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Where Has My Acid Gone? Understanding the Self-Catalyzed Esterification of Maleic Acid in Methanol During Salt Formation

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Supporting Information

ABSTRACT: The kinetics of the esterification of maleic acid in methanol have been investigated following the contamination of a batch of an API maleate salt with the corresponding monomethyl maleate salt. The esterification was found to be catalyzed by H^+ generated by the ionization of maleic acid, giving rise to an observed rate law with a one-and-a-half-order dependence upon the maleic acid concentration. On the basis of the measured rate constants over a range of temperatures a predictive model has been developed that will estimate the time taken to achieve a given degree of esterification as a function of temperature and maleic acid concentration. Rate constants have also been determined for the maleic acid-catalyzed esterification of monomethyl maleate. Neutralization of maleic acid through salt formation with triethylamine reduces the rate of esterification in a manner that is consistent with the degree of neutralization. The potential for the esterification of maleic acid in other alcohols and for the esterification of other carboxylic acids in alcohols is discussed in the light of these findings.

INTRODUCTION

The use of maleic acid to prepare salts of basic drugs is well established with examples such as enalapril maleate **1**,[1] amlodipine maleate **2**[2] and chlorpheniramine maleate **3**[3] currently on the market (Figure 1).

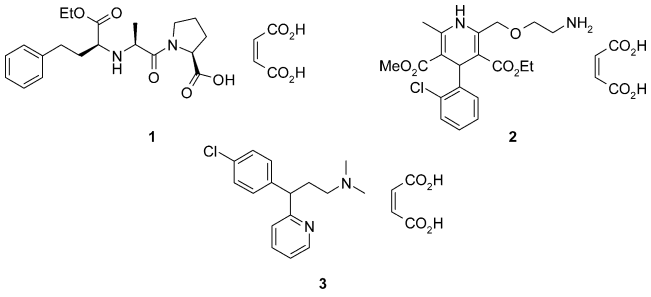

Figure 1. A selection of drugs marketed as maleate salts.

During the development of the process for the isolation of a pharmaceutical ingredient containing amine functionality as its maleic acid salt a problem was noted with the analytical closure of the isolated salt. Analytical investigations of this phenomenon found that the desired maleate salt was significantly contaminated with the monomethyl maleate salt. While this situation was satisfactorily resolved by a recrystallization, experimental studies of the reaction between maleic acid **4** and methanol were undertaken to understand where in the process the problem had arisen.

The acid-catalyzed esterification of maleic acid **4** by a range of alcohols has been studied.[4] However, no studies of the spontaneous esterification of maleic acid **4** in methanol have been undertaken. Investigations of the spontaneous esterification of other carboxylic acids under stoichiometric conditions have concluded that weak catalysis of the acids esterification is provided by the undissociated acid acting as a general acid catalyst.[5]

RESULTS AND DISCUSSION

The process used to prepare the maleate salt involved dissolving the API in hot methanol and screening this solution into the crystallizer. A solution of maleic acid **4** in methanol was prepared in a second vessel and was also screened into the crystallizer. This was followed by seeding and a cooling crystallization to yield the desired maleate salt. There are, therefore, two points in the process where the formation of monomethyl maleate **5** could potentially occur, either during the dissolution of the maleic acid **4**, and or during the salt formation.

Profiling the reaction between maleic acid and methanol at 60 °C by ^{1}H NMR spectroscopy demonstrated the esterification of maleic acid **4** to generate monomethyl maleate **5** to be relatively fast, giving approximately 35% reaction in one hour (Figure 2). It was also shown that monomethyl maleate **5** underwent further reaction to dimethyl maleate **6** (Scheme 1).

