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Exploring Reactive Carbocations in AqueousMicrodroplets

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ABSTRACT

Recent advancements in the study of reactive carbocations have unveiled their intriguing behavior in aqueous microdroplets, challenging traditional notions of stability and reactivity. We present a comprehensive investigation into the formation, detection, and reactivity of various carbocation intermediates within water microdroplets

Keywords: *Aqueous microdroplets, Carbocations, Reactive intermediates, Dehydrogenative aromatization.*

1 Introduction

Microdroplet chemistry has gained considerable attention over the years due to its ”catalytic” interface, which plays a crucial role in speeding up reactions.The unique environment within microdroplets, especially at the interface, can influence the way reactions occur, leading to faster and sometimes different reaction pathways than those observed in bulk phases.[1–4]

This phenomena is used to modify chemical compounds making it valuable in chemical derivatization. The acceleration and unique conditions in microdroplets pro- vide a platform for studying reaction mechanisms in detail. The rapid reaction rates in microdroplets are advantageous for high-throughput screening, allowing for the testing of numerous reactions or conditions in a short amount of time. This is particularly useful in drug discovery and materials science. Microdroplet chemistry aligns with green chemistry principles by reducing the amount of solvents and reagents needed forreactions. [5]

An ion containing a positively charged carbon atom is called a *carbocation*. The vinyl C_2H^+ cations, methenium CH^+, and methanium CH^+ are a few of the most basic examples. Carbocations containing multiple positively charged carbon atoms are also occasionally observed (e.g., ethylene dication C_2H^{2+}).[6]

As per the International Union of Pure and Applied Chemistry (IUPAC), a carbo- cation is defined as a cation that has an even number of electrons and a substantial amount of positive charge on its carbon atom. [[7]]

As a positively charged electron deficient carbon species are indispensable inter- mediates in organic chemistry due to their high reactivity and pivotal role in various chemical reactions. [1] Historically, evidence of alkyl carbocations was gleaned from kinetic studies, stereochemical investigations, product analyses, gas-phase ion chemistry, and various spectroscopic techniques.

Carbocation and carbonium ion were used interchangeably until Olah and asso- ciates discovered five-coordinate carbocations. While Olah offered a new description of a carbenium ion, which is a carbocation that only has two-center two-electron bonds with a three-coordinate positive carbon, the term ”carbonium ion” was originally used to describe to any sort of three-center two-electron bonding.[6]

The main challenge in capturing and characterising these fleeting intermediates stems from their rapid reactivity with nucleophiles in the system, which prevents their stabilization and observation. Due to their high reactivity, carbocations are often critical in many synthetic transformations and organic reaction pathways, including nucleophilic substitution, elimination, and rearrangement reactions, to form more stable intermediates.[2]

Despite their utility, carbocations are challenging to control due to their high reac- tivity and rearrangement propensity. The stability of carbocations is a crucial aspect of their chemistry and varies significantly based on their structure. Polar solvents can stabilise carbocations through solvation, while Lew is acids or metal catalysts can help stabilise and direct the reactivity of carbocations, allowing for more controlled reaction pathways.

The diverse chemistry of carbocations has received considerable attention, with carbocation-based synthetic reactions used in methodology development and targeted organic synthesis. Carbocations are conventionally known to be rapidly annihilated by the nucleophilic attack of water. Still, based on experiments and literature prece- dence that could primarily contribute to stabilising carbocations, here in the following review, we describe that reactive carbocation species can be captured and stabilised in water microdroplets by enhancing their lifetime at or near the air-water interface. The review article presented here delves into the history of carbocations, tracing their discovery and the evolution of our understanding of these intriguing intermediates in organic chemistry. It begins with an exploration of the early observations and theoretical models that first brought carbocations to the attention of chemists, highlighting the key experiments and figures that laid the groundwork for subsequent advancements.

The article then transitions to a comprehensive analysis of the current state of carbocation research. It examines the latest methods for synthesizing carbocations, detailing the innovative approaches that have been developed to generate these species under various conditions. These advancements have significantly broadened the scope of reactions that can be facilitated by carbocations, opening up new possibilities in synthetic chemistry.

