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Article

Selective Ammonolysis of Bioderived Esters for Biobased Amide Synthesis

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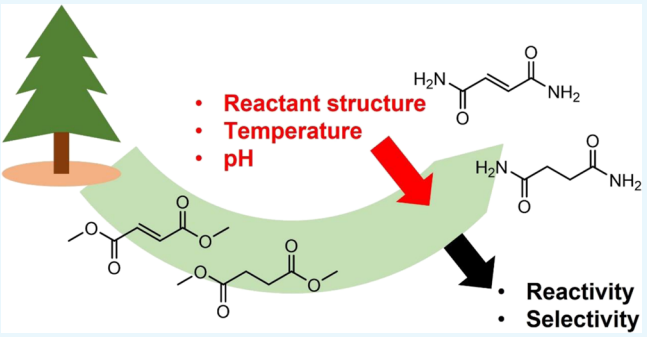
ABSTRACT: Amidation is an important reaction for bioderived platform molecules, which can be upgraded for use in applications such as polymers. However, fundamental understanding of the reaction especially in the presence of multiple groups is still lacking. In this study, the amidation of dimethyl fumarate, maleate, and succinate through ester ammonolysis was examined. The reaction networks and significant side reactions, such as conjugate addition and ring closing, were determined. A preliminary kinetic comparison among additional C_4 and C_6 esters showed a significant correlation between molecular structure and ammonolysis reactivity. Esters with a C═C double bond in the molecule backbone were found to have higher ammonolysis reactivity. To improve the selectivity to unsaturated amides rather than byproducts, the effects of thermal conditions and additives in dimethyl fumarate ammonolysis were examined. Lower temperature and decreasing methoxide ion concentration in the solution relative to the base case conditions increased the fumaramide selectivity from 67.1 to 90.6%.



INTRODUCTION

Utilizing biomass as a renewable carbon resource for sustainable chemical and fuel production has been a popular topic.[1] A critical issue in this area is the need to achieve a balance between selectivity and conversion efficiency. One approach to maximizing productivity of an overall biomass reaction system is the integration of biosynthesis and chemical catalysis.[2−5] Their integration has been demonstrated for a number of platform molecules based on well-developed reaction pathways.[6,7] Very commonly, the bio-based platform molecules have multiple functional groups, which can be subsequently used for further upgrading. However, the impact of the multifunctionality on the selectivity of the subsequent reactions remains an important area of research for using biomass as a chemical feedstock. This chemistry becomes particularly significant if the goal is to selectively maintain some of the functionality in the desired product. For example, fermentation-derived muconic acid can be readily hydrogenated to adipic acid, but it has been shown that the judicious selection of reaction conditions can lead to the highly selective production of 3-hexanedioic acid.[8,9] Synthesis of 3-hexanedioic acid, which can be incorporated in nylon-6,6, is interesting because the residual C═C double bond can be used to modify performance properties of the resulting nylon.[10] This exploration of novel transformation routes has the potential to lead to new molecules as well as to optimizing the efficiency of reaction pathways.[11] Additionally, understanding the conversion chemistry of multifunctional molecule reactions can be exploited to construct computational strategies for predicting promising platform molecules.[12]

One class of bioderived molecules that has been extensively studied is dicarboxylic acids due to their application in the polymer industry.[13−17] Among the candidates, fumaric acid can be produced *via* either chemical or biological pathways.[18,19] It has been considered as an interesting biobased intermediate,[20] due to its potential to be used in the production of a number of downstream chemicals. As with 3-hexanedioic acid, the double bond in the carbon chain provides a basis for further functionalization,[6] which could provide a means to synthesize advanced polymers.

Use of bioderived acids can proceed *via* hydrogenation, dehydrogenation, dehydration, amidation, and nitrilation. However, not all of the reactions have received similar attention. Hydrogenation, dehydrogenation, and dehydration reactions have been widely demonstrated for various biobased acids.[21−24] In contrast, reactions, such as amidation and nitrilation, to generate amides, nitriles, and amines have received less attention despite the importance of nitrogen-containing molecules. In many proposed nitrogen incorporation reaction pathways, amides are the first intermediates with subsequent conversion to nitriles and amines from primary amides.[25,26] However, the

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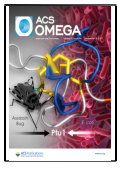

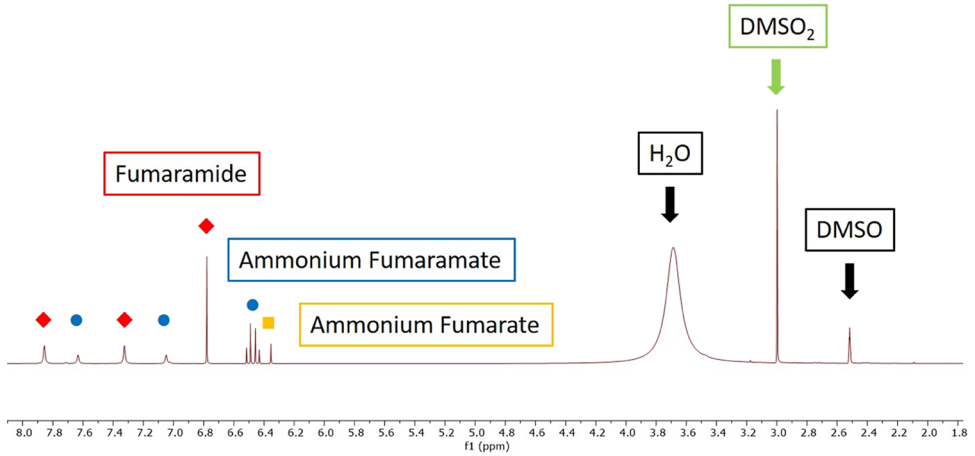

Figure 1. ^{1}H NMR spectrum of the reaction products of dimethyl fumarate ammonolysis in 7.0 M $NH_4OH_{(aq)}$ for 24 h at 25 °C.

