

Speed Limits for Acid–Base Chemistry in Aqueous Solutions

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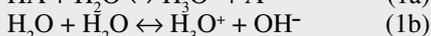
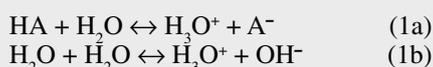
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Abstract: Proton transfer reactions, including acid–base recombination, are commonly considered to occur ‘nearly instantaneously’. However, their actual time scales may stretch far into the microsecond range, as acid–base reactions are diffusion controlled and the concentrations are low near neutral pH. The interplay of competing bases in the pH relaxation is illustrated using a model acid–base system consisting of *o*-nitrobenzaldehyde (oNBA) as a proton cage and acetate ions and hydroxyl ions as bases. The kinetically controlled behavior leads to highly counterintuitive states, *i.e.* acetate ions are transiently protonated for hundreds of nanoseconds despite the presence of a much stronger base OH[−].

Keywords: Neutralization · *o*-Nitrobenzaldehyde · pH-jump · pH-relaxation · Proton release

Introduction

Acid–base reactions are one of the principal categories of chemical transformations, and are typically thought of in terms of pH determining the protonation state of acids and bases in solution phase. Systems which undergo pH changes, due to ongoing reactions involving protons as reactants or products, can be thought of in terms of two fundamental steps: proton delivery and pH relaxation. When studied in water solutions, and therefore in most cases, these two steps are described by two very elementary chemical reactions: acid dissociation and autodissociation of water:



These two equations are an absolute corner stone of acid–base chemistry in Brønsted–Lowry definition which is one of the widest theories of chemical reactivity and explains all proton transfer reactions. Acid–base reactions have been extensively researched,^[1–5] are well understood in terms of their equilibria and many theories

regarding proton transfer mechanisms^[2,6–8] and diffusion processes,^[9–11] for solution phase systems are available. It is well established that proton transfers are one of the fastest chemical processes and even in diluted solution phase, when diffusion limited, due to the Grotthuss mechanism^[9] their rates exceed other known reactions.^[5,12,13] On these grounds, chemists often take the advantage of treating dissociation processes and pH equilibration as instantaneous in everyday scientific practice. As a consequence, most commonly acid–base systems are discussed exclusively in terms of the equilibrium picture of pK_a and pK_w, which are the equilibrium constants for reactions 1a and 1b, respectively. Describing acid–base systems by their pK_w, pK_a and complementary their pK_b values, bases would be neutralized from strongest to weakest and pH sums with pOH to pK_w by definition.

Adding a kinetic dimension to the acid–base reactivity opens a whole new space for consideration and experimental investigation. The first obvious but often overlooked conclusion corresponds to the reaction orders for acid dissociation and neutralization. Dissociation reaction 1a considered from left to right, follows a pseudo first order kinetics due to the large excess of water molecules available to uptake the released proton. The same is not true for neutralization which runs in the opposite direction. Neutralization reactions involve protons and bases which normally exist at similar concentration levels and the pseudo first order approximation cannot be used. Therefore apparent time scales of neutralization will be concentration dependent. For the text book example of H₃O⁺ and OH[−] recombination this rate is roughly 10¹¹ M^{−1}s^{−1}.^[1,11–13] Effectively it

sets a speed limit for acid–base equilibration in aqueous solutions already at the 100 μs time scale for near neutral conditions where the acid proton and hydroxyl concentrations fall below micromolar. These rate limitations can become crucial for fundamental understanding of time evolution of acid base systems.^[10,14–18] Naturally when rapid pH changes are initiated the ongoing relaxation must be taken into account for a relatively long period. On a more general note the remark applies to all systems in which protons are released or taken in a reaction. In these cases if the reactive steps occur on time scales faster than the relatively slow neutralization time scale, a stationary state for the reaction rather than the acid–base equilibrium will be established. This difference might have tremendous implications regarding the actual reaction mechanisms and kinetics.