Additional profiling experiments were undertaken at 60 °C in which a portion of the maleic acid **4** was neutralized by the addition of triethylamine to mimic the conditions of the salt formation. Comparison of the profiles for the loss of maleic acid **4** as a function of the amount of triethylamine used (Figure 3) clearly shows that partial neutralization slows the rate of

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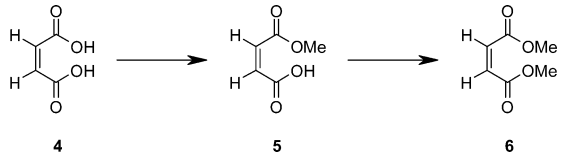
Scheme 1. Esterification of Maleic Acid 4 in Methanol



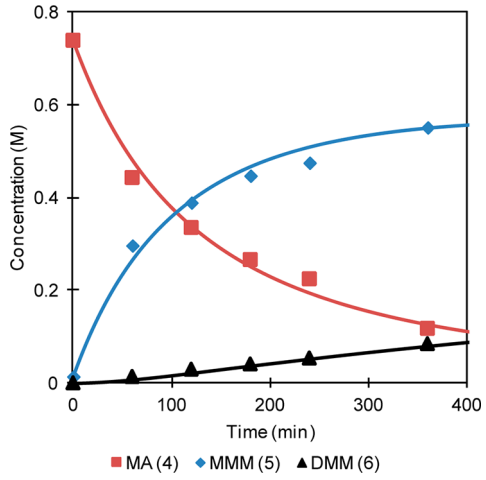


Figure 2. Reaction profile for the esterification of maleic acid in methanol at 60 °C.

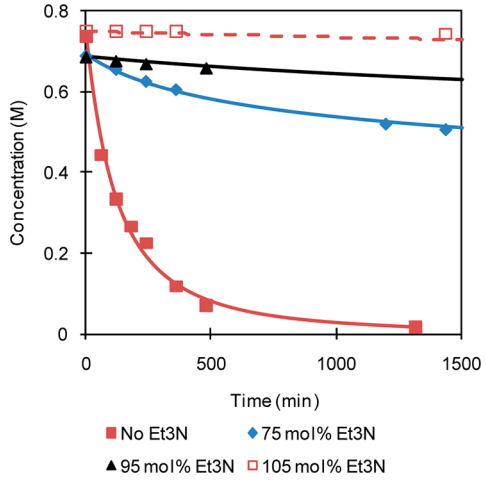


Figure 3. Influence of added triethylamine upon the loss of maleic acid in methanol at 60 °C.

esterification and that a slight excess of base essentially shuts down the reaction.

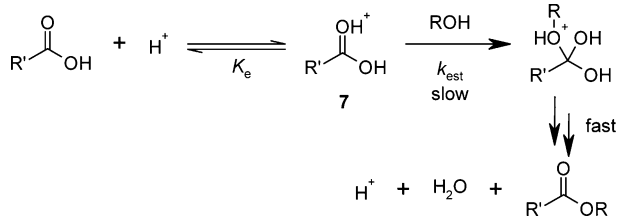
On the basis of these experiments it was possible to draw the conclusion that the observed esterification of maleic acid during processing occurred in the maleic acid solution prior to its charging to the crystallizer. The obvious solution to the problem would be to minimize the time for which the maleic acid solution in methanol is held prior to charging it to the crystallizer, although this may not be robust at scale due to the time required for dissolution and charging. A more thorough analysis of the profile data was therefore undertaken to understand the reaction kinetics and also the temperature dependence of the esterification reaction.

Kinetic Measurements. Reactions were profiled by ^{1}H NMR at a range of temperatures, with and without added triethylamine. An internal standard of 2,3,5,6-tetrachloronitrobenzene was used to ensure that reliable concentration vs time data were obtained. As the NMR samples were in some instances analyzed overnight it was necessary to add sufficient triethylamine to them to prevent further reaction occurring prior to analysis.

The work was carried out under a nitrogen atmosphere in a 100-mL jacketed reactor fitted with an overhead stirrer (PTFE paddle), using an external circulating bath to maintain the reaction temperature. In a typical experiment 1,2,4,5-tetrachloro-3-nitrobenzene (0.5 g, 1.92 mmol) was suspended in methanol (36.4 g, 46 mL). The suspension was heated to 50 °C to give a clear solution, and maleic acid **4** (5.0 g, 43.1 mmol) was charged and rinsed in with methanol (3.2 g, 4 mL). After the mixture stirred for 2 min, a 0.5 mL sample was withdrawn, added to a vial containing triethylamine (44 mg, 60 μL) and mixed thoroughly, diluted with methanol-d_4, and analyzed by ^{1}H NMR.[6] The experiment was maintained at 50 °C with periodic sampling to generate a concentration vs time profile such as Figure 1.

