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Review

Reactive Oxygen Species at Water−Hydrophobic Interfaces: How Controversy Advanced Understanding

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ABSTRACT: Aqueous interfaces can support chemistry that differs markedly from bulk solutions. Reports that reactive oxygen species form at water−hydrophobic interfaces under ambient conditions have opened an exciting but controversial area of interfacial chemistry. Many objections have been raised, from chemical contaminants to instrumental artifacts and alternative reaction pathways. This Review examines how those challenges have reshaped the field. They have moved the discussion from whether unusual redox chemistry can occur at water interfaces to where reactive species originate, how they are detected, and which mechanisms operate in different experimental regimes.

KEYWORDS: *reactive oxygen species, aqueous interfaces, chemical contaminants, instrumental artifacts, redox chemistry, hydroxyl radicals*

INTRODUCTION

Hydroxyl radicals are among the most reactive species in chemistry. Their formation is traditionally associated with ultraviolet excitation, ionizing radiation, electrical discharges, or transition-metal-mediated processes such as Fenton chemistry. Consequently, the suggestion that hydroxyl radicals could arise spontaneously at water−hydrophobic interfaces under ambient conditions was initially met with considerable skepticism. Although hydroxyl radicals dominated the early debate, subsequent studies have broadened the discussion to include a larger family of reactive oxygen species, such as hydrogen peroxide, singlet oxygen, superoxide, and water-derived radical cations.

The controversy was sparked by experiments from the Zare laboratory, beginning in 2019, in which Lee and co-workers reported evidence for hydroxyl-radical formation in pure water microdroplets.[1−4] An ion later observed at m/z 36 was assigned to the hydrogen-bonded complex $(H_3O^+{-}OH^\bullet)$,[5] which is also called the water dimer radical cation, $[(H_2O)_2]^{+\bullet}$,[6] and independent measurements revealed hydrogen peroxide (H_2O_2) and oxidation products characteristic of hydroxyl-radical chemistry. Because no external oxidant, catalyst, or irradiation source was intentionally introduced, these observations challenged conventional expectations regarding the chemical inertness of water. Figure 1 shows one fluorescence-based approach applied to detect H_2O_2 generation at water−hydrophobic interfaces, illustrating that smaller droplets are more reactive in generating H_2O_2.[7]

Over the following years, the initial interpretation encountered a succession of objections. Atmospheric ozone was proposed as the source of oxidation chemistry.[8,9] Another claim was pointing to ultrasonication as the only source of hydrogen peroxide.[10] Subsequently, the identity of the m/z 36 ion itself was questioned, with ammonia contamination suggested as an alternative explanation.[11,12] More recently, electrical discharges accompanying droplet formation were invoked as a source of reactive oxygen species.[13] Still other investigators proposed that some of the chemistry might arise inside the mass spectrometer rather than within the droplets themselves.[14]

Far from ending the discussion, these criticisms stimulated increasingly sophisticated experiments that combined orthogonal analytical methods, including spin trapping, fluorescence probes, nuclear magnetic resonance, isotopic substitution, and tandem mass spectrometry, with new interfacial platforms such as microbubbles, hydrophobic surfaces, soap films, and levitated droplets. Consequently, the scientific question has evolved from the detection of hydroxyl radicals and related ROS in interfacial water systems to the deeper mechanistic questions of where they originate, how they are spatially localized, and which pathways dominate under different experimental conditions. In retrospect, this controversy provides an instructive example of how skepticism, careful experimentation, and competing interpretations can advance scientific understanding.

THE INITIAL OBSERVATION

Interest in unusual chemical reactivity at aqueous interfaces emerged from the observation in the Cooks laboratory that reactions in microdroplets frequently proceed much faster than in bulk solution.[15−18] Lee and co-workers reported evidence that pure water microdroplets could generate hydroxyl radicals under ambient conditions. The principal observation was an ion at m/z 36, assigned to $(H_3O^+{-}OH^\bullet)$,[5,19] together with the