Moreover, the review addresses the cutting-edge techniques used for the detection and characterization of carbocations. It discusses the technological advancements that have made it possible to observe these transient species with greater accuracy and detail, providing deeper insights into their behavior and reactivity. The combination of novel synthetic methods and advanced detection techniques has propelled carbocation research forward, enabling chemists to harness their unique properties for a wide range of applications.

2 History of Carbocations

The journey of understanding carbocations, positively charged ions centered on a carbon atom, marks a significant chapter in the history of organic chemistry. This section traces the discovery and the evolving comprehension of carbocations, shedding light on their role in organic reactions and the contributions of key chemists in this field.[2]

2.1 Early Observations and Mysteries (Pre-1901)

Before the turn of the 20th century, organic chemists had documented numerous reactions involving rearrangements, substitutions, eliminations, additions, and poly- merizations. Despite this, these reactions exhibited peculiar behaviors that baffled scientists, as the bonding theories of the time could not account for these anomalies. The scientific community was at a standstill, lacking a coherent explanation for these peculiarities in organic transformations.[8]

2.2 The Breakthrough and Early Contributions (1901-1940)

The early 20th century marked a pivotal period in the understanding of organic chem- istry, particularly with the identification of carbocations. In 1901, A. H. Norris [3] and, independently, Kehrman and Wentzel [9], made groundbreaking discoveries that would lay the foundation for future research. Both parties reported the ionization of substrates in sulfuric acid, resulting in colored solutions which they identified as con- taining the triphenylmethyl cation. This was a monumental discovery, as it provided the first evidence of carbocations.

During the same period, notable chemists such as Julius Stieglitz, Adolf von Baeyer, and Moses Gomberg [10] made significant contributions to the study of carbocations. Initially, the discovery of cationic species involving carbon was met with skepticism and was considered little more than laboratory curiosities. Despite this, these early findings were critical as they hinted at the existence of reactive intermediates that played a crucial role in organic reactions.

2.3 The Mechanistic Revolution (1920-1970s)

By 1920, several notable carbocation-based reactions had been known for decades, including the pinacol rearrangement, Friedel–Crafts alkylation, and acid-catalyzed polymerizations of olefins. However, there was no awareness of the carbocation reaction intermediates. A critical insight was made by Meerwein and Van Emster in 1922[11], when they proposed “a rearrangement of the cation” for the acid-promoted isomer- ization of camphene hydrochloride. This pioneering idea was soon followed by

Ingold and Rothstein's suggestion of an SN1 mechanism and Whitmore's formal description of heterolytic bond cleavage at carbon. With further descriptions of alkene protona- tion, the carbocation was firmly established as one of the most important reactive intermediates in organic synthesis.[12, 13]

As aptly noted by Stang in his historical perspective on carbocation chemistry, this period ushered in "the golden age of mechanistic organic chemistry" from about the 1940s through the mid-1970s[14]. It was during this period that carbocations were thor- oughly investigated, leading to the development of many new synthetic methodologies, including those involving heteroatom-stabilized carbocations, allylic and homoallylic cations, rearrangements, cycloadditions, cascade reactions, and others.[15] Indeed, the "peculiarities of organic reactions" noted by Whitmore had become a valuable tool in the hands of synthetic organic chemists. This was succinctly stated by George Olah during his 1994 Nobel Prize (awarded to him "for his contribution to carbocation chemistry") award address when he stated, "Knowledge about mechanisms makes it possible to develop better and less expensive methods to prepare products of technical importance."[16]

2.4 Industrial and Academic Impact

The value of carbocationic synthetic chemistry cannot be overstated, as it continues to be a vital part of industrial and academic chemistry. For example, the petroleum industry uses alkylation unit chemistry (isobutylene or propene/isobutane/acid) to produce more than 1.6 million barrels per day of highly branched hydrocarbons for use in transportation fuels.[2] The critical C–C bond-forming step involves the reaction of a carbocation with the alkene, followed by hydride transfer from the isobutane to the carbocation. Likewise, the majority of phenol is still produced using the oxidation of cumene and the subsequent Hock rearrangement. Cumene itself is formed by the Friedel–Crafts alkylation of benzene with propene,[17] a reaction involving the 2-propyl cation.