Esterification Mechanism and the Development of a Kinetic Model. The standard acid-catalyzed esterification mechanism of carboxylic acids involves the rate-limiting attack of the alcohol upon the protonated carboxylic acid intermediate 7 (Scheme 2).[7] Treating the formation of intermediate 7 as a

Scheme 2. Mechanism for the Acid-Catalyzed Esterification of Carboxylic Acids



rapid pre-equilibrium it is possible to derive a simple third-order rate law (eq 1)[8] for the formation of an ester under conditions where the back reaction (hydrolysis) is insignificant. In our case this rate law simplifies to pseudo-first-order kinetics, as $[H^+]$ should be constant for an acid-catalyzed process and the methanol is present in such a large excess that its concentration is effectively unchanged.

$$-\frac{d[HA]}{dt} = \frac{d[ester]}{dt} = \frac{k_{est}[H^+][ROH][HA]_T}{K_e} \approx k'_{est}[HA]_T \quad (1)$$

Initial kinetic fitting of the experimental data for the esterification of maleic acid **4** with *Micromath Scientist*[9] was undertaken using a model based upon this mechanism, which contained two sequential first-order reactions (eq 2). This model successfully fitted the majority of the data with the exception of the data collected at 50 °C, where two experiments had been carried out using 0.4 and 0.8 M maleic acid solutions in methanol. The best-fit plot (Figure 4) arising from the simultaneous fitting of both data sets shows the model to be a reasonable description at the beginning of the reactions, but with significant deviation towards the end.

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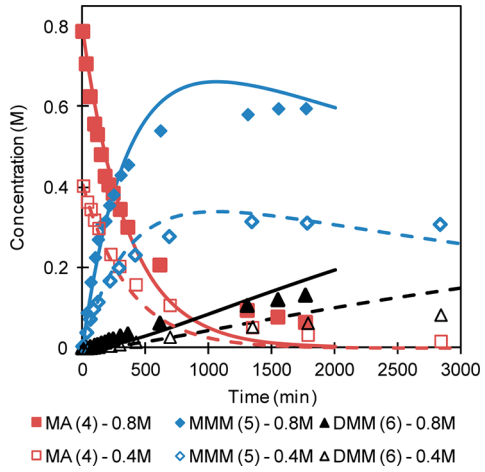

Figure 4. Maleic acid esterification in methanol at 50 °C; best-fit plots to a sequential first-order model.

$$-\frac{d[\mathbf{4}]}{dt} = k_1'[\mathbf{4}]$$
$$\frac{d[\mathbf{5}]}{dt} = k_1'[\mathbf{4}] - k_2'[\mathbf{5}]$$
$$\frac{d[\mathbf{6}]}{dt} = k_2'[\mathbf{5}] \quad (2)$$

Studies of the self-catalyzed esterification of monocarboxylic acids have found evidence of a general acid-catalyzed reaction, in which the un-ionized acid catalyses its own esterification.[5] This would give rise to a rate law with a second-order dependence upon the maleic acid **4** concentration.[10] Fitting a model on the basis of this mechanism gave a better fit than the simple first-order mechanism (Figure 5)[11] but still failed to reliably fit the loss of maleic acid **4** towards the end of the reaction.

