ACS Partner Journal

Journal of the American Society for Mass Spectrometry

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Research Article

Monoacylation of Symmetrical Diamines in Charge Microdroplets

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Cite This: *J. Am. Soc. Mass Spectrom.* 2021, 32, 531−536

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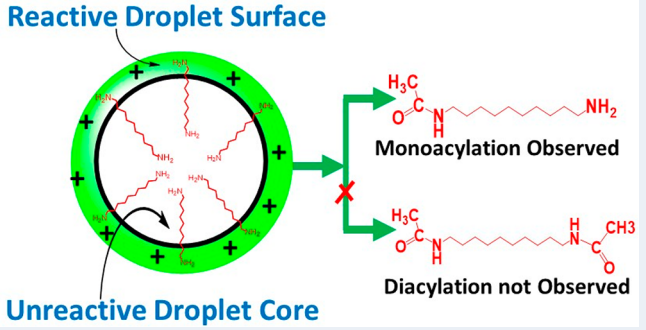
ABSTRACT: Monoacylation of symmetrical diamine is achieved when the primary α,ω-diamines (carbon numbers n = 3, 5 and 12) are diluted in ethyl acetate, and the resultant mixture is electrosprayed across a 10 mm distance in ambient air toward a mass spectrometer. The N-acylated product is formed in charged microdroplets without acidifying and activating agents and in the absence of heat. This result provided an insight into the orientation of the amines in the droplets, suggesting that the ester is activated to react with the amine at the droplet surface due to the high abundance of protons at the air−droplet interface.



KEYWORDS: *selective acylation, symmetric diamines, direct amidation, accelerated droplet chemistry, electrospray ionization*

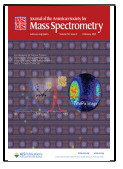
INTRODUCTION

Selective reactions of symmetrical functional groups are challenging. That is, selectivity becomes a major issue in organic reactions when two functionalities in a given molecule have very little difference in reactivity. The reactivity of charged microdroplets derived from electrospray has been attributed mainly to surface effects.[1−5] Therefore, there is a natural tendency to restrict two symmetrical functional groups at the opposite ends of a linear alkyl chain in two uniquely different environments in the charged droplet, one at the surface and the other inside the core of the droplet. This capability should in principle confer different reactivities to the two symmetrical functionalities without using any protecting groups. We test this hypothesis using N-acylation of symmetrical diamines in charged ethyl acetate microdroplets to afford stable amide bonds.

Amide bonds are one of the most important fundamental functional groups in organic chemistry, particularly because of their role in many biological systems.[6−8] Amides are present in biomolecules, fine chemicals, and drug candidates. Despite the ubiquitous nature of this functional group, there has not been any report on the direct amidation without prior activation of the carbonyl functional group. Almost all known synthetic routes use catalysts and other means of activation to enable the formation of the amide bond.[9−12] In particular, acetamides have many applications and are important to the polymer, agrochemical, and pharmaceutical industries.[13−15] Not surprisingly, these have been traditionally synthesized through the reaction of activated acylating agents (e.g., acetic anhydride and acetyl chloride) with amines. However, the toxicity and hygroscopic nature of acetic anhydride and acetyl chloride make them less favorable as acylating agents.[15] Other reported methods involve metal catalysts, both heterogeneous and homogeneous, which are often expensive and add further purification steps.[16,17]

In this work, we chose to examine the reactivity of symmetrical primary diamines toward common esters in an electrosprayed charged microdroplet environment. Esters are one of the most common functional groups in nature and can be readily isolated from flowers, fruits, and fats. Esters are more stable than carbonyl groups such as ketones, aldehydes, and carboxylic acids. The stability of esters has led to their applications as solvents and protecting groups for carboxylic acids. As alluded to earlier, charged microdroplets derived from electrospray ionization (ESI) have been reported to serve as reaction vessels where bimolecular organic reactions can be accelerated.[1,5,18−20] The factors influencing reaction rates in the charged microdroplet environment have been identified to include extreme pH effects due to the preferential localization of protons at the droplet surface, concentration effects as a result of solvent evaporation when droplets are allowed to travel in ambient air, and surface effects due to the presence of un-neutralized charged species at the air−droplet interface, which lowers the activation energy by reducing solvent effects. The pH effect was particularly important in designing this experiment because a recent report indicated that acetic acid is able to facilitate the conversion of amine to amide in the

