

pubs.acs.org/JACS



Aqueous Microdroplets Capture Elusive Carbocations

Anubhav Kumar, Supratim Mondal, and Shibdas Banerjee*

Cite This: J. Am	Chem. Soc. 2021, 143, 2459–2463	Read Online	
ACCESS	LII Metrics & More	E Article Recommendations	Supporting Information

ABSTRACT: Carbocations are short-lived reactive intermediates in many organic and biological reactions that are difficult to observe. This field sprung to life with the discovery by Olah that a superacidic solution allowed the successful capture and nuclear magnetic resonance characterization of transient carbocations. We report here that water microdroplets can directly capture the fleeting carbocation from a reaction aliquot followed by its desorption to the gas phase for mass spectrometric detection. This was accomplished by employing desorption electrospray ionization mass spectrometry to detect a variety of short-lived carbocations (average lifetime ranges from nanoseconds to picoseconds) obtained from different reactions (e.g., elimination, substitution, and oxidation). Solvent-dependent studies revealed that aqueous microdroplets outperform organic microdroplets in the capture of carbocations. We provide a mechanistic insight demonstrating the survival of the reactive carbocation in a positively charged aqueous microdroplet and its subsequent ejection to the gas phase for mass spectrometric analysis.

The long-standing search for the existence of alkyl carbocations in the twentieth century evolved through indirect evidence from kinetic, stereochemical, and product studies, conductivity measurements, gas-phase ion chemistry, and spectroscopic studies.¹ Because of its high reactivity toward nucleophiles present in the system, capture and characterization of the transient carbocation species became a major challenge until a breakthrough development in superacid chemistry. The pioneering work of Olah using superacid resulted in the first direct observation of alkyl carbocations by ionizing the corresponding alkyl fluoride in the excess superacid medium.^{1,2} Despite the remarkable progress of carbocation chemistry,¹⁻⁸ direct capture and isolation of the intermediate carbocation from a reaction mixture appears like a hunt for elusive species, as they are transient and exist in low concentrations (Supplementary Note 1).

Inspired by the recent findings of the mysterious nature of water microdroplets, 9^{-13} which differ sharply from the corresponding bulk phase, we attempted to directly capture and isolate elusive carbocation intermediates from the reaction aliquot using aqueous microdroplets followed by mass spectrometric detection. We find that positively charged water microdroplets can behave as a magic acid for the capture and stabilization of carbocations.

Figure 1 shows the experimental setup involving desorption electrospray ionization mass spectrometry (DESI-MS), a form of ambient ionization technique, which was employed in this study (Supplementary Note 2). We followed three different types of model reactions, such as elimination,¹⁴ substitution,¹⁵ and oxidation¹⁶ to examine the formation of a wide variety of short-lived carbocation species (e.g., tertiary, secondary, nonclassical, bridgehead, benzylic, and allylic) (Figure 2). Literature precedents show that the lifetime of these carbocation intermediates ranges from nanoseconds to picoseconds depending upon the reaction, which were estimated by laser flash photolysis, azide clocks, and theoretical calculations



Figure 1. DESI-MS experimental setup for capturing short-lived carbocations using microdroplets. A 10 μ L amount of a reaction aliquot was bombarded with charged microdroplets. This resulted in the immediate extraction of reactive species in the splashed microdroplets, from where the species were transferred to a high-resolution mass spectrometer for their detection on a time scale of milliseconds.

(Supplementary Note 3).¹⁷⁻²³ These reactions were conducted following the reported protocol (details in Supporting Information), which were proposed earlier to involve the intermediacy of carbocations.¹⁴⁻¹⁶

We began our investigation by impacting the positively charged water microdroplets (Figure 1) with the reaction

Received: December 1, 2020 Published: February 3, 2021







Figure 2. Model reactions performed to generate various types of short-lived carbocations 1-8 as intermediates (Table S1). The theoretical m/z value of each carbocation is shown in red next to their respective structures.

