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Consecutive reactions in an oleic acid and acetic anhydride reaction medium

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When mixing acetic anhydride and oleic acid, two consecutive reactions take place. The first one yields acetic-oleic anhydride (AOA) and acetic acid. In the second one, oleic acid reacts with AOA to form oleic anhydride at 5% in a mixture when the initial molar ratio is 1:1. Therefore, at equilibrium, the global reaction yields a mixture of AOA, acetic anhydride, oleic acid, acetic acid and oleic anhydride. Based on a new HPLC protocol, all the species of the reaction medium could be separated and quantified. This permitted for the first time to study the kinetics and thermodynamics of the reaction. In the 30–70 °C range, reactions were of order 2 with partial orders of 1 for each reactant. Equilibrium constants were determined for both reactions. Enthalpy, entropy and activation energies were calculated for the main reaction. The influence of molar ratio on the composition at equilibrium was also investigated. The synthesis of AOA could thus be understood and new data were obtained for this singular molecule scarcely cited in the CAS database.

Keywords: Consecutive reactions / Fatty acids / Kinetics / Mixed anhydride / Thermodynamics

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1 Introduction

Anhydride groups in organic chemistry are acylating agents appreciated for their high reactivity compared to carboxylic acids. Mixed anhydrides, *i.e.* with two different carboxylic acid radicals, are even more reactive due to the difference in the *pK* values of the two moieties of the asymmetric molecule [1]. Mixed anhydrides have found many applications in chemical processes, *e.g.* as key intermediates for the production of carbamates [2], in pharmaceutical prodrug synthesis [3] and in the esterification of cellulose [4].

Pure mixed anhydrides can be obtained by distillation, provided that the molecules have low molecular weight and show small differences between the lengths of the acyl moieties. Propionic-acetic anhydride can thus be isolated and seems to be stable enough to be stored at low temperature [5]. When the carboxylic chains are longer, decomposition may occur during distillation.

Another particularity of mixed anhydrides is the fact that they rearrange by reaction with carboxylic acids. If the latter

corresponds to one of the moieties of the mixed anhydride, the result is a symmetric anhydride: $R_1CO(O)COR_2 + R_1COOH \rightarrow R_1CO(O)COR_1 + R_2COOH$.

There exist four ways of synthesis of such mixed anhydrides. The most recent is the ketene process [6]. Ethenone, the smallest ketene, is the most employed to produce anhydrides by reaction with carboxylic acids. The reaction yields a mixed acetic-carboxylic anhydride [7–10].

Another method consists in the reaction of an acid chloride with a salt of a carboxylic acid, usually sodium or potassium salts [5, 11–13]. The reaction yields NaCl or KCl as by-product, which is very convenient for purification and for shifting the equilibrium.

A third method consists in the reaction of an acid chloride with a carboxylic acid. This method is not frequently used as it forms HCl as by-product.

The last synthesis approach is the reaction between a symmetric anhydride, usually acetic anhydride, and a carboxylic acid [8]. This reaction is equilibrated [10] and therefore the remaining carboxylic acids may cause the formation of symmetric anhydrides, as explained before. This occurs particularly if the mixed anhydride is not withdrawn by distillation from the reaction medium, which is unfortunately the most common case. Furthermore, in another context, this rearrangement feature is exploited when the opposite objec-

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tive is foreseen: the synthesis of symmetric anhydrides (usually fatty anhydrides). In this case, acetic acid is distilled off from the medium to favor the formation of the desired fatty anhydride [7, 9, 12].

In parallel, mixed anhydrides are present in industrial processes without being explicitly mentioned. For instance, in the preparation of cellulose acetate-butyrate, the acylating reagents added to the medium are acetic anhydride and butyric anhydride. As they are introduced into the same bath, there is *in situ* formation of the mixed acetic-butyric anhydride [4, 8].

There are few studies describing the mixed acetic-fatty anhydrides. In the particular case of acetic-oleic anhydride (AOA), there is only one reference in the literature [14] and it does not concern the synthesis. We will consider the synthesis of this molecule by reaction of acetic anhydride and oleic acid, the latter being a common renewable feedstock; and as this molecule finds industrial application in the chemical modification of wood [15].

