

One-Step, Catalyst-Free Formation of Phenol from Benzoic Acid Using Water Microdroplets

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ABSTRACT: Benzoic acid dissolved in water is electrosprayed (-4 kV) by using nitrogen gas at a pressure of 120 psi to form ~ 10 μm diameter microdroplets. Analysis with mass spectrometry (MS) and tandem mass spectrometry (MS^2) of the resulting microdroplets shows the direct formation of phenol via decarboxylation without any catalyst or added reagents. This process represents an ecofriendly, environmentally benign method for producing phenol and related aromatic alcohols from their corresponding aromatic acids. The mechanism of this transformation was unambiguously characterized using mass spectrometry, radical trapping, and ^{18}O labeling.

Phenol and its substituted derivatives are found in many natural products.^{1–4} Aromatic alcohol-containing scaffolds are widely used as synthetic intermediates in the perfume industry as well as in pharmaceuticals and textiles.^{5–10} For example, phenol, itself, acts as an antiseptic and is used in aerosol form to treat sore throats.¹¹ Similarly, the penicillin drug amoxicillin contains a phenol core, as do propofol, which is used to induce general anesthesia, and tolcapone, which is used to treat Parkinson's disease.^{12,13} Many other bioactive molecules—such as the flavoring agent vanillic acid and the antioxidant gallic acid—also contain phenols.¹⁴ Furthermore, phenols are common moieties in dyes, as evinced by picric acid, which is both a yellow dye and an important metal etchant.¹⁵

Owing to their numerous applications, there is high commercial demand for phenol derivatives. Historically, phenol was extracted from coal tar, but at the present time most phenol is derived from petroleum.^{16,17} Substituted phenols can be prepared using a variety of multistep transformations, such as diazotization of aniline to the diazonium salt followed by hydrolysis. Several other methods can be used to prepare phenols, but existing protocols require expensive starting materials, harsh reaction conditions, or naturally derived inputs.^{18–21} In this study, we describe the one-step decarboxylative hydroxylation of benzoic acid to obtain phenol, which is achieved without the addition of catalysts or other reagents. Advantages of this decarboxylative method include the stability and wide availability of benzoic acids; additionally, most benzoic acids are less expensive than their corresponding phenols. In light of these advantages, the direct synthesis of phenol from benzoic acid via decarboxylation is a valuable transformation.

Until now, only a few methods were available to prepare phenols from benzoic acids via decarboxylation.^{22–24} In 2021, Ritter et al. developed a copper-mediated decarboxylative hydroxylation of benzoic acids to generate phenols under mild conditions (at 35 $^{\circ}\text{C}$; Figure 1a). The scope of the reaction was further expanded to prepare other phenol derivatives from

their corresponding aromatic acids. In 2022, Liu et al. reported the decarboxylative oxidation of benzoic acid with an oxidizing agent, such as *m*-CPBA followed by hydrolysis, which occurred at room temperature and provided phenols in good yields (Figure 1a). To our knowledge, no catalyst-free method for the decarboxylative conversion of benzoic acid to phenol has been previously disclosed.

Recently, our group and others have utilized microdroplet chemistry to carry out various reactions and increase the rate of these reactions manifold.^{25–34} For example, we have utilized microdroplet chemistry to prepare formic acid as well as phenylacetic acid derivatives—including several pharmaceutically relevant drug molecules—in just a single step.^{35,36} We have further utilized this chemistry to prepare other interesting organic compounds in a single step;^{37,38} in related work, the Cooks group disclosed the late-stage functionalization of bioactive molecules using water microdroplet accelerated reactions.³⁹ In a continued expansion of the utility of this field, we disclose herein the catalyst-free, one-step decarboxylative hydroxylation of benzoic acid to phenol in water microdroplets at room temperature (Figure 1a). In our method we can obtain the phenol and substituted phenol derivatives without use of a metal catalyst or the addition of other reagents. This is accomplished under mild conditions, and the reaction rate via decarboxylation is much faster than that of bulk reactions.

