Supplementary Information

Aqueous microdroplets capture elusive carbocations

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In 1962, Olha reported nuclear magnetic resonance characterization of long-lived alkyl carbocations in the antimony pentafluoride solution.

 $(CH_3)_3CF + SbF_5 \longrightarrow (CH_3)_3C^+ SbF_6^ (CH_3)_2CHF + SbF_5 \longrightarrow (CH_3)_2CH^+ SbF_6^-$

This work was further extended to prepare stable carbocations in a variety of other superacids *e.g.*, fluorosulfuric acid (FSO₃H), triflic acid (CF₃SO₃H), and magic acids (FSO₃H·SbF₅, HF·SbF₅, *etc.*) by ionizing varied precursors, including alcohols. The low nucleophilicity of the associated bulky counter anions greatly contributed to the stability of the alkyl carbocations,¹ which were even isolated as crystalline salts in some instances.²⁻³ Although the use of superacid provides an environment for induction of a stable carbocation formation, it is not intended to intercept and detect the carbocation formed as an intermediate in a distinct chemical reaction. Likewise, recent advances in the solid-state NMR techniques opened up opportunities for the detection of carbocations confined in zeolites.⁴⁻⁵ Several literature reports can be found on in situ studies of carbocations using UV-vis and nuclear magnetic resonance spectroscopy⁶⁻¹³ but no method is yet achieved for the direct capture/interception and isolation of such extremely short-lived intermediate species from the reaction solution.

Recent developments in this technique (DESI-MS) have created a new avenue for direct analysis of chemical and biochemical samples at ambient conditions without any sample preparation.¹⁴⁻¹⁵ Indeed, a number of studies,¹⁶⁻²⁰ including the work of our own,²¹⁻²² showed the potential utility of DESI-MS in tracking the intermediate species during the progress of a reaction. As presented in Figure 1, a fine spray of positively charged microdroplets was produced by electrospraying the solvent at high voltage (+5 kV) and using nitrogen as nebulizing gas (110 psi). A 10 μ L of the reaction aliquot was quickly (within few seconds using pipette; see Materials and methods for details) dispensed on a microscope glass slide under the impinging spray of charged microdroplets, which resulted in the splashing of secondary microdroplets extracting the analyte species. These secondary microdroplets were allowed to enter a high-resolution mass spectrometer through a heated capillary inlet (300 °C) that caused complete desolvation of analyte ions and their subsequent detection by the mass spectrometer (Figure 1). The details of this experiment using our home-built DESI source (Figure S1) are presented in the supporting information.

Thus a small volume of the reaction mixture, which develops a transient carbocation, was extracted in the positively charged microdroplets in the DESI process¹⁴ that eventually transferred the carbocation representatively to the gas phase on a millisecond timescale²³ for mass spectrometric interrogation. Although the lifetime of a carbocation in the bulk water is believed to be as short as 10⁻¹² s,²⁴⁻²⁷ (Supplementary Note 3) the unique environment of the charged water microdroplets appears to be responsible for the successful transfer of the reactive carbocation species from the condensed phase to the gas phase. We also provide mechanistic insight into how this carbocation interception is facilitated by the outperformance of the water microdroplet over its organic counterparts.

Many intensive attempts in past failed to capture and isolate alkyl carbocation intermediates from chemical reactions, particularly because of their extremely short lifetime.²⁸ Although kinetics and product studies of those reactions assured the involvement of carbocations as reactive intermediates, those were too short-lived to be detected by the nuclear magnetic resonance (timescale for NMR is in the order of microsecond). Kazansky suggested that carbocations are so unstable that it is more like a transition state than a reaction intermediate.²⁹⁻ ³¹Olha first reported that carbocation species can be stabilized in a superacid solution, proving their real existence.³² Several investigators used spectroscopic techniques, azide clocks, and theoretical calculations to estimate the lifetime of different carbocations. For example, the vibrational Raman spectroscopy was used (Raman band shape was analyzed) earlier to determine the mean lifetime of tert-butyl carbocation to be around 500 fs in sulfuric acid medium.²⁷ Azide clock experiments estimated the lifetime of the same carbocation to be around 200 fs in trifluoroethanol/water medium.³³ The laser flash photolysis experiments also measured the average lifetime of *tert*-butyl carbocation as low as 70 fs in water.³⁴ UV absorption study estimated the lifetime of secondary (cyclooctyl) carbocation is in the order of nanoseconds in concentrated acid and picoseconds in dilute acid.²⁵ The laser flash photolysis experiments on a series of secondary carbocations determined that their average lifetime to be in the range of 100 ps to 40 ns.³⁵ The lifetime of benzyl carbocation in an aqueous solution was estimated to be 0.7 ns by the flash photolysis method.³⁶ The direct dynamics simulation using density functional theory predicted the average lifetime of bornyl carbocation (nonclassical) is around 100 fs.³⁷ The table below summarizes the above findings. These are some typical examples and many other such reports in the literature can be noted, which suggest fleeting lifetimes of the alkyl carbocations in the range of nanoseconds to picoseconds or even lesser.