In general, the reactions leading to acetic-fatty anhydrides are based on assumptions and hypotheses because of three reasons: (i) the complexity of the reaction medium, (ii) the high reactivity of the mixed anhydride – and therefore its high instability – and (iii) the fact that no efficient analytical methods have been available so far.

An HPLC method developed in parallel [16] permitted the determination of the composition of such media at different reaction times. We could then study the kinetics and thermodynamics of the equimolar reaction between acetic anhydride and oleic acid in order to determine the order of the reaction, the partial orders, the equilibrium constants, the activation energies, the speed rate constants, and other thermodynamic parameters. Finally, we studied the influence of the molar ratio (from 1:2 to 2:1) on the final composition of the reaction medium at equilibrium.

2 Materials and methods

2.1 Chemicals and standards

Acetic anhydride and oleic anhydride (both 99% GC purity) were purchased from Sigma-Aldrich (France) and were used without further purification. Phosphoric acid (85% in water) and other standards for chromatography were bought from Acros (France). Acetonitrile HPLC grade was obtained from Scharlau (Spain), and pure water from a Milli-Q (Millipore) water purification system.

2.2 HPLC analysis

Reversed-phase chromatography analysis based on a previous publication of the same authors [16] was performed in a liquid-phase chromatograph from Dionex including a P680 pump, a variable 20- μ L loop and a UVD340U diode array

UV detector set to 212 nm. The temperature of the column was set at 23 °C.

Samples (10 μ L) in acetonitrile were eluted through a C18 column (Varian: Polaris C18-A, 100 Å, 5 μ m; 250 \times 4.6 mm ID). Concentrations of samples in acetonitrile were between 4 and 6 g/L.

An initial flow rate of 1.5 mL/min¹ was set. An eluent gradient was used starting at $t = 0$ from 75:25 acetonitrile/water (with 0.02 wt-% phosphoric acid) to 100% acetonitrile in 5 min and then keeping at 100% acetonitrile. After 12 min of analysis, the flow rate was increased in 2 min up to 2.5 mL/min until the end of the analysis.

2.3 Kinetic and thermodynamic study of the reaction

Equimolar mixtures (ratio = 1 ± 0.001) were prepared with 890 mg oleic acid and 320 mg acetic anhydride, *i.e.* 1.3 mL of mixture in 1.5-mL vials. Samples were prepared in duplicate. During the preparation of all the vials, they were kept at 4 °C to prevent the reaction from starting. When all the vials were ready, they were simultaneously introduced into a Vor-Temp 56 shaking incubator previously heated to the desired temperature. Precision in temperature was ± 1 °C. Shaking agitation was set at 1300 rpm permitting a perfect mixing of the samples.

For sampling, two vials were instantly removed and cooled down with liquid nitrogen to stop the reaction. Samples were immediately analyzed by HPLC or stored at -18 °C. It is the average composition of the two vials of each sampling that is reported. Relative variation between the two concentrations was in all cases inferior to 2%. At room temperature, acetic anhydride and oleic acid are not miscible; the reaction can be considered as heterogeneous during the first minutes of the reaction. In this particular case, acetonitrile was used to dissolve the whole content of the vial to obtain a single phase for HPLC analysis.

3 Results and discussion

The equimolar reaction without catalyst between acetic anhydride and oleic acid was conducted for long enough time to attain the equilibrium (70 °C during 5 days). The composition of the reaction medium, continuously monitored by HPLC, showed since the first day constant concentrations of AOA, oleic anhydride and acetic acid. Acetic anhydride and oleic acid were still present in the medium. We cannot say, however, that the latter are only unreacted chemicals. They are also the by-products of all the reactions taking place (Fig. 1). The formation of oleic anhydride is the proof of the subsequent reaction (II) between the mixed anhydride and the fatty acid. They both co-exist in equilibrium.