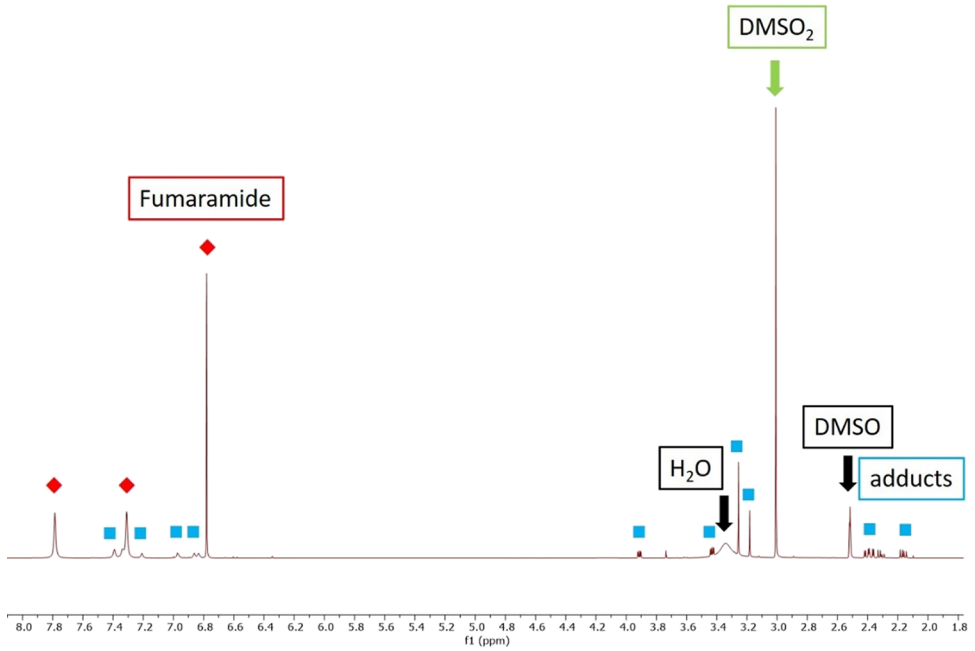

Figure 2. ^{1}H NMR spectrum of the reaction products of dimethyl fumarate ammonolysis in 7.0 M NH_3/methanol for 24 h at 25 °C.

efficacy of amidation reactions to generate primary amines while retaining unsaturation in the main carbon backbone has not been systematically examined.

Direct amidation of an acid has only been reported in the synthesis of secondary or tertiary amides.[27] Primary amidation is a more challenging reaction due to the high stability of ammonium salts. A more feasible approach is to synthesize a primary amide *via* ester ammonolysis.[28] For example, McMaster and Langreck synthesized fumaramide *via* diethyl fumarate ammonolysis, and they further dehydrated the product to form fumaric nitrile.[29] Structural effects are also crucial for applying ammonolysis to other esters. Gordon *et al.* reported the impact of alkyl and aryl groups, which replaced the hydroxyl group in ester ammonolysis.[30] Additionally, the structure of the ester can play a critical role. Kirsch and Kline tested ammonolysis on a series of substituted *p*-chlorophenyl and *p*-nitrophenyl benzoates, which provided insights into how electron withdrawal due to the substitution affected the reaction.[31]

As discussed, the ammonolysis reaction kinetics and mechanism have been studied for a number of molecules. However, most of those molecules only contained a single reactive moiety, which does not address conversion selectivity for multifunctional molecules. Given the potential multifunctionality of biomass-derived molecules, there is value in a more systematic evaluation of the amidation reaction. In this work, dimethyl fumarate was selected as a model molecule for a more detailed examination of unsaturated ester ammonolysis. The work was then further extended to additional potential biomass-derived C_4 and C_6 esters. By characterizing key side reactions and reaction rates of these esters, the impact of molecular attributes on ammonolysis was elucidated as to provide insights into the selection of the desirable biobased molecules for generating nitrogen-containing products.

RESULTS AND DISCUSSION

Dimethyl fumarate can be produced at high selectivity through a simple esterification of fumaric acid,[32] so dimethyl fumarate was selected as the representative model compound for studying the amidation reaction behavior of the bioderived unsaturated esters. The experiments were conducted in either water or

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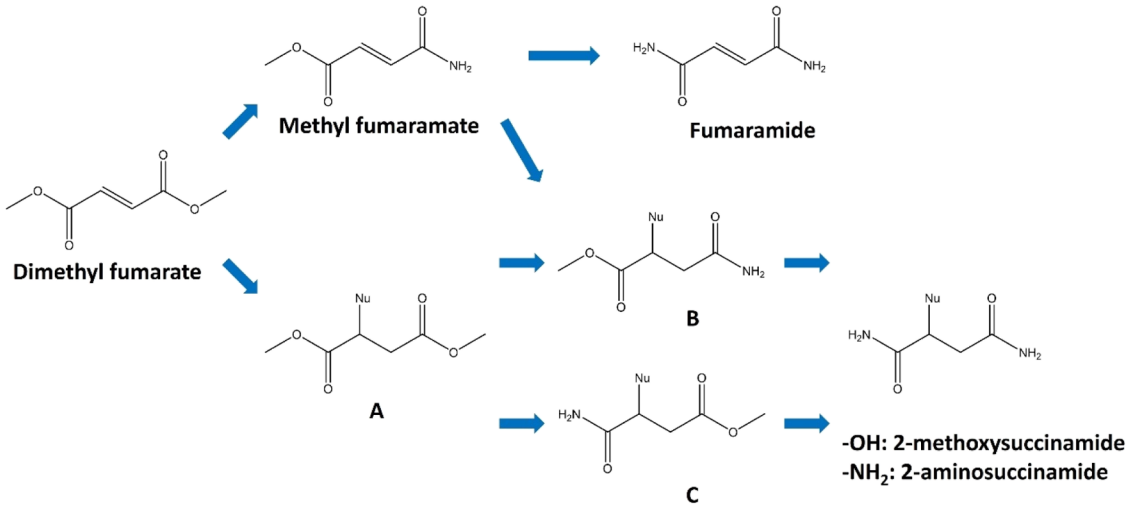
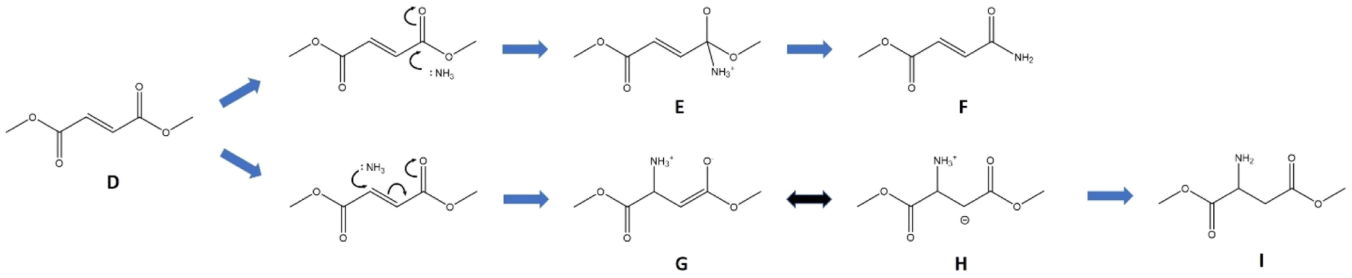
Scheme 1. Ammonolysis Reaction Network of Dimethyl Fumarate in NH_3/Methanol