Received: October 12, 2020
Revised: December 1, 2020
Accepted: December 17, 2020
Published: December 28, 2020



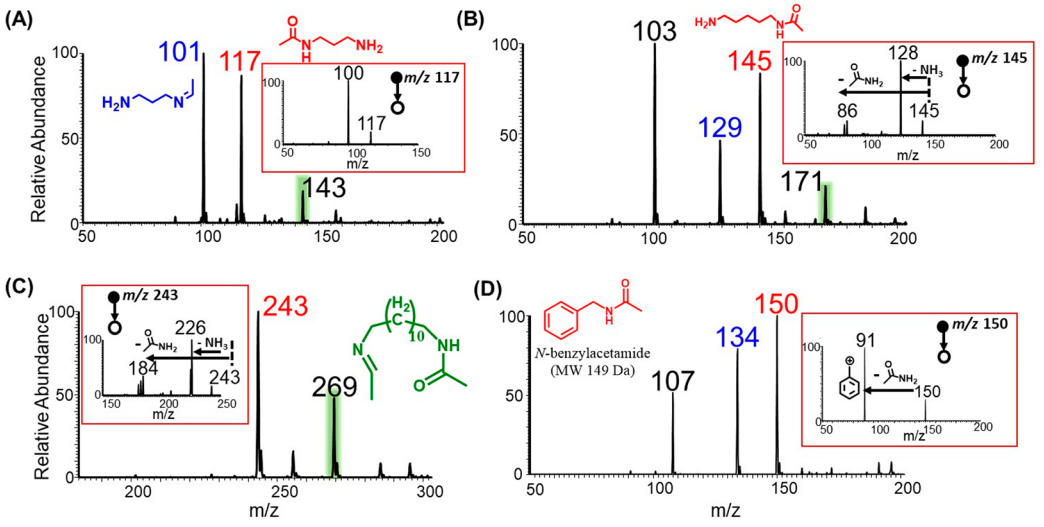


Figure 1. Positive-ion mass spectra recorded after electrospaying separate mixtures of ethyl acetate with (A) 1,3-diaminopropane, (B) 1,5-diaminopentane, (C) 1,12-diaminododecane, and (D) benzylamine. Inset spectra represent product-ion tandem MS/MS of monoacylated diamine reaction products at m/z 117, 145, 243, and 150, respectively, for A, B, C, and D using collision-induced dissociation. The peaks shaded with green backgrounds in A, B, and C represent a reaction product in which both alkylation and acylation occur in a single diamine molecule.

presence of esters when the reaction mixture is subjected to heat (80 °C) for an extended time period (20 h).[21] We hypothesized that, if the reaction between amines and esters is acid catalyzed, then it should be possible to accelerate this bimolecular reaction under the charged microdroplet environment without using acidifying agents or heat. This expectation has been met. The electrospray of an amine and ester mixture yields the corresponding N-acylated product in a seconds time scale. The elimination of the acetic acid catalyst from the droplet reaction system also provided a straightforward means to confirm the reaction mechanism by pinpointing the source of the acylation agent. This was not possible in the previous report because the use of acetic acid and esters meant that the same product would be produced, irrespective of whether the acetyl group was transferred from the acetic acid or acetate ester. Most importantly, we show that the unique droplet environment allows monoacylation of symmetrical diamines without prior protection steps.

EXPERIMENTAL SECTION

Mass Spectrometry. Reaction systems were monitored by a Thermo Fisher Scientific LTQ ion trap mass spectrometer (San Jose, CA, USA). Unless otherwise stated, MS parameters employed were as follows: 250 °C inlet capillary temperature, 5 kV spray voltage, 10 mm distance from the ESI ion source to the MS inlet, 60% S-lens voltage, 3 microscans, and 100 ms ion injection time. Spectra were recorded for at least 30 s, yielding an average of 300 individual scans. Thermo Fisher Scientific Xcalibur 2.2 SP1 software was utilized for the MS data collection and processing. Unless otherwise mentioned, tandem MS with collision-induced dissociation (CID) was performed for analyte identification. 30% (manufacturer's unit) and 1.5 Th (mass/charge units) for the isolation window of the normalized collision energy were selected for the CID tests.