Having eliminated pseudo-first-order and general acid-catalyzed (pseudo-second-order) mechanisms there remains the specific acid-catalyzed mechanism rejected by previous studies of the self-catalyzed esterification of carboxylic acids under stoichiometric conditions.[5a,b] Maleic acid **4**, pK_a 5.5 in methanol,[12] is considerably more acidic than the monomethyl maleate **5** produced in the reaction, which has a pK_a of 8.3 in methanol.[13] It is therefore reasonable to assume that monomethyl maleate **5** does not catalyze the esterification of maleic acid **4**, making it possible to relate the $[H^+]$ present in the reaction to the $[\mathbf{4}]$ (eq 3).[14]

$$[H^+] \approx \sqrt{K_a[\mathbf{4}]} \quad (3)$$

Substitution into eq 1 for $[H^+]$ and simplification again gives rise to a relatively simple rate law (eq 4) for the esterification of maleic acid **4**, which has a one-and-a-half-order dependence upon the $[\mathbf{4}]$. Similar use of the term for $[H^+]$ gives rise to an expression for the rate of esterification of monomethyl maleate **5** making it possible to write a model that describes the specific acid-catalyzed esterification reactions and includes the drop in acidity as the reaction proceeds (eq 4) due to the consumption of maleic acid **4**. Simultaneous fitting of the two sets of esterification data collected at 50 °C using different $[\mathbf{4}]$ to this model was successful (Figure 6) giving the tabulated best fit

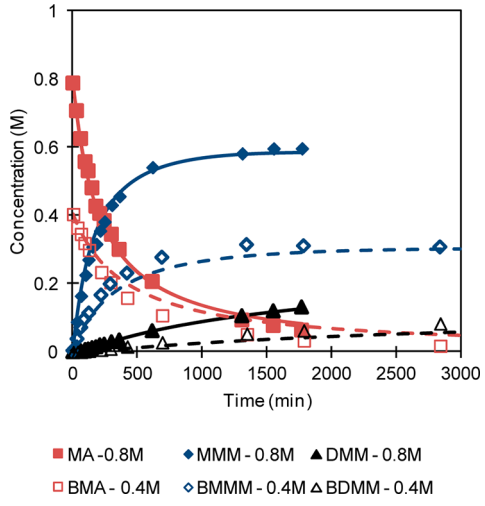

Figure 5. Maleic acid esterification in methanol at 50 °C; best-fit plots to a general acid-catalyzed model.

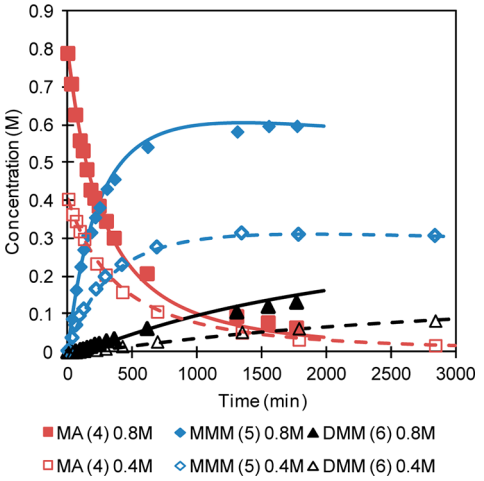

Figure 6. Maleic acid esterification in methanol at 50 °C; best-fit plots to a sequential one-and-a-half-order model.

Table 1. Best-fit rate constants for the self-catalyzed esterification of maleic acid 4 and monomethyl maleate 5 in methanol

temperature (°C)	$10^5 \times k_1$ ($M^{-1/2}$ s^{-1})	$10^6 \times k_2$ ($M^{-1/2}$ s^{-1})
60	15.5 ± 0.8[a]	18.3 ± 0.2
55	8.5 ± 0.2	10.8 ± 0.1
50	7.0 ± 0.2	7.5 ± 0.5
40	2.7 ± 0.2	3.5 ± 0.3
20	0.7 ± 0.1	–

[a]The quoted errors are the 95% confidence limits of the best-fit rate constants arising from the fitting.

values of the rate constants (Table 1).[15] The model also fitted the data generated by esterification reaction at other temperatures to give the quoted best-fit rate constants (Table 1).[16] The observation of the self −catalyzed esterification mechanism rejected by other workers[5a,b] in studies of the stoichiometric esterification of acetic acid may be due to the higher acidity of maleic acid when compared to acetic acid in methanol (Table 4). Additionally the previous studies were conducted in an

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almost equimolar mixture of acetic acid and methanol, which represents a very different solvent to the relatively dilute solutions (<1 M) in methanol studied in this work.

