, alcohol is added to a solution of the carboxylic acid and, after sufficient time has elapsed to ensure that the system is at equilibrium, the concentration of unreacted alcohol determined as above. Then, from a knowledge of the initial concentration of carboxylic acid and alcohol or ester, and the measured concentration of alcohol present at equilibrium, it is possible to calculate the equilibrium constant (eq 3)

$$K = \frac{[\text{ester}]_E [H_2O]}{[\text{carboxylic acid}]_E [\text{alcohol}]_E} \quad (3)$$

directly as illustrated in the following examples where the subscripts I and E have been used to designate initial and equilibrium concentrations, respectively.

In the case where ester is added to a solution and allowed to come to equilibrium, $[\text{alcohol}]_E$ is determined experimentally, $[\text{carboxylic acid}]_E$ is equal to $([\text{alcohol}]_E + [\text{carboxylic acid}]_I)$ and $[\text{ester}]_E$ is equal to $([\text{ester}]_I - [\text{alcohol}]_E)$. In the case where the reaction is initiated by addition of alcohol to a solution of the carboxylic acid, $[\text{alcohol}]_E$ is determined experimentally, $[\text{ester}]_E$ is equal to $([\text{alcohol}]_I - [\text{alcohol}]_E)$, and $[\text{carboxylic acid}]_E$ is equal to $([\text{carboxylic acid}]_I - [\text{ester}]_E)$.

EXPERIMENTAL SECTION

Materials. Acetic acid, obtained from Fisher Scientific, was distilled through a 20-cm Vigreux column from 1 wt % chromic acid. The fraction boiling at 117–118 °C was collected and stored in a glass vessel until used.⁷

Gold label (+99%) ethanol, methanol, 1-propanol, 1-butanol, 2-butanol, 1-pentanol, and 1-hexanol, obtained from Aldrich, were dried over anhydrous CaSO₄ for 3 days and then purified by distillation through a 20-cm Vigreux column. Fractions corresponding to the known boiling points of these compounds were collected.

Gold label (+99%) alkyl (methyl, ethyl, *n*-propyl, *n*-butyl, 2-butyl, *n*-pentyl, *n*-hexyl) acetates, obtained from Aldrich, were also purified by the procedure described above. Constant-

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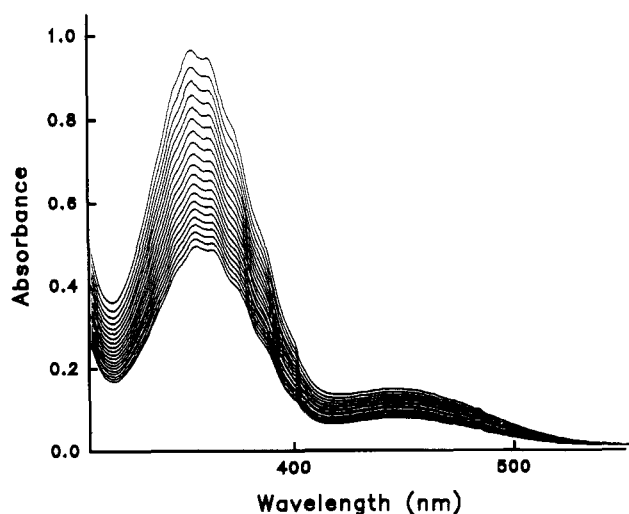


Figure 1. Sequential scans for the oxidation of ethanol by chromate. Spectra taken at 100-s intervals, top to bottom: [ethanol] = 0.103 M, [chromate] = 0.00051 M; temperature 25.0 ± 0.1 °C.

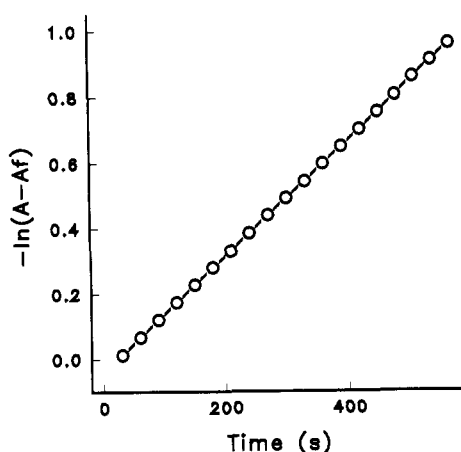


Figure 2. Typical pseudo-first-order rate plot for calculating k_2 : solvent, 50/50 (by volume) aqueous acetic acid; temperature 20.0 ± 0.1 °C; $[\text{HClO}_4] = 0.499$ M, [ethanol] = 0.103 M; slope $1.77 \times 10^{-3} \text{ s}^{-1}$; k_2 slope/[ethanol] = $0.0172 \text{ M}^{-1} \text{ s}^{-1}$; $r = 0.9999$.

boiling fractions were collected for each alkyl acetate and stored in sealed bottles.