Materials and Reagents. 1,12-Diaminododecane (98%) 1,5-diaminopentane, and 1,3-diaminopropane were ordered from Fisher Scientific (Columbus, OH, USA). Dodecylamine (98%) and propylamine (98%) were ordered from Acros Organics (New Jersey, USA). Methanol (99.9% HPLC grade), acetonitrile (99.9% HPLC grade), benzylamine, ethyl acetate, propyl acetate, butyl acetate, butyl butyrate, and benzyl benzoate were all obtained from Sigma-Aldrich (St. Louis, USA). Standard *N*-(3-aminopropyl) acetamide was purchased from Cayman Chemicals (Ann Arbor, USA).

Solution Preparations. For both 1,5-diaminopentane and 1,3-diaminopropane reactants, stock solutions were first prepared at 4 M concentrations in methanol and acetonitrile, respectively. Then, the working solutions were subsequently prepared through dilutions using the selected esters to make a final concentration of 100 μM. The high concentration of the stock solution ensures that the ester is the main solvent for the final working solution to be analyzed. Because of solubility issues, the stock solution of 1,12-diaminododecane was prepared at 500 μM using methanol, before the final dilution to 100 μM with the ester. All other amine solutions examined were prepared following the procedure described for 1,5-diaminopentane at similar concentrations.

RESULTS AND DISCUSSION

We examined the reactivity of different esters (e.g., ethyl acetate, propyl acetate, butyl acetate, butyl butyrate, and benzyl benzoate) toward three primary α,ω-diamines (carbon numbers n = 3, 5, and 12). The solutions of the amine substrates under investigation were prepared at a high concentration of 4 M in acetonitrile or methanol solvents prior to adding the esters to obtain an amine concentration of 100 μM. The esters were the main solvents/reagents in which the final working amines were prepared. This meant that the initial acetonitrile or methanol solvents were present in negligible (<0.05%) amounts during the reaction. The mixture, in the final concentration of 100 μM, was electrosprayed (5 μL/min flow rate, 100 psi N_2 nebulizer gas pressure, and 5 kV spray voltage) immediately upon ester addition. The resultant charged microdroplets derived from the electrospray process were transferred to a proximal mass spectrometer (across a 10 mm distance), enabling the characterization of reaction products in real-time without the need for sample workout. During mass spectrometry (MS) analysis, we noted that esters

https://dx.doi.org/10.1021/jasms.0c00384
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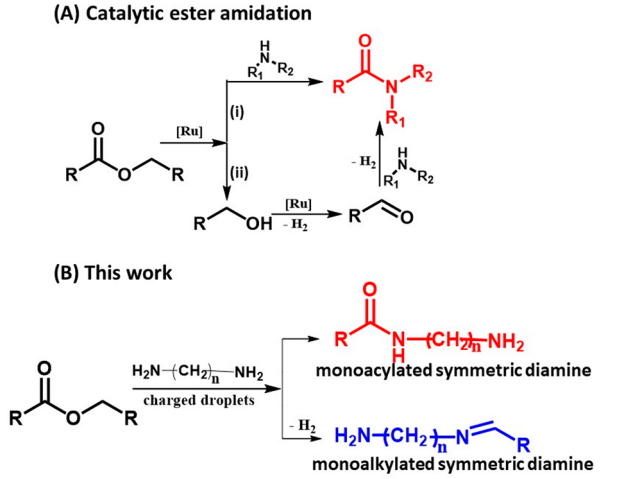
with longer carbon chains such as propyl acetate, butyl acetate, butyl butyrate, and benzyl benzoate were less reactive. Ethyl acetate was identified as the most effective acylation agent among the esters investigated, producing amide products instantaneously without requiring any external activation.

