Study of the Kinetics and Mechanism of the Production of *Iso*propyl Xanthic Anhydride

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Abstract:

Bis[*iso*propoxy(thiocarbonyl)] sulfide, also known as *iso*propyl xanthic anhydride, serves as a useful precursor to other organosulfur compounds and is also commercially important as a flotation agent in ore processing. The kinetics of the reaction between potassium *iso*propyl xanthate and ethyl chloroformate in which it is produced were studied in order to elucidate a mechanism and enable improvement of the yield. To determine the reaction kinetics, the concentrations of reaction species were monitored over time in seven reactions, each with different initial reactant concentrations, sampling intervals, and reaction times. The reaction was found to take place in two second order steps, in which one equivalent of potassium *iso*propyl xanthate first reacts with ethyl chloroformate to form the isolable intermediate *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate, which then reacts with another equivalent of potassium *iso*propyl xanthate to form the final product. Mathematical models of the reaction system were developed, and the rate constants of both steps were determined.

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Introduction and Objectives:

The reaction between potassium *iso*propyl xanthate and ethyl chloroformate has long been known, being first reported by Welde in 1877.[1] Its product, *iso*propyl xanthic anhydride, is used as a precursor for other organosulfur compounds,[2] for protection of amino acids in peptide synthesis,[3] and as a flotation agent in ore processing.[4] However, until now its mechanism had not been conclusively established. Previous evidence for *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate as an intermediate compound comes from its being detected as an impurity in the crude reaction product.[2] The first step, then, was thought to be a simple nucleophilic acyl substitution, and this research confirms that conjecture. The mechanism of the second step, however, was less clear.

In order to determine the mechanism of both steps and enable the improvement of the yield, the kinetics of the reaction were studied by monitoring the concentration of the reaction species over time in several experiments, each with different parameters. In the first set of experiments, potassium *iso*propyl xanthate was reacted with a stoichiometric amount of ethyl chloroformate under conditions shown to give good yields and enable easy recovery of product, and thus usable in a preparative method. In the next set, a twofold excess of ethyl chloroformate was used, and the reaction was diluted by various amounts, in order to provide contrasting initial conditions and thus ensure a robust model applicable under a wide variety of circumstances. Finally, to enable close study of the second reaction step, potassium *iso*propyl xanthate was reacted directly with *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate in a third set of experiments.

The data support a mechanism in which both steps are second order, and enable the determination of rate constants. The knowledge of the kinetics of this important reaction not only sheds light on the mechanism, but also enables the prediction of the concentration of product over time given initial reactant concentrations, which will certainly prove useful in the course of optimizing the yield.

Experimental Methods and Procedures

The concentrations of *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate and *iso*propyl xanthic anhydride were monitored over time under different initial conditions. Chemicals used were of ACS reagent grade, except potassium *iso*propyl xanthate and *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate, which were produced according to the procedures given below. In all experiments a small amount of *iso*propyl xanthic disulfide was present, due to its being an impurity on the order of 0.5% in the potassium *iso*propyl xanthate starting material. However, this did not pose a problem for quantitation of the concentration of *iso*propyl xanthic anhydride, as the NMR spectra of the two compounds are sufficiently different. All reactions were carried out at room temperature unless stated otherwise. NMR spectra were taken on a 500 MHz Varian instrument with deuterated chloroform as the solvent. All of the experiments were carried out using a 3:2 mixture of methanol and water. Under these conditions, the *iso*propyl xanthic anhydride precipitates as a fine suspension, but the mixture can be considered homogenous for the purpose of determining concentration. In fact, the solvent was initially chosen for preparative methods to enable facile collection of *iso*propyl xanthic anhydride by filtration.