Scheme 2. Mechanism of Dimethyl Fumarate Ammonolysis and Conjugate Addition[a]



[a]Nu = amine or methoxy group.

methanol. After a 24 h reaction at 25 °C in 7.0 M ammonia water solution, as shown in Figure 1, all of the dimethyl fumarate was converted to fumaramide, ammonium fumaramate, and ammonium fumarate, with yields of 39.6, 46.0, and 2.9%, respectively. The formation of partial hydrolysis products, ammonium fumaramate, and ammonium fumarate, was consistent with what was reported by Blackburn and Jencks.[33] They found that ester hydrolysis happens under basic conditions; hence, it is inevitable in aqueous ammonia, which is a weak base. To prevent the hydrolysis reaction, methanol was used instead of water as the solvent. Peaks corresponding to ammonium fumaramate and ammonium fumarate were absent from the spectrum (see Figure 2). In contrast, a 29.7% yield of adducts, such as 2-aminosuccinamide and 2-methoxysuccinamide, were formed as byproducts, at the expense of the fumaramide selectivity. After a 24 h reaction, a 63.5% fumaramide yield was obtained. Further, the ammonolysis reaction was conducted for 1 and 3 h to track the reaction products. The nuclear magnetic resonance (NMR) results for these runs are shown in Figures S1 and S2. Peaks in the range of δ = 3.60−3.20 ppm were detected, which were assigned to the unreacted ester intermediates (**A**, **B**, or **C** in Scheme 1), which indicated conjugate addition occurred.

The stability of fumaramide in the reaction system was tested under the same conditions. As shown in Figure S3, only trace amounts of byproducts were detected after 24 h and the amount of fumaramide remained essentially unchanged. The result suggested that once fumaramide was formed, it was not further converted to an adduct product. An important contributor to the result is the relative insolubility of fumaramide in methanol, which limits the opportunity for its further reaction. Importantly, fumaramide reactivity for conjugate addition was negligible (see Figure S3). The ammonolysis of dimethyl fumarate forms methyl fumaramate and then further reacts to form fumaramide.[29,34] Combining the observations discussed above, a reaction network for the ammonia−methanol system could be proposed in Scheme 1. Aside from ammonolysis, conjugate addition occurred in the reaction system, so adducts were formed by the addition of ammonia or methanol to the C═C double bond. The reaction time was further extended to 48 h with the results shown in Figure S4. For this longer time, the yields of the major products remained unchanged, which indicated that these products were either stable in the NH_3/methanol solution or fully precipitated from the solution.

The proposed reaction mechanisms for ester ammonolysis and conjugate addition are shown in Scheme 2. Ammonia can react as a nucleophile and attach to the α-carbon in the carboxylic acid group with the electron on the α-carbon being partially transferred to the oxygen-forming intermediate **E**. Then, the amine cation can donate a proton to the methoxy group to create a methanol leaving group leading to the formation of an amide group, **F**. In parallel to the ester ammonolysis, conjugate addition can occur through nucleophilic attachment on the C═C double bond. The nucleophilic molecules in the solution can react with the ester and form intermediate **G** or **H**, as shown in Scheme 2. Finally, the proton transfers to form an amine or methoxy group as given by **I**. The NMR spectrum in Figure 2 supported the existence of amine and methoxy groups. The singlets at 3.26 and 3.28 ppm were assigned to the three protons in the methoxy group.