More recent technologies include the methanol-to-gasoline (MTG)[18] and methanol-to-olefins (MTO) [19] processes developed by Mobil. Solid-state NMR stud- ies have suggested mechanisms involving a "hydrocarbon pool" within the channels of the acidic zeolite catalyst. The catalytic sites are shown to possess carbocationic inter- mediates, such as the 1,3-cyclopentadienyl cation and 1,1,2,4,6-pentamethylbenzenium cation. These carbocation intermediates are thought to be the basis for C–C bond-forming reactions in the MTG and MTO processes.[20]

The diverse chemistry of carbocations has also received considerable attention from the academic community, with carbocation-based synthetic reactions being used in methodology development and targeted organic synthesis. Despite the long history of synthetic carbocation chemistry, this continues to be an area of intensive research. New methodologies are being developed for C–C bond construction, functional group manipulation, activation of sp^3 carbons, and rearrangements of carbon skeletons. Many of the classical organic reactions continue to be developed and applied to innovative synthetic conversions, including the total syntheses of natural products. Carbocations have also been used in several recent asymmetric synthetic methodologies.[4, 21, 22][23] As our understanding of carbocations continues to evolve, their historical journey provides valuable insights into the development of organic chemistry as a discipline.

Table 1: Timeline of Significant Discoveries and Developments in Carbocation Chemistry

Year	Event/Discovery	Researchers	Details
1891	Report on the reaction of bromine with tropylidene (cycloheptatriene)	G. Merling [24]	Product: C_7H_7Br, identified later as tropylium bromide.
1902	Discovery of triphenylmethanol color changes in concentrated sulfuric acid	Norris and Kehrman [6]	Triphenylmethyl chloride forms orange complexes with alu-minum and tin chlorides. Recognized salt-like character.
1902	Recognition of the carbocationic system	Adolf von Baeyer [25]	Identified stable trityl carbocation used as an organocatalyst.
1899	Proposal of carbocations as reactive intermediates	Julius Stieglitz [26]	Carbocations proposed as intermediates in organic reactions.
1922	Study of Wagner–Meerwein rearrangement	Hans Meerwein [11]	Further development of carbocation theory.
Various	Involvement in SN1 reaction, E1 reaction, and rearrangement reactions like Whitmore 1,2 shift	-	Carbocations involved in several key organic reactions.
-	Initial skepticism and rejection by the Journal of the American Chemical Society	Chemical establishment	Reluctance to accept carbocations as valid intermediates.

Year	Event/Discovery	Researchers	Details
1958	First NMR spectrum of a stable carbocation in solution	Doering et al.[27]	Heptamethylbenzenium ion observed by treating hex- amethylbenzene with methyl chloride and aluminum chloride.
1960	Preparation of the stable 7-norbornadienyl cation	Story et al.[28]	Reacted norbornadienyl chloride with silver tetrafluoroborate insulfur dioxide at minus 80 °C.
1962	Direct observation of tert-butyl carbocation	Olah	Observed by NMR on dissolving tert-butyl fluoride in magic acid.
-	NMR of norbornyl cation and proton-scrambling observation	Schleyer et al[29]	NMR spectrum reported, show- ing proton-scrambling over abarrier.

3 Spontaneous Transformation of Phenol to Phenyl Carbocations

3.1 Phenol Stability

Phenol (C_6H_5OH) is a notable aromatic compound, characterized by the presence of a hydroxyl group (-OH) directly attached to a benzene ring. It serves as a critical aromatic feedstock in the synthesis of various value-added chemicals. The stability of phenol can be attributed to its resonance stabilization. In this context, the lone pair of electrons on the oxygen atom of the hydroxyl group delocalizes into the aromatic pie- system of the benzene ring. This electron delocalization enhances the overall stability of the molecule by spreading the negative charge over the ortho and para positions of the ring. As a result, phenol exhibits increased stability compared to other poten- tial derivatives, making it relatively resistant to forming carbocations under standard conditions [30].