In recent decades, chemical research has been exploring new time regimes that reach down to the femtosecond domain with modern laser spectroscopy techniques. Pump-probe spectroscopy (conceptually similar to flash photolysis) is a powerful tool to see molecules act ‘live’ during reactions and structural reorientations. In such experiments, two laser pulses are sent to the sample. The first one initiates the chemical process, the second one is used to collect transient spectra of the sample, and hence its chemical structure, at a given time after the process has been initiated. The most obvious application of pump probe spectroscopy involves studies of photoreactions that are directly initiated by light. However, other, more indirect chemical triggers broaden the range of applications of pump probe spectroscopy to very different classes of chemical reactions. One example is that of temperature

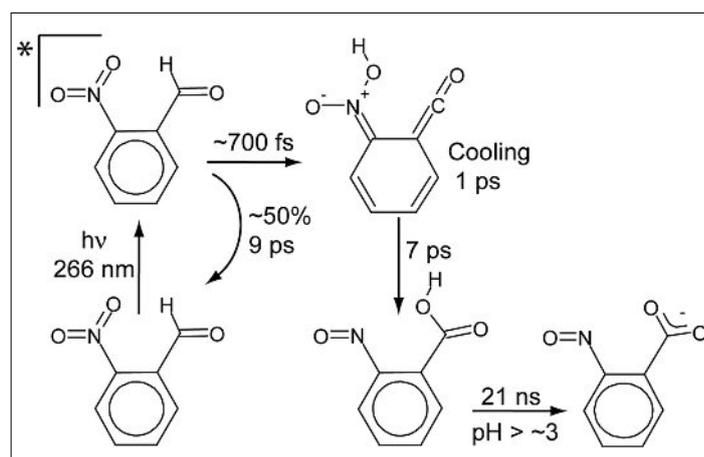
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jumps,^[19,20] that may shift the chemical equilibrium between several compounds, so the kinetics leading to a new equilibrium can be followed. Rapid proton release, on the other hand, can trigger acid–base reactions^[4,14,21,22] and protonation-dependent structural changes, such as protein folding.^[23–25] Executing pH jump experiments,^[14,15,17,26] and more generally speaking investigating dynamics of acid–base systems, there are always two critical aspects that need to be understood beforehand: starting with reaction 1a, how fast are protons delivered to the system? And related to any acid–base equilibria 1b, how are these protons distributed after their release?

There are two principal mechanisms of proton release in photoacids: excited state dissociation, when the electronic excitation decreases the pKa value of an existing dissociable proton,^[15,26–29] and caged protons, *i.e.* molecules in which an acidic proton is created in a photochemical reaction.^[30–32] Understanding their functionality is essential to answer the first fundamental question of how fast can they deliver free protons? In the case of the excited state dissociation, the actual proton release is the only step that needs to be discussed. For proton cages the problem gains complexity as the proton release depends on the reaction mechanism and kinetics in which the cage rearranges. Proton delivery in this case might happen from the final product or already during the reaction if an intermediate form is capable of acid dissociation. In this paper, a model system for pH jumps will be discussed. The experiments were conducted with *o*-nitrobenzaldehyde (*o*NBA) as an optically triggered proton source^[30] and acetate ions as a simple proton acceptor.^[14]

*o*NBA Proton Cage

Ortho-nitrobenzaldehyde is a caged proton molecule undergoing an internal redox reaction initiated by UV irradiation (Scheme 1). It produces *o*-nitrosobenzoic acid, a medium-strong carboxyl acid with pKa ~3. The reaction has been known for over a century^[33] but its details remained controversial, in particular regarding the actual proton release time. The well-established first step of the reaction mechanism involves a ketene intermediate being formed as a result of a hydrogen transfer from the aldehyde group onto the nitro substitute.^[34,35] Already this step results in the formation of a highly acidic -NOOH group, which was sometimes postulated to dissociate during the reaction.^[36] Further details of the reaction depend strongly on the solvent and are discussed controversially in literature.^[30,35,37–40] We recently



Scheme 1. Mechanism of the photoreaction of *o*NBA in water.

combined time resolved UV pump–IR probe spectroscopy (TR-IR) with *ab initio* molecular dynamics (AIMD) and obtained a consistent picture of the reaction from the reactant's photoexcitation up to the final product formation.^[30] The reaction is summarized in Scheme 1.