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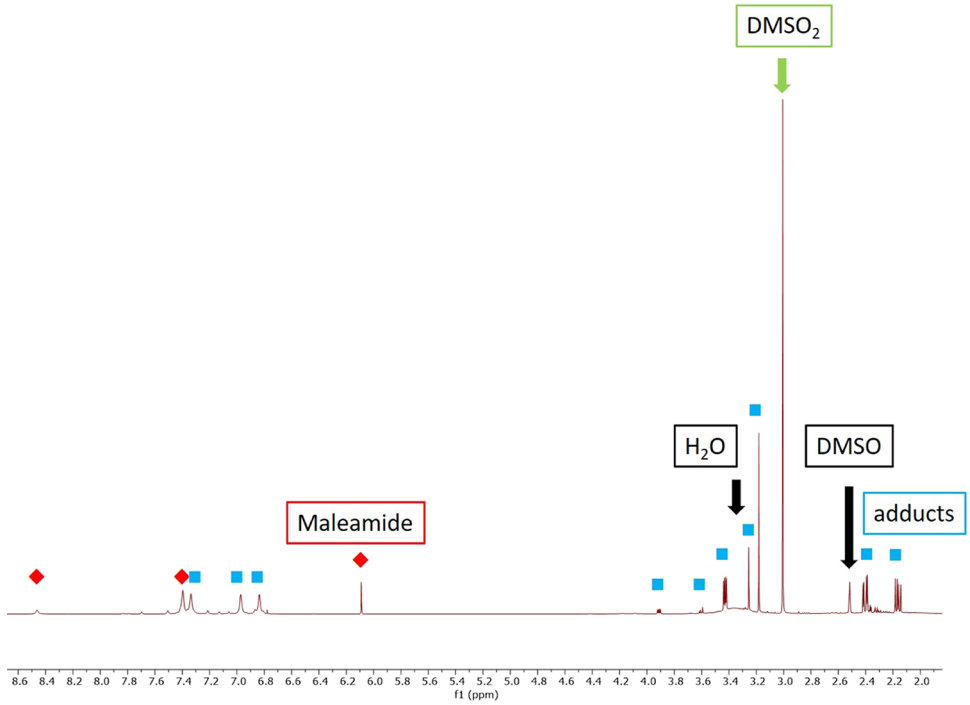

Figure 3. ^{1}H NMR spectrum of the reaction products of dimethyl maleate ammonolysis in 7.0 M NH_3/methanol for 24 h at 25 °C.

Furthermore, the two peaks at 3.43 and 3.91 ppm indicated that two adducts were formed; these peaks were assigned to the hydrogen bonded to the C on which the nucleophile was added. Of note, conjugate addition products (Figure S9) were also observed in the ammonolysis of the monoester counterpart, methyl crotonate.

To examine the geometric effect of the diester, the reaction results for dimethyl fumarate were compared with that of dimethyl maleate under the same reaction conditions. The NMR spectrum given in Figure 3 revealed no peaks characteristic of dimethyl maleate, indicating that the conversion reached 100%. The yield to the unsaturated diamide was only 14.3%, which was much lower than that for the trans-isomer, dimethyl fumarate. A significantly higher selectivity to adducts, 66.1%, was determined from the peak intensities. Other saturated by-products were observed as can be seen with the peaks from δ = 2.13 to 2.43 ppm. The geometric difference between dimethyl fumarate and dimethyl maleate possibly increased the probability of the nucleophilic attack in the reaction mechanism in Scheme 2. The results suggested that a steric hindrance from the trans-isomer can diminish the nucleophilic attack on the C═C double bond. In contrast, the less restricted structure of the cis-isomer allowed the nucleophile to have a higher addition reactivity to the C═C double bond.

While NMR is effective for product identification, it requires replacing the deuterated solvent, but the ammonolysis reaction is then unavoidable during the sample preparation drying process. To obtain temporal results, high-performance liquid chromatography (HPLC) analysis was used. In Figure 4, the concentration of the reactants and products were measured as the reaction proceeded, all the concentrations were normalized by the reactants. Unfortunately, accurate quantification for each intermediate is challenging due to low concentrations and high molecule diversity. As shown in Figure 4, dimethyl fumarate reacted faster than dimethyl maleate. The structure of the cis- or trans-isomer not only affected the overall selectivity but also changed the ammonolysis reaction rate.

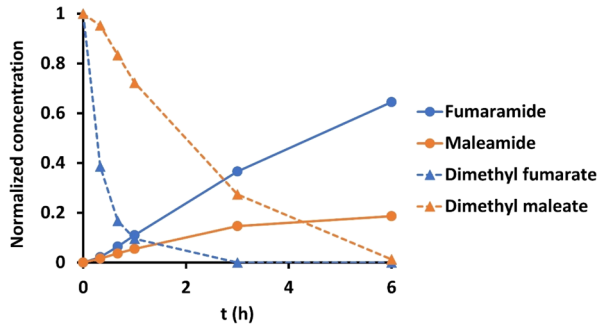

Figure 4. Amide production from dimethyl fumarate and dimethyl maleate ammonolysis in 7.0 M NH_3/methanol at 25 °C.

To understand how a C═C double bond in the backbone affected the reaction, dimethyl fumarate, and dimethyl maleate results were compared with that of dimethyl succinate. In dimethyl succinate ammonolysis, the conversion only reached 70.6% after 24 h. The products were identified using HPLC−MS and NMR and quantified by HPLC. The products were methyl succinamate, succinamide, and a ring product, succinimide. The product distribution is shown in Figure 5. To examine how succinimide was formed in the system, the dimethyl succinate was replaced with methyl succinamate and succinimide. The related NMR results are shown in Figures S6 and S7. Both the methyl succinamate and succinimide were found at the same ratio in either case, so it appeared that they readily interconverted at reaction conditions in the ammonia/methanol solution. Unlike with the C═C double bonds, the C−C bonds permitted the free rotation of the molecule, so the succinimide ring could for due to the nucleophilic attack between the amide group and the intramolecular carbon in the other ester group. The overall reaction network for dimethyl succinate is illustrated in Scheme 3.

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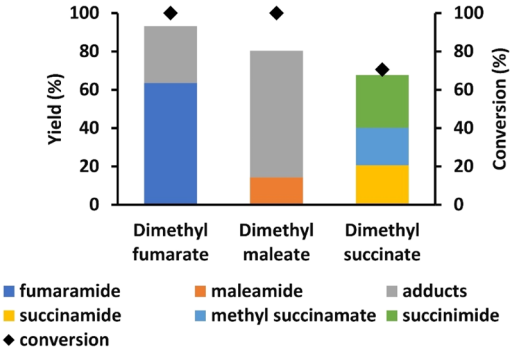


Figure 5. C_4 diester product distributions in the 7.0 M NH_3/methanol solution under 25 °C for 24 h.