Other syntheses were conducted until equilibrium in a temperature range of 30–70 °C. In all cases, the five molecules cited above were present. The final compositions of the media

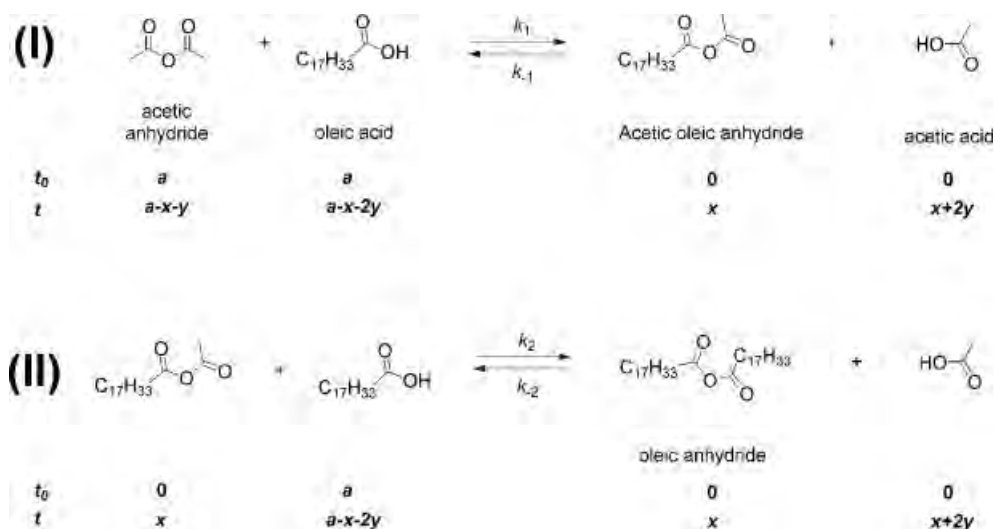


Figure 1. Proposed mechanism for the reaction between acetic anhydride and oleic acid.

were not identical, but were maintained within a narrow range. Regardless of the reaction temperature, the molar fraction of oleic anhydride was always less than 4% for a 1:1 molar ratio.

The example of the slowest reaction, *i.e.* conducted at 30 °C for 5 days, is shown in Fig. 2. The lack of miscibility in the first minutes of the reaction did not alter the smooth trend of the curves. Three parts can be distinguished in the concentration *vs.* time curves. From 0 to 4 h, the consumption of the two initial reagents is equimolar. The formation of AOA and acetic acid is also equimolar. From 4 to 40 h, reaction II becomes significant as shown by the formation of oleic anhydride. The consumption of oleic acid is higher than that of acetic anhydride. The former reacts with AOA to yield oleic anhydride. The concentration of acetic acid is particularly high as it is formed from both reactions I and II. In the final stage of the reaction, from 40 h, the concentrations of all the substances reached a plateau. No degradation of the molecules was observed till 120 h.

The study on the kinetics of reaction I involves defining the speed law of the reaction. As it is impossible to integrate the speed law of two consecutive equilibrated reactions, we made the following assumption: Reaction II is negligible compared to reaction I. In this case, $y = 0$ during all the reaction. It is therefore the *apparent* speed of formation of AOA that will be determined.

In order to determine the speed law, we made the hypothesis that reaction I was of order 2 with partial order of 1 for each reactant.

The speed rate can then be described as $dx/dt = k_1(a-x)^2 - k_{-1}x^2$.

After integration, we obtain:

$$\frac{1}{(A-B)a^2} \ln \frac{(1-Bx)}{(1-Ax)} = k_1 t \quad (1)$$

$$A = \frac{1}{a} + \frac{1}{a\sqrt{K_1}}$$

$$B = \frac{1}{a} - \frac{1}{a\sqrt{K_1}}$$

where K_1 is the constant of equilibrium for reaction I and a is the initial molar fraction of acetic anhydride and oleic acid. (Fig. 1).

According to our assumption, the formation of AOA depends only on the first equilibrium (reaction I). It is important to note that this approximation does not permit to determine the real speed rate constants. Indeed, the formation of oleic anhydride consumes part of the AOA; the rate constant is therefore under-evaluated. The latter has been called *apparent* speed rate.

The apparent speed law of reaction is therefore $dx/dt = k'_1(a-x)^2 - k'_{-1}x^2$ and the integrated law becomes a function of k'_1 . It is thus necessary to replace in the integration K_1 , which is dependent on k_1 and k_{-1} and not k'_1 and k'_{-1} , by its expression as a function of the concentration at equilibrium, x_e .