In contrast to other types of carbocations, such as tertiary carbocations, which can stabilize the positive charge through hyperconjugation or resonance, the phenyl car- bocation is significantly less stable. The phenyl carbocation ($C_6H_5C^+$) remains highly electron-deficient due to the ineffective overlap between the p-orbital of the carboca- tionic carbon and the pie-system of the benzene ring. This poor overlap prevents the effective delocalization of the positive charge, making the phenyl carbocation highly reactive and short-lived. This inherent instability has traditionally made the direct observation and study of phenyl carbocations challenging under standard laboratory conditions. In bulk solution, these intermediates rapidly react with nucleophiles or solvents, reverting to more stable forms and thus evading direct detection and char- acterization. Studying these species typically requires extremely low temperatures or highly controlled environments, often necessitating sophisticated techniques and equipment [30].

To facilitate the C–O functionalization of phenol derivatives, chemists often employ expensive transition metal catalysts. These catalysts provide the necessary activation energy and stabilization required for the cleavage of the C–O bond, thus enabling various synthetic transformations. Despite their utility, the use of such catalysts intro- duces complexity and additional costs to chemical processes. Moreover, the use of environmentally hazardous substances in these catalysts often contradicts the prin- ciples of green chemistry. While these catalytic processes are essential for organic synthesis and the formation of complex molecules from simpler phenol derivatives, their environmental and economic impacts must be carefully considered [31].

3.2 Phenol Transformation in Microdroplets

The study of carbocation intermediates traditionally poses significant challenges in bulk solution due to their transient nature. Recent advancements in microdroplet chemistry offer a novel approach to investigating these reactive intermediates. A groundbreaking study by Nandy et al. [32] demonstrated the spontaneous generation of phenol carbocations within microdroplets. By introducing phenol into microdroplets containing isotopically labeled water, they observed the conversion of phenol to its isotopically labeled analogue. This observation indicated an equilibrium between phe- nol and the phenyl carbocation (Ph+) in these microenvironments. Notably, their study predicted that approximately 68 percent of phenol in water microdroplets was transformed into Ph+, followed by nucleophilic reactions facilitated by the aqueous medium.

This transformation underscores the unique properties of microdroplets in stabiliz- ing reactive intermediates that are otherwise difficult to observe in bulk phases. The confined environment of microdroplets appears to lower the activation energy required for carbocation formation, thus enabling these reactions to proceed spontaneously and at an accelerated rate.

Subsequent research has further explored the implications of this discovery. Meng et al. [33] extended this work by demonstrating a one-step, catalyst-free method for the formation of phenol from benzoic acid using water microdroplets. This method lever- ages the spontaneous generation of reactive intermediates in microdroplets to achieve high-efficiency transformations without the need for external catalysts. The findings suggest that microdroplet chemistry can streamline synthetic processes, reducing the reliance on traditional catalytic systems and potentially minimizing environmental impact.

Additionally, Meng et al. [34] highlighted the superfast formation of $C(sp^2)N$, $C(sp^2)P$, and $C(sp^2)S$ vinylic bonds in water microdroplets. The rapid formation of these bonds further demonstrates the unique reactivity observed in microdroplet environments. Their study illustrated that the confined space and high surface-to- volume ratio of microdroplets not only accelerate reaction kinetics but also enable the formation of bonds that are otherwise challenging to achieve under conventional conditions.

Wang et al. [35] also contributed to this growing body of knowledge by demon- strating ultrafast C–C and C–N bond formation reactions in water microdroplets, facilitated by the spontaneous generation of carbocations. Their work emphasizes the potential of microdroplet chemistry to revolutionize synthetic methodologies, enabling rapid and efficient formation of complex molecules. The spontaneous generation of carbocations in these environments opens new avenues for exploring carbocation chemistry in previously impractical ways.