aliquot sampled at 5 min after starting the reaction to directly capture and detect the aforementioned carbocations (1-8), Figure 2) in the liquid DESI-MS.²⁴ Figure 3 shows ion signals of those different types of carbocation species detected in the positive ion mode DESI-MS (Table S1). The high mass accuracy and resolution of the MS instrument allowed reliable identification of these transient fleeting intermediates (m/z)accuracy ≤ 1 ppm) from the corresponding reactions (Table S1). We also calculated the spectral accuracy, wherever possible, by matching the simulated and experimental isotopic distribution patterns (Figure S2). Figure S3 shows the extracted ion chronogram of the tert-butyl carbocation as a representative example indicating that the carbocation was detected immediately upon dispensing the reaction aliquot in the DESI source. This observation suggests that the same species was absent in the blank background. No carbocation signal was detected from the control experiments (no reagent added) with the precursor solution (Figure S4) and some typical products (Figure S5). We also intercepted the above carbocations at different time intervals, and their ion signal intensities were plotted against the reaction time, providing us with temporal profiles (insets of Figure 3a-h) of the carbocation abundance (normalized to 1) during the reaction. We further confirmed the feasibility of the water microdroplets for intercepting the same carbocation species from different reactions by changing the reagents added to a typical substrate. For example, exo-norborneol was considered as the substrate for two different reactions, such as elimination (Figures 2 and 3d) and a substitution (Figure S6). Detection of the 2norbornyl cation from both these reactions suggests that this carbocation detection using water microdroplets in DESI-MS is likely to be a general method, although the detection efficiency should depend on the carbocation concentration in the reaction.



Figure 3. Microdroplets generated in the DESI source (Figure 1) rapidly transferred the elusive carbocations from the reaction aliquot to the mass spectrometer for their subsequent detection (a-h, Table S1). The insets show the temporal evaluation of the carbocation formation (intensity normalized to 1) allowing their real-time monitoring.

In another set of experiments, we screened microdroplets of different solvents to examine their carbocation-capturing efficiencies. We selected seven different types of electrospray-friendly solvent systems²⁵ (Table S2) for capturing four typical carbocations (1, 2, 4, and 6 in Figure 2), and the results are presented as histograms in Figure 4a–d. The data indicated the



Figure 4. Screening of spray solvents and voltages to elucidate the mechanism of carbocation interception. Four typical species, e.g., tertiary (1), secondary (2), nonclassical (4), and benzylic (6) carbocations, were considered in the assessment of DESI spray solvents (a–d) and voltages (e–h). Ion intensities are presented as mean \pm SD from the triplicate analysis. An ion evaporation mechanism is illustrated in the lower panel (i) to demonstrate the feasibility of intercepting short-lived carbocations using positively charged aqueous microdroplets.

superior performance of microdroplets composed of water compared to that of organic or binary aqueous-organic solvents in intercepting the carbocation species from an ongoing reaction. For example, the highly unstable tert-butyl carbocation was only detected by water spray, while other solvent sprays failed (Figure 4a) to do so. The tuning of solvent flow rate (5–50 μ L/min) and sheath gas flow (100– 170 psi back pressure) could not establish the better performance of organic microdroplets than that of aqueous microdroplets (data not shown). This phenomenon can be ascribed by the high polarity of water and its microdroplet surface, which is discussed later. Relatively less polar solvents (methanol, acetonitrile, and their binary mixtures) either could not intercept (Figure 4a,b) or poorly intercepted (Figure 4c,d) the intermediate carbocation species depending on the nature and stability of the carbocation. For example, carbocation intermediates 4 and 6 are somewhat better stabilized by resonance when compared with 1 and 2 and thereby detected with less polar solvents, albeit poorly, as mentioned above.