Preparation of potassium *iso*propyl xanthate:

CS_2 (484 mL, 8.01 mol) was slowly added over 10 minutes with vigorous stirring to a solution of KOH (436 g, 7.77 mol) in *iso*propanol (2.5 L) and water (100 mL) in an ice bath at 5 °C. The reaction mixture was stirred for an additional five minutes, after which the cream-colored precipitate which had formed was collected by vacuum filtration on a Buchner funnel, washed with ethyl acetate (500 mL), and dried under vacuum overnight. Yield: 972.8 g (72%)

Preparation of *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate:

Ethyl chloroformate (100 mL, 1.04 mol) was added all at once with stirring to a solution of potassium *iso*propyl xanthate (183 g, 1.04 mol) in *iso*propanol (980 mL) and water (420 mL) in an ice bath at 5 °C. Stirring continued for an additional two hours, after which the product was extracted into $CHCl_3$ (1 L), washed with water (3 x 300 mL), dried with anhydrous $MgSO_4$ (125 g) and concentrated by rotary evaporation to yield a yellow oil (180.3 g, 83%). [NMR δ 5.75 (septet, J = 6.2 Hz, 1 H), 4.32 (q, J = 7.1 Hz, 2 H), 1.45 (d, J = 6.2 Hz, 6 H), 1.33 (t, J = 7.1 Hz, 3 H)].

Preparation of *Iso*propyl Xanthic Anhydride:

Ethyl chloroformate (25 mL, 0.26 mol) was added slowly over 5 minutes with stirring to a solution of potassium *iso*propyl xanthate (91.5 g, 0.52 mol) in methanol (420 mL) and water (280 mL). Stirring continued for an additional hour, during which time a fine yellow precipitate formed. The precipitate was collected by vacuum filtration on a Buchner funnel and dried under vacuum to yield a yellow powder (47.34 g, 76%). For purification, it was recrystallized from boiling hexanes

(235 mL), yielding yellow crystals (38.52 g, 62%). [NMR δ 5.74 (septet, J = 6.5 Hz, 2 H), 1.45 (d, J=6.5 Hz, 12 H)]

Reaction 1: General Procedure:

Ethyl chloroformate (25 mL, 0.26 mol) was added with stirring to a solution of potassium *iso*propyl xanthate (91.5 g, 0.52 mol) in methanol (420 mL) and water (280 mL). Every five minutes for the next hour, 25 mL of reaction mixture were removed. Each portion was extracted with brine (20 mL) and diethyl ether (20 mL), dried with anhydrous $MgSO_4$ (5g), and concentrated by rotary evaporation. At the end of the hour, the remaining reaction mixture was worked up in the same way, but with proportionately greater amounts (285 mL of brine and ether and 75 g drying agent).

Reactions 2 through 7:

To study other aspects of the reaction, six more reactions were performed using essentially the same procedure but with different initial conditions, sampling intervals, and reaction times. Reaction 2 was still the overall reaction, but run on a longer time scale. In Reactions 3, 4, and 5, a twofold excess of ethyl chloroformate was used, and the reactants were diluted by various amounts. In Reactions 6 and 7, potassium *iso*propyl xanthate was directly reacted with the intermediate.

Reaction Number:	Reaction Duration (hr.):	Sampling Interval (min.):	Solvent Volume (mL):	Potassium *Iso*propyl Xanthate used (mol):	Ethyl Chloroformate used (mol):	Intermediate used (mol):
1	1	5	700	0.52	0.26	0
2	4	15	700	0.52	0.26	0
3	1	5	700	0.52	0.52	0
4	0.5	5	700	0.13	0.13	0
5	0.5	5	1400	0.052	0.052	0
6	1	5	700	0.26	0	0.26
7	2	10	700	0.26	0	0.26

Results and Discussion

The reaction between potassium *iso*propyl xanthate and ethyl chloroformate is proposed to take place in a two-step process. In the first step, one equivalent of potassium *iso*propyl xanthate reacts by nucleophilic acyl substitution with one equivalent of ethyl chloroformate to form the intermediate compound *S*-ethoxycarbonyl-*O*-*iso*propyl dithiocarbonate (Figure 1).