In summary, the transformation of phenol in microdroplets provides a compelling example of the power of microdroplet chemistry to stabilize and utilize reactive inter- mediates. The ability to generate and observe carbocations in such environments not only enhances our understanding of fundamental chemical processes but also paves the way for innovative applications in synthetic chemistry. These studies collectively highlight the versatility and efficacy of aqueous microdroplets as a powerful tool for facilitating a diverse range of chemical transformations.

3.3 Discussion

In a recent visionary article, Shaik [36] discussed the potential of electric-field-aided chemistry by 2050, projecting how such advancements could accelerate reactions and revolutionize chemical synthesis. This forward-looking perspective resonates with recent developments in microdroplet chemistry, as exemplified by the work of Nandy et al. [32]. Their study, which demonstrated the spontaneous generation of phenol carbo- cations, highlights the transformative potential of confined environments and electric fields in facilitating complex chemical transformations.

Building upon this foundation, Meng et al. [34] further emphasized the accelerated reaction kinetics and unique bond formation capabilities within microenvironments. Their research underscores the transformative impact of microdroplet chemistry on synthetic methodologies.

Additionally, Kumar et al. [37] provided mechanistic insights into the synthesis of phenol using microdroplets. By employing custom-designed sampling sources com- bined with mass spectrometry and isotope labeling experiments, their study confirmed that air nitrogen reacts with water at the air–water interface, fixing molecular nitro- gen into its oxides (NO, NO_2, and N_2O) and acids (HNO_2 and HNO_3) at trace levels without any catalyst. This evidence not only advances our understanding of chemi- cal processes in microdroplets but also offers critical insights into the origins of these gases in the early atmosphere, as corroborated by Liu et al. [38].

In summary, the transformation of phenol in microdroplets exemplifies the signifi- cant potential of microdroplet chemistry to stabilize and utilize reactive intermediates. The ability to generate and observe carbocations in such confined environments not only advances our fundamental understanding of chemical processes but also paves the way for innovative applications in synthetic chemistry. Collectively, these studies underscore the versatility and power of aqueous microdroplets as a tool for facilitat- ing a broad range of chemical transformations, aligning with visionary perspectives on the future of chemistry as proposed by Shaik and others. The ongoing exploration of microdroplet chemistry promises to further revolutionize synthetic methodologies, making them faster, more efficient, and environmentally sustainable.

4 Dehydrogenative Aromatization

For cyclohexane, cyclohexene, and cyclohexadiene, dehydrogenation is the simplest pathway to aromatization. Among them, hexadiene is more prone to aromatization since the activation barrier decreases with degree of unsaturation. Normally, dehydrogenation is a redox process. DA is the reverse of arene hydrogenation. As such, hydrogenation catalysts are effective for the reverse reaction. For example, Platinum- catalyzed dehydrogenations of cyclohexanes and related feedstocks are the largest scale applications of this reaction [39]

DA of cyclic ketones is a pivotal reaction in the synthesis of functionalized aromatic compounds and hydrogen transfer–related technologies. Traditional DA strategies often rely on precious metals and harsh reaction conditions, including high tempera- tures , extra oxidants and bases which pose significant challenges for sustainable and efficient synthesis. [40] [41] .

Many researchers have developed numerous methods that are recently related to development of cyclic ketones like [42] and [43] Recently, a milder approach using iodine (I2) has been proposed, offering a promising alternative under ambient conditions.

This section explores the traditional DA strategies, the proposed I2-mediated approach, and the mechanistic insights and reaction optimization achieved through recent studies.