The electrospray voltage is known to contribute charges in the microdroplet,²⁶ and that can also contribute to increased focusing of charged microdroplets into the MS inlet. To investigate the effect of DESI spray voltage, we tuned the voltage from 0 to +5 kV for the detection of the above carbocations (Figure 4e–h). We observed that the carbocation detection efficiency improved on increasing the voltage of the water spray. However, the opposite effect was observed for carbocations wherever detected by the acetonitrile spray (Figures 4g,h), indicating better carbocation detection with no voltage applied to the acetonitrile spray. This result has also been separately shown in Figure S7, which could be attributed to the high volatility of the acetonitrile and its rapid droplet evolution involved in the DESI process (Supplementary Note 4).

All the above observations collectively suggested that water microdroplets outperformed the organic microdroplets considered in this study for the capture and detection of several short-lived and elusive carbocation intermediates. One may wonder why the intermediate carbocations survived in the aqueous microdroplet although they are highly susceptible to be attacked by the nucleophilic water forming alcohol. It appears that this microdroplet phenomenon is strikingly different from that of the corresponding bulk phase.^{7,27–29} Indeed, this observation can be attributed to the emerging field of microdroplet chemistry demonstrating the unusual process that could occur in a tiny droplet.^{9–11,13,27,30–33}

Although we are unable to conclusively establish the mechanism of the carbocation interception at present, we rationalize a viable mechanism for the same (Figure 4i) based on what has been presented. An electrospray microdroplet, produced under a positive potential, is highly acidic because of the accumulation of protons by the solvent oxidation.^{25,26} Unlike a normal Brønsted acid, these protons lack their counteranions (conjugate base) in the droplet. Moreover, these protons are likely distributed on or nearer to the microdroplet surface with equidistant spacing to minimize the potential energy.^{34,35} This unique polar environment of the air-liquid interface possibly facilitates the carbocation capture. When the charged microdroplet impacts the reaction aliquot on the microscope glass slide, it causes the splashing of secondary microdroplets encapsulating the chemical and reactive intermediate species from the reaction aliquot. A charged species can be destabilized inside the charged microdroplet by a huge Coulomb force of repulsion imparted by the surface protons.³¹ Therefore, the carbocation (R^+) can exist as an intimate or tight ion pair in association with a counteranion X^- (e.g., the leaving group or other anions) inside the charged microdroplet, or R⁺ can also exist preferentially on the charged surface to minimize the Coulomb force of repulsion. The existence of intimate ion pairs inside charged microdroplets was also proposed before by Fenn.³⁴ The mechanism of DESI suggests that secondary microdroplets evolve through repeated solvent evaporation and the Coulomb fission assisted by the flow of a sheath gas and the heated MS inlet capillary (Figure 1).³⁶ When the intimate ion pair (R^+X^-) in the vanishing charged droplet encounters the surface by its Brownian dynamics, the attractive interaction between the counteranion (X⁻) and surface protons might weaken the interaction between R^+ and X^- (Figure 4i). The thermal activation $(k_{\rm T})$ and Coulomb repulsion may subsequently provide sufficient energy to desorb the intrinsically charged carbocation species (R^+) from the highly charged

droplet surface with concomitant neutralization of the counteranion (X^-) by binding with a proton on the surface (Supplementary Note 5).

When we investigated the influence of different spray solvents on carbocation interception, we found that the carbocation signal was highest from water spray, and in some instances, the carbocation was only captured by water or water containing organic solvent spray (Figure 4a–d). This result appears anomalous because, in contrast to other organic solvents (Table S2), water is a better nucleophile for attacking the carbocation and thereby decreasing its average lifetime.

However, this phenomenon can be attributed to the high charge (H⁺) density¹² and electric field^{26,35} on the aqueous microdroplet surface, leading to effective desorption of carbocations (Supplementary Note 6). Moreover, the reactivity of carbocations with water is likely to be decreased on the microdroplet surface, where water density sharply vanishes within a nanometer.^{37–41}