As $K_1 = x_e^2/(a-x_e)^2$, we obtained the following integrated law:

$$\frac{x_e}{2a^2 - 2ax_e} \ln \frac{(x_e - (\frac{2x_e}{a} - 1)x)}{(x_e - x)} = k'_1 t \quad (2)$$

The plot of Eq. (2) for experimental results at 30, 40, 50, and 70 °C gives a linear correlation (Fig. 3). The slope values correspond to k'_1 . We can deduce from these results that reaction I behaves as a second-order reaction with partial orders of 1 for each reactant. Once this hypothesis has been confirmed, it is now necessary to study and determine the real speed rates of reaction I and to determine its thermodynamic parameters.

This time, we can restrict our first assumption: Reaction II is negligible but only in the first minutes of the reaction; *i.e.* $y = 0$ as long as y is inferior to 0.5%. This permits to evaluate the *real* speed rate constants.

The plot of Eq. (1), involving K_1 (Fig. 4), shows linear trends for each temperature followed by a non-linear trend. On the scale of time, the linear part is maintained only for a

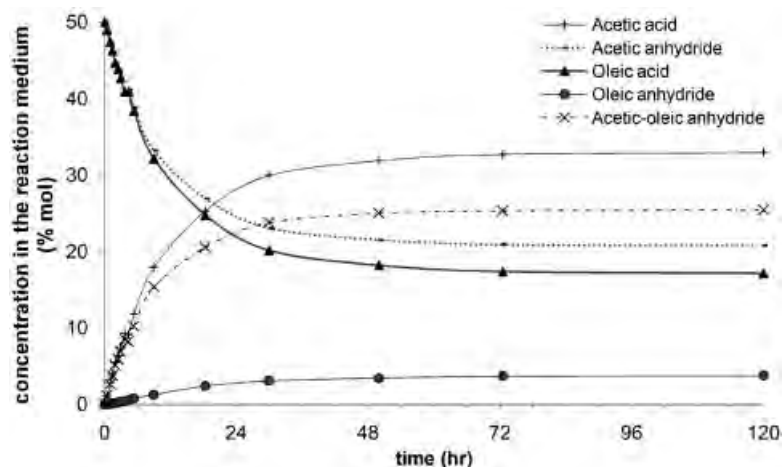


Figure 2. Kinetics of the equimolar reaction between oleic acid and acetic anhydride at 30 °C.

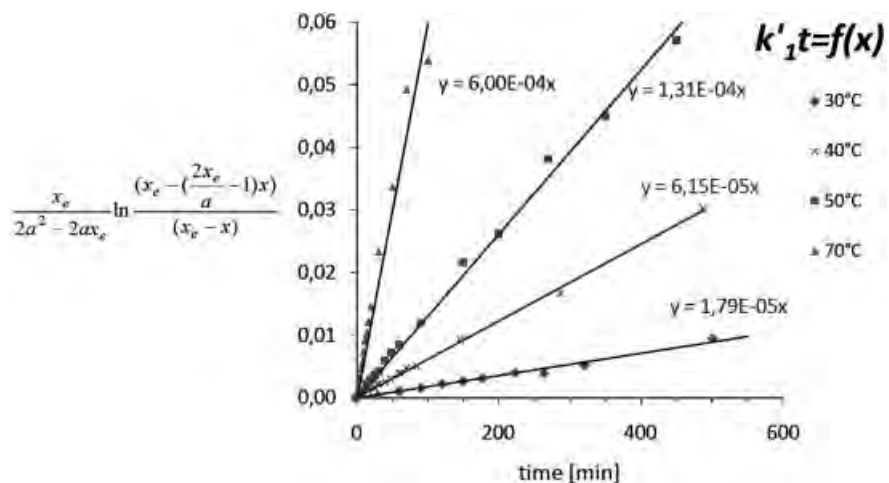


Figure 3. Apparent kinetic plots considering $x = x_e$.