The ketene intermediate can be clearly identified in the TR-IR data by a characteristic band representing the =C=O group, presented in Fig. 1A. The band appears within a few hundred femtoseconds after

photo-excitation. It disappears with a 7 ps time constant as the reaction progresses to the second intermediate – nitrosobenzoic acid – which can be identified by the carboxylic acid C=O band (Fig. 1B). The acid finally dissociates on a 21 ns time scale, which is manifested by vanishing of the C=O band and the accompanying rise of the carboxylate peaks (Fig. 1C). Hence, the proton is delivered to the system with a 21 ns time constant.^[30]

For the second reaction step from

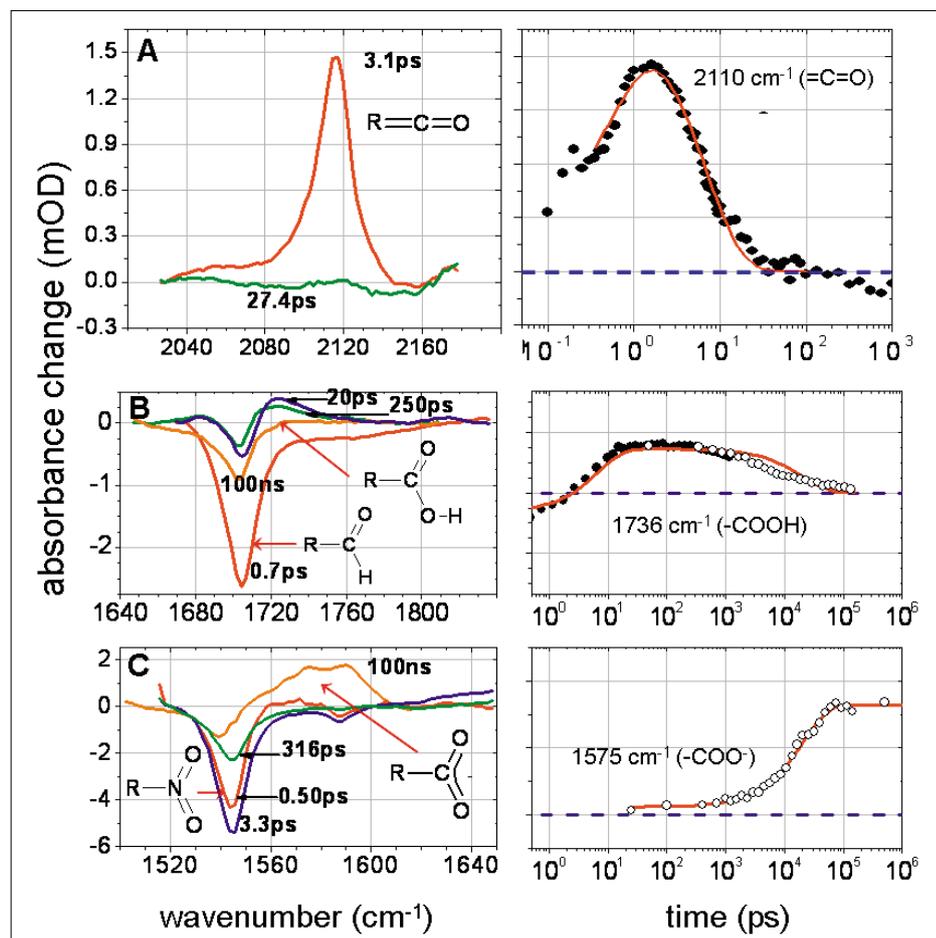


Fig. 1. Time-resolved difference IR spectra illustrating the *o*NBA photo reaction. A) ketene band and kinetics of formation and disappearance of the first intermediate, B) the carbonyl stretch region with bands of the aldehyde and carboxyl group, kinetic trace shows the formation and dissociation of nitrosobenzoic acid, C) The nitro and carboxylate bands and carboxylate appearance kinetics. Adapted from ref. [30].