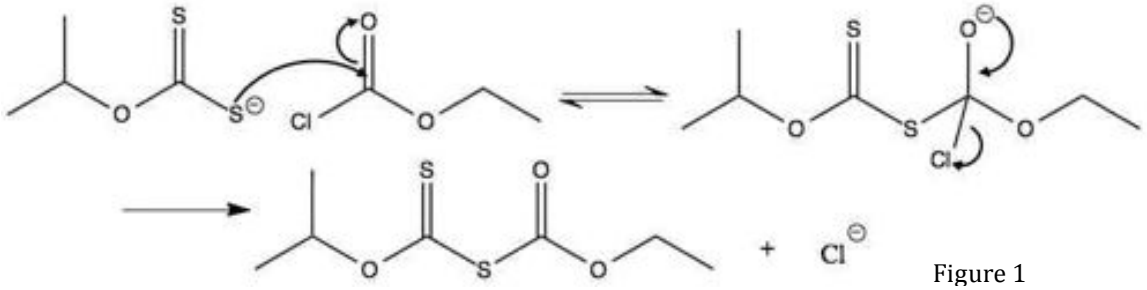

Figure 1

In the second step, the intermediate reacts with an additional equivalent of potassium *iso*propyl xanthate to form the final product. This step is proposed to be similar to a transthioesterification, except with an irreversible expulsion of carbonyl sulfide that drives the reaction forwards (Figure 2).

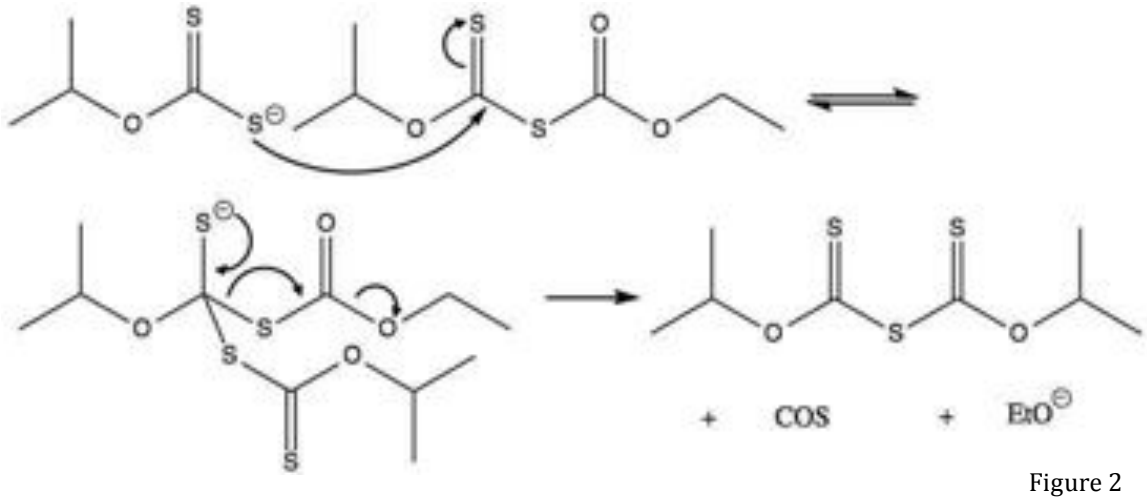

Figure 2

This mechanism implies that the second step is slower than the first, since thioesters are less reactive than acid chlorides towards nucleophilic acyl substitution, and that both steps are second order overall. Thus, the rate law is:

$$\frac{dA}{dt} = -k_1 AB$$

$$\frac{dB}{dt} = -k_1 AB$$

$$\frac{dC}{dt} = k_1 AB - k_2 AC$$

$$\frac{dD}{dt} = k_2 AC$$

where A is the concentration of potassium *iso*propyl xanthate, B is the concentration of ethyl chloroformate, C is the concentration of intermediate, and D is the concentration of final product. Taking note that

$$A = A_0 - C - 2D$$

$$B = B_0 - C - D$$

where A_0 and B_0 are the respective initial concentrations, the rate law can be rewritten:

$$\frac{dC}{dt} = k_1(A_0 - C - 2D)(B_0 - C - D) - k_2(A_0 - C - 2D)C$$

$$\frac{dD}{dt} = k_2(A_0 - C - 2D)C$$

This system of nonlinear differential equations is not analytically solvable, so numerical methods must be used. However, k_2 can easily be determined by direct reaction of intermediate with potassium *iso*propyl xanthate, such as in Reactions 6

and 7. In this case only step two of the overall reaction occurs, so the reaction is a simple second order one. The integrated rate law is thus:

$$\frac{1}{C} - \frac{1}{C_0} = k_2 t$$

The rate constant is easily computed by regression on the intermediate concentration with respect to time (Figure 3).