$$-\frac{d[\mathbf{4}]}{dt} = \frac{k_{est}\sqrt{K_a[\mathbf{4}]}\,[MeOH][\mathbf{4}]}{K_e} = k_1[\mathbf{4}]^{3/2}$$

$$\frac{d[\mathbf{5}]}{dt} = k_1[\mathbf{4}]^{3/2} - k_2[\mathbf{5}][\mathbf{4}]^{1/2}$$

$$\frac{d[\mathbf{6}]}{dt} = k_2[\mathbf{5}][\mathbf{4}]^{1/2} \quad (4)$$

The temperature dependence of the best-fit rate constants was analyzed in terms of the Arrhenius equation. Both rate constants gave a good fit to the linearised form of the equation (eq 5) as may be seen from Figure 7. The best fit values of the

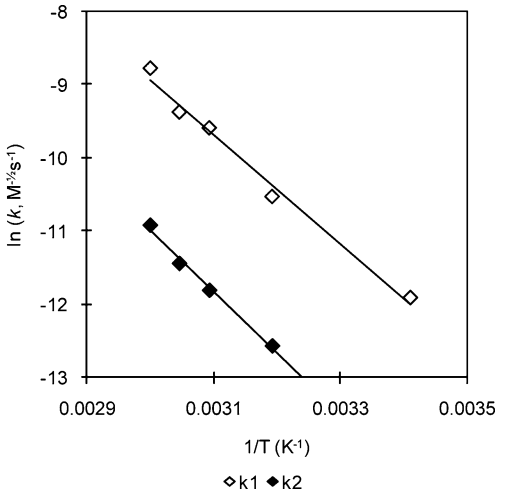

Figure 7. Arrhenius plot for the maleic acid-catalyzed esterification of maleic acid (**4**, k_1) and monomethyl maleate (**5**, k_2).

activation energy, E_a and ln A are tabulated (Table 2) and may be used to estimate the rate constants at other temperatures.

$$k = A\cdot e^{-E_a/RT}$$

$$\Rightarrow \ln k = \ln A - \frac{E_a}{RT} \quad (5)$$

Table 2. Best-fit activation parameters for the maleic acid-catalyzed esterification of maleic acid 4 and monomethyl maleate 5

acid	E_a (kJ mol^{-1})	ln A (M$^{-1/2}$ s^{-1})	R^2
4	62.4	13.60	0.988
5	70.2	14.37	0.991

Development of a Predictive Tool. It is possible to predict the degree of esterification to be expected at a particular time for a given maleic acid concentration and temperature by using the rate laws that describe the system (eq 4) coupled with the best-fit Arrhenius parameters. However, the software routinely available to process chemists will not run this simulation with ease.

In many cases it will be adequate to know how much of the maleic acid **4** has been lost to esterification, without knowing how much of the monomethyl maleate **5** has itself undergone esterification. This reduces the number of differential equations to be solved in a practical model of the loss of maleic acid **4** in the system from three to one (eq 6). Solution of this differential equation (eq 6)[17] gives rise to an expression (eq 7), which relates the maleic acid **4** concentration at a given time to the initial maleic acid concentration $[\mathbf{4}]_0$ and the rate constant k_1 for the esterification of maleic acid.

$$-\frac{d[\mathbf{4}]}{dt} = k_1[\mathbf{4}]^{3/2} \quad (6)$$

$$[\mathbf{4}] = \left(\frac{1}{2}\left(\frac{2}{\sqrt{[\mathbf{4}]_0}} + k_1 t\right)\right)^{-2} \quad (7)$$

Rearrangement of eq 7 and substitution for k_1 in terms of the best-fit Arrhenius parameters (Table 2) gives an equation (eq 8), which predicts the time taken to reach a specified extent of conversion, depending upon the temperature (in K) and initial maleic acid concentration. Using eq 8 it was possible to predict the effect of changes to the concentration and maleic acid solution hold temperature required for process accommodation upon the safe hold time for the maleic acid solution. This is illustrated in Figure 8 which plots the time required for 5% of

