Superacid Chemistry on Mildly Acidic Water

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# Superacid Chemistry on Mildly Acidic Water

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ABSTRACT The mechanism of proton transfer across water−hydrophobic media boundaries is investigated in experiments in which the protonation of gaseous *n*-hexanoic acid (PCOOH) upon collision with liquid water microjets is monitored by online electrospray mass spectrometry as a function of pH. Although PCOOH(aq) is a very weak base ($pK_{BH^+} < -3$), PCOOH(g) is converted to $PC(OH)_2^+$ on pH < 4 water via a process that ostensibly retains some of the exoergicity of its gas-phase counterpart, $PCOOH + H_3O^+ = PC(OH)_2^+ + H_2O$, $\Delta G < -22$ kcal mol^{-1}. The large kinetic isotope effects observed on H_2O/D_2O microjets, $PC(OH)_2^+/PC(OH)OD^+ = 88$ and $PC(OH)OD^+/PC(OD)_2^+ = 156$ at pD = 2, and their inverse dependences on pH indicate that PCOOH(g) hydronation on water (1) involves tunneling, (2) is faster than H-isotope exchange, and (3) is progressively confined to the outermost layers as water becomes more acidic. Proton transfers across steep water density gradients appear to be promoted by both dynamic and thermodynamic factors.

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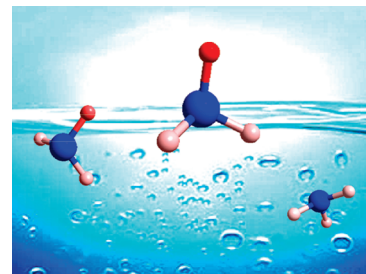
Various classes of chemical reactions have been found to proceed faster and/or along different pathways at water boundaries with hydrophobic phases.[1−4] These phenomena have been tentatively ascribed to the peculiar structure or acidity of interfacial water.[5−9] Herein, we advance the notion that they are due both to the onset of favorable thermochemistry and to the unique dynamics of proton transfer under steep water density gradients. We point out that these two conditions should generally arise during catalytic events within enzyme active sites.[10−19]

In the laboratory, Brönsted acidity scales are based on proton activity relative to a realizable standard state, or the position of equilibria among conjugated acid/base pairs. Uniform proton activity/chemical potential across phases in thermodynamic equilibrium ensures that local acidity (defined, e.g., as the pH of bulk water relative to a local standard state) is a global acidity, even at water boundaries of widths commensurate with the range of intermolecular forces.[20,21] The acidity of interfacial water is therefore identical to the acidity of bulk water (in the same standard state). Alternatively, A is said to be a stronger (Brönsted) acid than B in any given medium if protons would bind preferentially to B. Because hydronium, H_3O^+, can protonate most organic compounds in the gas phase (reaction R1)[22,23] but only relatively strong bases in bulk water (reaction R2)[24,25]

$$B(g) + H_3O^+(g) \rightarrow BH^+(g) + H_2O(g) \qquad (R1)$$

$$B(aq) + H_3O^+(aq) \rightarrow BH^+(aq) + H_2O(l) \qquad (R2)$$
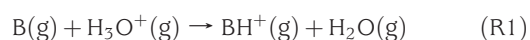
it is apparent that the extent of protonation of Brönsted acids and bases on water's surface is determined not only by (global) acidity but, critically, by their hydration status therein. It is a remarkable fact that most nonalkanes have

gas-phase basicities (GB) larger than H_2O, GB(B) > GB(H_2O) = 158 kcal mol^{-1},[26] and are readily protonated by H_3O^+(g), as evinced by the versatility of proton-transfer reaction mass spectrometry.[27] The larger stabilities of $(H_2O)_n \cdot H_3O^+$ versus $(H_2O)_n \cdot BH^+$ clusters,[28] however, render the free energies of reactions that generate, annihilate, or interconvert charged species at water's surfaces (such as reaction R3) sensitive functions of *n* or, equivalently, of water density, ρ_w, particularly about $\rho_w \approx 0$.[29,30] The empirical eq E1 encodes such functionality

$$B(s) + H_3O^+(s) \rightarrow BH^+(s) + H_2O(s) \qquad (R3)$$
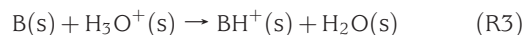
$$\Delta G_3(\rho_w) = \Delta G_1 + (\Delta G_2 - \Delta G_1)\rho_w{}^\alpha \qquad 0 < \alpha < 1 \quad (E1)$$

The exoergicity of gas-phase proton transfers, $\Delta G_1 = $ GB(H_2O) − GB(B) < 0, is therefore expected to be exquisitely tunable and eventually reversed with great economy of motion within interfacial layers. Our report underscores the importance of this phenomenon.