Kinetic Methods. A sample (1.8 mL) of 5.54 M HClO_4 was mixed with 10.0 mL of glacial acetic acid and diluted to 20.0 mL with doubly distilled water to give 0.499 M HClO_4 (50/50 by volume). After this solution was kept in a thermostatically controlled water bath for 20 min, an aliquot (2.0 mL) was removed and transferred to a quartz cuvette placed in the thermostated cell compartment of a Hewlett-Packard 8485A spectrophotometer. An appropriate amount of an alcohol was added to the solvent giving a concentration in the range of 0.03–0.12 M. About 1 μL of concentrated chromate solution was added to give an absorbance of ~ 1.0 (0.0005 M chromic acid), and the rate of reduction of chromic acid was determined by monitoring the decrease in absorbance at 355 nm (Figure 1). A typical pseudo-first-order rate plot, used for calculating k_2 , has been reproduced in Figure 2.

At equilibrium, reached after 12 h at constant temperature, the pseudo-first-order rate constant for oxidation of the alcohol was again determined by use of the same procedure under identical conditions. A typical rate plot, used for the calculation of $[\text{alcohol}]_E$, has been reproduced in Figure 3.

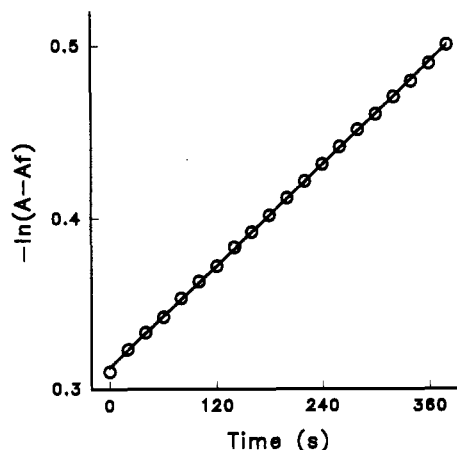


Figure 3. Typical rate plot for calculation of the concentration of ethanol at equilibrium: solvent, 50/50 (by volume) aqueous acetic acid; temperature 20.0 ± 0.1 °C; $[\text{HClO}_4] = 0.499$ M; slope $4.58 \times 10^{-4} \text{ s}^{-1}$; $r = 0.9996$; [ethanol] = slope/ $k_2 = 0.0266$ M.

Table 1. Esterification Equilibrium Constants

ester ^a	K^b	K^c
methyl acetate	5.9 ± 0.2	5.9 ± 0.2
ethyl acetate	9.2 ± 0.1	9.7 ± 0.1
<i>n</i> -propyl acetate	9.4 ± 0.3	10.2 ± 0.7
<i>n</i> -butyl acetate	10.4 ± 0.5	11.6 ± 0.7
<i>s</i> -butyl acetate	4.2 ± 0.1	4.3 ± 0.3
<i>n</i> -pentyl acetate	10.7 ± 0.4	12.2 ± 0.3
<i>n</i> -hexyl acetate	11.0 ± 0.2	11.9 ± 0.6

^a Experimental conditions: temperature 20.0 ± 0.1 °C; $[\text{HClO}_4] = 0.499$ M. The solvent is 50/50 water/acetic acid. All values are averages of at least three determinations. ^b Equilibrium constant obtained by allowing a solution of the alcohol and acetic acid to come to equilibrium. ^c Equilibrium constant obtained by allowing a solution of the ester to come to equilibrium.