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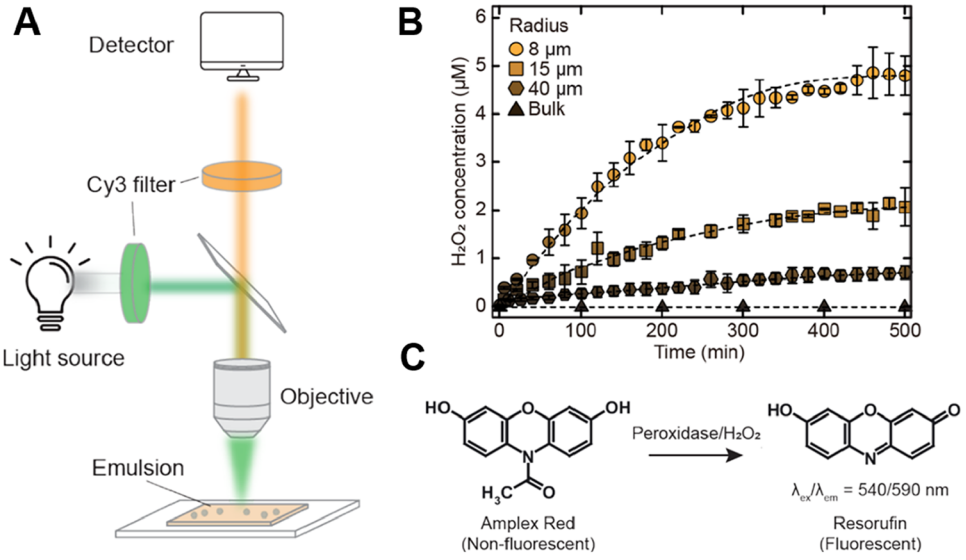

Figure 1. Detection of hydrogen peroxide generation at water–hydrophobic interfaces. (A) Fluorescence microscopy setup for monitoring H_2O_2 formation in water-in-oil emulsion droplets. (B) Time-dependent H_2O_2 formation for droplets of different radii and for bulk solution, showing greater peroxide accumulation in smaller droplets. (C) Amplex red assay in which H_2O_2, in the presence of peroxidase, converts nonfluorescent amplex red to fluorescent resorufin. Adapted with permission from ref 7. Copyright 2025 American Chemical Society.