In a recent study, trimethylamine, Me_3N(g), a strong base both in bulk water ($pK_{BH^+} = 9.8$) and in the gas phase (GB = 227 kcal mol^{-1}), could be captured as Me_3NH^+(s) on water only at pH < 4 (rather than at pH < pK_{BH^+}) in a process clearly controlled by the unavailability of interfacial H_3O^+(s) in the pH > 4 range rather than by unfavorable thermochemistry.[5] It must be emphasized that such finding strictly implies that H_3O^+ actually emerges to the surface of pH < 4 water, where it can protonate impinging Me_3N(g) molecules during collision times (not that the surface of 4 < pH < 7

Scheme 1. Creation of a Microjet in the Spraying Chamber of an Electrospray Mass Spectrometer by Injecting Acidified Water through an Electrically Grounded Nebulizer[a]
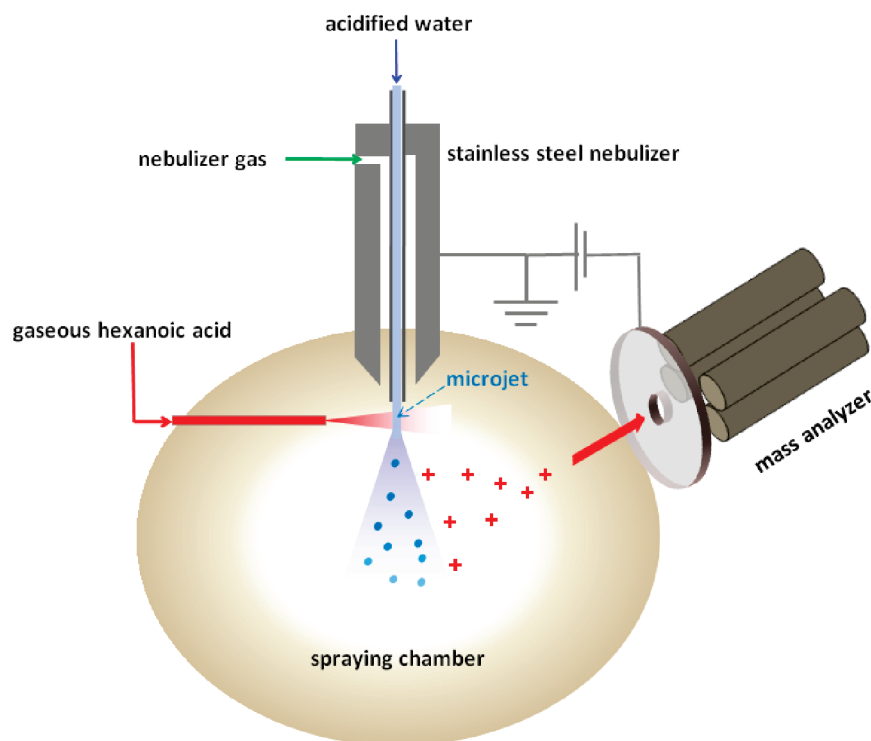
[a] The microjet is briefly exposed to hexanoic acid vapors before it is broken up (at ~10 μs) into charged microdroplets by the fast nebulizer gas. Upon subsequent solvent evaporation, ions in excess are ultimately ejected from the microdroplets via field desorption and detected by mass spectrometry within 1 ms.

water is necessarily "basic"). On the basis of the preceding considerations, herein, we explore the possibility that $H_3O^+(s)$ could protonate bases weaker than $Me_3N(g)$, that is, whether $H_3O^+(s)$ is a stronger proton donor than $H_3O^+(aq)$ of the same nominal acidity. In other words, we inquire whether the thermochemistry of reaction R3 approaches that of reaction R1 or R2 on water's surface.