In Figure 5, the products from dimethyl fumarate, dimethyl maleate, and dimethyl succinate are compared after 24 h ammonolysis reactions. The conversion of dimethyl succinate was much lower than for dimethyl fumarate or dimethyl maleate. Complete conversion was reached for dimethyl fumarate and dimethyl maleate ammonolysis, including converting the intermediates into diamides, as shown in Figures 2 and 3. The yields of fumaramide and maleamide were 63.5 and 14.3%, respectively. Additionally, the adducts were converted to diamides as well. In contrast, the dimethyl succinate conversion was only 70.6% with a 19.6% yield of succinamide. It was clear that diamide formation from dimethyl fumarate was much faster than for dimethyl succinate. There are several possible reasons for this difference. First, the ring-closing reaction with dimethyl succinate would decrease the methyl succinamate concentration thereby decreasing the rate of succinamide formation. Even though intermediates **A**, **B**, and **C** in Scheme 1 can be formed in dimethyl fumarate ammonolysis, the amine or methoxy group side chain could reduce the ring-closing reaction leading to a high diamide formation from the adducts. The NMR spectrum in Figures 2 and 3 show that no ring structure was formed. Second, the conjugated C═C double could delocalize the electron density of the α-carbon, inducing higher ammonia nucleophilic attack rates, as shown from the mechanism in Scheme 2. This phenomenon was consistent with the conversion results in Figure 5. In dimethyl fumarate and dimethyl maleate ammonolysis, most of the products were found to be diamides, including those from the adducts. In contrast, only 70.6% of dimethyl succinate was converted.

One of the goals of the studies was to develop more generalized knowledge about the amidation activity for a range of potential biomass-derived esters. To do this, the reaction rate constants for a set of di- and mono-esters were determined. In contrast to the above studies, low ammonia concentration and ester concentration 0.7 M were used to determine initial reaction rates corresponding to low ester conversions. Stirring rates from 200 and 500 rpm were tested with the results given in Table S2. It appeared that 300 rpm was sufficient to overcome mass transfer, while also eliminating spurious solution vortices that were observed with stirring rates above 400 rpm. Therefore, the stirring rate was held at 300 rpm for the reaction studies. For determining the rate expression corresponding to dimethyl fumarate, the ammonia concentration was varied from 0.175 to 1.05 M with the overall reaction targeted to 10% conversion at each condition. The effect of the ammonia concentration on the reaction rate for dimethyl fumarate is shown in Figure 6, with the reaction rate defined as the consumption rate of dimethyl fumarate, as given in eq 3.

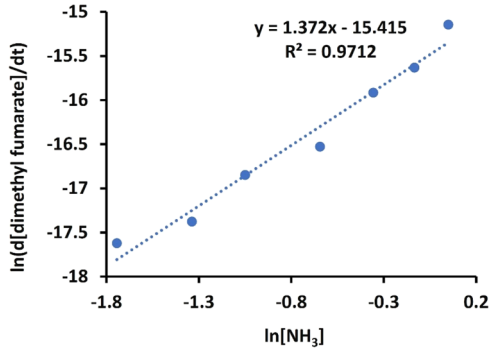
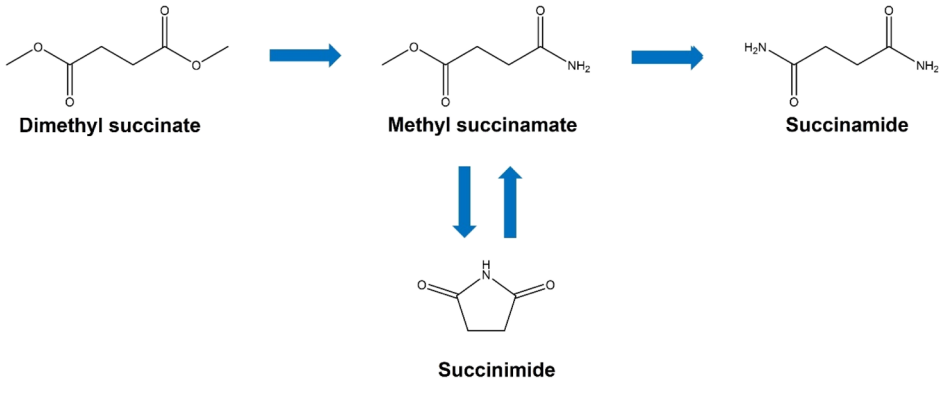


Figure 6. Ammonia concentration *vs* reaction rate in dimethyl fumarate ammonolysis at 25 °C.

For the ammonia concentration range used, the apparent reaction order with respective to ammonia was determined to be 1.37. This value was close to the 1.5 value that has been reported for ammonolysis reactions.[35] However, in the current study, the measured ammonia order of 1.37 would be a combination of both ammonolysis and conjugate addition. Given the previously reported value and the small changes in selectivity between the two reactions across the ammonia values in the current study, a value of 1.5 was used to determine the apparent rate constants for different molecules. Therefore, the model used for comparison is given in eq 1

$$r_{app} = k_{app}[\text{ester}][NH_3]^{1.5} \quad (1)$$

Scheme 3. Ammonolysis Reaction Network of Dimethyl Succinate in NH_3/Methanol



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The apparent rate constants for a range of reactants as determined from the experimental results and subsequent calculation using eq 1 are given in Table 1. As seen in the table,

Table 1. Ammonolysis Reaction Rates at 25 °C in 0.7 M NH_3/Methanol Solution

molecules	rate constant $k_1 \times 10^2$ (min^{-1} $M^{-1.5}$)
dimethyl fumarate	419
dimethyl maleate	34.6
dimethyl succinate	2.96
dimethyl 3-hexendioate	7.43
dimethyl adipate	2.39
methyl crotonate	6.52
methyl butyrate	1.26
dimethyl fumarate with NH_4CH_3COO (2.8 M)	61.2

dimethyl fumarate and dimethyl maleate had rate constants larger than that for dimethyl succinate with that of dimethyl fumarate being 2 orders of magnitude greater than that for dimethyl succinate. The selectivity between the two reactions relied on the ammonia concentration. While the quantification of the reaction products was more difficult at the lower conversions used for determining the apparent rate constants, it did appear that the conjugate addition occurred at a relatively higher rate than under the conditions used in Figure 5, so some of the reactivity difference could be attributed to the unsaturated molecules allowing conjugate addition. However, the significant differences of the rate constants, k_{app}, could not be merely assigned to conjugate addition, so the conclusion that the conjugate C═C double bond affected the α-carbon electron density still seemed to apply.