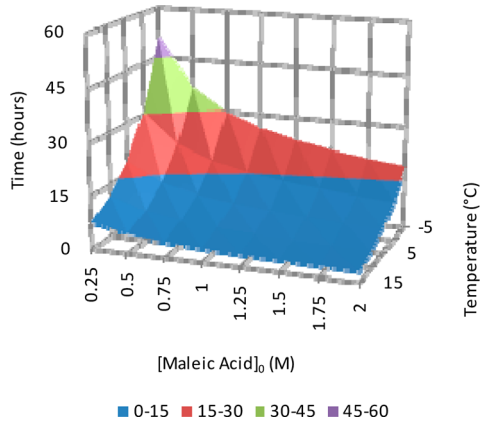

Figure 8. Predicted time (in hours) for 5% esterification of maleic acid **4** in methanol as a function of temperature and initial maleic acid concentration.

the maleic acid **4** to be lost vs temperature and initial maleic acid concentration $[\mathbf{4}]_0$. It is clear from these predictions that the preparation and storage of solutions of maleic acid in methanol should take place at low temperatures if the progress of the self-catalyzed esterification is to be minimized.

$$t(\text{in s}) = \frac{\left(\frac{2}{\sqrt{[\mathbf{4}]}} - \frac{2}{\sqrt{[\mathbf{4}]_0}}\right)}{8.06\times 10^5\cdot e^{-7505/T}} \quad (8)$$

Wider Relevance. In theory the self-catalyzed esterification of maleic acid in methanol reported here is likely to occur in other alcoholic solvents, although the extent will depend upon both the esterification rate constant and the acid dissociation constant, K_a of maleic acid in the relevant alcohol. While acid dissociation constants are not available for maleic acid in other alcohols they are available for a range of substituted acetic acids in methanol ethanol and propan-2-ol (isopropanol).[13] Selected values are tabulated (see Table 3) and show that the acidity of the acids decreases upon going from methanol to propan-2-ol

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with ethanol occupying an intermediate position. It is likely that other carboxylic acids will display similar behavior, lowering the risk of autocatalytic esterification with decreasing acidity.

Table 3. Comparison of the pK_a values of a range of substituted acetic acids in methanol, ethanol, and propan-2-ol

acid	pK_a (MeOH)[a]	pK_a (EtOH)[a]	pK_a (2-PrOH)[a]
acetic	9.7	10.3	11.3
chloroacetic	7.8	8.2	9.2
dichloroacetic	6.3	7.3	7.8

[a]From ref 13.

The catalytic behavior exhibited by maleic acid with respect to its esterification in methanol may also be exhibited by other carboxylic acids. Therefore, an assessment of the relative risk of such reactions may be obtained by comparing available acid dissociation constants for a range of carboxylic acids in methanol (see Table 4), which clearly show that maleic and oxalic[18] acids pose the greatest risk, while other commonly used salt forming acids (fumaric[19] and succinic) represent a far lower risk.

Table 4. Comparison of the acidities of a range of carboxylic acids in methanol and water

acid	pK_a (MeOH)	pK_a (H_2O)	relative acidity[a]
maleic	5.5 (5.9)[b,c]	1.9[d]	1
oxalic	6.1[e]	1.2[e]	0.5
malonic	7.5[e]	2.9[e]	0.1
citric	7.6[b]	2.7[f]	0.09
tartaric	7.7[b]	3.0[f]	0.08
fumaric	7.8 (8.0)[b,e]	3.0[e]	0.07
succinic	9.1[e]	4.2[e]	0.02
acetic	9.8 (9.7)[e,g]	4.75[e]	0.007

[a]Relative to a 1 M solution of maleic acid in methanol based on eq 3. [b]See ref 12. [c]Kolthoff, I. M.; Chantooni, M. K., Jr. *Anal. Chem.* **1978**, *50*, 1440. [d]Dahlgren, G.; Long, F. A. *J. Am. Chem. Soc.*, **1960**, *82*, 1303. [e]Chantooni, M. K., Jr.; Kolthoff, I. M. *J. Phys. Chem.*, **1975**, *79*, 1176. [f]Serjeant E. P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*; IUPAC Chemical Data Series, No. *23*; Pergamon Press: Oxford, 1979. [g]See ref 13.