We chose hexanoic acid, PCOOH, GB(PCOOH) = 187 kcal mol^{-1} > GB(H$_2$O),[26] pK_{BH^+} < −3,[31] as a suitable probe in experiments where reactive events on the surface of aqueous microjets exposed to PCOOH(g)/N$_2$(g) mixtures for ~10 μs are monitored by online electrospray ionization mass spectrometry (ESI-MS). A flow of 50 μL min^{-1} of water (whose pH had been adjusted using concentrated HCl) was injected as a liquid microjet via an electrically grounded pneumatic nozzle (bore diameter: 100 μm) into the spraying chamber of an ESI mass spectrometer held at 1 atm and 293 K (Scheme 1). The fast nebulizer gas (N$_2$) soon tore up the outer layers of the microjet into microdroplets carrying ion excesses of either sign.[32] Excess ions were eventually field-ejected to the gas phase from evaporating microdroplets, mass-analyzed, and detected within 1 ms. The PC(OH)$_2^+$ ESI-MS signals detected in these experiments therefore correspond to species produced on the outermost layers of the microjet upon brief exposure to PCOOH(g).[5,33] We had previously verified that this setup operates as a linear transfer device, that is, ESI-MS signals are directly

proportional to ion concentrations (up to a few mM) in the interfacial layers of the microjets prior to their breakup.[5,34] See Experimental Methods and Figure S1 in the Supporting Information, SI, for further details. The present study focuses on the evolution of PC(OH)$_2^+$ (m/z = 117) ESI signals as functions of pH and solvent deuteration.

Figure 1 shows the PC(OH)$_2^+$ ESI mass spectral m/z = 117 signal intensities, I_{117}, detected on (1) aqueous microjets exposed to 77 ppbv PCOOH(g) and (2) microjets containing 1 mM PCOOH(aq), as functions of the pH of the bulk liquid. If all PCOOH(g) collisions with the surface of microjets yielded PC(OH)$_2^+$, that is, its uptake coefficient were $\gamma \approx 1$, we estimate that < 1.5 × 10^{11} PC(OH)$_2^+$(s) cm^{-2} would be generated upon exposure to 77 ppbv PCOOH(g) for 10 μs.[5] As a reference, a 1 mM interfacial layer that is δ = 1 × 10^{-7} cm deep contains 6 × 10^{10} PCOOH(aq) cm^{-2}. It is apparent that the reactive uptake of PCOOH(g) via protonation approaches 100 % efficiency, whereas predissolved PCOOH(aq) (pK_{BH^+} < −3) is minimally protonated at pH > 1. We infer that PCOOH(g) is directly captured as PC(OH)$_2^+$(s) on the surface of pH < 4 water via proton transfer from H_3O^+(s) before it becomes hydrated. Thermochemical considerations suggest that most nonalkane gases could be similarly protonated on the surface of pH < 4 water, albeit, perhaps, at different rates. Competitive substrate protonation versus hydration at water−hydrophobic media interfaces is the key condition for H_3O^+(s) to manifest itself as a superacid.[35]
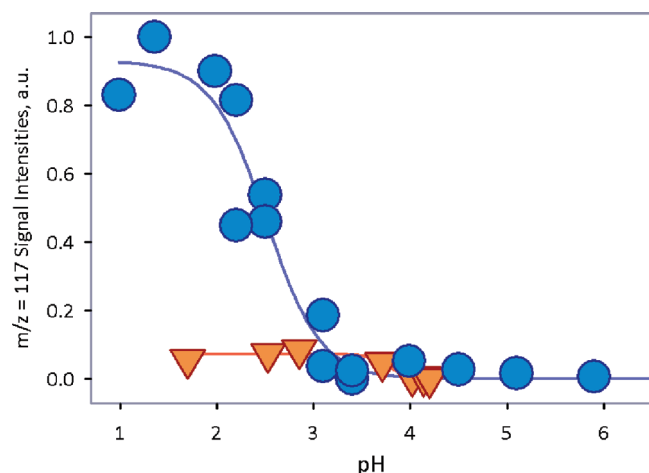
Figure 1. Protonation of hexanoic acid (PCOOH) on water. $PCOOH_2^+$ ESI-MS $m/z = 117$ signal intensities as functions of pH. Blue circles: Signals from $PCOOH_2^+$ produced on aqueous microjets exposed to 77 ppbv PCOOH(g) for 10 μs. The blue line is a titration curve with $pH_{1/2} = 2.5$. Tan triangles: $PCOOH_2^+$ signals from 1 mM PCOOH(aq) microjets. All experiments are in 1 atm of $N_2(g)$ at 293 K.