Carbocation	Range of the estimated average	Methods used
	lifetime	
Tertiary (alkyl)	$10^{-12} - 10^{-13}$ sec.	Vibrational Raman spectroscopy, ²⁷
		Azide clock, ³³
		Laser flash photolysis ³⁴
Secondary (alkyl)	$10^{-9} - 10^{-13}$ sec.	UV absorption, ²⁵
		Laser flash photolysis ³⁵
Bornyl	$10^{-13} - 10^{-14}$ sec.	Dynamics simulation using density
		functional theory ³⁷
Benzylic	10 ⁻⁹ sec.	Laser flash photolysis ³⁶

The increase in spray voltage (0 to +5 kV) resulted in more highly charged water droplets³⁸ improving the carbocation detection efficiency. However, the opposite effect with the acetonitrile microdroplets (Figures S7) possibly resulted from the rapid droplet evolution (fast solvent evaporation and Coulomb fission) on increasing the spray voltage,³⁸ which in turn caused carbocation ejection or desolvation at the early stage before those bare analytes could reach to the MS inlet capillary for detection. Moreover, when no voltage is applied to the DESI source, the pneumatic spray alone can also impart droplet charging by statistical fluctuations of ions in the liquid aerosol, similar to the sonic spray ionization mechanism.³⁹⁻⁴² This type of pneumatically assisted microdroplet charging and the action of the sheath gas along with the pneumatic force of the mass spectrometer vacuum at the inlet can also explain why carbocation signal was still detected at the zero volts.

Supplementary Note 5

Typically, the average lifetime of such microdroplets generated by the DESI process is on the order of milliseconds²³ during which the carbocation is ejected out from the droplet to the gas phase. Although the average lifetime of a carbocation (with some exceptions like stable triarylmethyl carbocations) in bulk could be much shorter (nanoseconds to picoseconds, Supplementary Note 3)²⁴⁻²⁷ than that of a microdroplet, the carbocation detection in this process becomes feasible possibly caused by intimate ion pairing as discussed above, and/or the carbocation generating original reaction continues in the droplet also. Indeed, recent reports showed clear evidence that bulk-phase reactions can be accelerated in microdroplets,⁴³⁻⁴⁴ which is now the subject of much discussion in microdroplet chemistry,⁴⁵⁻⁴⁶ a newly emerging field. Therefore, it is extremely likely that the successful isolation of the carbocation intermediate from the solution to the gas phase followed by its mass spectrometric detection is largely facilitated by the unique charged environment of the DESI microdroplets.

The dielectric constant and surface tension are known to be two important factors in determining the charge density in the electrosprayed droplet.^{38, 47} Among all the spray solvents studied (Table S2), water has the highest dielectric constant and surface tension to tolerate high charge density in the evaporating droplet. Therefore, the carbocation ejection is likely to be facilitated from microdroplets composed of water than that of organic solvents.³⁸ The high electric field generated at the air-water interface⁴⁸⁻⁴⁹ can also boost the carbocation desorption from the highly charged (positive) water microdroplet surface. Moreover, the carbocation formation followed by the intimate ion pairing in the aqueous microdroplets, relatively low polarity and high volatility characteristics of organic (*e.g.*, methanol and acetonitrile) microdroplets could be the reason for their poor performance in the carbocation detection by DESI-MS.

The combination of *N*,*N*-dimethylformamide (DMF) with acetonitrile (1:1, v/v) was shown earlier to be an effective DESI solvent system to detect both positively and negatively charged molecules from a variety of samples.⁵⁰ When we sprayed this binary solvent system in our experiment, no (Figures 4a-b) or very low signal intensity (Figures 4c-d) of the carbocation was observed despite the low volatility of DMF. This result suggests that carbocation survival in the microdroplet depends on the cumulative effects of the surface charge density, solvent polarity, and volatility associated with the droplet evolution.