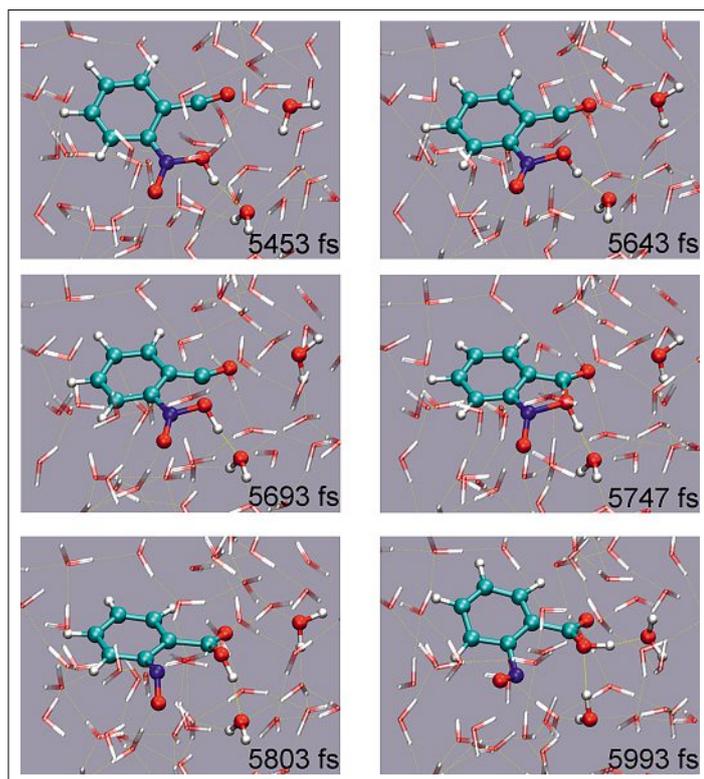


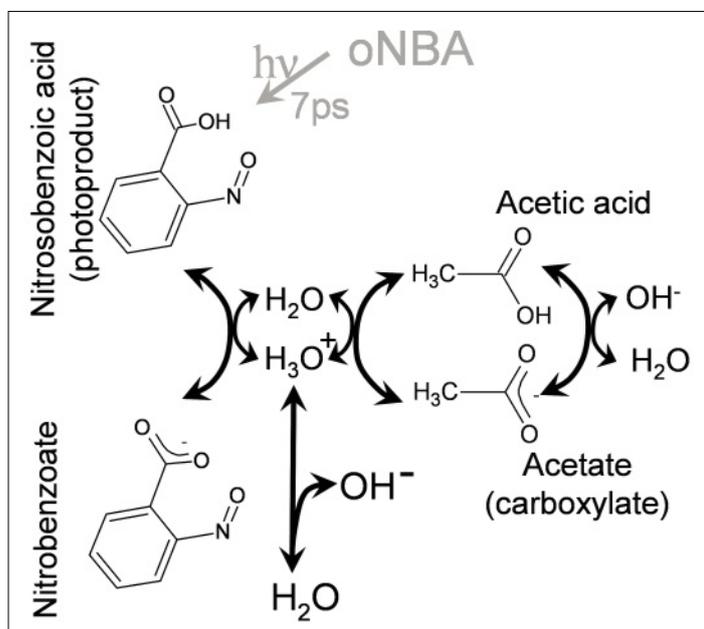
Fig. 2. Snapshots from an *ab initio* molecular dynamics simulation starting from the ketene intermediate in aqueous solution. The formation of the acid takes place after about 5.5 ps, and leads directly from the ketene to the acid. The transfer of the OH group is assisted by a hydrogen-bonded water molecule. Adapted from ref. [30].