It is a widely accepted fact that the hydrophobic carbon chain in alkyl amines is typically exposed at the charged droplet surface with the polar amine functional group inserted into the core of the droplet.[22−24] We anticipated this configuration to hinder primary alkyl amines from participating effectively in reactions occurring at the air−droplet interface, where the acylating ester reagent is expected to be activated due to the high abundance of protons at the droplet surface. Therefore, we elected to start our investigation on N-acylation reactions using diamines instead of monoamines. By utilizing diamines, we ensured that at least one of the amine functional groups would be exposed at the droplet surface to enable surface reactions.

A positive-ion mode mass spectrum recorded after electrospraying a solution containing a mixture of 1,3-diaminopropane (MW 74 Da) and ethyl acetate is provided in Figure 1A. The expected amide product, *N*-(3-aminopropyl) acetamide (MW 116 Da), was detected as a protonated $[M + H]^+$ species at m/z 117 in high abundance. The identity of this ion was confirmed through tandem MS (MS/MS) analysis using collision-induced dissociation (CID), which fragmented predominantly to give a product ion at m/z 100 via ammonia loss (see inset, Figure 1A). We further compared the MS/MS of *N*-(3-aminopropyl) acetamide derived from the droplet reaction conditions to the MS/MS recorded from a standard *N*-(3-aminopropyl) acetamide (Figure S1) and found the two spectra to be identical, confirming the assigned structure. In a similar manner, the N-acylation of 1,5-diaminopentane (MW 102 Da) by ethyl acetate is observed to give *N*-(5-aminopentyl) acetamide (MW 144 Da) after electrospraying the reaction mixture (Figure 1B). The reaction product was detected at m/z 145 during ESI MS. MS/MS analysis (inset, Figure 1B) registered two competitive fragmentation pathways to give product ions at m/z 128 and 86, formed by the loss of ammonia (MW 17 Da) and acetamide (MW 59 Da), respectively. Also, from a 500 μM methanolic stock solution of 1,12-diaminododecane (MW 200 Da), ethyl acetate was added to produce a final concentration of 100 μM 1,12-diaminododecane. ESI-MS analysis of this reaction mixture registered an abundant peak at m/z 243 (Figure 1C), which corresponds to the N-acylated reaction product *N*-(12-aminododecyl) acetamide (MW 242 Da). The MS/MS spectrum for *N*-(12-aminododecyl) acetamide is shown as the inset in Figure 1C, which is also observed to fragment by losing ammonia and acetamide to give product ions at m/z 226 and 184, respectively. Aside from the linear diamines, we also investigated the possible N-acylation of amine with aromatic substituents, benzylamine. Although benzylamine is a primary monoamine, it reacted favorable under the charged microdroplet environment (Figure 1D), forming the N-acylated product at m/z 150 (reasons for this reactivity are discussed later).

These results are important because catalytic ester amidation is rare. Ru-pincer systems are the best known examples, which allow direct ester amidation via nucleophilic substitution at the carbonyl carbon. However, this catalytic system mostly requires strong nucleophiles such as secondary amines (Scheme 1A).[11] The use of secondary amines also prevents

Scheme 1. Schematic Illustration of (A) Ru-Based Catalytic Acylation of Secondary Amines Compared with (B) Droplet-Based Monoacylation of Symmetrical Diamines



the possible formation of imine, due to the involvement of the aldehyde intermediates illustrated in pathway (ii) in Scheme 1A. A nickel-catalyzed coupling method was recently found to allow direct amidation using nitroarenes.[25] Other direct ester amidation methods involve the use of stoichiometric amounts of promoters such as trimethylaluminum (average temperature 100 °C, total reaction time ∼18 h),[26] *tert*-butoxide (in the presence of air for in situ superoxide generation, total reaction time ∼30 min)[27] and bislithium amide (cold temperature (−70 °C), total reaction time ∼2 h).[28] In the current study, no transition metal catalyst or promoters are required; yet, the reaction is found to be completed in a seconds time scale following the electrospray of the ester/diamine mixture (Scheme 1B) at room temperature and pressure. The monoacylated diamine reaction products formed from this droplet-based reaction system are important intermediates of several well-established drugs.[29−32] Traditionally, the formation of monoacylated symmetric diamine is challenging due to the fact that the two amine functional groups in the starting diamine have almost identical reactivity, making it difficult to achieve selectivity in the bulk-phase reactions. Currently, the simplest approach to achieve monoacylation from symmetrical diamines is through BOC protection of one amine in an acidic medium, although yields of this step are often low.