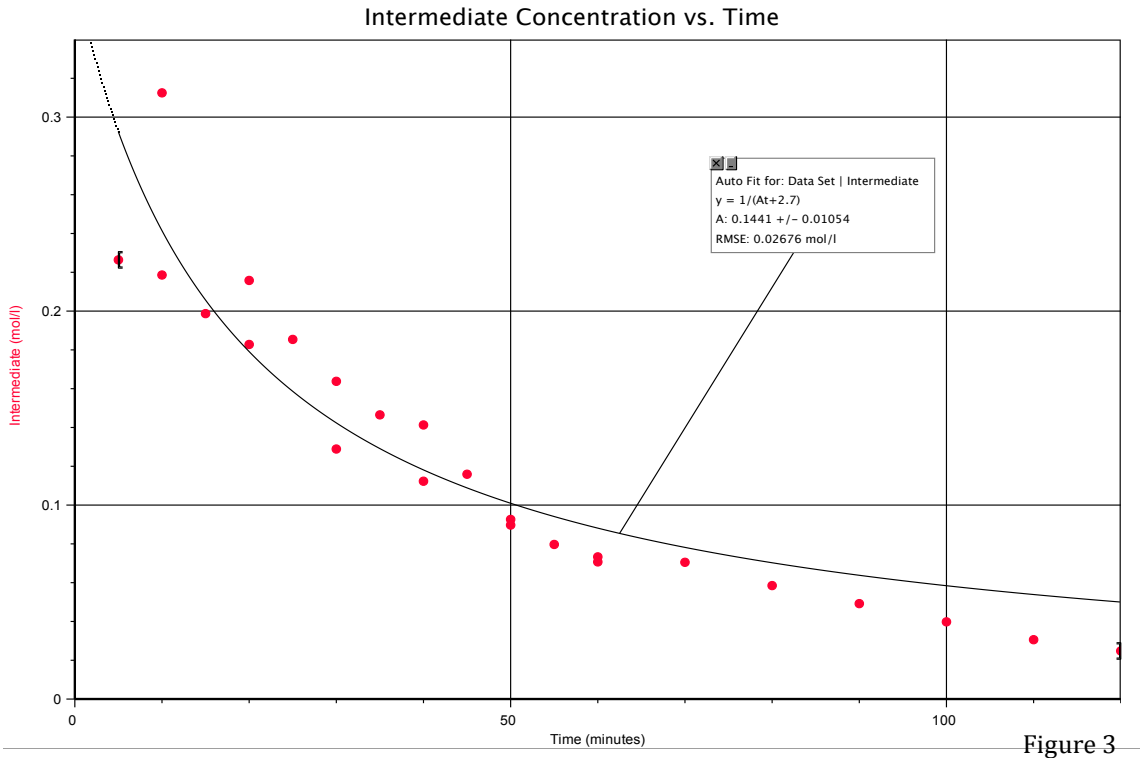

Figure 3

k_2 was found to be $0.144 \pm 0.011 \frac{\text{L}}{\text{mol}*\text{s}}$. Because k_2 is known, k_1 can also be found. The numerical integration of the system of differential equations was performed in Wolfram Mathematica, and k_1 was found by regression on the intermediate concentration to be $0.620 \pm 0.032 \frac{\text{L}}{\text{mol}*\text{s}}$ (Figure 4).