the ketene to nitrosobenzoic acid, AIMD simulations in explicit solvent are feasible, thanks to the small size of the molecule, its short lifetime and the reaction occurring the ketene's ground state. Fig. 2 shows the actual event of the ketene molecule, undergoing a solvent-assisted OH transfer from the nitrogen atom to the carbonyl carbon, resulting in the formation of a protonated carboxylic acid. This reaction step occurs within a few bond oscillations with no intermediate identified between the ketene and carboxyl acid molecules, as has been postulated in literature.^[35,37–39] Averaging over many such trajectories, we obtained a reaction time of 7 ps, in perfect agreement

with the experiment. Within that short period, no event of direct proton dissociation of the ketene intermediate has been observed. We will see in the next section why proton dissociation is typically much slower.

pH Jump Relaxation

Following the sudden proton release, the acid–base system is driven to an extreme non-equilibrium condition, that leads to very counter-intuitive states.^[14] This is illustrated in experiments by adding acetate to a solution of *o*NBA. In this



Scheme 2. Acid-base equilibrium establishing in acetic acid solution upon *o*NBA delivered pH-jump.

simple-looking model system, a relatively complex set of entangled acid-base equilibria has to be considered, as demonstrated in Scheme 2. Fig. 3 shows the result of pump-probe experiments in dependence of pD (experimental data were collected in heavy water solutions). Near neutral pH, the expected outcome of the experiment was observed. Due to a large excess of CH_3COO^- and delivered protons compared to OH^- ions, Scheme 2 simplifies and the two equilibria involving hydroxyl groups can be neglected. For these solutions, the pH jumps showed protonation of the carboxylates on a time scale matching the proton release. The proton release could be identified as the rate-limiting step and proton transfer brings the system to its new equilibrium directly.

The picture is more complicated in the experiments performed in initially alkaline solutions, where presence of hydroxyl group includes competition of two possible neutralization reactions. An equilibrium-based picture of acid–base chemistry would suggest that presence of the OH^- ions should diminish the magnitude of the recorded acetate protonation signal, as some of the released protons will be taken by hydroxyls. This thinking builds on the implicit assumption that stronger bases will be protonated favorably over weaker ones, which is, of course, true for the final equilibrium state. Nevertheless, Scheme 2 shows a complex network of proton transfer steps, which may take many routes before reaching the final equilibrium. In the data (Fig. 3), nearly all traces show initial

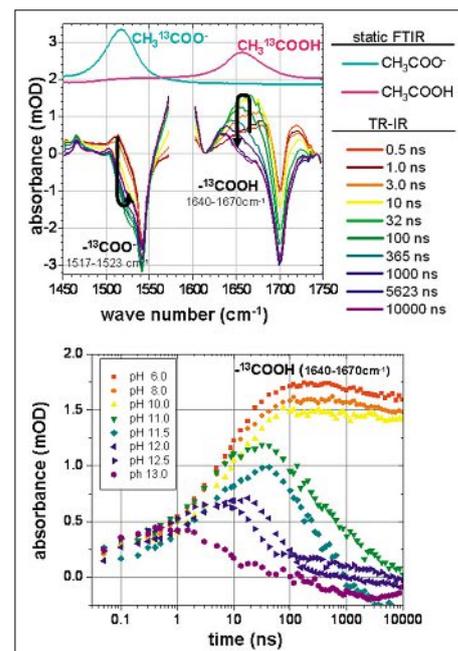


Fig. 3. Time-resolved difference IR spectra in the carboxyl and carboxylate region (exemplary sample at pD = 11). Kinetic traces showing appearance of protonated acetic acid extracted from the IR data. Adapted from ref. [14].