Aside from C_4 diacids, C_6 diacids are also important monomers in the polymer industry, so two C_6 esters, dimethyl adipate and dimethyl 3-hexenedioate, were tested as they can be derived from biomass.[9] As shown in Table 1, dimethyl 3-hexendioate and dimethyl adipate reacted much slower than dimethyl fumarate and dimethyl maleate. This result was consistent with the postulate that conjugate unsaturated bonds might play a significant role in ammonolysis reactivity. While dimethyl 3-hexenedioate contains a C═C double bond, it is not conjugated to either ester group and the electronic interaction is much weaker than in the conjugated ones. However, as with the C_4 diacids, the unsaturated dimethyl of 3-hexenedioate apparent rate constant was still higher for dimethyl adipate. Another difference between dimethyl adipate and its C_4 counterpart, dimethyl succinate, was that no cyclic product was observed in the ammonolysis of the former, likely due to the higher stability of the C_5 ring. Finally, the ammonolysis of the monoamides, methyl crotonate and methyl butyrate was also screened. Again, the presence of the C═C double bond in methyl crotonate enhanced its reactivity relative to the saturated methyl butyrate. Comparing methyl crotonate and dimethyl fumarate, a higher conversion rate of dimethyl fumarate was observed, which can be attributed to several possible factors. First, there are more reactive moieties in the diester than the monoester and as the conversion rate accounts for either, the rate for the diesters can be higher. Second, the conjugate structure of dimethyl fumarate could delocalize the electron on the C═C bond and stabilize an intermediate, such as **E** in Scheme 2. In contrast, the methyl group near the C═C bond in the methyl crotonate has an electron-donating effect, which could lead to a lower chance of a nucleophilic attack on the ester group.

To conclude the study, reaction conditions were screened to maximize diamide selectivity for the ammonolysis of unsaturated dimethyl fumarate. Given the competitive parallel reactions leading to either fumaramide or adducts, the temperature was the first reaction variable examined. Reaction time was allowed to vary so that the reaction products at the different temperatures were all determined when 95% of the ester groups were converted. As shown in Figure 7, the

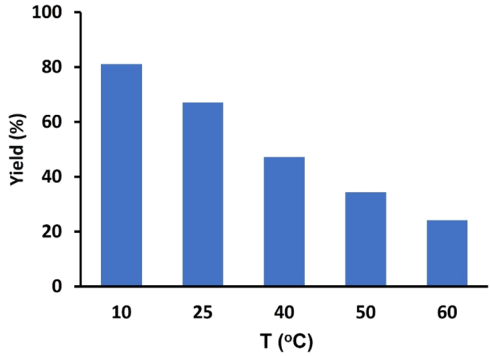

Figure 7. Fumaramide yields under different reaction temperature in 7.0 M NH_3/methanol when over 95% ester groups were converted.

fumaramide yield decreased from 81.1 to 24.1% when the temperature was increased from 10 to 60 °C. Overall, the activation energy for conjugate addition appeared to be higher than that for ammonolysis as the byproduct adducts were increasingly favored at higher temperatures.

The effect of additives on selectivity and reactivity were also studied. Several salts and bases have been proposed for catalyzing ester ammonolysis.[36−39] However, those reports mainly focused on how additives affected the ammonolysis of monoesters, so little information is available on the selectivity when multifunctional esters are reacted. With the increasing complexity of the reactants, controlling the selectivity of ammonolysis is also more challenging. Ammonium acetate was added into the glass vial reactors to exam the effects of ammonium salts on the ammonolysis reactions. As shown in Table 1, ammonium acetate addition caused a decrease of the reaction rate constant from 419 to 61.2 min^{-1} $M^{-1.5}$. This result was consistent with that reported by Betts and Hammett[40] As can be noted in eq S8, the presence of additional ammonium ions would impact the methoxide ion concentration leading to a decrease in the value of the base-catalyzed ammonolysis term and a subsequent lower overall conversion rate. Both ammonolysis and conjugate addition can be catalyzed by a base, but the relative sensitivity to the base concentration might not be the same for the reactions. Therefore, the effect of base concentration and type on reaction selectivity was examined.

Dimethyl fumarate ammonolysis in the presence of additives were conducted in a 7.0 M ammonia solution for 24 h with the results summarized in Figure 8. All of the runs led to complete conversion of the dimethyl fumarate, but as seen from runs 1−6, the fumaramide yield increased with increasing concentration of NH_4CH_3COO. The yield without NH_4CH_3COO was 67.1% and in the presence of 2.8 M NH_4CH_3COO reached 84.3%. These results were likely driven by the changing ammonium ion concentration buffering the solution, which would drastically reduce the methoxide ion concentration. The change in

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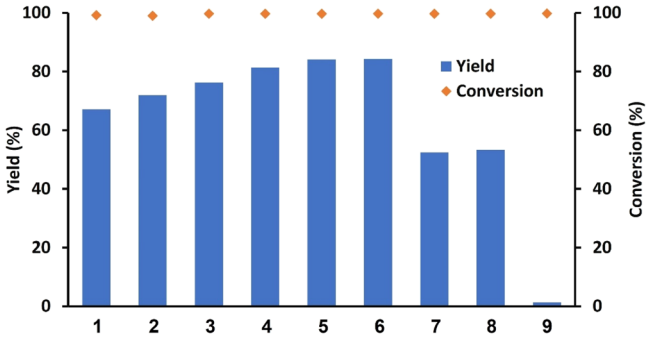