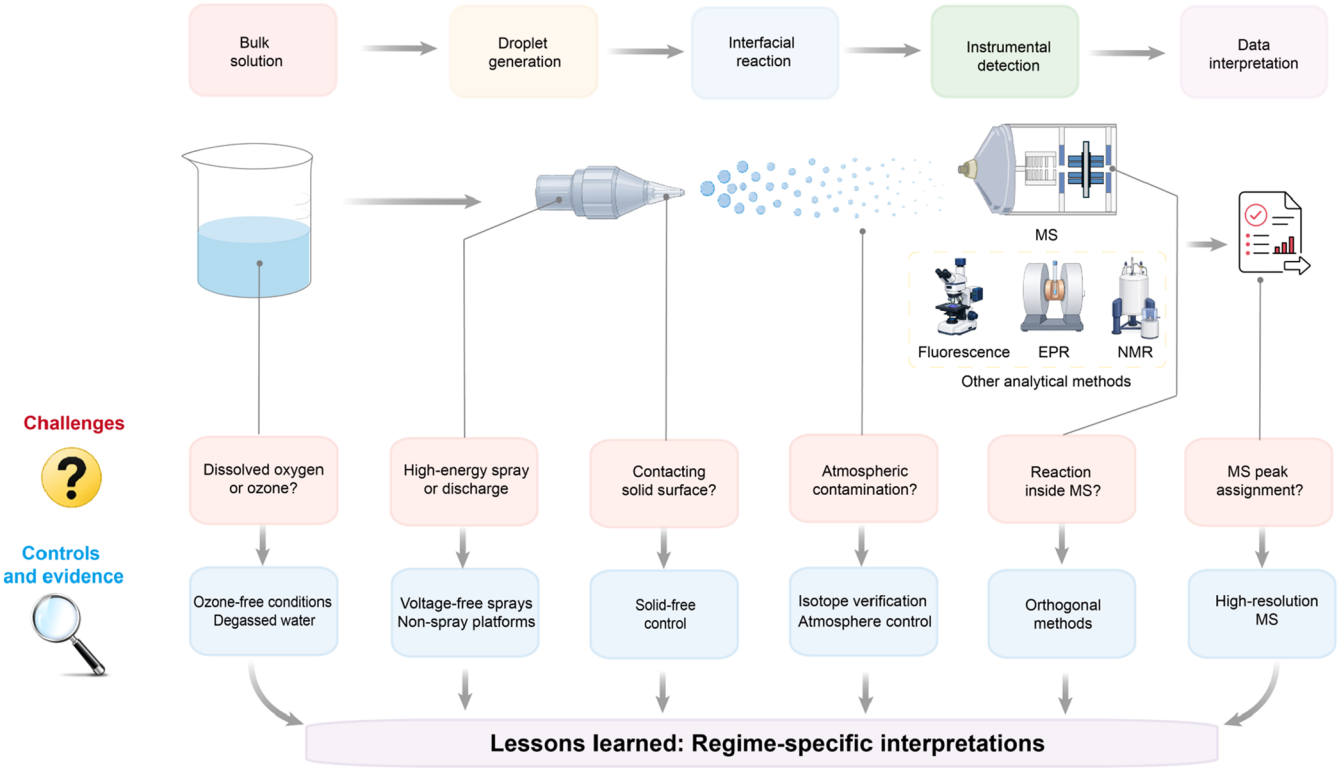

Figure 2. Workflow, challenges, and controls for evaluating ROS formation at water–hydrophobic interfaces. Proposed artifacts or alternative pathways can arise during droplet generation, interfacial reaction, instrumental detection, and data interpretation. The corresponding controls help distinguish high-energy spray or mass-spectrometric effects from regime-specific interfacial chemistry.

detection of hydrogen peroxide and oxidation products characteristic of hydroxyl-radical chemistry.

The claim was provocative because no external oxidant, catalyst, or irradiation source was supplied. The work suggested that the distinctive environment of the water-hydrophobic interface, where hydrogen bonding is necessarily incomplete and strong local electric fields exist,[20−24] could promote charge separation, electron transfer, and radical formation. Although these ideas were consistent with growing appreciation of the special properties of interfaces, many investigators questioned whether the observations might instead arise from extrinsic artifacts (Figure 2).

The following sections examine these challenges in a regime-specific way. Each case is considered in terms of why the concern arose, what evidence limits its scope, and what questions remain unresolved.

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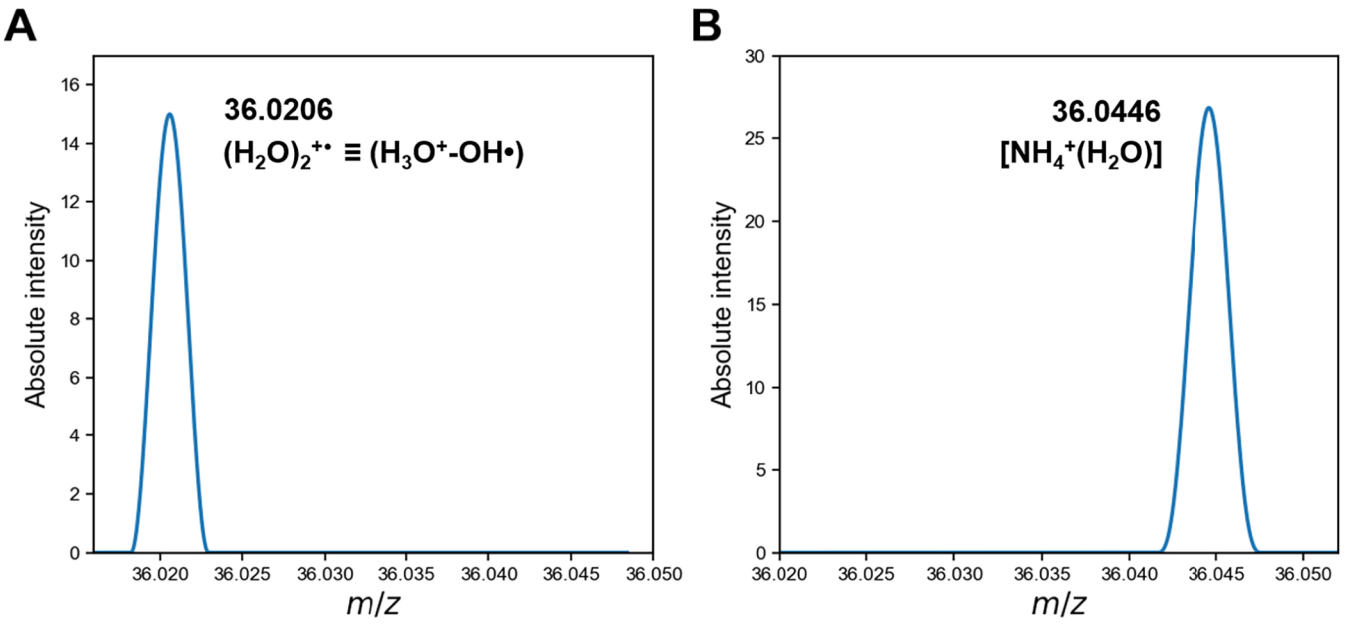