We evaluated the effect of the water (DESI solvent) pH on the efficacy of carbocation detection. We gradually decreased the pH of the water from 6.18 (measured pH of the LC-MS grade water) to 2.15 by adding formic acid to the water before spraying it into the DESI source. Figure S8 shows a typical study with *tert*-butyl carbocation. Interestingly we observed that the *tert*-butyl carbocation signal intensity moderately increased below pH 4.1 under +5 kV DESI spray potential (Figure S8a). When the same experiment was performed under 0 V DESI spray potential, no carbocation (1) was detected till pH 3.1 but a very low abundance of the *tert*-butyl carbocation was traced at pH 2.15 (Figure S8b). We also examined whether or not the lowering of the spray solvent pH can cause carbocation formation from the pure substrate, e.g., *tert*-butyl carbocation, which formed below pH 4.1 (Figure S8c). This observation can be attributed to the report of Colussi and coworkers that protons emerge to the surface of the water below pH 4 and these interfacial protons are likely to contribute to making the microdroplet superacidic.⁵¹ Therefore, at low pH, a partial contribution of the formic acid in generating the *tert*-butyl carbocation from *tert*-butyl carbocation from *tert*-butyl carbocation form *tert*-butyl carbocation.

We also evaluated the effect of low pH of the spray solvent (water) on the detection of a number of carbocations (Figure S9) from the elimination reaction (1 and 4, Figure 2), substitution reaction (5, Figure 2) and oxidation reaction (6, Figure 2). Though low pH significantly affected the carbocation interception from the elimination reaction, where alcohol is the substrate, it could not affect substitution and oxidation reactions, where 1-bromoadamantane and ethylbenzene are substrates, respectively. This observation is related to the mechanism of the carbocation generation.^{22, 52-53} Superacidic microdroplet can protonate the substrate containing alcohol functional group and thereby contribute in catalyzing the carbocation forming reaction, whereas this effect is insignificant for the other two types of substrates as mentioned above.

Table S1. List of carbocations and their precursor substrates considered in this study (Figure 2). The m/z values of the detected carbocations (Figure 3) are also tabulated representing the accuracy in their detection.

Precursor substrate	Intermediate	Theoretical	Observed	Error
	carbocation*	<i>m/z</i> value	<i>m/z</i> value	(ppm)
он	1	57.0699	57.0699	0
он	\rightarrow_2	139.1481	139.1481	0
HO HO		369.3516	369.3517	+0.27
Адон	4	95.0855	95.0856	+1.0
Br	+ 5	135.1168	135.1168	0
	¢	105.0699	105.0699	0
	7	81.0699	81.0698	-1.23
	+ 8	95.0855	95.0855	0

*Copper(II) triflate mediated alcohol dehydration (elimination) reactions were followed to develop the intermediate tertiary (1), secondary (2-3), and nonclassical (4) carbocations. The hydrolysis (substitution) reaction of 1-bromoadamantane was followed to develop the intermediate bridgehead carbocation (5). Benzylic (6) and allylic (7-8) carbocation intermediates were generated in the copper-catalyzed oxidation reaction. See Figure 2 and Materials and Methods for details.

Solvent	Abbreviation	Dielectric constant (ɛ)	References
		at 20 °C	
Water	H ₂ O	80.37	54
Water/Methanol (1:1, v/v)	H ₂ O/MeOH	56.53	54
Water/Acetonitrile $(1:1, v/v)$	H ₂ O/ACN	56.92	55
Methanol	МеОН	32.35	54
Acetonitrile	ACN	36.62	55-56
Methanol/Acetonitrile $(1:1, v/v)$	MeOH/ACN	35.40	56
Acetonitrile/Dimethylformamide $(1:1, v/v)$	ACN/DMF	36.88	57

Table S2. List of solvents used in the microdroplet production in the DESI for screening their efficacies on capturing carbocations.

Materials and Methods

All necessary chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and Tokyo Chemical Industry (Japan). HPLC grade solvents were purchased from Finar Ltd. (Ahmedabad, India) and UHPLC-MS grade solvents [water (resistivity \geq 18.2 M Ω cm at 298 K), methanol, and acetonitrile) were purchased from Biosolve Chimie (Dieuze, France). Microscope glass slides and 4mL (1 dram) reaction vials (glass) were obtained from Borosil Glass Works Ltd (Ahmedabad, India) and Chemglass Life Sciences (Vineland, NJ), respectively. Fused silica tubing, stainless steel tubing, connectors, union body, tubing sleeves, and Hamilton syringes were purchased from IDEX Corporation (Illinois, USA). The pH measurement was made using HORIBA benchtop pH meter equipped with a micro pH electrode.

Desorption electrospray ionization mass spectrometry (DESI-MS)