Scheme 2. Protonated Hexanoic Acid Tautomers (A and B) and the Product (C) of Their Collisionally Induced Dissociations (CIDs)
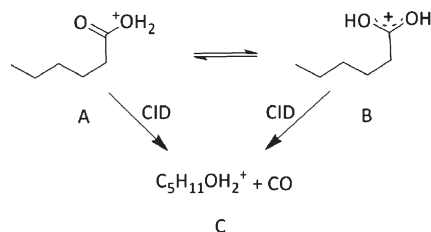
In this regard, we would like to point out that the probability of CH_3COOD H-isotope exchange on neutral $H_2O(l)$ is larger than that of its uptake,[36] suggesting that the hydration of polar acetic acid is already slower than interfacial H-exchange.

In our experiments, PCOOH(g) protonation via reaction R3 leads to oxonium (A) or carboxonium (B) species,[37] which fragment to the oxonium C ($m/z = 89$) via neutral CO losses (Scheme 2)[38] rather than into the acylium PCO^+ ($m/z = 99$, not shown) plus H_2O, as reported elsewhere.[39]

Figure 2 shows the mass spectrum obtained by exposing H_2O/D_2O (5/95) microjets at pD = 3.2 [pD = pH(measured) + 0.4] to PCOOH(g). It is apparent that the ratio of the isotopologues' raw signals, $\rho = PC(OH)_2^+/PC(OH)(OD)^+ \approx 2.78$, is much larger than that expected from the ratio of H/D abundances, H/D = 5/95 = 0.053, or from a process displaying a normal kinetic H-isotope effect KIE < 12,[40] $\rho < 12 \times 0.053 = 0.64$. Notice that $I_{119}:I_{118}:I_{117}/1:0.105:0.003$ signal intensities should be expected for fully exchanged hydronated PCOOH. KIE values, KIE = 0.053 × ρ(corrected), calculated from ratios of corrected experimental signal intensities, ρ(corrected) = I_{117}/I_{118}(corrected), as functions of pD are shown in Figure 3. I_{118}(corrected) takes into account the ^{13}C contribution of I_{117} to I_{118} signals, I_{118}(corrected) = I_{118}(measured) − 0.065 × I_{117}(measured).
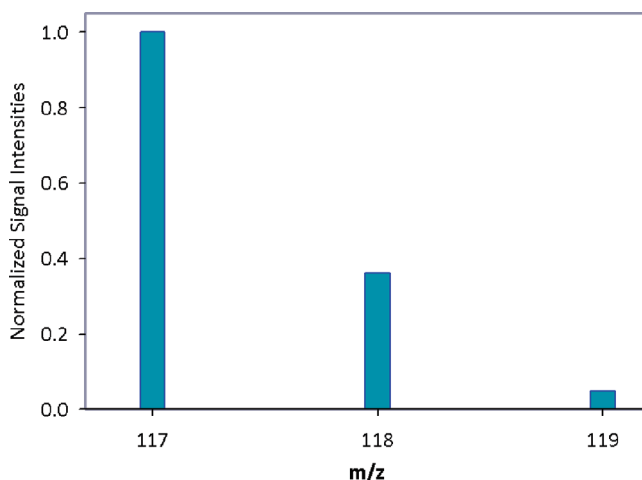
Figure 2. ESI mass spectrum of hydrated hexanoic acid, $m/z = 117$ [$PC(OH)_2^+$], 118 [$PC(OH)(OD)^+$], and 119 [$PC(OD)_2^+$], on H_2O/D_2O (5/95) microjets at pD = 3.2 exposed to 77 ppbv PCOOH(g). See text for details.
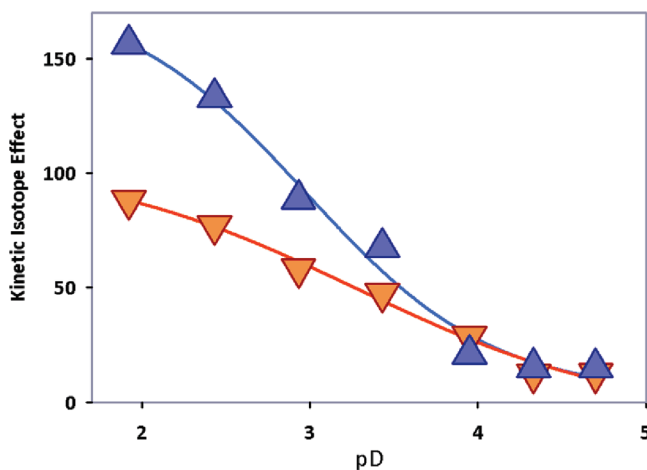