Figure 3. High-resolution mass spectra of (A) sprayed pure water and (B) sprayed water in contact with ammonia vapor.

THE OZONE CHALLENGE

One of the earliest objections focused on atmospheric ozone. Because ozone is a potent oxidant and is ubiquitously present in air, it was proposed that ozone dissolved in water, rather than intrinsic interfacial processes, might account for the observed hydrogen peroxide and oxidation products.[8,9]

This possibility deserved careful consideration. Indeed, the history of chemistry contains many examples in which trace contaminants masqueraded as new phenomena. The ozone hypothesis therefore stimulated experiments designed to control gas composition, minimize atmospheric contamination, and compare different droplet-generation conditions. Measurements performed under dark, ozone-free conditions with degassed water, and under controlled gas environments revealed trends that are difficult to reconcile with ozone contamination alone. Peroxide formation persisted when ozone was minimized, and the yield depended on droplet or interfacial geometry rather than simply on ambient-air exposure. These observations do not exclude ozone chemistry in all settings, but they show that ambient ozone alone cannot account for the broader set of results.[3,25,26] Although ozone may contribute under some circumstances, ambient ozone alone cannot account for the broader set of observations obtained across different laboratories, platforms, and analytical methods.

Thus, the ozone controversy, rather than invalidating the original observations, led to more rigorous controls and a deeper appreciation of the role of dissolved gases in interfacial chemistry. More broadly, recent work has shown that ozone can participate productively in interfacial microdroplet chemistry.[27−29] As will be discussed later, ozone can be generated through electrical discharge between microdroplets.[30] For example, replacing nitrogen with air or oxygen can markedly increase the observed hydrogen peroxide yield.[31,32] This controversy helped shift the role of gas-phase species from uncontrolled contaminants to variables that can be deliberately controlled in interfacial reaction studies.

THE AMMONIA CHALLENGE

A second controversy concerned the identity of the ion at nominal m/z 36. This peak in low-resolution mass spectra is frequently observed when water microdroplets are sprayed into air. Several studies suggested that ammonium-containing clusters, particularly $[NH_4^+(H_2O)]$, arising from ubiquitous atmospheric ammonia contamination, might contribute to or even dominate this signal originally assigned to $(H_3O^+{-}OH^\bullet)$.[11,12,33] This proposal emphasized an important principle in mass spectrometry: identical nominal masses observed at low mass resolution do not necessarily correspond to identical chemical species. When pure water is sprayed into air, high-resolution mass spectrometry (HRMS) shows a distinct peak at m/z = 36.0206 (consistent with the result from Chen and co-workers[34]) from $(H_3O^+{-}OH^\bullet)$ and no detectable peak at m/z = 36.0444 from $[NH_4^+(H_2O)]$, as shown in Figure 3A. The ammonium-water cluster observed at m/z 36.0446 becomes prominent only when the droplet plume is deliberately exposed to ammonia vapor (Figure 3B). Experimental and processing details for the spectra in Figure 3 are provided in Supporting Information.