Predicted and Measured Intermediate Concentration vs. Time

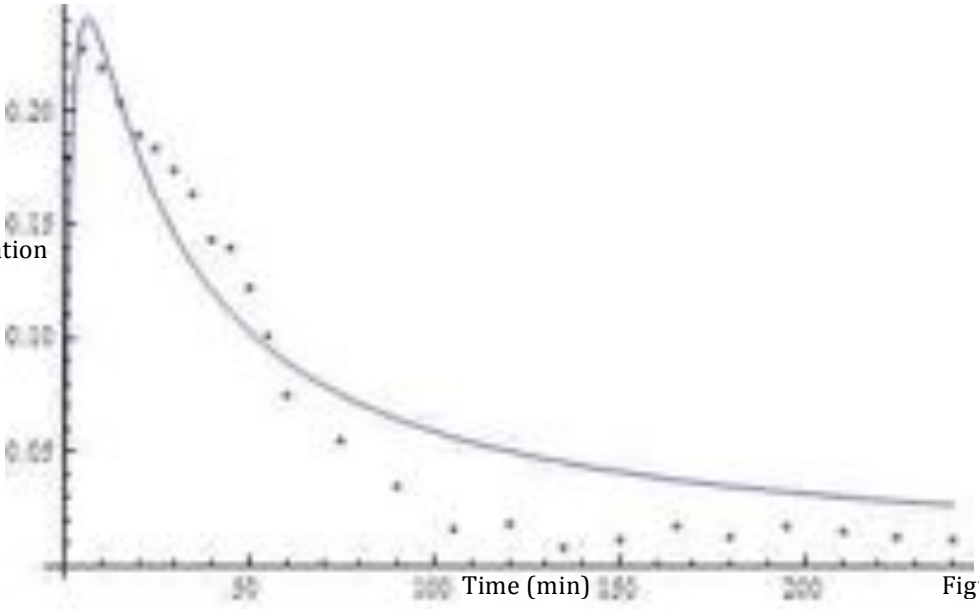

Figure 4

While this model accurately predicts the intermediate concentration at early times, it overpredicts the concentration at late times (Figure 4), both in the overall reaction and in the direct reaction of intermediate with potassium *iso*propyl xanthate. This is probably due to the slow decomposition of intermediate by hydrolysis, which would most likely be a first order process.[5] Also, in calculating the concentration of isopropyl xanthic anhydride, the model assumes theoretical yields for the reaction, resulting in overprediction (Figure 5). To account for non-ideal yields, the predicted product concentration was scaled down by a factor of 0.76, which corresponds with observed yields in the preparative method.