Figure 8. Additive ion effect on amidation selectivity. Ammonolysis reaction in 7.0 M NH_3/methanol solution for 24 h at 25 °C. (**1**: none additive, **2**: 0.35 M NH_4CH_3COO, **3**: 0.7 M NH_4CH_3COO, **4**: 1.4 M NH_4CH_3COO, **5**: 2.1 M NH_4CH_3COO, **6**: 2.8 M NH_4CH_3COO, **7**: 0.7 M $NaCH_3COO$, **8**: 0.7 M KCH_3COO, **9**: 0.7 M $NaCH_3O$).

methoxide ion concentration would affect the base-catalyzed reaction for both ammonolysis and conjugate addition. Given the lower reaction rate but increasing selectivity, it can be concluded that the sum of k_{amm} and k_{add} was reduced, but the k_{add} was reduced more significantly. The impact of ammonium salts was also examined since their impact should be attenuated relative to ammonium acetate as they would lead to a higher equilibrium concentration of CH_3O^-. In runs 7 and 8, the NH_4CH_3COO was replaced with $NaCH_3COO$ or KCH_3COO leading to yields of 52.4 and 53.3%, respectively, which was diminished from the 71.9% with ammonium acetate. $NaCH_3O$ was introduced in run 9 leading to a drastic yield reduction to 1.3%, which was due to directly providing the nucleophile, CH_3O^-. The increased methoxide ion concentration had the dual negative effect of providing a strong nucleophile for enhancing conjugate addition and raising the pH. Therefore, the choice of salt added to the reaction system has a significant impact on the product selectivity. While the conjugate addition is a side reaction for unsaturated amide production, it could be positively applied to modify the unsaturated moiety to generate unique chemicals that could be targeted for other applications.[41]

As the lower reaction temperature and addition of ammonium acetate increased the yield of fumaramide, they were examined together to see if the selectivity could be further increased. As can be seen in Figure 9, the use of both reaction condition modifications led to a further increase in selectivity. Combining a reaction temperature of 10 °C in the presence of 2.1 M ammonium acetate led to the complete conversion of the dimethyl fumarate with a fumaramide selectivity of 90.6%, which was the highest value achieved in the study.

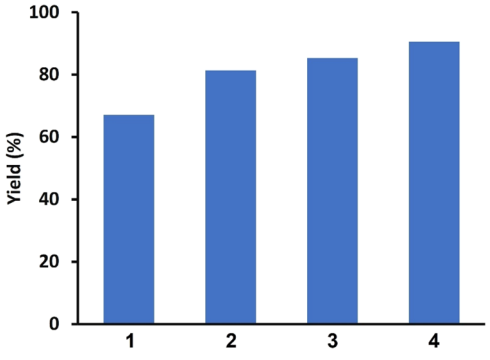

Figure 9. Conditions for maximizing fumaramide production when over 95% ester groups were converted. (**1**: 25 °C, **2**: 25 °C with 2.1 M ammonium acetate, **3**: 10 °C, **4**: 10 °C with 2.1 M ammonium acetate).

CONCLUSIONS

The development of the biobased chemicals can be greatly aided by identifying promising bioderived intermediates that can be subsequently converted to a diversity of chemicals. A range of carboxylic acids can be accessed, which could serve as key intermediates if their conversion to the desired molecules could be selectively achieved. Amidation is one of the reactions that could diversify products from carboxylic acids. This work examined the ammonolysis of dimethyl fumarate and other esters to determine the potential of converting unsaturated esters to nitrogen-containing chemicals, while maintaining the unsaturation.

With ammonia as the reactant, the primary competing reaction for the desired ammonolysis product was conjugate addition. The selectivity to unsaturated amide depended strongly on the reaction temperature and pH of the solvent. Decreasing the reaction temperature from 60 to 10 °C increased the selectivity from 24.1 to 81.1%. In addition to the temperature, the control of the NH_4^+ and CH_3O^- ion concentrations in the solution strongly impacted selectivity. Overall, higher solution pH values decreased the CH_3O^- ion concentration, leading to a higher selectivity to fumaramide. Ultimately, a 90.6% fumaramide yield was achieved when both the lower temperature and introduction of ammonium acetate to suppress conjugate addition was used.

Systematic studies were performed to compare the ammonolysis products from C_4 esters as well as the apparent kinetics of several C_4 and C_6 esters. Due to geometric effects, dimethyl fumarate showed a higher selectivity to the unsaturated amide than dimethyl maleate. In contrast, without the C=C double bond, no conjugate addition was observed for dimethyl succinate but a ring product formed during the reaction, which affected the overall amide production rate. Also, a general trend was observed in that the apparent conversion rates became higher with a C=C double bond molecule, which was likely attributable to both conjugate addition and an electronic effect.

Overall, this study found critical factors for selectively converting unsaturated esters to unsaturated amides, which included the control of the solvent, temperature, and pH. Furthermore, the isomer comparison showed the importance of selecting the appropriate bioderived molecules for further conversions. As expected, the molecular structure of the intermediate carboxylic acid strongly affects ammonolysis selectivity and reactivity, so the intermediate molecule selection should consider subsequent transformations in the development of biobased chemicals.

EXPERIMENTAL SECTION

Reagents and Materials. 7.0 M ammonia in methanol solution (Acros Organics, 9t8%), methanol (Fisher Scientific, Certified ACS), dimethyl fumarate (Sigma-Aldrich, 97%), dimethyl maleate (TCI America, 97%), dimethyl succinate (TCI America, 98%), dimethyl *trans*-3-hexenedioate (TCI America, 98%), dimethyl adipate (TCI America, 99%), methyl crotonate (Acros Organics, 98%), methyl butyrate (TCI America, 99%), succinamide (TCI America, 98%), succinimide (TCI America, 98%), methyl succiniamate (TCI America, 98%), fumaramide (TCI America, 96%), maleamide (TCI America, 98%), adipamide (TCI America, 98%), crotonamide

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(TCI America, 98%), butyramide (TCI America, 98%), deuterated dimethyl sulfoxide (Cambridge Isotope Laboratory Inc, 99.96%), and dimethyl sulfone (Sigma-Aldrich, 98%) were used as received.

