Chemical Science

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Cite this: *Chem. Sci.*, 2019, **10**, 8253

Comment on "The chemical reactions in electrosprays of water do not always correspond to those at the pristine air–water interface" by A. Gallo Jr, A. S. F. Farinha, M. Dinis, A.-H. Emwas, A. Santana, R. J. Nielsen, W. A. Goddard III and H. Mishra, *Chem. Sci.*, 2019, 10, 2566

Agustín J. Colussi *[a] and Shinichi Enami [b]

Received 27th February 2019
Accepted 11th April 2019

DOI: 10.1039/c9sc00991d

rsc.li/chemical-science

Recently, Gallo *et al.* (*Chem. Sci.*, 2019, 10, 2566) investigated whether the previously reported oligomerization of isoprene vapor on the surface of pH < 4 water in an electrospray ionization (ESI) mass spectrometer (*J. Phys. Chem. A*, 2012, 116, 6027 and *Phys. Chem. Chem. Phys.*, 2018, 20, 15400) would also proceed in liquid isoprene–acidic water emulsions. Gallo *et al.* hypothesized that emulsified liquid isoprene would oligomerize on the surface of acidic water because, after all, isoprene, liquid or vapor, is always a hydrophobe. In their emulsion experiments, isoprene oligomers were to be detected by *ex situ* proton magnetic resonance (^{1}H-NMR) spectrometry.

Gallo *et al.*'s expectation did not pan out: ^{1}H-NMR spectrometry could not detect isoprene oligomers in the non-aqueous phases recovered from their emulsions. This seemingly disappointing outcome led Gallo *et al.* to speculate that "*reactions of isoprene in aqueous electrosprays (must be) driven by non-equilibrium conditions… due to the rapid evaporation of water leading to highly concentrated droplets and partially hydrated hydronium ions*".[1] Here, we explain that this speculation is a non sequitur because Gallo *et al.*'s failure to detect isoprene oligomers in their emulsion experiments was in fact to be expected.

Gallo *et al.*'s expectation that emulsified isoprene would be protonated and oligomerize "on water" (*i.e.*, at a molecularly thin liquid isoprene–water interface) ignores extensive studies on organic synthesis in water as a reaction medium.[4] These studies indicate that, given the significant mutual solubilities of water and liquid isoprene (see below), the interfacial boundary between these two liquids is diffuse. As a result, isoprene reactions in water emulsions take place "in water" rather than "on water". Therefore, the fundamental reason why isoprene oligomers were not formed in Gallo *et al.*'s "in water" experiments was the lack of the partially hydrated hydroniums that are thermodynamically required to protonate isoprene and initiate its cationic oligomerization.

In any case, even if isoprene had oligomerized to some extent in Gallo *et al.*'s emulsions, the "missing" ^{1}H-NMR isoprene oligomers signals strictly meant that isoprene oligomerization, if any, was undetectable by ^{1}H-NMR. As a rule, the absence of evidence is not evidence of absence.

For all these reasons, we consider that Gallo *et al.*'s negative results on isoprene oligomerization "in water" emulsion experiments are moot, if not irrelevant, about the oligomerization of gas-phase isoprene on the surface of pH < 4 water previously reported by our group.[2,3]

Gallo *et al.*'s implicit assumption of the chemical equivalence of gas-phase isoprene–water and liquid isoprene–water interfaces ignores that, in contrast with the sharp gas–water interfaces, the boundaries between partially soluble hydrophobic liquids and water are diffuse.[4] This is the case of the isoprene–water system. Available mutual solubility data indicate that in isoprene–water emulsions the aqueous phase is 10 mM in isoprene, and the hydrophobic phase (where Gallo *et al*. assumed isoprene would be protonated and oligomerize) is 15 mM in water at 300 K throughout.[5] At this concentration, it is well known that isoprene reactions in water emulsions take place "in-water" rather than "on-water".[4] These are hardly the conditions that would support the existence of the partially hydrated hydroniums needed to protonate isoprene.[6] Partially hydrated hydroniums, however, may conceivably exist under certain conditions at the sharp air–water interface, where the concentration of condensed water drops from 55.5 M to zero in ~1 nm, *i.e.*, within a couple of molecular diameters.[7] We concur with Gallo *et al.* that isoprene is a hydrophobe, only that there is more to chemistry than that.