Figure 1b shows the setup of a typical microdroplet experiment. Benzoic acid (20 μM) is dissolved in water. The solution is injected into a fused silica capillary (i.d. 70 μm , o.d. 350 μm) by a syringe pump with an injection speed of 5 $\mu\text{L}/$

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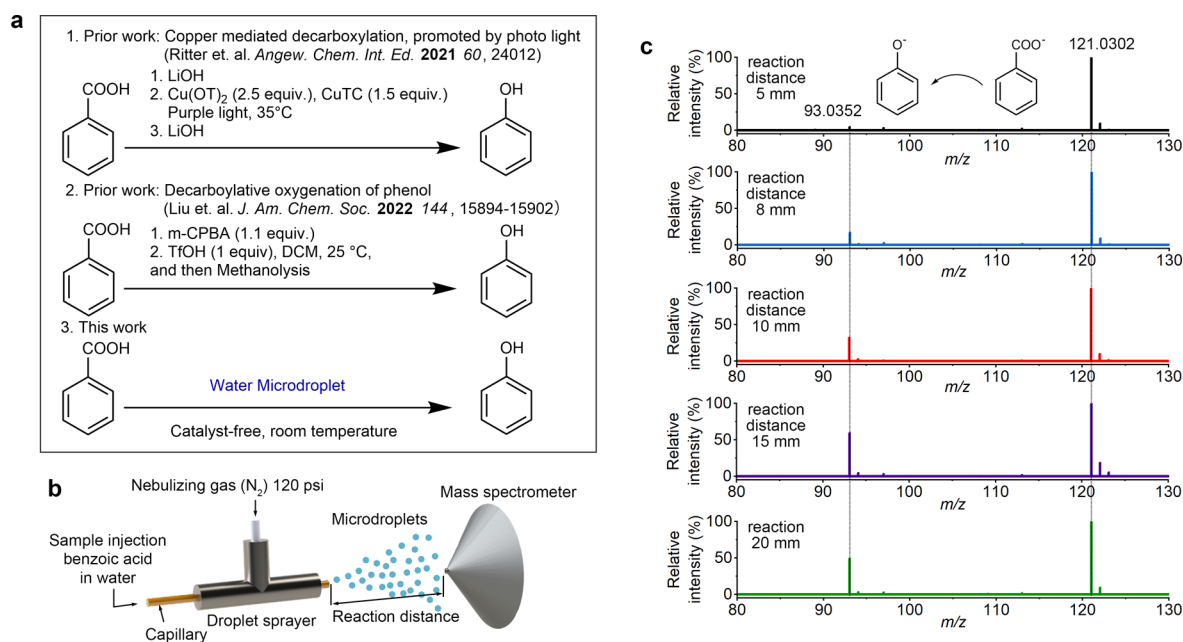


Figure 1. (a) Synthesis of phenol from benzoic acid via decarboxylation. (b) Schematic diagram of the experimental setup. (c) Mass spectra of microdroplets containing benzoic acid at different reaction distances from 5 to 20 mm.

min. N₂ (99.999% purity, 120 psi) is used as the nebulizing gas to generate benzoic acid-containing water microdroplets. A negative voltage (−4 kV) is applied to the microdroplet sprayer. Our previous study has shown that hydroxyl radicals can form without any external voltage.³⁵ The purpose of applying a high voltage is to obtain a higher electric field at the water–gas surface for accelerating the reaction (Figure S1). The chemical components of the water microdroplets were directly detected with a high-resolution mass spectrometer (Orbitrap Velos Pro, Thermo Fisher Scientific, Waltham, MA). In the water microdroplet experiment, the distance between the sprayer and MS inlet is considered as the reaction distance. Figure 1c shows the mass spectra of water microdroplets containing benzoic acid with different reaction distances from 5 to 20 mm, recorded in negative mode. In the spectra, the peak at *m/z* 121.0302 represents deprotonated benzoic acid, whose molecular formula is [C₇H₅O₂][−], and the peak at *m/z* 93.0352 represents deprotonated phenol, whose molecular formula is [C₆H₅O][−]. Results show that when we spray microdroplets containing benzoic acid into the mass spectrometer, phenol can be detected, which demonstrates that phenol can form in water microdroplets from benzoic acid. Our previous experiment has shown that the jet velocity of the microdroplets generated by the sprayer is about 83 m/s while the nebulizing gas pressure is 120 psi.⁴⁰ Therefore, by changing the reaction distance, we can modulate the reaction time between 60 and 240 μs. As shown in Figure 1c, as the reaction time increases from 60 to 180 μs, we obtain increasing signal intensities of deprotonated phenol (C₆H₅O[−]). When the reaction time is increased to 240 μs, the signal intensity tends to be stable. This result indicates that phenol can be obtained from benzoic acid in water microdroplets in less than 200 μs, which may not be achieved by other approaches.