Traditional DA Strategies and Limitations

Metal-free I2-mediated DA has attracted increasing attention to address such cost and safety concerns.[44, 45] In 1980, The I2-mediated DA of cyclic ketones was initially described by Tamura and Yoshimoto, who also converted a number of cyclic ketones to aromatics in MeOH. The reaction demonstrated efficacy at a slightly increased temperature of approximately 70 °C, yielding 53–86 percent aromatic ethers. [46] Over the years,I2 has been a universal mediator in numerous organic synthesis processes over the years because of its low toxicity, abundance, multivalence states, and affordability.[47]

Traditional methods for DA typically involved the use of precious metal (PM) cata- lysts, such as palladium,(Pd) ,platinum(Pt) ,and ruthenium(Ru) often in combination with oxidants. [48, 49] Yamaguchi et al. reported a heterogeneous catalyst consisting of a highly dispersed Pd–Au alloy on CeO2 to facilitate aliphatic C–H bond activa- tion to achieve DA from aliphatic cyclic precursors. The reaction, was conducted at 100 °C, leading to the dehydrogenation of cyclohexanone to cyclohexenone and phe- nol with high selectivity. [50] Ding et al. developed an organic polymer-supported Pd compound that can promote the aromatization of 10 substituted cyclic ketones with satisfactory efficiencies. ([51]) .This heterogenous catalytic system avoided using oxi- dants and extra additives to develop a green process but also need a high temeprature of 140 °C.

The above-mentioned studies have enhanced our fundamental understanding of DA. However, the use of PM catalysts may not be sustainable or environmentally friendly. While these methods can be effective, they have several limitations:

High Cost and Scarcity of Catalysts: Precious metals and complicated ligands appli- cations are expensive and not readily available, making large-scale applications applications and subsequent products separation economically unfeasible.

1. Harsh Reaction Conditions: The need for high temperatures and strong oxidants not only increases energy consumption but also limits the substrate scope to thermally stable compounds.
2. Environmental and Safety Concerns: The use of toxic and hazardous oxidants raises safety issues and environmental concerns, necessitating the development of greeneralternatives.
3. Limited Selectivity: Traditional methods often struggle with product selectivity, leading to mixtures of desired and undesired products.

Proposal and Characterization of the I2-Mediated DA Approach

To address these limitations, a novel I2-mediated DA approach has been proposed, which operates under milder conditions [52]. This method uses I2 as a mediator to facilitate the dehydrogenation of substituted unsaturated cyclic ketones, achieving aromatization at ambient temperature. The characterization of this approach involved several analytical techniques:

1. Time-Resolved Proton Nuclear Magnetic Resonance (NMR): NMR spectroscopy was employed to monitor the reaction progress in real-time, providing insights into dehydrogenation of the aliphatic C-H bond on the cyclic ketone.
2. Density Functional Theory (DFT) Calculations: DFT calculations were performed to predict the energy profiles and identify the most favorable pathways for the reaction, helping to elucidate the mechanism at the molecular level.
3. Substrates Scope Study and Solvent Screen: Substrates scope investigation firstly discovered the carbocation formation for some reactants, and the solvent screen study proved that this DA of cyclic ketones could executed in various solvent and more favored in polar solvent including alcohols, DMSO and water.
4. Mass Spectrometric Analyses: Desorption electrospray ionization–mass spectrome- try (DESI-MS) was used to detect transient species and intermediates, in different solvents revealing the presence of a carbocation intermediate,in different reaction pathway which had been overlooked in previous studies.

Mechanistic Insights and Reaction Optimization

The combination of experimental and computational techniques allowed for the devel- opment of a unified mechanism for the I_2-mediated DA approach. Key findings include:

1. **Carbocation Formation**: The detection of a carbocation intermediate suggested a new pathway for the reaction, where I_2 facilitates the removal of hydrogen atoms on α/γ-position, leading to the formation of a highly reactive carbocation that undergoes subsequent aromatization.
2. **Product Selectivity**: Depending on the solvent used, the reaction could yield either phenol ether or phenol. This solvent-dependent selectivity was attributed to the different stabilization effects of the carbocation intermediate in various solvents.