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[a] *Linde Center for Global Environmental Science, California Institute of Technology, Pasadena, California 91125, USA. E-mail: ajcoluss@caltech.edu*

[b] *National Institute for Environmental Studies, 16-2 Onogawa, Tsukuba 305-8506, Japan*

Technical issues may have also adversely affected Gallo *et al.*'s ability to detect isoprene oligomers in their experiments. Even if isoprene had been protonated and oligomerized in water emulsions to some extent, ^{1}H-NMR may not have been the appropriate technique to track these processes. The reason is that in Gallo *et al.*'s hands, ^{1}H-NMR was four orders of magnitude less sensitive than ESI-MS.[1] The intrinsically lower sensitivity of ^{1}H-NMR spectrometry *vs.* ESI-MS would have been further compounded in their experiments by the fact that any of the isoprene oligomers that could have been formed at the putative isoprene–water interface would have been diluted into the bulk of the recovered hydrophobic phase samples analyzed by ^{1}H-NMR. By assuming emulsified isoprene droplets of $\rho = 10$ μm radius, and interfacial layers $\delta = 1$ nm thick, the estimated dilution factor: $\gamma = 3\delta/\rho = 3 \times 10^{-4}$, would have decreased the relative sensitivity of ^{1}H-NMR by additional four orders of magnitude. Thus, since there is no reason to expect that the extent of isoprene oligomerization would be the same on gas–water and liquid–water interfaces it is apparent that, even after considering the long contact times of emulsion experiments, it would have been difficult to detect small concentrations of isoprene oligomers by ^{1}H-NMR.

Gas-phase ion thermodynamic data alone (*i.e.*, without recourse to *ab initio* calculations or molecular dynamics simulations) show that only partially hydrated hydronium ions can protonate gas-phase isoprene.[6,8] It seems neither necessary to invoke non-equilibrium effects at the air–water interface to envision the existence of partially hydrated hydroniums in the interfacial gas–water region where, as indicated above, the concentration of liquid water drops precipitously from 55.5 M to zero in ~1 nm under normal conditions.

Could partially hydrated hydroniums only be present in highly concentrated evaporating water droplets?[1] The droplets in question are those produced by aerodynamic nebulization of water microjets in the spraying chamber of ESI mass spectrometers.[9] Extensive studies have shown that the nebulization process generates primary micro-sized droplets (diameters < 10 μm),[10,11] which carry net charges produced in the statistical separation of anions from cations upon fragmentation of the liquid microjets.[12,13] Under the electric fields applied to deflect them towards the entrance to the mass analyzer section, the residence times of charged microdroplets in the spraying chamber typically are a few milliseconds. Quite to the point, recent experiments revealed that in this time scale there is minimal evaporation from water microdroplets speeding at $\sim$80 m s^{-1} in dry air at 1 atm (*i.e.*, under typical ESI-MS conditions).[14]

The negligible evaporation of microdroplets in the spraying chamber means that they are not "highly acidic", *i.e.*, that their acidities largely remain those of the injected aqueous solutions. Therefore, the acidity of liquid microdroplets in electrospray experiments is well defined, given by the pH measured in the bulk solutions prior to injection. It should be realized that this condition is otherwise implicit in the fact that the protonation of gas-phase isoprene and other gases on acidic water follows well-defined titration curves as functions of pH, with equivalence points at pH $\sim 3.5 \pm 0.5$.[2,14,15] Mist of microdroplets of random sizes undergoing significant evaporation, in contrast, would not be expected to have well-defined acidities.