When the product distribution derived from the droplet reactions (Figure 1) is examined, two diamine orientations in the charged microdroplets are expected (Scheme 2A): (i) in the first configuration, one amine functional group in the diamine is exposed at the reactive air−droplet interface with the other amine buried in the neutralized droplet bulk; (ii) the second diamine orientation involves having the two amine functional groups exposed at the air−droplet interface while the hydrophobic alkyl chain is anchored in the droplet in a U-shaped configuration. In this later case, we expect both amines to react. Accordingly, three distinct (major) reaction products can be identified in Figure 1: monoacylated diamine (red font), monoalkylated diamine, which spontaneously lose H_2 to yield the corresponding imine (blue font), and mixed bis-functionalized diamine product, having both acylation and alkylation on a single diamine molecule (green font). If one assumes that these reactions occur at the air−droplet interface, then it is reasonable to suggest that the bis-functionalized

https://dx.doi.org/10.1021/jasms.0c00384
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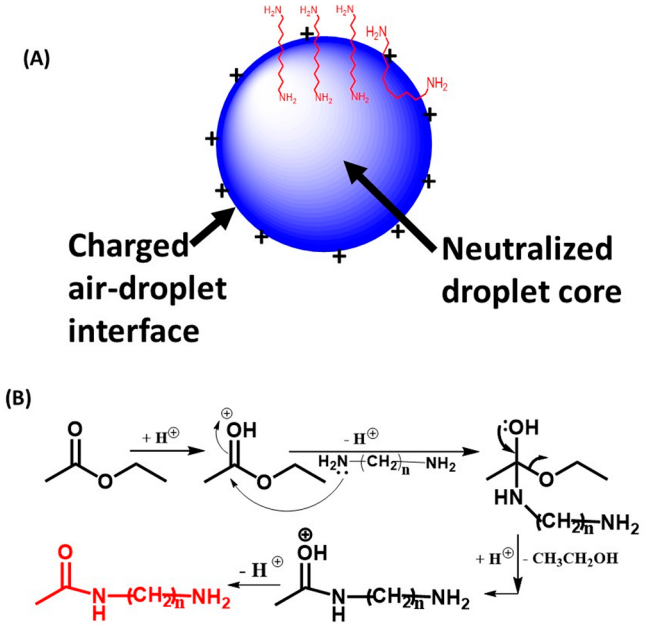
Scheme 2. (A) Schematic Illustration Depicting the Two Possible Diamine Orientations in the Charged Microdroplet; (B) Possible Reaction Mechanism Leading the Acid-Catalyzed Monoacylation of Diamines (n = 3, 5, and 12) at the Charged Ethyl Acetate Droplet Surface[a]



[a]In (A), the majority of the diamines will orient themselves in the droplets with one of the amine groups exposed at the reactive droplet surface while few molecules will have both amines exposed at the air−droplet interface in a U-shaped configuration.

diamine product was formed via the U-shaped diamine orientation in which both amines were exposed to the droplet surface. On the basis of the relative ion intensities, the mixed bis-functionalized diamine products from 1,3-diaminopropane and 1,5-diaminopentane (the peaks are highlighted with a green background in Figure 1A,B) were estimated to be ∼10% and 13% of the total reaction products, respectively. This indicates that only a small fraction of the diamine reactants have both amine functional groups exposed at the droplet surface. However, this fraction increased to ∼50% (see m/z 269 in Figure 1C) for 1,12-diaminododecane due to the increased chain length. Interestingly, detectable amounts of the homo bis-acylated product from 1,3-diaminopropane were not observed. For 1,5-diaminopentane and 1,12-diaminododecane, trace amounts of the homo bis-acylated products were detected at m/z 187 and 285, respectively. Although this might require further investigation, it is important to note that the relative ion intensities recorded for this product type might not reflect the true yield, compared with the monoacylated and monoalkylated products, since the presence of two amide groups can reduce the ionization efficiency of the homo bis-acylated product.