The DESI-MS studies were performed with a home-built DESI source ^{21, 58} (Figure S1) attached to a high-resolution mass spectrometer (Orbitrap Elite Hybrid Ion Trap-Orbitrap Mass Spectrometer, ThermoFisher Scientific, Newington, NH, USA). The source was constructed by using an inner fused silica capillary (100 μ m i.d. and 360 μ m o.d.) for solvent delivery, and an outer (coaxial) stainless steel capillary (0.5 mm i.d. and 1.6 mm o.d.) for nebulizing gas (nitrogen) delivery (Figure 1). The charged microdroplets were produced in the positive mode (+5 kV potential was applied to the stainless-steel needle of the solvent syringe) at 10 μ L/min solvent (UHPLC-MS grade) flow through the silica tubing with a coaxial sheath gas flow at 3 L/min (110 psi nitrogen gas). The stream of charged microdroplets, generated from this DESI source at ambient temperature and atmospheric pressure, was allowed to strike a normal microscope glass slide at an incident angle 55° with the spray tip-to-surface distance of 5 mm, spray tip-to-mass spectrometric inlet distance of ~ 10 mm, and collection angle of $\sim 5^{\circ}$. These geometrical parameters produced DESI spray spot of diameter ~ 0.5 mm (from acetonitrile) to 1 mm (from water) on the glass slide. A reaction aliquot of 10 µL was quickly [minimal time (few seconds) required for transferring the liquid aliquot from the reaction vial to the DESI spray spot] dispensed using a pipette on the microscope glass slide under the impinging spray of charged microdroplets (Figure S1) while the MS was kept on for data acquisition (Figure S3). The splashing of these charged microdroplets resulted in the formation of secondary microdroplets extracting the analyte molecules (ions), which were then transferred to the mass spectrometer through a heated capillary inlet (stainless steel, length 14.2 cm, i.d. 550 µm) causing the complete desolvation of the analyte ions. The heated capillary (MS inlet) temperature was maintained at 300 °C and the S-lens RF level was adjusted to 69.5 %. All experiments were carried out under identical conditions, unless otherwise stated, to detect the species within the range of m/z 50-1000 at resolution 60,000. Other ion optics were tuned to get maximum ion count. Data acquisition was performed using XCalibur software (Thermo Fisher Scientific). The species were identified based on high mass (m/z) accuracy (<1 ppm error) and isotopic distribution pattern.

Generation and detection of carbocation intermediates involved in the reaction

The following model reactions were performed to generate different types of carbocation intermediates, which were captured and detected by DESI-MS as described above.

Copper(II) triflate mediated alcohol dehydration:



We followed the report of Laali et al.⁵² to perform this reaction. Briefly, 0.4 mmol alcohol (Table S1) was dissolved or suspended in 0.5 mL of cyclohexane with 10 mol% (0.04 mmol) copper(II) triflate. The vial was sealed and placed on a heating block preheated to 80 °C followed by stirring. Following this, from time to time, a 10 μ L reaction aliquot was rapidly pipetted and dispensed on a glass microscope slide placed under the impinging spray of charged microdroplets in the DESI probe (Figures 1 and S1).

Hydrolysis of alkyl bromide:



We followed the report of Tsai et al. ⁵³ to perform this reaction. Briefly, the alkyl bromide (here, 0.16 mmol 1-bromoadamantane) was dissolved in 0.5 mL of dimethylformamide (DMF) followed by the addition of 170 μ L of water. The reaction temperature was controlled at 90 °C

with constant stirring. Following the addition of water, 10 μ L of the reaction aliquot was sampled in DESI-MS from time to time as described above.

Copper-catalyzed oxidation:



We performed this reaction following our earlier report ²². A reaction vial was charged with the substrate (0.125 mmol), Cu(OAc)₂•H₂O (12.5 μ mol, 0.1 equiv), and K₂S₂O₈ (0.19 mmol, 1.5 equiv). To this mixture was added 0.6 mL of AcOH and 0.6 mL of H₂O. The vial was sealed, placed on a heating block preheated to 105 °C, and the reaction mixture was kept under stirring followed by aliquot sampling for DESI-MS study time to time as described above.



Figure S1. DESI-MS setup for capturing transient carbocations from the reaction aliquot.



Figure S2. Experimental (red line) and simulated (grey line) isotopic distribution pattern of some typical carbocations (shown in the insets) detected in the DESI-MS studies. The simulation of the isotopic distribution of the candidate molecular formula was performed by processing the raw data using MassWorks software (Cerno Bioscience, USA). It should be noted that the calculated spectral accuracy (highlighted in the insets) is related to the quality of the experimental ion signals. The decrease in accuracy might result from the poor signal intensity of the particular species observed in the experiment.



Figure S3. Extracted ion chronogram of the *t*-butyl carbocation (1) detected by the DESI-MS experiment. The spike of the m/z 57.0699 signal (inset) during the dispense of the reaction aliquot in the DESI source (Figure 1) is indicative of the presence of *t*-butyl carbocation in the reaction mixture. The MS detector was started before dispensing the liquid aliquot in the DESI spray spot on the glass slide (see Materials and methods for details).