Based on the product formation, the conversion of phenol from benzoic acid was identified from the mass spectral peak intensities of the starting material and the product. The conversion rate of phenol from 20 μM benzoic acid is about 30% at a reaction time of 180 μs at a reaction distance of 15

mm. Based on the standard addition method, the yield of phenol is calculated to be about 4.7% (Figure S2).

Figure 2a shows the proposed mechanism of the formation of phenol from benzoic acid in water microdroplets, which was determined by using mass spectrometry. First, water is ionized at the air–water interface because of the strong electric field and contact electrification^{41–45} (eq 1), followed by the formation of hydroxyl and hydrogen radicals (eq 2). Also,

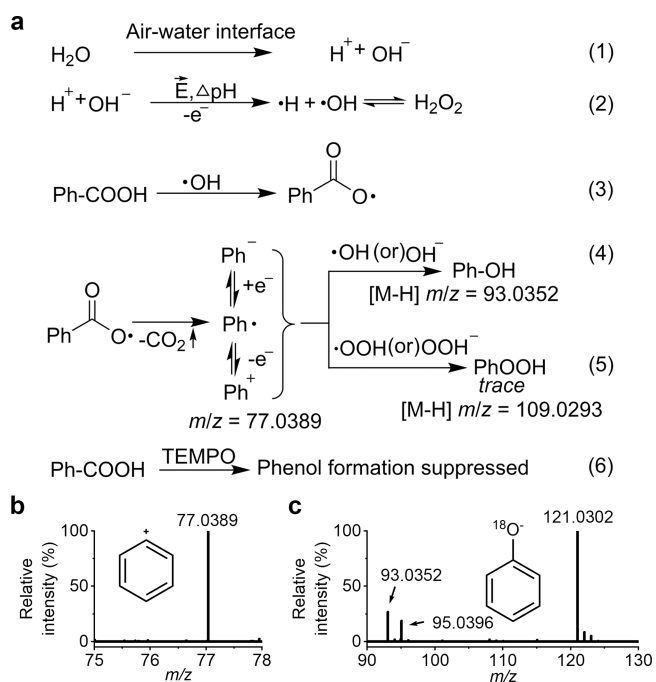


Figure 2. (a) Proposed mechanism for the formation of phenol from benzoic acid in water microdroplets. (b) Mass spectrum of the phenyl cation intermediate in sprayed water microdroplets containing benzoic acid. (c) Mass spectrum of chemical components in H₂¹⁸O microdroplets containing benzoic acid.