Table 1. Reactions included in the kinetic mode of the acid base system with their equilibrium and kinetic constants

Reaction	K_+	k_-
1) $\text{NBD} + \text{D}_2\text{O} \leftrightarrow \text{NB}^- + \text{D}_3\text{O}^+$ $\text{pK}_a = 2.9$	$1 \cdot 10^8 \text{ s}^{-1\text{a}}$	$8 \cdot 10^{10} \text{ M}^{-1}\text{s}^{-1\text{a}}$
2) $\text{ACD} + \text{D}_2\text{O} \leftrightarrow \text{AC}^- + \text{D}_3\text{O}^+$ $\text{pK}_a = 5.3^{[41]}$	$2.8 \cdot 10^5 \text{ s}^{-1\text{b}}$	$8 \cdot 10^{10} \text{ M}^{-1}\text{s}^{-1[42]}$
3) $\text{D}_2\text{O} + \text{D}_2\text{O} \leftrightarrow \text{OD}^- + \text{D}_3\text{O}^+$ $\text{pK}_a = 16.5^{[1]}$	$2.6 \cdot 10^{-6} \text{ s}^{-1\text{b}}$	$8.4 \cdot 10^{10} \text{ M}^{-1}\text{s}^{-1[1]}$
4) $\text{AC}^- + \text{D}_2\text{O} \leftrightarrow \text{ACD} + \text{OD}^-$ $\text{pK}_a = 11.2^{\text{c}}$	$6 \cdot 10^{-2} \text{ s}^{-1\text{b}}$	$1 \cdot 10^{10} \text{ M}^{-1}\text{s}^{-1\text{d}}$

Note: Water is printed in bold as by convention it was included in the pK values with a constant concentration of 55 M and is not treated explicitly in the kinetic rate constants (convention commonly used for pK_a and pK_b). Non standard symbols: ACD – deuterized acetic acid, AC^- – acetate ion, NBD – deuterized nitrosobenzoic acid, NB^- – nitrosobenzoate ion. ^aForward rate k_+ fitted to experimental data, back reaction rate k_- assumed to the same as for acetate protonation (reaction 2). The pK_a is calculated from k_+ and k_- (see Eqn. (3)). ^bCalculated based on the equilibrium constant and the rate constant for the opposite reaction (see Eqn. (3)). ^cCalculated based on pK_a of ACD and D_2O ($\text{pK}_a^{(4)} = \text{pK}_a^{(3)} - \text{pK}_a^{(2)}$). ^dFree parameter of the kinetic model adjusted to match the experimental data.

protonation of the acetate ions. For pD exceeding 11, this protonation is transient and all of the acetic acid formed is finally consumed. Since the time scale of the acetic acid deprotonation is clearly pD dependent, the protons were scavenged by the competing hydroxyl groups. Hydroxyl is a very strong base, certainly stronger than acetate. Nevertheless, acetate is transiently protonated in the first step. Hence, the pK_a , *per se*, has no kinetic meaning for the neutralization reaction.

Despite the fact that this observation might contradict the common chemical intuition, it does not violate any known acid–base theory. It merely reflects the fact that the neutralization reaction is diffusion controlled, since no driving force leads the free proton to the most basic anion. Protonation happens, rather, on a first-found-first-neutralized basis, as each neutralization event is thermodynamically allowed, regardless of the strength of the base. Hence, the released protons will first preferably neutralize the base that exists at a higher concentration. For the experimental conditions in Fig. 3 (*i.e.* 20 mM acetate solution and about 3 mM proton release), that will be acetate up to pD ≈ 11 –12, where the hydroxyl concentration reaches the same range. As equilibration proceeds, protons captured on the weaker base (acetate) will form a relatively strong acid, which will then redissociate to react directly or through the detour of water with the stronger base (hydroxyl).

A more detailed understanding of the pH equilibration can be obtained from a kinetic model of the proton transfer network shown in Scheme 2. A summary of the elementary reaction steps and their kinetic parameters is presented in Table 1. The result is shown in Fig. 4, where the lowest plot agrees very well with the experimental data (Fig. 3). The upper plots illustrate what actually happens on the rather indirect way to pH relaxation in the experiment. For ex-

ample, free protons in the form of H_3O^+ are nearly never present in the experiment and are quickly picked up by either the COO^- or the OH^- groups available. Also deduced from the kinetic modeling can be the ionic product, $\text{pH} + \text{pOH}$, which in equilibrium is expected to hold