Figure 3. Kinetic isotope effects (KIEs) for the hydronation of gaseous hexanoic acid (PCOOH) on H_2O/D_2O (5/95) microjets exposed to 77 ppbv PCOOH(g) as functions of pD. Tan downward triangles and curve: KIE = (95/5) × I_{117}/I_{118}(corrected). Blue upward triangles and curve: KIE′ = (95/5) × I_{118}(corrected)/I_{119}(corrected). See text for details.

Noticeably, KIE′ = ρ'/0.053 values calculated from the ratio $\rho' = PC(OH)(OD)^+/PC(OD)_2^+ = I_{118}$(corrected)/$I_{119}$(corrected) become increasingly larger than KIE at lower pD, revealing that proton transfer becomes progressively faster than (neutral) H-atom exchange in more acidic water.

Our observations are consistent with the direct protonation of PCOOH(g) on the surface of water by minimally hydrated H_3O^+(s) (Figure 4). The thermochemistry of reaction R1 ultimately merges into that of reaction R2 via to the cumulative hydration energy differences between $(H_2O)_n \cdot H_3O^+$ and $(H_2O)_m \cdot PC(OH)_2^+$ cluster ions.[28] The exothermicity/exoergicity ($\Delta S_1 \approx \Delta S_2 \approx 0$) of reaction R1 gradually decreases as conditions shift from gas-phase ($\rho_w = 0$) to bulk water ($\rho_w = 1$ g cm^{-3}). The final outcome is that proton exchange between fully hydrated species becomes endothermic/endoergic. In essence, the protonation of PCOOH(aq) requires
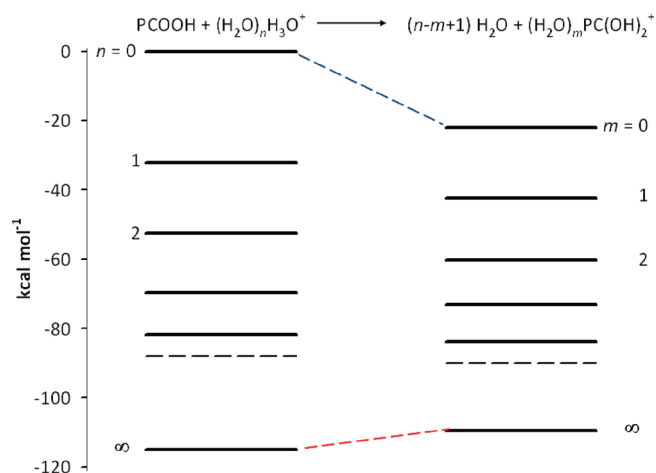
Figure 4. Enthalpy diagram for the protonation of hexanoic acid PCOOH by H_3O^+ under increasing solvation. Data adapted from Meot-Ner,[28] by assuming (1) similar solvation enthalpies for protonated hexanoic acid—water and protonated acetic acid—water clusters and (2) $\Delta H_{hydration}(H_3O^+(g)) = -115$ kcal mol^{-1}.[41,46]