The challenge also prompted investigations using isotopic substitution, tandem mass spectrometry, temperature variation, salt effects, gas-purging experiments, and comparisons across droplet-generation methods. These studies revealed a more complicated picture than originally appreciated. Ammonia-associated ions can contribute under some conditions, particularly when a higher ammonia concentration is present or when ionization conditions favor hydrated ammonium clusters. However, subsequent work demonstrated that ammonia contamination alone cannot account for the broad range of observations,[34−38] including isotope effects and independent measurements based on fluorescence probes,[25] spin trapping,[39] nuclear magnetic resonance (NMR),[40] and chemical reactivity.[2,18] More recent work further suggests that nominal m/z 36 should be interpreted in relation to the experimental regime in which it is produced, including water source, sample history, ion-transfer conditions, hydrogen−deuterium exchange (HDX) and other isotopic behaviors[41]

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(see Supporting Information), and neighboring ion signatures, rather than as a single condition-independent contamination marker.[35] An important lesson emerged from this debate: no single measurement should be expected to establish the existence of radicals unequivocally. Confidence instead arises from the convergence of multiple independent lines of evidence.

THE SOLID SURFACE CHALLENGE

It is proposed that ROS is only formed by water in contact with solid surfaces, such as metals, metal oxides, and silicon.[9,31,42] However, several counterexamples exist, such as the formation of H_2O_2 at the water−oil interface,[43] bubble interface,[44] or container-free levitated water droplets.[45] Metal-free hydrophobic polystyrene−divinylbenzene resins also generate H_2O_2 under ambient stirring, with isotope labeling identifying O_2 as the predominant oxygen source.[46] In a recent water−molten-polymer study, an all-PTFE control showed an $^{\bullet}OH$ production driven by microdroplets. It also reported no change in $^{\bullet}OH$-mediated reactions after matched metal additions in bulk solutions.[47] Together, these results support ROS production without solid−water contact.

THE DISCHARGE CHALLENGE

It has been claimed[48,49] that only negatively charged droplets can induce ROS production, but it has been shown that both negatively and positively charged droplets yield ROS.[50] A more recent proposal[13] attributed radical formation to electrical discharges associated with droplet generation. High electric fields, corona discharges, and microscopic spark events are well-known to produce reactive oxygen species, making this explanation plausible for electrospray systems.

Unlike earlier objections, however, the discharge hypothesis did not deny the existence of hydroxyl radicals. Instead, it addressed their origin.[13,48] Experiments demonstrated that electrical discharges can indeed generate hydroxyl radicals under certain circumstances, emphasizing the importance of electrohydrodynamic processes accompanying droplet formation.

Ironically, these studies are related to an unexpected discovery. Investigations of charge separation and droplet interactions led to the observation of microscopic electrical discharges between droplets and bubbles carrying different amounts of charge. These events, termed "microlightning," were accompanied by photon emission and were found to drive chemical transformations resembling those observed in the classical Miller−Urey experiment.[51] Related microlightning chemistry has also been shown to initiate a wide range of oxidation in water droplets and gas bubbles in water, suggesting that transient electrical events can couple charge transfer, gas-phase oxidants, and interfacial reaction pathways.[30,52,53] Microlightning has subsequently been implicated in sulfur transformations in seawater[54,55] and has been proposed as a possible contributor to prebiotic chemistry on the early Earth.[51]

At the same time, ROS chemistry has been observed in systems lacking electrospray conditions, including microbubbles,[44,56,57] hydrophobic microfilms,[58] biomolecular condensates in cells,[59−66] rain,[40] dewdrops driving the flowering of plants,[67,68] and droplets generated without externally applied voltages.[45,69] Such observations suggest that electrical discharges constitute one pathway among several rather than a universal explanation.

WERE THE REACTIONS PRODUCED INSIDE THE MASS SPECTROMETER?

Because mass spectrometry has served as the principal analytical tool in many studies, some investigators suggested that chemistry itself might occur inside the instrument. According to this view, collisions with atmospheric interfaces or ion optics might create reaction products absent from the original droplets.[14]

Several observations argue against this interpretation. Product abundances frequently increase with flight time prior to entering the mass spectrometer, indicating that reactions occur in droplets before sampling.[70] Moreover, analogous chemistry has been detected by other means than mass spectrometry, as discussed above. These observations suggest that mass spectrometry serves primarily as a sensitive window into interfacial chemistry rather than its source.