$$\text{pKw} = \text{pH} + \text{pOH} \quad (2)$$

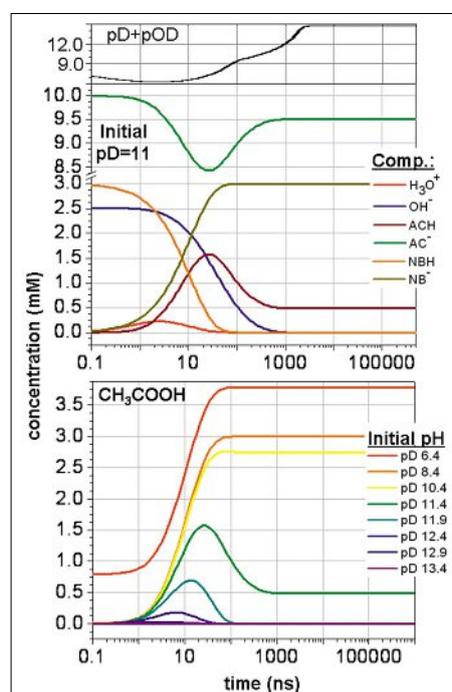


Fig. 4. Kinetic model calculations. Upper panel: Time evolution of concentration of all acids and bases in the solution and of the ionic product of water in a sample of initial pD = 11.4. Lower panel: Time evolution of the acetic acid concentrations following a pD jump in samples of different initial pD. Abbreviations: ACD – deuterized acetic acid, AC^- – acetate ion, NBD – deuterized nitrosobenzoic acid, NB^- – nitrosobenzoate ion. Initial conditions and parameters for the simulation: $c_{\text{NBD}} = 2.5 \text{ mM}$, $c_{\text{AC}^-} = 10 \text{ mM}$, pK_a values and rate constants as in Table 1. Adapted from ref. [14].

where pKw is 14 or 14.6 in the case of heavy water, respectively. The time evolution of the ionic product is illustrated in Fig. 3 (top plot). It can be seen in the plot that its transient values can go many units below the expected equilibrium value, indicating that the concentrations of hydronium and hydroxyl ions are orders of magnitude higher than in equilibrium. It takes about 3 μs to fully relax to the equilibrium value, a time scale governed by the mutual diffusion coefficient and the concentrations of the various acid–base compounds. Closer to neutral pH, this time would increase to $\approx 100 \mu\text{s}$.

A striking observation in Table 1 is the almost universal base neutralization rate for reactions 1, 2, 3 of $k_- \approx 8 \cdot 10^{10} \text{ M}^{-1}\text{s}^{-1}$. The rate is universal because it is governed by the proton diffusion constant through the Grotthus mechanism, thus the association step is essentially barrier-less. Together with the definition of the equilibrium constant this universality of k_- implies that the acid dissociation rate k_+ is directly related to the pK_a :

$$\text{pK}_a = \log k_- - \log k_+ \quad (3)$$

For moderately strong to weak acids, taking pK_a values in range of 0 to 6, acid dissociation rates range from 10^{11} s^{-1} to 10^5 s^{-1} , corresponding to time range between 10 ps and 10 μs . This time range, in turn, justifies why the proton of the highly acidic -NOOH group in the ketene intermediate cannot dissociate within its 7 ps lifetime. For an effective competition with that short lifetime, its pK_a would need to be around 0, which is rather unlikely for an organic acid. Reaction 4 is significantly slower because it is related to the slower diffusion rate of an OH^- .

Based on the mechanistic understanding of the diffusion controlled pH equilibration, experimentalists can take advantage of these kinetic aspects when designing pH jump experiments. In case of multi-base systems, in which equilibrium protonation of the investigated molecule is excluded due to an insufficient proton release in an alkaline environment, transient protonation of a weak base can still take place in a certain time window. The protonation priority and the duration of the time window in which the molecule stays protonated can be tuned, within chemically feasible limits, by adjusting the concentrations.

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