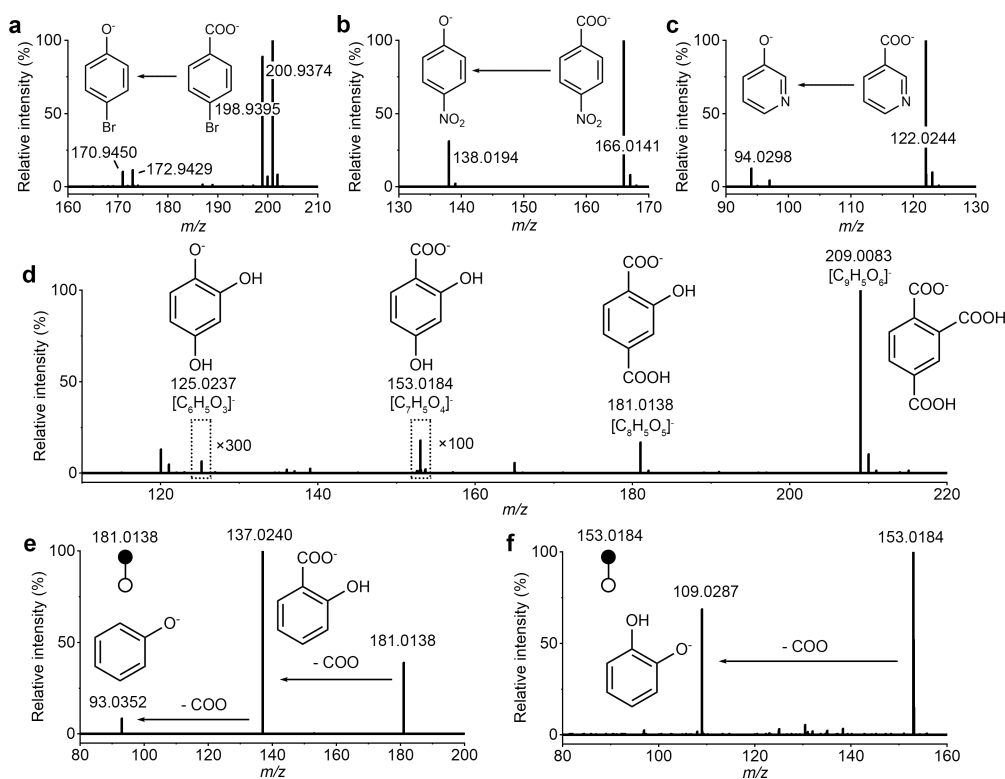


Figure 3. Formation of multiple molecules with a phenol core from reagents containing an aryl-COOH group in water microdroplets. Mass spectra of the microdroplets containing (a) 4-bromobenzoic acid, (b) 4-nitrobenzoic acid, (c) nicotinic acid, and (d) 1,2,4-benzenetricarboxylic acid. (e) MS² spectrum of the peak at m/z of 181.0138 shown in (d). (f) MS² spectrum of the peak at m/z of 153.0184 shown in (d).

the hydroxyl radical formation from the hydroxide anion will be accelerated at the surface of a corona bubble.⁴⁶ Hydrogen atom abstraction from benzoic acid yields a benzoate radical (eq 3). Liberation of $-\text{COO}^-$ leads to the phenyl radical, which can be intercepted by the hydroxyl radical to form phenol (eq 4). Alternatively, the phenyl radical can lose an electron to form a phenyl carbocation, which can then be intercepted by water and/or hydroxide. Figure 2b shows the mass spectrum of the phenyl carbocation intermediate in sprayed water microdroplets containing benzoic acid. C_6H_5^+ at $m/z = 77.0389$ can be clearly detected by MS under positive ion mode. In addition, our previous research has shown that hydrogen peroxide can form at the air–water interface.⁴⁷ In this study, we confirmed this result again. The phenyl radical and/or phenyl cation can react with $\cdot\text{OOH}$ or OOH^- in water microdroplets to form phenyl hydroperoxide ($\text{C}_6\text{H}_5\text{OOH}$) (eq 5). Based on our experimental results, we also considered a Hofmann-like rearrangement mechanism, but we did not detect any of the required benzoyl hydroperoxide or benzoyl peroxide intermediates, so this is ruled out. The deprotonated product at m/z of 109.0293 can be observed from the mass spectrum of water microdroplets containing benzoic acid (Figure S3). The source of the hydroxyl group was unambiguously identified through a ¹⁸O-labeling experiment. When a solution of benzoic acid in H_2^{18}O (97%) was electrosprayed, we observed the formation of ¹⁸O-labeled phenolate anion at m/z of 95.0396 in negative ion mode (Figure 2c). This result clearly explains that the source of hydroxyl group oxygen is from water, not from benzoic acid. To verify the mechanism, we added 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), a common radical trap, to a benzoic acid solution. With the addition of 3 equiv of TEMPO,

phenol formation was clearly suppressed (Figure S4), which indicated the involvement of radical intermediates in this reaction.