Reactions occur at the air−droplet interface where charged species (H^+) reside. A possible mechanism for monoacylation of the diamine occurring at the droplet surface is illustrated in Scheme 2B. In this schematic illustration, the high abundance of surface protons derived from the electrospray process (e.g., from a trace amount of water or methanol) activate the ethyl acetate at the droplet surface and enable the primary amine located at the droplet surface to attack the carbonyl carbon, resulting in the elimination of ethanol. A similar acid-catalyzed pathway is thought to be responsible for the production of monoalkylated diamine products, except that in this case a more stable acetic acid is eliminated after the initial protonation of the oxygen attached to the ethyl group in ethyl acetate. This monoalkylated diamine is observed to lose hydrogen gas (H_2) instantaneously to yield the corresponding imine at m/z 101, 129, and 227 for 1,3-diaminopropane, 1,5-diaminopentane, and 1,12-diaminododecane, respectively (Figure 1A−C). The intensity of these monoalkylated diamine products decreased with increasing chain length, with only trace amounts recorded for 1,12-diaminododecane at m/z 227. The tandem MS characterization of the monoalkylated diamine products is provided in Figure S2.

The above results suggest that the orientation of the symmetrical diamines in the charged microdroplet affects their reactivity. Considering the fact that the longer 1,12-diaminododecane has a higher (∼50%) capacity of exposing both of its amino groups at the droplet surface compared with the shorter diamines, we hypothesized that shorter chain aliphatic monoamines such as propylamine should be less reactive in charged ethyl acetate droplets. On the other hand, dodecylamine can be expected to be more reactive (relative to propylamine) since it will have more of the amine functionality exposed at the droplet surface as opposed to being buried at the droplet core as would be expected for the shorter monoalkylamine. The results for these investigations are in Figure 2, where we compared the reactivity of propylamine and

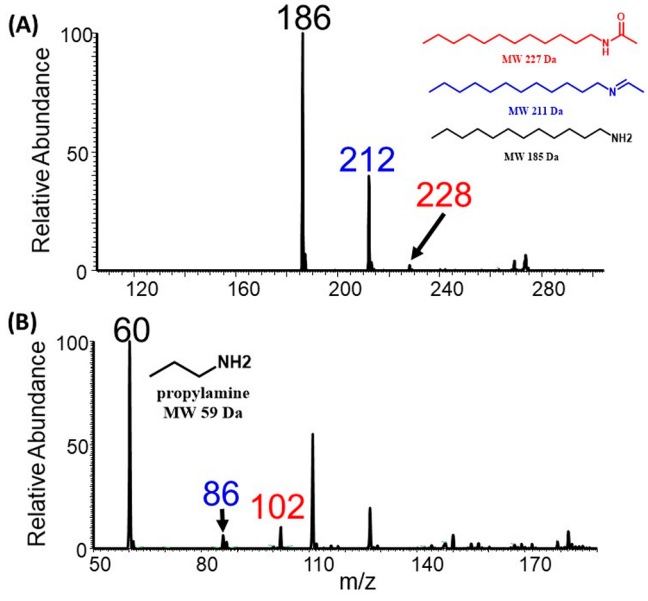


Figure 2. Positive-ion mode ESI-MS spectra for a 100 μM solution of (A) dodecylamine and (B) propylamine in ethyl acetate.

dodecylamine in ethyl acetate droplets. Both the N-acylated and N-alkylated reaction products were observed for both monoamines, but the corresponding ion intensities were much smaller compared to that of the corresponding diamines (i.e., 1,3-diaminopropane and 1,12-diaminododecane). This result is consistent with how we expect the alkylamines to insert in charged droplets with the amine groups mostly buried inside the droplet hindering reaction. When one compares the reaction efficiency among the two monoamines, the reaction product ion intensities (total for both acylation and alkylation) were observed to increase with chain length with dodecylamine

https://dx.doi.org/10.1021/jasms.0c00384
J. Am. Soc. Mass Spectrom. 2021, 32, 531−536

affording slightly more products due to the increased number of exposed amine groups.