Reaction Optimization: By exploring a wide range of substrates and optimizing reaction conditions, the researchers were able to achieve phenolic product yields ranging from 17% to 96%. Notably, some substrates underwent efficient DA in water, achieving yields of 95–96% at temperatures below the boiling point of water.

3. **Mechanistic Elucidation**: The combined spectroscopic and computational stud- ies provided strong evidence for the formation mechanism and the specific location of the carbocation intermediate. This mechanistic understanding allowed for precise control over the reaction conditions to maximize yield and selectivity.

In summary, the I_2-mediated DA approach offers a mild and efficient alternative to traditional DA methods. By leveraging the unique properties of iodine and optimizing reaction conditions, this strategy overcomes the limitations of conventional methods, providing a greener and more sustainable pathway for the synthesis of functionalized aromatic compounds.

5 Enhanced Detection of Carbocation Intermediates via Surface Modification

5.1 Surface Chemistry In Mass Spectrometric analysis

Surface chemistry plays a pivotal role in mass spectrometric analysis, particularly when investigating reactions and transformations at the interface of different phases. This discipline focuses on the study of chemical processes occurring at surfaces and interfaces, which is crucial for understanding the behavior of molecules in various environments, including biological, environmental, and industrial contexts.[53]

Mass spectrometry (MS) is a powerful analytical technique used to measure the mass-to-charge ratio of ions. It provides detailed information about the molecular weight and structure of compounds, making it indispensable in fields such as proteomics, metabolomics, and chemical analysis. The integration of surface chemistry principles into mass spectrometric techniques has significantly enhanced the ability to analyze complex samples with high sensitivity and specificity.[54]

5.1.1 Importance of Surface Chemistry in Mass Spectrometry

Surface chemistry is integral to mass spectrometric analysis for several reasons:

1. Enhanced Ionization Efficiency: The efficiency of ionization is a critical factor in mass spectrometry. Surface-active sites can facilitate the ionization process, improving the detection limits of analytes. Techniques such as Matrix-Assisted Laser Desorp- tion/Ionization (MALDI) and Electrospray Ionization (ESI) heavily rely on surface interactions to generate ions from analytes in solid and liquid phases, respectively.
2. Microdroplet Chemistry: The study of reactions in microdroplets has emerged as a significant area of interest. Microdroplets provide a high surface-to-volume ratio, creating unique microenvironments that can stabilize reactive intermediates and accel- erate reaction kinetics. This phenomenon is particularly useful for studying transient species like carbocations, which are challenging to observe in bulk phases. [55]

3. Surface-Induced Fragmentation: In techniques such as Surface-Induced Dissociation (SID), the interaction of ions with surfaces induces fragmentation. This process provides structural information about the analytes, aiding in the identification and characterization of complex molecules.
4. Surface-Enhanced Raman Scattering (SERS): Although not a mass spectro- metric technique perse, SERS is often coupled with MS to enhance the detection and analysis of surface-bound species. The amplification of Raman signals by sur- face plasmons on metallic surfaces allows for the sensitive detection of low-abundance analytes.
5. Sample Preparation and Deposition: The preparation of samples on specific surfaces can influence the outcome of mass spectrometric analysis. Techniques like thin-layer chromatography (TLC) combined with MS use surface properties to sep- arate and identify compounds in mixtures. The choice of surface can affect the desorption/ionization process, impacting the accuracy and reproducibility of results.

2.1.1 Advances in Surface Chemistry for Mass Spectrometric Analysis

Recent advances in surface chemistry have led to innovative approaches in mass spectrometric analysis:

1. Nanostructured Surfaces: The development of nanostructured surfaces, such as nanopillars and nanowires, has improved the sensitivity and specificity of MS. These surfaces enhance ionization efficiency and provide unique platforms for studying surface-bound reactions.
2. Microfluidic Devices: Integration of microfluidic devices with mass spectrometry allows for the precise control of sample flow and reaction conditions. These devices exploit surface chemistry principles to manipulate small volumes of fluids, enabling high-throughput and real-time analysis. [55]
3. Ambient Ionization Techniques: Techniques such as Desorption Electrospray Ion- ization (DESI) and Direct Analysis in Real Time (DART) utilize surface interactions to ionize samples in their native environments. These ambient ionization methods expand the applicability of MS to a wider range of samples, including those that are difficult to analyze using traditional techniques.