In a separate experiment, an appropriate amount of the ester (0.3–0.9 mmol) was added to 10.00 mL of the solvent, and the solution was allowed to come to equilibrium by keeping it at constant temperature for 12 h. The concentration of the alcohol present was then determined (as described above) by transferring 2.00 mL of the solution to a cuvette, adding 1 μL of concentrated chromate solution, and monitoring the rate of reaction. Because chromic acid has an intense absorbance band at ~ 360 nm, it is possible to use a very small concentration of oxidant and thereby ensure that the amount of alcohol consumed in the oxidation reaction will be inconsequential with respect to total concentrations of ester, carboxylic acid, and alcohol. Oxidation of a small amount of alcohol will therefore have an insignificant effect on the magnitude of the measured constants.

RESULTS AND DISCUSSION

The determination of concentrations from reaction rate studies is a well-established methodology that has been used extensively in situations where direct observation is either impossible or impractical.⁸ In this particular example, it has been possible to determine the amount of alcohol present in a solution containing a great excess of acetic acid and smaller amounts of the corresponding alcohol and alkyl acetate. To

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the best of our knowledge, no other reliable methods for obtaining esterification constants for aliphatic compounds have been published.

The accuracy of the approach used in this work is quite high because chromium(VI) is not reduced at comparable rates by other compounds present.⁹ In theory, it should be possible, by use of the appropriate software, to also apply this approach in situations where more than one of the reactants or products is oxidized. For example, it is feasible to treat theoretically the use of an oxidant that reacts with both alcohols and esters at comparable rates, provided that the rate constants for both reactions are known. However, our experience to date has been that such systems yield results with rather large uncertainties.

Another limitation of the methodology, of course, is related to the need to find reactions that can be easily monitored and that occur at an appropriate rate under a particular set of conditions. For example, the procedure described here could not be used under basic conditions because chromate does not react with alcohols at appreciable rates in neutral or basic solutions.⁹ Under such conditions, it would be necessary to use a different oxidant, such as permanganate, which readily reacts with alcohols in alkaline solutions.¹⁰

From the results obtained in this study, summarized in Table 1, it can be seen that comparable equilibrium constants are obtained by both procedures; i.e., by allowing a solution of alcohol and acetic acid to form an equilibrium amount of alkyl acetate, or by starting from the ester and allowing it to form an equilibrium amount of acetic acid and alcohol. A third possible way of estimating the equilibrium constant, by measuring the rates of the forward and reverse reactions ($K = k_f/k_r$), was not practical in this case because of the very slow rate at which equilibrium is established under these conditions.

A Taft plot¹¹ for the equilibrium is linear (Figure 4) with a ρ value of -1.8 ± 0.1 , thereby indicating that electron-donating substituents shift the equilibrium to the ester side. This can be understood by considering contributing resonance

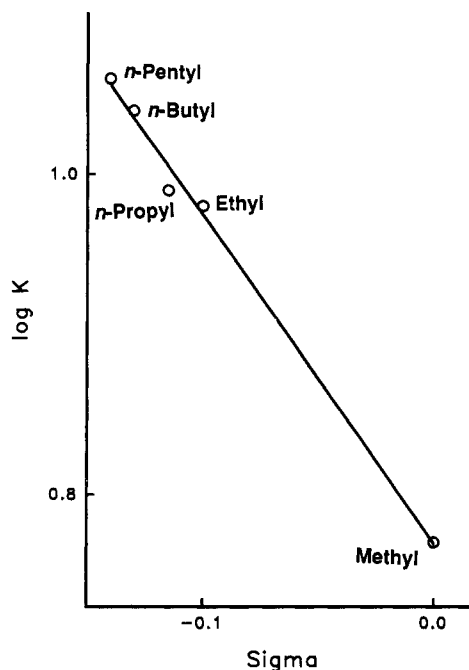
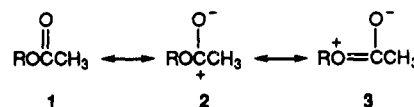


Figure 4. Taft plot illustrating the electronic effects on the esterification equilibrium constants: solvent, 50/50 (by volume) aqueous acetic acid; temperature 20.0 ± 0.1 °C; $[\text{HClO}_4] = 0.499$ M; slope, -1.8 ± 0.1 ; $r = 0.994$.

structures, 1–3, that are also believed to be responsible for the dipole moments exhibited by these compounds.¹²



PRECAUTION

Chromic acid is a known carcinogen¹³ and should be handled with appropriate care.

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