Predicted and Measured *Iso*propyl Xanthic Anhydride Concentration vs. Time

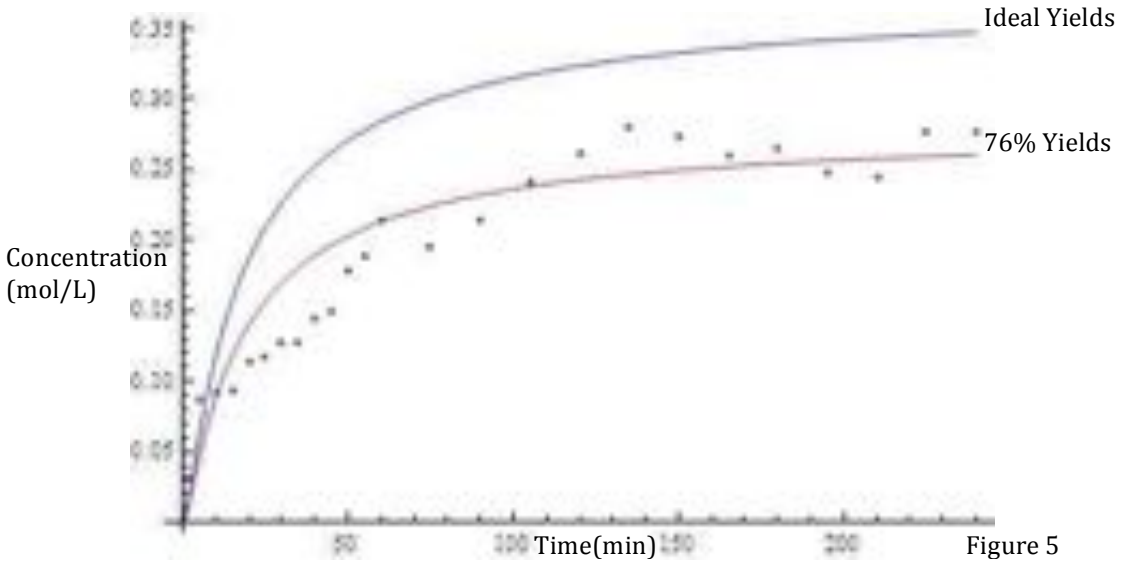

Figure 5

The corresponding model in which the second step is first order was also considered. However, the predictions of this model do not agree with observations. The model predicts a slower initial rise of intermediate concentration in the overall reaction than that observed, and underpredicts the intermediate concentration for large times (Figure 6).

First Order Predicted and Measured Intermediate Concentrations vs. Time

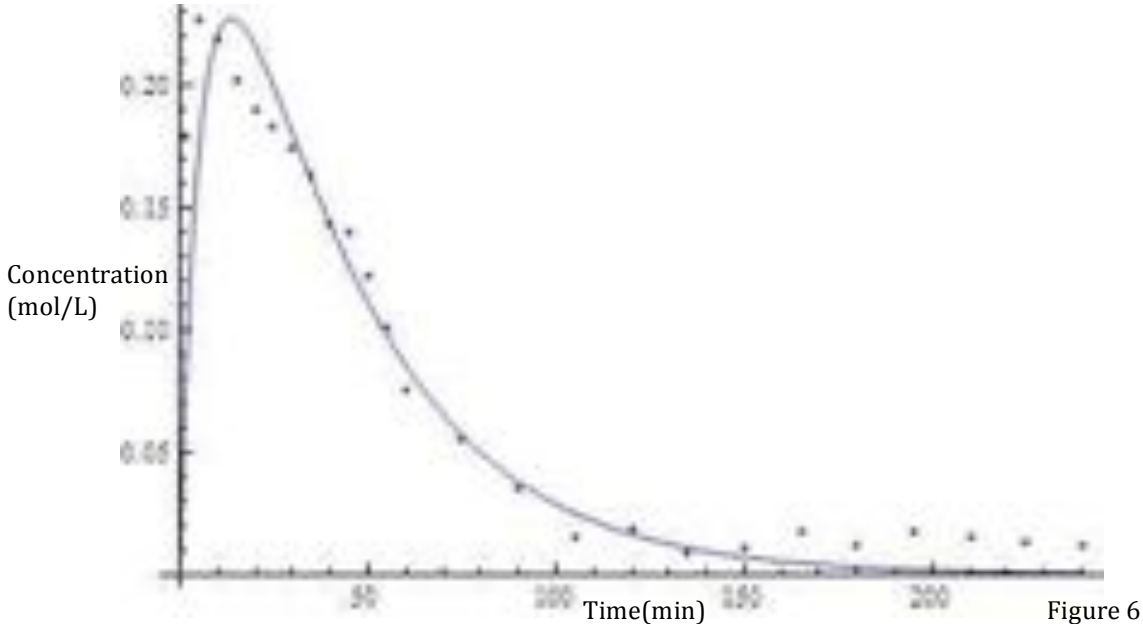

Figure 6

While the overprediction of the second order model at large times can be explained by decomposition of the intermediate, there is no rational explanation for the underprediction of the first order model. Thus, it is clear that the observed intermediate concentration matches better with a second order model than with a first order one.

Moreover, when the reaction was diluted (in reactions 3, 4, and 5), the rate decreased by the square of the dilution factor. When the reaction was diluted by a factor of four, the rate decreased by a factor of 16.8 ± 2.8; when the reaction was diluted by a factor of twenty, the rate decreased by a factor of 354 ± 53 (Figure 7). This decrease in rate proportional to the square of the dilution further supports second order kinetics overall.