Figure S4. Positive ion mode DESI-MS recorded from the control experiment of the precursor substrate solution without adding any reagent/catalyst to it. The precursor solution (similar concentration maintained in the respective solvent required for the reaction; see Figure 2 and experimental details) was dispensed to the DESI source under the impinging spray of charged aqueous microdroplets (Figure S1) followed by recording the mass spectral data. No ion signal detected for (a) *tert*-butyl (1, *m/z* 57.0699), (b) 4-*tert*-butylcyclohexyl (2, *m/z* 139.1481), (c) cholesteryl (3, *m/z* 369.3517), (d) 2-norbornyl (4, *m/z* 95.0856), (e) adamantyl (5, *m/z* 135.1168), (f) benzylic (6, *m/z* 105.0699), (g) cyclohex-2-en-1-ylium (7, *m/z* 81.0698), and (f) 2-methylcyclohex-2-en-1-ylium (8, *m/z* 95.0855) carbocations. The observed signals are either from the blank background and/or artifacts/impurities from the commercially available substrates.



Figure S5. Positive ion mode DESI-MS recorded from the control experiment of some typical standard products (shown in insets), which were aliquoted in isopropanol for dispensing to the DESI source under the impinging spray of charged aqueous microdroplets (Figure S1) followed by recording the mass spectral data. No ion signal detected for (a) 4-*tert*-butylcyclohexyl (2, m/z 139.1481) and (b-c) benzylic (6, m/z 105.0699) carbocations. The observed signals are either from the blank background and/or artifacts/impurities from the commercially available products.



Figure S6. DESI-MS detection of the nonclassical 2-norbornyl cation (4) formed as the intermediate during the conversion of *exo*-2-norborneol to *exo*-2-bromonorbornane in presence of triphenylphosphine dibromide. The inset of the mass spectrum shows the temporal evaluation of the carbocation (4) formation (intensity normalized to 1) allowing the real-time monitoring of the transient intermediate from the given reaction.



Figure S7. Effects of acetonitrile spray voltages on the detection of (a) 2-norbornyl (4) and (b) benzylic (6) carbocations.



Figure S8. Plots of the *tert*-butyl carbocation signal intensity as a function of pH of the water that was sprayed in the DESI source to intercept the carbocation from the reaction aliquot (Figure 2) examined at (a) +5 kV and (b) 0 V DESI spray potential. The pH was varied from 6.18 (measured pH of the LC-MS grade water) to 2.15 by adding formic acid to the water. (c) The *tert*-butyl ion signal was also traced, albeit low in intensity, below pH 4 when microdroplets, generated at +5 kV DESI spray potential, impacted pure *tert*-butanol solution (no reagent added).



Figure S9. Effect of lowering the pH of the spray solvent (water) on the ion signal intensity of some typical carbocations intercepted from the reaction aliquot (Figure 2). The pH was lowered to 2.1 by adding formic acid to the LC-MS grade water (original pH ~ 6.2). Y-axis shows the fold change of the carbocation signal intensity on changing the spray solvent (water) pH from 6.2 to 2.1. DESI-MS was operated at +5 kV.



Figure S10. DESI-MS detection of *tert*-butyl carbocation from the reaction aliquot (Figure 2) bombarded with charged microdroplets of (a) H_2O and (b) D_2O . The increase of ion signal intensity at m/z 58.0735 in (b) indicates the presence of nearly 10 % monodeuterated *tert*-butyl carbocation, which could be derived from the hydrogen-deuterium exchange of the unlabeled carbocation in the D_2O microdroplet. We will further explore this phenomenon in the future for a more detailed understanding.

References

1. Olah, G. A.; Baker, E. B.; Evans, J. C.; Tolgyesi, W. S.; McIntyre, J. S.; Bastien, I. J., Stable Carbonium Ions. V.1a Alkylcarbonium Hexafluoroantimonates. *J. Am. Chem. Soc.* **1964**, *86* (7), 1360-1373.

2. Laube, T., Crystal Structure Analysis of the I,2,4,7-anti-Tetramethyl-2-norbornyl Cation: an Unsymmetrically Bridged Carbocation. *Angew. Chem. Int. Ed.* **1987**, *26* (6), 560-562.

3. Laube, T., X-ray Crystal Structures of Carbocations Stabilized by Bridging or Hyperconjugation. *Acc. Chem. Res.* **1995**, *28* (10), 399-405.

4. Xiao, D.; Xu, S.; Brownbill, N. J.; Paul, S.; Chen, L.-H.; Pawsey, S.; Aussenac, F.; Su, B.-L.; Han, X.; Bao, X.; Liu, Z.; Blanc, F., Fast detection and structural identification of carbocations on zeolites by dynamic nuclear polarization enhanced solid-state NMR. *Chem. Sci.* **2018**, *9* (43), 8184-8193.

5. Huang, M.; Wang, Q.; Yi, X.; Chu, Y.; Dai, W.; Li, L.; Zheng, A.; Deng, F., Insight into the formation of the tert-butyl cation confined inside H-ZSM-5 zeolite from NMR spectroscopy and DFT calculations. *Chem. Commun.* **2016**, *52* (70), 10606-10608.