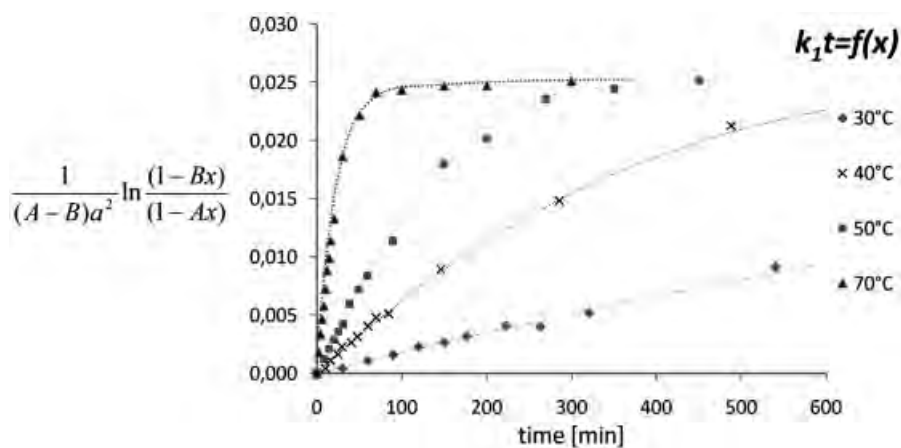


Figure 4. Kinetic plots considering K_1 .

few minutes at the highest temperature (70 °C) and up to 4 h at 30 °C. During these periods, the formation of oleic anhydride is negligible. When it becomes significant, the general

law (Eq. 1) is no longer valid. The formation of AOA depends then on the apparent model (Eq. 2). In this case, the concentration of AOA, x , instead of following the general model,

tends to a plateau, x_e , which depends on the two reactions and not only on reaction I. For further calculations, we will consider only the linear part of Fig. 4. The expanded view of this plot and the slope values (corresponding to k_1) are presented in Fig. 5.

From these values and the relation $K = k_1/k_{-1}$, where k_{-1} is the speed rate of the inversed reaction I, we could calculate the k values presented in Table 1. It is important to specify that the values of K_1 and K_2 were determined experimentally at time equal to 5 days, which can be considered 'infinite'. The equations used are:

$$K_1 = \frac{[AOA]_e * [Acetic acid]_e}{[Acetic anhydride]_e * [Oleic acid]_e}$$

$$K_2 = \frac{[Oleic anhydride]_e * [Acetic acid]_e}{[AOA]_e * [Oleic acid]_e}$$

We can observe that k_1 is always superior to k'_{-1} . This can easily be explained by the fact that in the apparent model (Eq. 2) a part of the consumed AOA is not taken into account as it reacted to form oleic anhydride. Moreover, the speed rate at 70 °C is 45 times greater than at 30 °C, showing a big dependence on temperature.

Another thermodynamic parameter determined for reaction I is the activation energy. Based on the Arrhenius law, we calculated the activation energies by plotting $\ln(k) = E/RT + \ln(A)$ (Fig. 6). We obtained $E_{+a} = 80.4$ kJ/mol and $E_{-a} = 78.4$ kJ/mol for the straight and the inversed reactions, respectively. These values are very close, indicating that the equilibrium state is barely dependent on the reaction temperature.

As $\Delta G_0 = \Delta H_0 - T\Delta S_0 = -RT \ln(K)$, plotting $\ln(K_1)$ as a function of $1/T$ permitted to determine other thermodynamic constants of reaction I (Fig. 7): $\Delta H_{01} = 2473.8$ J/mol and $\Delta S_{01} = 14.96$ J/K. The reaction is therefore endothermic as these values are both positive. We could have also given ΔH_{02} and

Table 1. Speed rate constants and equilibrium constants for the equimolar reaction.

T [°C]	k_1 [s ⁻¹]	k_{-1} [s ⁻¹]	K_1	K_2
30	1.85E-05	7.84E-06	2.36	2.84
40	6.92E-05	3.13E-05	2.21	2.74
50	1.43E-04	5.89E-05	2.43	2.35
70	8.29E-04	3.22E-04	2.57	3.32

ΔS_{02} values. However, the concentration of oleic anhydride, which is the main indicator of reaction II, is determined with a relatively high uncertainty due to its low concentration. In order to study the kinetics and thermodynamics of reaction II, it would be better to follow the kinetics of an equimolar reaction between oleic anhydride and acetic acid. This was not done because the price of such experiments would be extremely high due to the expensiveness of pure oleic anhydride.