Based on the mechanism above, we hypothesized that other compounds containing an aryl-COOH group could be reactive in water microdroplets and generate the corresponding molecules with a phenol core via a similar pathway. To verify this hypothesis, we prepared 20 μM solutions of 4-bromobenzoic acid, 4-nitrobenzoic acid, and nicotinic acid in water. These solutions were used to generate microdroplets using the same methods described above. When the three solutions were sprayed into the mass spectrometer, we observed the corresponding phenol derivatives from these starting materials (Figure 3a–c). The product of 4-bromophenol has two isotope peaks ($\text{C}_6\text{H}_4\text{O}^{79}\text{Br}^-$ and $\text{C}_6\text{H}_4\text{O}^{81}\text{Br}^-$), whose m/z values are 170.9450 and 172.9429 (Figure 3a). The ratio of these two peaks exactly matches with the isotopic ratio of bromine. This result further verified the formation of the corresponding aromatic alcohol products in water microdroplets. Figure S5 shows the MS² spectrum of the peak at m/z of 172.9429 shown in Figure 3a. We observed the peak at the m/z of 80.9170, which is $^{81}\text{Br}^-$, a fragment from the collision-induced dissociation (CID) of $\text{C}_6\text{H}_4\text{O}^{79}\text{Br}^-$. Interestingly, the heterocyclic compound pyridinecarboxylic acid formed the corresponding alcohol compound, which is observed at m/z of 94.0298.

Similarly, we added 1,2,4-benzenetricarboxylic acid to water and made a solution of 20 μM concentration. By spraying the water microdroplets containing 1,2,4-benzenetricarboxylic acid to the mass spectrometer, the reaction of polybasic acid was studied. Figure 3d shows the mass spectrum of the generated water microdroplets, in which the peak at m/z of 209.0083

represents the deprotonated starting material ($C_9H_5O_6^-$). The peaks at m/z of 181.0038, 153.0184, and 125.0237 represent the three decarboxylated products $C_8H_5O_5^-$, $C_7H_5O_4^-$, and $C_6H_5O_3^-$, respectively. We were able to observe all three decarboxylation products, which indicates the mild nature of water microdroplets (Figure 3d). Figure 3e shows the MS^2 spectrum of the peak at a m/z of 181.0138. As shown, we can observe the peaks at m/z of 137.0240 and 93.0352, which are $C_7H_5O_3^-$ and $C_6H_5O^-$, fragments from the CID of the monodecarboxylated product. Also, Figure 3f shows the MS^2 spectrum of the peak at a m/z of 153.0184, the double decarboxylated product of 1,2,4-benzenetricarboxylic acid. The peak at $m/z = 109.0287$ represents the CID fragment of $C_7H_5O_4^-$. We also performed experiments on 4-fluorobenzoic acid, 4-chlorobenzoic acid, 4-iodobenzoic acid, *p*-toluic acid, 4-methoxybenzoic acid, and 2-naphthoic acid under similar conditions. The corresponding alcoholic products were observed in the water microdroplets. Mass spectra of water microdroplets containing these molecules are shown in Figures S6–S11.

In summary, we report the decarboxylative hydroxylation of benzoic acids to phenol using water microdroplets. Notably, this transformation occurs under mild conditions and without a catalyst and can be applied to a variety of aromatic acids. The products were analyzed and further confirmed with literature data. We investigated the mechanism of this reaction using MS^2 analysis and used this tool to confirm the presence of all proposed intermediates; ^{18}O -labeling and radical trapping experiments further validated our mechanistic hypotheses. Furthermore, we were able to trap phenyl hydroperoxide, consistent with our previous work on the formation of hydrogen peroxide in water microdroplets. In conclusion, this study further highlights the unique features of water microdroplets and sheds light on the mechanisms of other microdroplet-promoted reactions. Work to scale up this transformation and expand its scope is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Data Availability Statement

Data are available from the corresponding authors upon reasonable requests.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c08638>.

Yield calculation; capture radicals with TEMPO; detection of multiple products; MS^2 spectra of products (PDF)

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Author Contributions

Experiments were performed by Y.M. and E.G. The manuscript was written by all authors.

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Notes

The authors declare no competing financial interest.

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