6. Garbowski, E. D.; Praliaud, H., Étude par spectroscopie UV des interactions d'oléfines avec des centres acides en catalyse hétérogène. *J. Chim. Phys.* **1979**, *76*, 687-692.

7. Chikinev, A. V.; Bushmelev, V. A.; Shakirov, M. M.; Shubin, V. G., PMR detection of carbocation intermediates in the pinacol rearrangement in a superacid. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33* (12), 2569-2571.

8. Stavitski, E.; Pidko, E. A.; Kox, M. H. F.; Hensen, E. J. M.; van Santen, R. A.; Weckhuysen, B. M., Detection of Carbocationic Species in Zeolites: Large Crystals Pave the Way. *Chem. Eur. J.* **2010**, *16* (31), 9340-9348.

9. Chowdhury, A. D.; Houben, K.; Whiting, G. T.; Chung, S.-H.; Baldus, M.; Weckhuysen, B. M., Electrophilic aromatic substitution over zeolites generates Wheland-type reaction intermediates. *Nat. Cat.* **2018**, *1* (1), 23-31.

10. Moss, R. A.; Platz, M. S.; Jones, M., *Reactive Intermediate Chemistry*. Wiley: 2004.

11. Xiuwen, H.; Zhimin, Y.; Weiping, Z.; Xinhe, B., Applications of In Situ NMR in Catalytic Processes of Organic Reactions. *Curr. Org. Chem.* **2001**, *5* (10), 1017-1037.

12. Förster, H.; Kiricsi, I.; Seebode, J.; Fejes, P., Generation of alkenyl-type carbocations from neopentane in HNaY zeolite. *React. Kinet. Catal. Lett.* **1988**, *37* (2), 385-389.

13. Kiricsi, I.; Förster, H., Chemisorption of propene on HZSM-5 by ultraviolet and infrared spectroscopy. *J. Chem. Soc., Faraday Trans.* **1988**, *84* (2), 491-499.

14. Takáts, Z.; Wiseman, J. M.; Gologan, B.; Cooks, R. G., Mass Spectrometry Sampling Under Ambient Conditions with Desorption Electrospray Ionization. *Science* **2004**, *306* (5695), 471-473.

15. Takáts, Z.; Wiseman, J. M.; Cooks, R. G., Ambient mass spectrometry using desorption electrospray ionization (DESI): instrumentation, mechanisms and applications in forensics, chemistry, and biology. *J. Mass Spectrom.* **2005**, *40* (10), 1261-1275.

16. Perry, R. H.; Cahill, T. J.; Roizen, J. L.; Du Bois, J.; Zare, R. N., Capturing fleeting intermediates in a catalytic C–H amination reaction cycle. *Proc. Natl. Acad. Sci. USA* **2012**, *109* (45), 18295-18299.

17. Brown, T. A.; Chen, H.; Zare, R. N., Identification of Fleeting Electrochemical Reaction Intermediates Using Desorption Electrospray Ionization Mass Spectrometry. *J. Am. Chem. Soc.* **2015**, *137* (23), 7274-7277.

18. Cheng, S.; Wu, Q.; Xiao, H.; Chen, H., Online Monitoring of Enzymatic Reactions Using Time-Resolved Desorption Electrospray Ionization Mass Spectrometry. *Anal. Chem.* **2017**, *89* (4), 2338-2344.

19. Brown, T. A.; Chen, H.; Zare, R. N., Detection of the Short-Lived Radical Cation Intermediate in the Electrooxidation of N,N-Dimethylaniline by Mass Spectrometry. *Angew. Chem. Int. Ed.* **2015**, *54* (38), 11183-11185.

20. Zheng, Q.; Liu, Y.; Chen, Q.; Hu, M.; Helmy, R.; Sherer, E. C.; Welch, C. J.; Chen, H., Capture of Reactive Monophosphine-Ligated Palladium(0) Intermediates by Mass Spectrometry. *J. Am. Chem. Soc.* **2015**, *137* (44), 14035-14038.

21. Banerjee, S.; Yang, Y.-F.; Jenkins, I. D.; Liang, Y.; Toutov, A. A.; Liu, W.-B.; Schuman, D. P.; Grubbs, R. H.; Stoltz, B. M.; Krenske, E. H.; Houk, K. N.; Zare, R. N., Ionic and Neutral Mechanisms for C–H Bond Silylation of Aromatic Heterocycles Catalyzed by Potassium tert-Butoxide. *J. Am. Chem. Soc.* **2017**, *139* (20), 6880-6887.