That the positively charged microdroplet surface has a crucial role in the carbocation capture is further supported by the voltage-dependent study as discussed before (Figure 4eh). The detection of the resonance stabilized carbocations (Figure 4g,h) at 0 V, the temporal evaluation of the carbocation formation (insets of Figure 3a-h), and absence of the carbocation signal at the zero time point (insets of Figure 3a-h) and in the control study (Figures S4 and S5) collectively suggest that those carbocations were indeed the intermediates in the original reactions (Figure 2), which is consistent with the literature reports.^{14–16} We were not able to detect carbocations (data not shown) from the same reactions (Figure 2) when we sprayed negatively charged water microdroplets at -5 kV in the DESI-MS. This result further substantiates the importance of the positive charges (protons) for providing the stability to the carbocation in the microdroplet (Figure 4i). In some cases, though not for all, the reduction of the spray solvent (water) pH improved the carbocation detection efficiency (Supplementary Note 7, Figures S8 and S9). Moreover, the carbocation (1) was also found to undergo hydrogen-deuterium exchange when captured by the microdroplets of heavy water (Figure S10). It should be noted that this study is not intended to measure the absolute concentration of carbocations in the original reaction aliquot, which is experimentally challenging, and also might suffer from the possibility of the loss of a fraction of carbocations by their reactions during the DESI spray.

Nevertheless, this anomalous carbocation chemistry in aqueous microdroplets inspires us to further explore the mysterious power of aqueous microdroplets in the future. This study lays the foundation of a fairly straightforward MS method for directly detecting elusive carbocation intermediates using inexpensive water spray on a minimal amount of reaction aliquot.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12512.

Supplementary notes, materials and methods, and mass spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

Shibdas Banerjee – Department of Chemistry, Indian Institute of Science Education and Research Tirupati, Tirupati 517507, India; orcid.org/0000-0002-3424-8157; Email: shibdas@iisertirupati.ac.in

Authors

- Anubhav Kumar Department of Chemistry, Indian Institute of Science Education and Research Tirupati, Tirupati 517507, India
- Supratim Mondal Department of Chemistry, Indian Institute of Science Education and Research Tirupati, Tirupati 517507, India

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c12512

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by SERB, India (grant numbers SB/S2/RJN-130/2017 and ECR/2018/001268). The authors thank S. Mutyam for his help with the HRMS instrumentation.

REFERENCES

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

(2) 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.
(3) Kiricsi, I.; Förster, H. Chemisorption of propene on HZSM-5 by ultraviolet and infrared spectroscopy. *J. Chem. Soc., Faraday Trans.* 1

1988, 84 (2), 491-499.
(4) Garbowski, E. D.; Praliaud, H. Étude par spectroscopie UV des interactions d'oléfines avec des centres acides en catalyse hétérogène.

J. Chim. Phys. Phys.-Chim. Biol. 1979, 76, 687–692. (5) Naredla, R. R.; Klumpp, D. A. Contemporary Carbocation Chemistry: Applications in Organic Synthesis. Chem. Rev. 2013, 113

(9), 6905-6948.
(6) 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.

(7) Ishizuka, S.; Matsugi, A.; Hama, T.; Enami, S. Chainpropagation, chain-transfer, and hydride-abstraction by cyclic carbocations on water surfaces. *Phys. Chem. Chem. Phys.* **2018**, 20 (39), 25256–25267.

(8) 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.

(9) Lee, J. K.; Samanta, D.; Nam, H. G.; Zare, R. N. Spontaneous formation of gold nanostructures in aqueous microdroplets. *Nat. Commun.* **2018**, *9* (1), 1562.

(10) Lee, J. K.; Walker, K. L.; Han, H. S.; Kang, J.; Prinz, F. B.; Waymouth, R. M.; Nam, H. G.; Zare, R. N. Spontaneous generation of hydrogen peroxide from aqueous microdroplets. *Proc. Natl. Acad. Sci. U. S. A.* **2019**, *116* (39), 19294–19298.

(11) Lee, J. K.; Samanta, D.; Nam, H. G.; Zare, R. N. Micrometer-Sized Water Droplets Induce Spontaneous Reduction. J. Am. Chem. Soc. 2019, 141 (27), 10585–10589.

Journal of the American Chemical Society

pubs.acs.org/JACS

(12) 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.

(13) 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.

(14) 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.