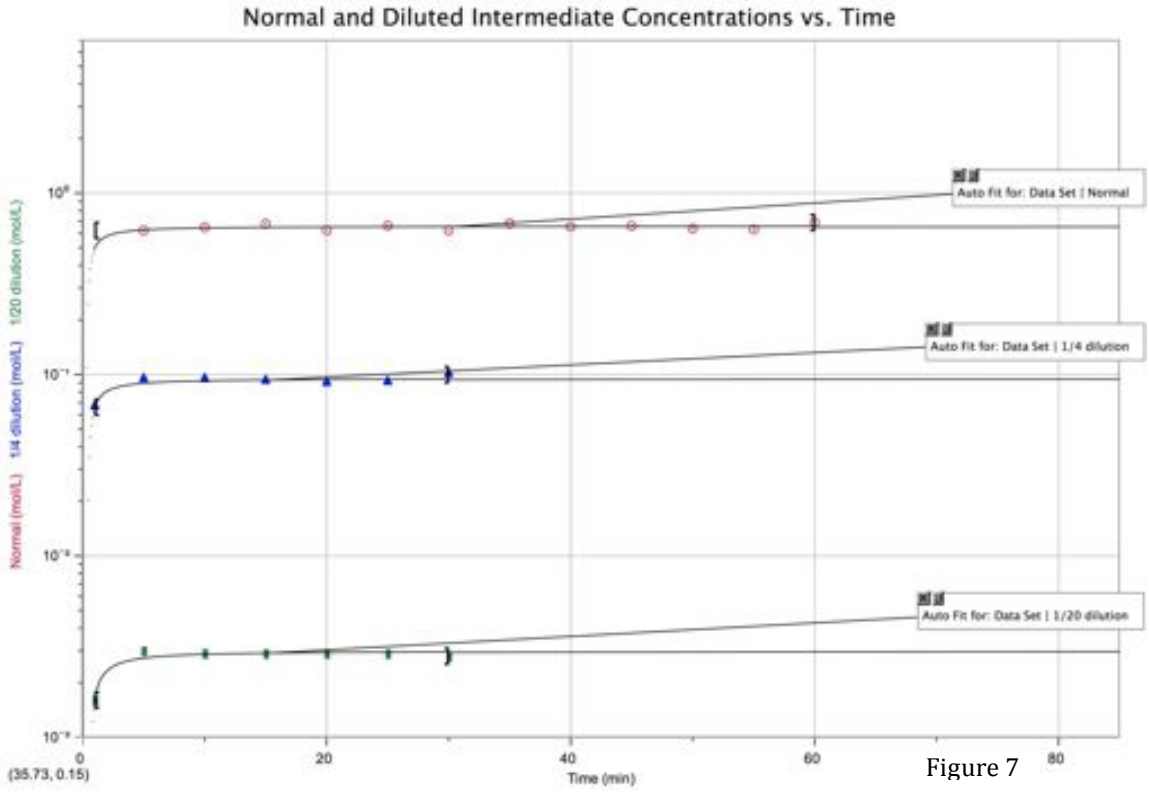

Figure 7

In conclusion, the reaction between ethyl chloroformate and potassium *iso*propyl xanthate was found to take place by a two-step mechanism in which both steps are second order. This supports the proposed mechanism, since nucleophilic acyl substitutions (including transthioesterifications) are known to be second order. The mathematical models presented accurately predict the concentrations of intermediate and product on short and medium timescales, but do not account for decomposition via hydrolysis. Therefore, more experimentation is needed to determine the rate of decomposition of intermediate. However, given that the target compound is reasonably stable under the reaction conditions employed,[5] decomposition is not likely to be a major issue for any preparative method based on this work.