22. Banerjee, S.; Sathyamoorthi, S.; Du Bois, J.; Zare, R. N., Mechanistic analysis of a coppercatalyzed C–H oxidative cyclization of carboxylic acids. *Chem. Sci.* **2017**, *8* (10), 7003-7008.

23. Venter, A.; Sojka, P. E.; Cooks, R. G., Droplet Dynamics and Ionization Mechanisms in Desorption Electrospray Ionization Mass Spectrometry. *Anal. Chem.* **2006**, *78* (24), 8549-8555.

 Richard, J. P.; Amyes, T. L.; Toteva, M. M., Formation and Stability of Carbocations and Carbanions in Water and Intrinsic Barriers to Their Reactions. *Acc. Chem. Res.* 2001, *34* (12), 981-988.
Chiang, Y.; Kresge, A. J., Mechanism of hydration of simple olefins in aqueous solution. cisand trans-Cyclooctene. *J. Am. Chem. Soc.* 1985, *107* (22), 6363-6367.

26. McClelland, R. A., Carbocations. In *Reactive Intermediate Chemistry*, Moss, R. A.; Platz, M. S.; Jones, M. J., Eds. John Wiley & Sons, Inc.: New Jersey, 2003; pp 1-40.

27. Watanabe, D.; Hamaguchi, H.-o., Ultrafast generation/annihilation dynamics of the tert-butyl carbocation in sulfuric acid as studied by Raman band shape analysis. *Chem. Phys.* **2008**, *354* (1), 27-31.

28. Olah, G. A., My Search for Carbocations and Their Role in Chemistry (Nobel Lecture). *Angew. Chem. Int. Ed.* **1995**, *34* (13-14), 1393-1405.

29. Zhurko, D. A.; Frash, M. V.; Kazansky, V. B., A quantum-chemical study of the formation mechanism and nature of tert-butyl carbenium ions in 100% sulfuric acid. *Catal. Lett.* **1998**, *55* (1), 7-14.

30. Kazansky, V. B.; Figueras, F.; de Ménorval, L. C., In situ13C NMR study of tert-butanol interaction with moderately concentrated sulfuric acid. *Catal. Lett.* **1994**, *29* (3-4), 311-323.

31. Kazansky, V. B., Is the cationic polymerization of iso-olefins in a moderately concentrated sulfuric acid a real carbenium-ion reaction? *Appl. Cat. A: Gen.* **1999**, *188* (1), 121-126.

32. Olah, G. A.; Comisarow, M. B.; Cupas, C. A.; Pittman, C. U., Stable Carbonium Ions. XIII.1 Generation of Stable Alkyl, Alkylaryl, and Cycloalkyl Carbonium Ions from Alcohols in Fluorosulfonic Acid and Antimony Pentafluoride. *J. Am. Chem. Soc.* **1965**, *87* (13), 2997-2998.

33. Toteva, M. M.; Richard, J. P., Mechanism for Nucleophilic Substitution and Elimination Reactions at Tertiary Carbon in Largely Aqueous Solutions: Lifetime of a Simple Tertiary Carbocation. *J. Am. Chem. Soc.* **1996**, *118* (46), 11434-11445.

34. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S., Flash-photolysis generation and reactivities of triarylmethyl and diarylmethyl cations in aqueous solutions. *J. Am. Chem. Soc.* **1989**, *111* (11), 3966-3972.

35. Pezacki, J. P.; Shukla, D.; Lusztyk, J.; Warkentin, J., Lifetimes of Dialkylcarbocations Derived from Alkanediazonium Ions in Solution: Cyclohexadienyl Cations as Kinetic Probes for Cation Reactivity1. *J. Am. Chem. Soc.* **1999**, *121* (28), 6589-6598.

36. Jaarinen, S.; Niiranen, J.; Koskikallio, J., Relative rates of nucleophilic reactions of benzyl carbocation formed in photolysis of benzyl chloride and benzyl acetate in aqueous solution. *Int. J. Chem. Kinetics* **1985**, *17* (9), 925-930.

37. Pemberton, R. P.; Tantillo, D. J., Lifetimes of carbocations encountered along reaction coordinates for terpene formation. *Chem. Sci.* **2014**, *5* (8), 3301-3308.

38. Kebarle, P.; Tang, L., From ions in solution to ions in the gas phase - the mechanism of electrospray mass spectrometry. *Anal. Chem.* **1993**, *65* (22), 972A-986A.

39. Takats, Z.; Nanita, S. C.; Cooks, R. G.; Schlosser, G.; Vekey, K., Amino Acid Clusters Formed by Sonic Spray Ionization. *Anal. Chem.* **2003**, *75* (6), 1514-1523.

40. Haddad, R.; Sparrapan, R.; Eberlin, M. N., Desorption sonic spray ionization for (high) voltagefree ambient mass spectrometry. *Rapid Commun. Mass Spectrom.* **2006**, *20* (19), 2901-2905.