To ensure that the difference in reactivity between propylamine and dodecylamine is not due to differences in proton affinities, we examined the reactivity of benzylamine in ethyl acetate droplets. All things being equal, we expect reduced reactivity as the basicity of the amine increases. This is due to the tendency for the more basic amine to be protonated at the droplet surface. This expectation is consistent with the observed results where dodecylamine (gas-phase basicity (ΔG) = 879.9 kJ/mol) showed more reactivity toward ethyl acetate than propylamine (ΔG = 883.9 kJol/mol). However, the results also show that amine basicity alone is not the contributing factor since marked reactivity was observed for benzylamine (Figure 1D) although its gas-phase basicity (ΔG = 878.4 kJ/mol) is the same as that for dodecylamine. We believe this result points to other effects such as the orientation of the amine at the droplet surface. The high electric field at the curved droplet surface can cause the aromatic amine to orient perpendicular to the field and expose the primary amine to the activated ethyl acetate groups at the droplet surface. In this regard, the number of amine groups exposed at the droplet surface for acylation and alkylation will be greater for the case of aromatic benzylamine than the linear dodecylamine and thus more reactive.

The reactivity of the diamines in ethyl acetate solvent was also examined in bulk-solution phase without the addition of any catalyst. Here, 100 μM solutions of the diamines were prepared in ethyl acetate and left to stand in solution for at least 10 min. After the specified reaction time, an aliquot (10 μL) of the diamine solution was analyzed using noncontact nanoelectrospray ionization (nESI) MS. The smaller nanodroplets generated by the nESI platform are known to be less reactive than the microdroplets derived from the conventional ESI source and therefore can give an accurate estimation of the reaction yield occurring in solution prior to electrospray.[2,18,33] The use of noncontact mode nESI further reduces the possible effects from the analytical process by avoiding electrochemical reactions and via the formation of even smaller droplets (due to smaller flow rates).[34] The noncontact nESI-MS spectra recorded for the three diamines after 10 min of a solution-phase reaction with ethyl acetate are shown in Figure S3A,B, where we observed the formation of the monoalkylated products for 1,3-diaminopropane and 1,5-diaminopentane at m/z 101 and 129, respectively. This result suggested the monoalkylated reaction products observed in the droplet experiments were possibly formed in solution before the electrospray. Although the monoacylated products were not detected within the 10 min of bulk solution phase reaction time, trace amounts of this product were observed for 1,5-diaminopentane at m/z 145 when the reaction time was increased to 30 min (Figure S4). This shows the acceleration power of the charged droplets in accelerating organic reactions, representing an enhancement factor ≫30×. For 1,12-diaminododecane, neither the monoacylated nor the monoalkylated products were detected after a 10 min reaction with ethyl acetate in bulk solution phase (Figure S3C), illustrating the necessity of a suitable catalyst for such reactions. Instead, we observed the more reactive 1,12-diaminododecane to be trapped in some other (unidentified) species that dissociated to release the protonated diamine at m/z 201 upon collisional activation in the gas phase (Figure S3D). This is contrary to the droplet experiment, which due to the presence of H^+ at the droplet surface, afforded a clean product.

CONCLUSIONS

In summary, we have identified ethyl acetate as an efficient acyl source for the N-acetylation of symmetrical diamines, which is made possible by the ability of the electrospray platform to screen different reactions conditions in a short amount of time. The charged microdroplet reaction system was most effective toward aliphatic primary diamines and aromatic primary amines. We ascribe the effective N-acylation of 1,3-diaminopropane, 1,5-diaminopentane, and 1,12-diaminododecane to surface effects, which is supported by the less efficient double acylation products due to the insertion of one amine functional group inside the core of the droplet. The weakly polar, relatively less volatile, and high eluent strength of ethyl acetate made it particularly suitable as an electrospray solvent. Proper solvent optimization should expand the scope of the current reaction to other esters.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jasms.0c00384.

Additional experimental details; comparison of MS/MS from a standard compound with experimental data (Figure S1); MS/MS of dehydrogenated monoalkylated reaction products (Figure S2); spectra for the bulk-phase reaction (Figure S3 and S4) (PDF)

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Author Contributions

‖E.A.-G. and E.A. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences, Condensed Phase and Interfacial Molecular Science, under award number DE-SC0016044.

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https://dx.doi.org/10.1021/jasms.0c00384
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