The enthalpy of formation of AOA ($\Delta H_f = -939.9$ kJ/mol) could be calculated from the ΔH_{01} value and the ΔH_f of the reagents and products of reaction I. The latter were obtained from the DIPPR 801 compilation from the AIChE [17].

Finally, we conducted several syntheses with different molar ratios of acetic anhydride and oleic acid. Figure 8 shows that the final composition of the mixture at equilibrium is clearly dependent on the initial ratio of reagents. Nevertheless, AOA is always present in the medium at a molar percentage between 20 and 25%, regardless of the molar ratio of the reactants. An optimum seems to be found at around the equimolar mixture.

The present work and the understanding of the reactions involved in the synthesis of mixed anhydrides may also help to understand why they are unstable. Traces of water may hydrolyze the mixed anhydride. The corresponding carboxylic acids act as initiators of a rearrangement leading to the

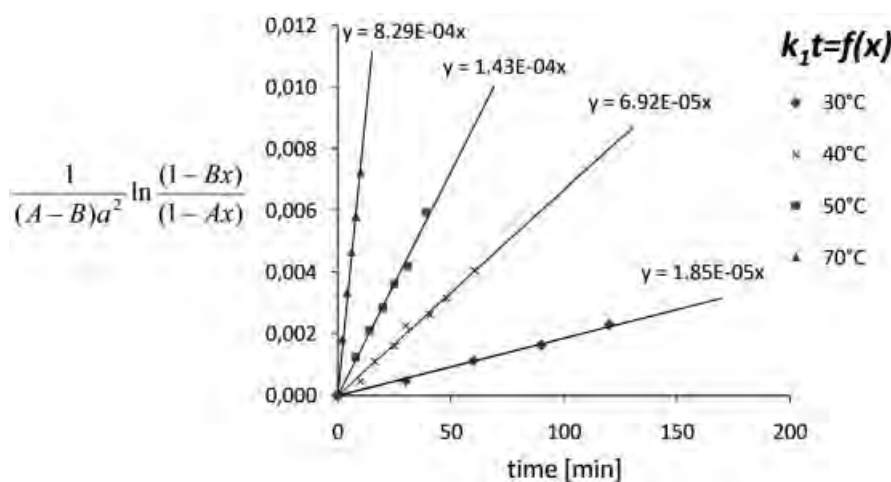


Figure 5. Kinetics of reaction I for experiments in which $y < 0.5$ mol-%.

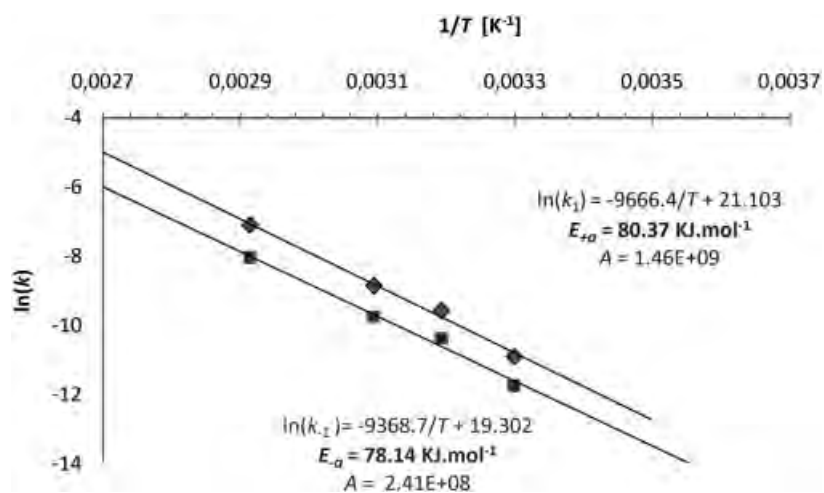


Figure 6. Arrhenius-type graph for the determination of the activation energies.