In addition, if the interfacial protonation of the weak base gas-phase isoprene (proton affinity = 826.4 kJ mol^{-1})[8] were due to "*the rapid evaporation of water leading to highly concentrated droplets and partially hydrated hydronium ions*", then stronger gas-phase bases should be protonated on less acidic water. However, both gas-phase trimethylamine,[16] a much stronger base (proton affinity = 981.8 kJ mol^{-1}) than isoprene,[8] and the very weak gas-phase base hexanoic acid[17] (proton affinity $\sim$ 791 kJ mol^{-1})[18] are also protonated on the surface of pH < 4 water. Together, these findings strongly suggest the emergence of significant concentrations of efficient proton donors, the "partially hydrated hydroniums", to the surface of pH < 4 water.[19] Note that the pH (hydronium activity) of the air–water interface is identical to the pH of bulk water (as required by thermodynamics),[20] but the concentration and reactivity of interfacial hydroniums can be different from the fully hydrated hydroniums in bulk water.

Regarding the occurrence of gas-phase ion–molecule reactions in our isoprene oligomerization experiments on the surface of pH < 4 water,[2,15,21] we want to call attention to the lack of protonated isoprene monomer and oligomer signals in the ESI mass spectra of 1 mM isoprene *dissolved* in a 1 : 1 (v/v) water–acetonitrile mixture in the $1.9 \leq \text{pH} \leq 4.6$ range.[2,3] The fact that isoprene was not protonated in these experiments, in which *both isoprene and acidic water were present*, excludes gas-phase ion–molecule reactions in our ESI mass spectrometer. It further demonstrates that dissolved isoprene is not protonated on the liquid side of the gas–water interface. Incidentally, since water is known to inhibit cationic polymerizations,[22] the fact that the polymerization of gas-phase isoprene proceeds at all on the surface of pH < 4 water is additional, albeit indirect, evidence of the low concentration of water on the gas-side of the interface.

Regarding the possible effects of electric fields in electrospray experiments on isoprene oligomerization, we have found that neither the polarization voltage nor the drying gas temperature in the heated capillary section of the mass analyzer influence oligomer distributions in the 1.5 kV to 4.0 kV, 150 °C to 350 °C ranges.[3] Furthermore, we found that in our experimental setup under our operating conditions, the applied electric fields only affect the residence time of charged microdroplets in the spraying chamber of the mass spectrometer.[23,24] Nebulizer gas velocities, in contrast, have a significant and predictable effect on absolute and relative ion signal intensities,[9] confirming that droplet charging is largely an aerodynamic rather than a purely electrodynamic phenomenon.

Finally, it is essential to understand that the expression "electrospray ionization mass spectrometers" designates a class rather than a single type of instrument. The main differences between different instruments reside in the configuration and operating conditions of the many available ion sources.[25] Therefore, results obtained under particular conditions must be validated by ancillary experiments, as we have done in the case the interfacial oligomerization of gas-phase isoprene.[2,3] For this reason, we abstain from speculating about Gallo *et al.*, electrospray measurements performed by polarizing the liquid injector at 6 kV to 8 kV relative to the grounded entrance to the mass analyzer.[1] These conditions are quite different from our experiments in which the entrance to the mass analyzer was polarized to ≤4 kV relative to the grounded liquid injector.

From the preceding considerations, we conclude that Gallo *et al.*'s statement: "*experimental and theoretical results demonstrate that chemistries in aqueous electrosprays do not necessarily correspond to those at the pristine air–water interface and oil–water emulsions at NTP. These findings also contradict the previous claims of the superacidity of the pristine air–water interface as the bulk acidity approaches pH* $\sim$ *3.6*"[1] is an unwarranted conjecture drawn from an erroneous interpretation of their own results due to the oversight of basic concepts and available information.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

AJC acknowledges support from the National Science Foundation USA, grant AGS-1744353. SE acknowledges support from the JSPS KAKENHI grant numbers 15H05328, 15K12188 and 19H01154. We are indebted to Dr Marcelo I. Guzman (University of Kentucky) and Dr Shinnosuke Ishizuka (NIES) for valuable critical comments.

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