strongly acidic conditions because the hydration energy of hydronium $\Delta H_{hyd}(H_3O^+) = -115$ kcal mol^{-1},[41] significantly exceeds those of larger ions, such as $PC(OH)_2^+$.[24,42] A similar situation will develop whenever $H_3O^+(s)$ encounters proton acceptors on the surface of pH < 4 water.[43] The vast database on gas-phase proton affinities[26] anticipates that $H_3O^+(s)$ could protonate both strong bases, such as trimethylamine ($pK_{BH^+} = 9.8$),[5] and very weak ones, such as PCOOH(aq) ($pK_{BH^+} < -3$), alkenes and carbonyls, that is, the protonating potential of $H_3O^+(s)$ greatly exceeds that of $H_3O^+(aq)$ of the same acidity. Because the protonation of carboxylic acids in condensed media requires superacidic conditions,[31,37] H_3O^+-(s) formally behaves as a superacid in present experiments. Thus, phenomenological evidence, thermodynamics, and the fact that the isoelectric point of water falls in the 2 < pH < 4 range at all inert hydrophobic interfaces[44] suggest that the protonation of neutral species approaching water from hydrophobic media should be a general phenomenon. At this point, it should be apparent that the statements "hydronium emerges to the surface of pH < 4 water" and "interfacial hydronium behaves as a superacid" are not contradictory because they refer to different phenomena. The negative charge of droplets and bubbles above the isoelectric point strictly implies that hydroxide approaches the air/water interface closer than hydronium (by reasons that have been analyzed elsewhere)[44,45] but provides no evidence about whether hydronium or hydroxide are available to incoming proton acceptors/donors. Whether the surface of water is basic in the 4 < pH < 7 range, that is, whether it can accept protons from strong and weak acids, remains to be demonstrated experimentally.[5]

The water's surface is not a "surface" but a highly inhomogeneous, discrete layer where water density vanishes within a nanometer. Therefore, the presence of hydronium/hydroxide ions somewhere in the interfacial layer, as inferred from calculations or surface-specific spectroscopies,[47–52] does not imply that these species can actually proton transfer to/from interfacial acceptors/donors. Because acidity is essentially a relative concept, it is not immediately obvious how the protonating ability of water's surface could be deduced from its structure. In plain terms, water's surfaces are not more or less acidic than bulk water, and the degree of protonation/deprotonation of specific species on water's surfaces is not univocally determined by their molecular configurations. Enzyme function arises not only from the structure of their active sites but from the nature and role of near-surface water.[53] Attempts at deducing the acidity of water's surface from its structure are therefore akin to expecting to hear the sound of one hand clapping.

The KIE associated with the hydronation of PCOOH(g) at the air/water interface is about an order of magnitude larger than that expected from semiclassical transition-state theory for gas-phase reactions, KIE < 12.[54–57] Rigorous analysis of kinetic isotope effects in homogeneous liquid phases involves, however, extensive conformational averaging of solvent modes.[40] A self-consistent interpretation of the KIE results of Figure 3 of proton transfer at the air—water interface should deal, in addition, with decreasing solvent participation along the reaction coordinate. Such a task is beyond the scope of this report,[58] but we notice that proton transfers in enzymatic reactions often display "abnormally" large KIEs[59] and hint that this circumstance may be associated with the steep water density gradients in which they take place. The increasingly larger and diverging KIE and KIE' values observed at lower pH further suggest that these behaviors could result from proton transfers across progressively thinner reaction barriers as $H_3O^+(s)$ emerges to the outermost water layers. Within the context of present findings, previous statements in the literature reflecting that "most reactions that take place in solution do not occur in the gas phase and vice versa" and that "clearly, a quantitative knowledge of solvation forces might lead to the understanding and manipulation of enormous new areas of chemistry"[43] and that "it is a common misconception to consider enzymatic reactions as actually taking place `in water'"[3,12,14,15,59–61] seem apropos and more farsighted than ever.

Summing up, we report that gaseous hexanoic acid molecules are readily protonated upon collision with the surface of mildly acidic pH < 4 water in a process that displays exceedingly large kinetic H-isotope effects. We ascribe these phenomena to the action of minimally solvated interfacial hydronium as "superacidic" proton donors and suggest that they may be common to chemistry at water interfaces with most hydrophobic media.

SUPPORTING INFORMATION AVAILABLE Additional data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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