(15) 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. *Mater. Express* **2016**, 6 (3), 220–228.

(16) Banerjee, S.; Sathyamoorthi, S.; Du Bois, J.; Zare, R. N. Mechanistic analysis of a copper-catalyzed C-H oxidative cyclization of carboxylic acids. *Chem. Sci.* **201**7, *8* (10), 7003–7008.

(17) McClelland, R. A., Carbocations. In *Reactive Intermediate Chemistry*; Moss, R. A.; Platz, M. S.; Jones, M. J., Eds.; John Wiley & Sons, Inc.: NJ, 2003; pp 1–40.

(18) 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. Kinet.* **1985**, *17* (9), 925–930.

(19) 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.

(20) Chiang, Y.; Kresge, A. J. Mechanism of hydration of simple olefins in aqueous solution. cis- and trans-Cyclooctene. J. Am. Chem. Soc. **1985**, 107 (22), 6363–6367.

(21) 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.

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

(23) 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.

(24) Miao, Z.; Chen, H. Direct analysis of liquid samples by desorption electrospray ionization-mass spectrometry (DESI-MS). *J. Am. Soc. Mass Spectrom.* **2009**, *20* (1), 10–19.

(25) 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.

(26) 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.

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

(28) Ishizuka, S.; Matsugi, A.; Hama, T.; Enami, S. Interfacial Water Mediates Oligomerization Pathways of Monoterpene Carbocations. J. Phys. Chem. Lett. **2020**, 11 (1), 67–74.

(29) Ishizuka, S.; Fujii, T.; Matsugi, A.; Sakamoto, Y.; Hama, T.; Enami, S. Controlling factors of oligomerization at the water surface: why is isoprene such a unique VOC? *Phys. Chem. Chem. Phys.* **2018**, 20 (22), 15400–15410.

(30) Banerjee, S.; Zare, R. N. Syntheses of Isoquinoline and Substituted Quinolines in Charged Microdroplets. *Angew. Chem., Int. Ed.* **2015**, *54* (49), 14795–14799.

(31) Banerjee, S.; Prakash, H.; Mazumdar, S. Evidence of Molecular Fragmentation inside the Charged Droplets Produced by Electrospray Process. J. Am. Soc. Mass Spectrom. **2011**, 22 (10), 1707.

(32) Nam, I.; Lee, J. K.; Nam, H. G.; Zare, R. N. Abiotic production of sugar phosphates and uridine ribonucleoside in aqueous microdroplets. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114* (47), 12396–12400.

(33) Wei, Z.; Li, Y.; Cooks, R. G.; Yan, X. Accelerated Reaction Kinetics in Microdroplets: Overview and Recent Developments. *Annu. Rev. Phys. Chem.* **2020**, *71* (1), 31–51.

(34) Fenn, J. B. Ion formation from charged droplets: Roles of geometry, energy, and time. J. Am. Soc. Mass Spectrom. **1993**, 4 (7), 524–535.

(35) 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.

(36) 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.

(37) 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.

(38) Enami, S.; Hoffmann, M. R.; Colussi, A. J. Proton Availability at the Air/Water Interface. J. Phys. Chem. Lett. 2010, 1 (10), 1599–1604.

(39) Colussi, A.; Enami, S. Detecting Intermediates and Products of Fast Heterogeneous Reactions on Liquid Surfaces via Online Mass Spectrometry. *Atmosphere* **2019**, *10*, 47.

(40) Enami, S.; Mishra, H.; Hoffmann, M. R.; Colussi, A. J. Protonation and Oligomerization of Gaseous Isoprene on Mildly Acidic Surfaces: Implications for Atmospheric Chemistry. *J. Phys. Chem. A* **2012**, *116* (24), 6027–6032.

(41) Enami, S.; Hoffmann, M. R.; Colussi, A. J. Dry Deposition of Biogenic Terpenes via Cationic Oligomerization on Environmental Aqueous Surfaces. J. Phys. Chem. Lett. **2012**, 3 (21), 3102–3108.