References:

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Appendix A: Concentration Data:

Reaction Number	Time (min)	iPrxa Product concentration (mol/L)	Intermediate concentration (mol/L)
Reaction 1: Overall reaction (short timescale)			
1	1	0.031	0.179
1	5	0.087	0.228
1	10	0.092	0.219
1	15	0.094	0.203
1	20	0.114	0.190
1	25	0.117	0.183
1	30	0.128	0.175
1	35	0.128	0.163
1	40	0.144	0.143
1	45	0.149	0.140
1	50	0.178	0.122
1	55	0.189	0.101
1	60	0.214	0.075
Reaction 2: Overall reaction (long timescale)			
2	15	0.111	0.194
2	30	0.162	0.153
2	45	0.207	0.076
2	60	0.192	0.077
2	75	0.196	0.056
2	90	0.214	0.035
2	105	0.241	0.016
2	120	0.262	0.019
2	135	0.281	0.009
2	150	0.273	0.012
2	165	0.260	0.018
2	180	0.265	0.012
2	195	0.248	0.008
2	210	0.244	0.015
2	225	0.276	0.013
2	240	0.277	0.012

Reaction Number	Time (min)	iPrxa Product concentration (mol/L)	Intermediate concentration (mol/L)
Reaction 3: 2x excess ethyl chloroformate			
3	5	0.0348	0.622
3	10	0.0202	0.648
3	15	0.0000	0.675
3	20	0.0107	0.624
3	25	0.0115	0.661
3	30	0.0135	0.624
3	35	0.0092	0.679
3	40	0.0087	0.653
3	45	0.0133	0.659
3	50	0.0076	0.638
3	55	0.0121	0.631
3	60	0.0074	0.688
Reaction 4: 2x excess ethyl chloroformate, 4x dilution			
4	1	0.0001	0.0660
4	5	0.0023	0.0936
4	10	0.0044	0.0936
4	15	0.0060	0.0915
4	20	0.0071	0.0892
4	25	0.0068	0.0903
4	30	0.0088	0.0997
Reaction 5: 2x excess ethyl chloroformate, 20x dilution			
5	1	0.0000	0.0016
5	5	0.0002	0.0030
5	10	0.0003	0.0029
5	15	0.0004	0.0029
5	20	0.0006	0.0029
5	25	0.0006	0.0029
5	30	0.0006	0.0028

Reaction Number	Time (min)	iPrxa Product concentration (mol/L)	Intermediate concentration (mol/L)
Reaction 6: Second step reaction (short timescale)			
6	5	0.0435	0.2062
6	10	0.0487	0.1991
6	15	0.0617	0.1807
6	20	0.0761	0.1663
6	25	0.0890	0.1697
6	30	0.0942	0.1493
6	35	0.104	0.133
6	40	0.123	0.102
6	45	0.142	0.106
6	50	0.183	0.083
6	55	0.195	0.073
6	60	0.195	0.068
Reaction 7: Second step reaction (medium timescale)			
7	10	0.0806	0.3125
7	20	0.0807	0.3158
7	30	0.211	0.129
7	40	0.184	0.141
7	50	0.235	0.093
7	60	0.265	0.071
7	70	0.280	0.070
7	80	0.292	0.058
7	90	0.290	0.049
7	100	0.297	0.040
7	110	0.308	0.031
7	120	0.324	0.025

Appendix B: Adjustment for Mechanical Losses:

In the course of experimentation, it was found that the amount of product collected at each time point was skewed downwards by mechanical losses during workup, which largely came from the product being absorbed by filter paper during removal of the drying agent. In theory, losses in this fashion are not dependent on amount of product, only on concentration of product in the extraction solvent. Therefore, it is possible to adjust for them by comparing the amount collected from the last small reaction sample and the amount collected from the final extraction of product.

For example, in Reaction 1, 0.972 g of organics were collected from the 25 mL removed at 55 minutes, and 26.22 g were collected from the 425 mL remaining at 60 minutes. Assuming the concentration varied little compared to the amount of mechanical losses during the intervening 5 minutes,

$$\frac{26.22\text{g} + x}{425\text{mL}} = \frac{0.972\text{g} + x}{25\text{mL}} \rightarrow x = 0.606\text{ g}$$

where x is the amount of product lost. The amounts of mechanical losses for the other reactions were calculated in the same manner, and the concentrations presented here have been adjusted to account for mechanical losses. However, because mechanical losses are not completely constant, they remain the main source of error in the data. In future work, more solvent may be used for extraction to reduce this source of error.