CONCLUSIONS

The esterification of maleic acid in methanol in the absence of other acids has been probed kinetically and found to proceed via a mechanism in which maleic acid catalyses its own esterification. The low degree of ionization of maleic acid in methanol gives rise to an observed rate law in which the rate of esterification exhibits a one-and-a-half-order dependence upon the maleic acid concentration. On the basis of the observed temperature dependence of the esterification rate constant and the rate law it is possible to model the time taken for a given level of esterification as a function of temperature and maleic acid concentration, making it possible to set a shelf life upon maleic acid solutions in methanol during manufacture. Partial neutralization of the maleic acid creates a buffer system and significantly reduces the acidity of the medium, which in turn reduces the rate of esterification, meaning that salt formation stabilizes the solution with respect to esterification.

It is likely that the rate law exhibited by the esterification of maleic acid in methanol will also be exhibited in other alcoholic solvents and potentially by other carboxylic acids in alcohols. However, it is expected that the risk of esterification will be greatest in methanol with carboxylic acids of similar or higher acidity relative to maleic acid.

EXPERIMENTAL SECTION

Materials. Methanol used in the kinetic experiments was HPLC grade and purchased from Fisher Scientific. Dimethyl maleate (96%), maleic acid (≥99%), maleic anhydride (99%), methanol-d_4 (99.8 atom % D), 1,2,4,5-tetrachloro-3-nitrobenzene (99%) and triethylamine (99%), were purchased from Sigma-Aldrich and used as supplied.

Preparation of Monomethyl Maleate. Maleic anhydride (20 g, 1.0 molar equiv) and methanol (6.54 g, 1.0 molar equiv) were charged to a 150-mL four-necked, round-bottomed flask and stirred (magnetically) under a nitrogen atmosphere for 30 min. The mixture was then heated to 50 °C and allowed to react for 45 min. After cooling to ambient, residual methanol was removed under vacuum on a rotary evaporator with a bath temperature of 55 °C to give a crude oil, 25.44 g (95%). Its identity was confirmed by ^{1}H NMR (400 MHz, DMSO-d_6) by comparison to the previously published spectrum.[20] This material was used as a locator sample without further purification.

ASSOCIATED CONTENT

Supporting Information

Figure S1 for ^{1}H NMR spectrum of a reaction sample (TIF); PDF with derivation of eq 1; derivation of the rate law for the general acid-catalyzed mechanism; table comparing the fitting of the different models considered; derivation of eq 3; sample Micromath Scientist model file; Figures S2, S3, and S4 for best-fit plots for the self-catalyzed esterification of **4** at 60, 55, and 40 °C, respectively; solution of eq 6. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) See Figure S1 in the Supporting Information for a sample ^{1}H NMR spectrum of a reaction sample.
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(8) See the Supporting Information for a derivation of eq 1.
(9) *Micromath Scientist*, v3.0; Micromath: St. Louis, MO, 2005. Using a Runge–Kutta fourth order approach to numerical solution of the differential equations.
(10) See the Supporting Information for the derivation of the rate laws required to describe the general acid-catalyzed mechanism.
(11) See Table S1 in the Supporting Information for a comparison of the parameters arising from fitting different rate laws to the data collected at 50 °C.
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(14) See the Supporting Information for a derivation of eq 3.
(15) A copy of the model used to fit the two sets of data generated at 50 °C to eq 4 is provided in the Supporting Information.
(16) See Figures S2, S3, and S4 in Supporting Information for the best-fit plots arising from fitting data collected at 60, 55, and 40 °C respectively to eq 4.
(17) See the Supporting Information for a solution to eq 6.
(18) We have encountered problems with the esterification of oxalic acid in propan-2-ol when preparing the oxalate salt of an intermediate.
(19) Holding a solution of fumaric acid in propan-2-ol for 24 h at greater than 60 °C failed to give rise to detectable levels of esterification.
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