CONVERGENT EVIDENCE FROM INDEPENDENT METHODS

The strongest argument for interfacial reactive-oxygen chemistry rests not on any single measurement but on the consistent results obtained from independent techniques that do not share the same sources of error. For example, hydrogen peroxide has been quantified by interference-free ^1H NMR, including under rigorously ozone-free conditions;[26,40] by single-droplet electrochemistry at a platinum ultramicroelectrode, a method that requires neither mass spectrometry nor electrospray;[71] and by time-resolved fluorescence of individual droplets confined to a surface, which localizes the generation rate at the droplet interface itself.[72] Hydroxyl radicals have likewise been probed by methods beyond the disputed m/z 36 assignment. They can be trapped as fluorescent adducts in dark, ozone-free chambers,[25] detected by surface-enhanced Raman nanosensors,[73] and distinguished from superoxide by electron paramagnetic resonance using appropriate spin traps.[74] This interfacial chemistry also oxidizes organic aerosol particles in darkness,[75] and across these studies the measured yields vary with physical parameters, such as relative humidity,[76−79] solution pH,[80] and specific-ion effects,[81] without correlation with a contaminant signal.

The strength of this case lies precisely in what the methods do not share. NMR and electrochemistry techniques are insensitive to the disputed m/z 36 ion; the condensation[3] and soap-film[58] techniques involve no spray, nozzle, or applied potential; and the characteristic dependence of yield on interfacial curvature is common to each one.[7,82] Moreover, the phenomenon is not restricted to a single laboratory. The spontaneous generation of peroxides and their resulting oxidative ability has been independently confirmed by single-droplet electrochemistry on sonicated emulsions,[83] by high-throughput imaging of individual droplets,[84] by calibrated redox probes,[85] and by detailed studies of ionization and reaction in charged microdroplets.[86] No single proposed artifact appears sufficient to rationalize the full range of reported observations. At the same time, different proposed artifacts or alternative pathways may contribute to different points in the experimental workflow and with different importance across experimental regimes. It is therefore essential to compare platforms, identify where reactive species are generated, and distinguish intrinsic interfacial chemistry from contributions introduced during generation, transport, or detection.

TOWARD A UNIFIED PICTURE

Viewed historically, each of the challenges described above sharpened a different aspect of the problem. The ozone challenge emphasized the need to control gas-phase composition and trace oxidants. The ammonia controversy

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underscored the need for rigorous mass-spectral assignments and orthogonal methods of detection. The discharge hypothesis highlighted the role of charge separation, electric fields, and electrohydrodynamic phenomena. The possibility of in-source chemistry emphasized the need to distinguish reactions occurring before sampling from those introduced during detection. The emerging picture is unlikely to be governed by a single universal mechanism. Instead, hydroxyl-radical formation appears to depend on multiple factors, including curvature,[7] dissolved gases,[31] ionic composition,[87] charge separation,[88] and, under some circumstances, electrical discharges.[13,48] Such complexity is perhaps unsurprising given the extraordinary heterogeneity of water interfaces.

The question has therefore evolved from asking whether hydroxyl radicals exist at water−hydrophobic interfaces to understanding the conditions under which they form and the mechanisms responsible. In this sense, controversy has served not as an impediment to progress but as its catalyst.