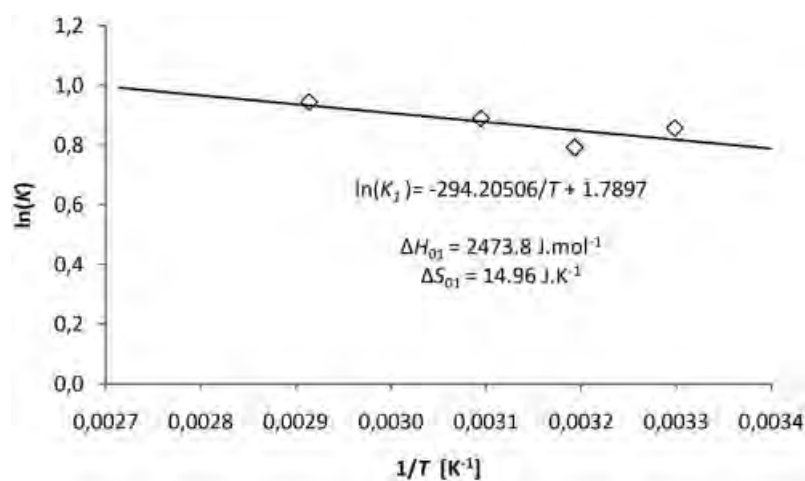


Figure 7. Thermodynamic values for reaction I.

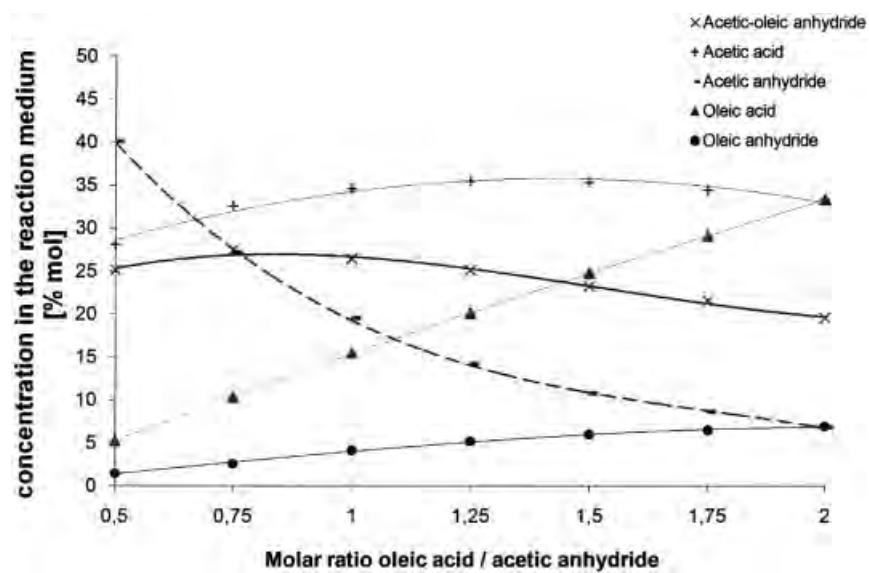


Figure 8. Composition of the mixture for different molar ratios of oleic acid/acetic anhydride at equilibrium at 70 °C.

formation of symmetric anhydrides (reaction II or reaction I inversed). At the end, one molecule of water can be responsible for a great conversion rate of AOA to symmetric anhydrides.

4 Conclusions

The equimolar reaction between acetic anhydride and oleic acid without any catalyst can be described as two consecutive equilibrated reactions. At equilibrium, five molecules coexist: acetic acid, AOA, acetic anhydride, oleic acid and oleic anhydride. The speed rate depends largely on the temperature. At 70 °C, the reaction attains equilibrium in 90 min. This time can easily be reduced at higher temperatures. Equations allow the prediction of the equilibrium at less than 10 min at 100 °C. The influence of molar ratio is smaller than that of temperature; however the optimum was situated at around 1.

The order of the main reaction (I) is 2, and it is expected that the consecutive reaction (II) follows the same behavior. Moreover, both reactions are endothermic and the composition at equilibrium is barely dependent on temperature.

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Conflict of interest statement

The authors have declared no conflict of interest.

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