Ammonolysis Reaction. In a typical reaction test, 1.4×10^{-4} mol of an ester was dissolved in 2.0 mL of the ammonia solution in a 10 mL thick-walled glass vial with a magnetic stir bar. Loaded reactors were placed in a water bath or a silicon oil bath, depending on the reaction temperature. The reaction temperature and stir bar agitation were controlled by a Fisher Isotemp hot plate stirrer. In the experiments at 10 °C, a water bath was cooled by a chiller through a copper coil. The reactors were transferred into an ice bath to stop the reaction and air-dried to remove methanol and ammonia. Prior to analysis, the dry products were dissolved in different solvents according to the analytical method, as described for the respective analytical methods.

Analytical Methods. *NMR Analysis.* NMR analysis was applied for the identification and quantification of products. Dimethyl sulfone was used as the internal standard for product quantification. The dried products were dissolved in deuterated dimethyl sulfoxide (DMSO-d_6) along with 600 μL of the internal standard. Because the ice bath kept the products at a low temperature, it was assumed that only methanol and ammonia evaporated and all products remained in the reactor. The NMR experiments were conducted with a Bruker AVANCE III 600 spectrometer.

The NMR identification used was dimethyl fumarate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 3.76 (s, 6H, $-CH_3$), 6.80 (s, 2H, C=C) ppm; methyl fumaramate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 3.74 (s, 3H, $-CH_3$), 6.59 (d, 1H, C=C), 6.99 (d, 1H, C=C), 7.53 (s, 1H, $-CONH_2$), 7.93 (s, 1H, $-CONH_2$) ppm; ammonium fumaramate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 6.44 (d, 1H, C=C), 6.50 (d, 1H, C=C), 7.05 (s, 2H, $-CONH_2$), 7.63 (s, 2H, $-CONH_2$) ppm; ammonium fumarate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 6.35 (s, 1H, C=C) ppm; fumaramide: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 6.78 (s, 2H, C=C), 7.31 (s, 2H, $-CONH_2$) 7.79 (s, 2H, $-CONH_2$) ppm; dimethyl maleate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 3.76 (s, 6H, $-CH_3$), 6.80 (s, 2H, C=C) ppm; maleamide: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 6.09 (s, 2H, C=C), 7.40 (s, 2H, $-CONH_2$), 8.46 (s, 2H, $-CONH_2$) ppm; dimethyl succinate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 2.58 (s, 4H, $-CH_2$), 3.60 (s, 6H, $-CH_3$) ppm; methyl succinamate: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 2.34 (t, 2H, $-CH_2$), 2.48 (t, 2H, $-CH_2$), 3.58 (s, 3H, $-CH_3$), 6.79 (s, 1H, $-CONH_2$), 7.33 (s, 1H, $-CONH_2$) ppm; succinamide: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 2.27 (s, 4H, $-CH_2$), 6.72 (s, 2H, $-CONH_2$), 7.27 (s, 2H, $-CONH_2$) ppm; and succinimide: ^{1}H NMR (DMSO-d_6, 600 MHz), δ = 2.58 (s, 4H, $-CH_2$), 10.17 (s, 1H, $-NH$) ppm.

HPLC-PDA/QDa and GC–MS/FID Analysis. Diesters and other reaction products were analyzed using a HPLC system, equipped with a Waters e2695 separation module, Jupiter 4 μm Proteo 90 Å column (250 × 4.60 mm) and Waters ACQUITY H-Class photodiode array (PDA) detector. For quantification, 50% (v/v) 5 mM sulfuric acid in methanol (HPLC grade) was used as the mobile phase. For molecule identification, the sulfuric acid solution was replaced with 0.5 mM acetic acid, and the samples were analyzed through a Waters ACQUITY QDa detector. The dried products were dissolved in a 1:1 v/v methanol/water solution. Using the same preparation as for HPLC analysis, the products from methyl crotonate and methyl butyrate reactions were analyzed with an Agilent 7890A GC–MS equipped with a DBWAX column (30 m, 0.25 mm, 0.25 μm), flame ionization detector (FID), and 5795C mass spectrometer.

Kinetic Model. For the kinetic study, the initial ester concentration remained the same, but the ammonia concentration was reduced to maintain a low conversion. A proposed mechanism for the ammonolysis of monoesters by ammonia was initially reported by Betts and Hammett.[40] They considered the ammonia–ammonium ion equilibrium and proposed an approximately 3/2 reaction order for the ester. A second ester ammonolysis model was developed by Bunnett and Davis based on a mechanism reported by Hawkins and Tarbell.[35,42] In that model, Lewis base-catalyzed chemistry was also included in the mechanism. Application of this model could be used to describe the variety of reaction orders for ammonia observed in other studies.[31,43,44]

In the current work, which examined the ammonolysis of unsaturated esters, the formation of adducts through conjugate addition was also observed. From the NMR analysis, both amine and methoxy groups were observed to have formed. Therefore, an adduct formation term was added to the model, so that the overall apparent reaction rate of ester conversion was modeled with

$$r_{app} = \frac{\mathrm{d[unsaturated\ ester]}}{\mathrm{d}t} \tag{2}$$

$$r_{app} = r_{amm} + r_{add} \tag{3}$$

where r_{amm} is the ammonolysis rate and r_{add} is the conjugate addition rate. Both reactions have been reported to be base-catalyzed. A more detailed presentation of the proposed kinetic expressions for the model is given in the Supporting Information. Selectivity and yield were defined as per the following equations in this work

$$\text{selectivity} = \frac{\text{mole of unsaturated amide formed}}{\text{mole of reacted reactant}} \times 100\% \tag{4}$$

$$\text{yield} = \frac{\text{mole of unsaturated amide formed}}{\text{mole of total reactant}} \times 100\% \tag{5}$$

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04750.

Structure of tested ester, ^{1}H NMR spectra, GC–MS results, proposed kinetic models, and agitation rate selection (PDF)

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Notes

The authors declare no competing financial interest.

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