TWO REGIMES OF REACTIVE-OXYGEN CHEMISTRY

Much of the apparent contradiction disappears once physically distinct systems are treated separately rather than grouped together. At one extreme lie strongly activated configurations: high-voltage nanoelectrospray and atmospheric-sampling inlets can themselves accelerate and ionize otherwise neutral droplets to very high energies, generating reactive ions through discharge and other high-energy processes.[14] In such systems the measurement may itself produce part of the chemistry it records. At the other extreme lie minimally perturbed systems that nevertheless generate reactive oxygen species: water vapor condensed onto cold, inert substrates,[3] stationary soap films,[58] acoustically levitated droplets,[45] and contactless, unactivated droplets,[69] none of which involve a spray, a nozzle, or an applied potential. A result obtained in one regime cannot be assumed to carry over to another. Across these regimes, ROS formation from stable molecular species still requires a driving force. In minimally perturbed systems, the key question is how local interfacial processes can provide this driving force without an imposed macroscopic voltage or obvious high-energy activation. O_2-dependence should be interpreted in this context. Dissolved O_2 is not itself the origin of the interfacial driving force, but it provides an available electron-accepting channel for peroxide formation. Replacing nitrogen with air or oxygen measurably increases the peroxide yield,[26] showing that O_2 participates directly in this pathway. Because dissolved and gas-phase O_2 is nearly ubiquitous in water exposed to air, its role differs from that of trace contaminants such as ammonia. Its participation therefore reframes the central claim rather than refuting it: the mechanistic question becomes how charge separation and electron transfer at the interface are coupled to O_2 reduction. Recent Marcus-type treatments of interfacial electron transfer, including tunneling effects, provide a possible kinetic framework for this O_2-dependent pathway, with interfacial OH^- serving as the electron donor and O_2 as the electron acceptor.[89,90] This kinetic picture is also consistent with an important quantitative convergence between independent NMR studies. Although the two studies differed in mechanistic interpretation, both reported H_2O_2 formation in the same low-micromolar range under O_2-rich nebulization conditions: 2.00 ± 0.05 μM from the Zare study and 3.0 ± 0.2 μM from the Mishra study.[9,26] This agreement shifts the emphasis from whether peroxide can be detected under these conditions to how O_2-dependent interfacial redox chemistry is initiated and sustained. Other regime-specific pathways should be considered separately; for example, cavitation occurs in mists generated by ultrasound[10] or liquid−solid contact.[9,31,42]

BEYOND THE HYDROXYL RADICAL

Despite the focus of the early controversy on hydroxyl radicals, the discussion has broadened to a larger family of reactive oxygen species and related redox intermediates. Hydrogen peroxide remains the species for which the strongest quantitative evidence exists.[1−4] Singlet oxygen has been reported to form at the air−water interface under dark conditions,[91] while superoxide has been implicated by spin-trapping experiments.[74] Water-derived radical ions, including the water dimer radical cation, have also been detected and characterized by high-resolution mass spectrometry (Figure 3) and electron paramagnetic resonance.[34] In addition, paired water radical cation/anion chemistry has been proposed to enable simultaneous oxidation and reduction within a single droplet,[92] linking interfacial radical chemistry to broader redox reactivity rather than to a single oxidizing species.

This expansion shifts the question from whether a single radical is present to how interfacial environments distribute reactivity among multiple oxidative and reductive pathways. The relative importance of these species likely depends on oxygen availability, charge state, pH, salt composition, interface type, droplet or bubble generation method, and detection conditions. In this sense, the hydroxyl-radical controversy opened a broader inquiry into interfacial redox chemistry rather than ending with the assignment of any one reactive intermediate.

These mechanisms have come to be described in a common mechanistic framework. Separation of charges through contact electrification that accompanies the formation of droplets results in strong interfacial electrical fields,[79] which have been observed in Stark-effect measurements and probe-free interfacial electric-field measurement by 3D TEM[23] as well as confirmed by simulation;[21] their function in the redox chemistry has been examined in detail,[93] and their magnitude has been measured directly at oil−water interfaces.[22] Disrupted hydrogen bonding at the surface, partial solvation,[88,94,95] along with these electric fields, lowers the barrier to the interfacial electron transfer $H^+ + OH^- \rightarrow {}^{\bullet}H + {}^{\bullet}OH$.[88,95−97] Recombination of hydroxyl radicals leads to the production of hydrogen peroxide, while O_2 undergoes reductions leading to the formation of superoxide and singlet oxygen,[27,91] in addition to a water radical cation formed with a solvated electron. Curvature unifies these phenomena: as a droplet contracts, its interfacial field intensifies and the yield of reactive species rises accordingly.[7,82] Spectroscopic measurements on planar air−water interfaces show no strong, long-lived electric fields,[98] which is consistent with a lack of interfacial curvature.