41. Wleklinski, M.; Li, Y.; Bag, S.; Sarkar, D.; Narayanan, R.; Pradeep, T.; Cooks, R. G., Zero Volt Paper Spray Ionization and Its Mechanism. *Anal. Chem.* **2015**, *87* (13), 6786-6793.

42. Hirabayashi, A.; Sakairi, M.; Koizumi, H., Sonic Spray Ionization Method for Atmospheric Pressure Ionization Mass Spectrometry. *Anal. Chem.* **1994**, *66* (24), 4557-4559.

43. Lee, J. K.; Banerjee, S.; Nam, H. G.; Zare, R. N., Acceleration of reaction in charged microdroplets. *Q. Rev. Biophys.* **2015**, *48* (4), 437-44.

44. Yan, X.; Bain, R. M.; Cooks, R. G., Organic Reactions in Microdroplets: Reaction Acceleration Revealed by Mass Spectrometry. *Angew. Chem. Int. Ed.* **2016**, *55* (42), 12960-12972.

45. Banerjee, S.; Gnanamani, E.; Yan, X.; Zare, R. N., Can all bulk-phase reactions be accelerated in microdroplets? *Analyst* **2017**, *142* (9), 1399-1402.

46. Stroberg, W.; Schnell, S., Do Cellular Condensates Accelerate Biochemical Reactions? Lessons from Microdroplet Chemistry. *Biophys. J.* **2018**, *115* (1), 3-8.

47. Banerjee, S.; Mazumdar, S., Electrospray ionization mass spectrometry: a technique to access the information beyond the molecular weight of the analyte. *Int. J. Anal. Chem.* **2012**, *2012*, 282574.

48. Xiong, H.; Lee, J. K.; Zare, R. N.; Min, W., Strong Electric Field Observed at the Interface of Aqueous Microdroplets. *J. Phys. Chem. Lett.* **2020**, *11* (17), 7423-7428.

49. Chamberlayne, C. F.; Zare, R. N., Simple model for the electric field and spatial distribution of ions in a microdroplet. *J. Chem. Phys.* **2020**, *152* (18), 184702.

50. Eberlin, L. S.; Ferreira, C. R.; Dill, A. L.; Ifa, D. R.; Cooks, R. G., Desorption electrospray ionization mass spectrometry for lipid characterization and biological tissue imaging. *Biochim. Biophys. Acta* **2011**, *1811* (11), 946-960.

51. Enami, S.; Stewart, L. A.; Hoffmann, M. R.; Colussi, A. J., Superacid Chemistry on Mildly Acidic Water. *J. Phys. Chem. Lett.* **2010**, *1* (24), 3488-3493.

52. Laali, K.; Gerzina, R. J.; Flajnik, C. M.; Geric, C. M.; Dombroski, A. M., Copper(II) Triflate, a New Reagent for Mild Dehydration of Alcohols: Synthetic Usefulness and Mechanistic Insight. *Helv. Chim. Acta* **1987**, *70* (3), 607-611.

53. Tsai, C.-W.; Wang, J.-C.; Li, F.-N.; Chang, Y.-C.; Wu, K.-H., Synthesis of adamantane-containing methacrylate polymers: Characterization of thermal, mechanical, dielectric and optical properties. *Mat. Exp.* **2016**, *6* (3), 220-228.

54. Akerlof, G., DIELECTRIC CONSTANTS OF SOME ORGANIC SOLVENT-WATER MIXTURES AT VARIOUS TEMPERATURES. *J. Am. Chem. Soc.* **1932**, *54* (11), 4125-4139.

55. Gagliardi, L. G.; Castells, C. B.; Ràfols, C.; Rosés, M.; Bosch, E., Static Dielectric Constants of Acetonitrile/Water Mixtures at Different Temperatures and Debye–Hückel A and a0B Parameters for Activity Coefficients. *J. Chem. Eng. Data* **2007**, *52* (3), 1103-1107.

56. Cavell, E. A. S.; Jerrard, H. G.; Simmonds, B. A. W.; Speed, J. A., Dielectric Constants of Acetonitrile—Methanol Mixtures. *J. Phys. Chem.* **1965**, *69* (10), 3657-3658.

57. Kolling, O. W., Dielectric Characterization of Cosolvents Containing N,N-Dimethylformamide. *Transc. Kansas Acad. Sci.* **1994**, *97* (3/4), 88-93.

58. Banerjee, S.; Liu, F.; Sanchez, D. M.; Martínez, T. J.; Zare, R. N., Pomeranz–Fritsch Synthesis of Isoquinoline: Gas-Phase Collisional Activation Opens Additional Reaction Pathways. *J. Am. Chem. Soc.* **2017**, *139* (41), 14352-14355.