Functionalized Surfaces: The use of chemically functionalized surfaces can selectively capture and analyze specific analytes. This approach enhances the selectivity and sensitivity of MS, particularly in complex biological matrices where target analytes are present at low concentrations. [56]

6 Discussion

Recent advancements in the study of reactive carbocations within aqueous microdroplets have significantly challenged traditional notions regarding their stability and reactivity. Our comprehensive investigation into the formation, detection, and behavior of various carbocation intermediates in water microdroplets has yielded several intriguing findings, which are discussed below.

6.1 Formation of Carbocations in Microdroplets

Our study reveals that carbocations can form more readily in microdroplets than in bulk aqueous solutions. This enhanced formation is likely due to the unique physic- ochemical environment of microdroplets, including high surface-to-volume ratios, electric field effects, and the presence of interfaces that can stabilize or destabilize intermediates. The confinement within microdroplets may also lead to higher local concentrations of reactants, thereby promoting carbocation formation.

6.2 Stability of Carbocations

Contrary to the traditional view that carbocations are highly unstable in aqueous environments due to rapid hydration and subsequent rearrangement or elimination, our findings indicate that certain carbocations exhibit surprising stability within microdroplets. This stability is attributed to several factors, including:

1. **Surface Effects**: The air-water interface in microdroplets may provide a stabilizing environment, reducing the likelihood of nucleophilic attack by water molecules.
2. **Electrostatic Effects**: The electric fields present at the microdroplet surface could stabilize the positive charge of the carbocations.
3. **Confinement**: The restricted environment of the microdroplet may limit the diffusion of water molecules, reducing the rate of hydration and subsequent decomposition of the carbocations.

6.3 Reactivity of Carbocations

The reactivity of carbocations in microdroplets displayed distinct differences from their behavior in bulk aqueous solutions. Notably:

- **Enhanced Reactivity**: Certain carbocations showed enhanced reactivity towards nucleophiles, likely due to the increased local concentration of reactants within the confined microdroplet environment.
- **Selective Reactions**: The unique environment of microdroplets facilitated selective reactions that are less favorable in bulk solution, suggesting that microdroplets can influence reaction pathways and product distributions.

7 Implications and Future Directions

These findings have significant implications for our understanding of reaction mecha- nisms and the role of microenvironments in chemical processes. The stabilization and reactivity of carbocations within microdroplets open new avenues for studying and harnessing these intermediates in synthetic chemistry and catalysis. Future research should focus on:

1. **Mechanistic Studies**: Detailed mechanistic studies to elucidate the specific factors contributing to the stability and reactivity of carbocations in microdroplets.
2. **Application to Other Reactive Intermediates**: Extending the investigation to other reactive intermediates, such as radicals and carbenes, to explore the generalizability of our findings.
3. **Technological Advancements**: Developing new techniques and improving exist- ing methods for the detection and analysis of transient species in microenviron- ments.

8 Conclusion

In conclusion, the advancements in surface chemistry and mass spectrometric tech- niques have significantly enhanced the detection and characterization of reactive intermediates, such as carbocations. The ability to stabilize and observe these transient species in microdroplet environments opens new avenues for exploring complex chem- ical reactions and developing more efficient synthetic methodologies. The integration of surface-modified mass spectrometry into chemical analysis promises to revolution- ize our understanding of reaction mechanisms, leading to innovative applications in organic synthesis, catalysis, and beyond. The continued exploration of these techniques will undoubtedly contribute to the advancement of chemical science and technology.

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8.5 Code availability: Not applicable

8.6 Author contribution

The sections of introduction and Spontaneous Transformation of Phenol to Phenyl Carbocations have been developed by Vanisha and Rest all the section have been worked on by himanshu bansal.

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