OUTLOOK

What began as a dispute over a mass-spectral assignment has become a broader investigation of where reactive oxygen species (ROS) form at water−hydrophobic interfaces and which pathways dominate under different conditions. Successive challenges involving ozone, ammonia, electrical discharge, and in-source chemistry prompted more rigorous controls and orthogonal measurements. The result is a more discriminating picture that separates intrinsic interfacial

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chemistry from contributions introduced during droplet generation, transport, or detection.[51,99]

This distinction also applies to energetic and kinetic arguments. Thermodynamic analyses based on homogeneous bulk reactions provide useful constraints, but they do not by themselves identify the operative pathway at a heterogeneous interface. The relevant question is which pathway is accessible in the local interfacial environment, where charge separation, solvation asymmetry, dissolved gases, and geometry can change both the driving force and the rate of electron transfer.

This developing understanding creates opportunities in atmospheric and environmental chemistry, prebiotic synthesis, and interfacial catalysis.[51,100−104] The central question is therefore no longer confined to the identity of one radical or one signal. It is why water−hydrophobic interfaces are chemically active and what additional reactivity may emerge from the same physical conditions.

BROADER IMPLICATIONS: WATER−HYDROPHOBIC INTERFACES AS REACTIVE ENVIRONMENTS

Bulk water is often treated as an electrically neutral solvent, but that description becomes incomplete at an interface. Hydrogen bonding is disrupted, solvation becomes asymmetric, and ions and dipoles acquire nonuniform distributions. Even interfacial pH is therefore experimentally and conceptually subtle.[15,105−107]

These coupled changes can generate strong local electric fields and promote charge separation, including through contact electrification when water encounters a hydrophobic phase.[108−111] Electrostatics is thus not merely a boundary condition; together with altered hydrogen bonding and solvation, it can reshape the energetics of interfacial electron transfer.

One proposed elementary step is electron transfer between H^+ and OH^- to form $^{\bullet}H$ and $^{\bullet}OH$, a process strongly disfavored in bulk water but potentially enabled at the interface by local electric fields, disrupted hydrogen bonding, and quantum tunneling.[89,90] The resulting radicals and related charge carriers can initiate secondary reactions with aqueous solutes or molecules in the adjoining hydrophobic phase. The interface is therefore not simply a dividing surface, but a region in which otherwise inaccessible chemical pathways may begin.[112]

Curvature provides an important geometric factor. Bending a polarized interface changes the cancellation of interfacial dipoles and charge distributions and can modify the local electric field. At the same time, curvature alters the surface-to-volume ratio, solute partitioning, gas exchange, diffusion distances, and the residence of short-lived intermediates. These coupled effects help explain why ROS formation and other reactions become more pronounced as droplets or bubbles become smaller and their curvature increases (Figure 1B).[7,82]

The implications extend beyond oxygen-centered chemistry. Microdroplet and microbubble systems have also been explored for the ambient formation of ammonia, nitrate, nitrite, and urea from nitrogen-containing gases.[32,113−116] Whether such reactions can be made efficient or scalable remains unresolved, but they illustrate the breadth of chemistry made possible where water meets a hydrophobic phase.

After years of scrutiny, the central conclusion no longer rests on a single mass-spectral peak, analytical method, or experimental platform. Ozone, ammonia, electrical discharge, and in-source chemistry may contribute to particular regimes, but none accounts for the full body of observations obtained across independent methods and interfacial systems. Taken together, the evidence convincingly shows that ROS are formed at water−hydrophobic interfaces. The remaining challenge is not simply to ask whether this chemistry occurs, but to determine how curvature, electric fields, contact electrification, charge separation, dissolved gases, and interfacial structures select the reactive species and govern their rates. Water−hydrophobic interfaces are not passive boundaries; they are reactive environments whose chemistry is shaped, and often amplified, by geometry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.6c11851.

Open-air nebulization experimental details; ammonia-vapor control experiments; high-resolution m/z 36 profile spectra and data processing details; hydrogen−deuterium exchange analysis; and isotope-labeled nitrogen and acetone-capture verification of ammonia generation (PDF)

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