pH-Regulated Chemical Oscillators

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CONSPECTUS: The hydrogen ion is arguably the most ubiquitous and important species in chemistry. It also plays a key role in nearly every biological process. In this Account, we discuss systems whose behavior is governed by oscillations in the concentration of hydrogen ion. The first chemical oscillators driven by changes in pH were developed a quarter century ago. Since then, about two dozen new pH oscillators, systems in which the periodic variation in pH is not just an indicator but an essential prerequisite of the oscillatory behavior, have been discovered. Mechanistic understanding of their behavior has grown, and new ideas for their practical application have been proposed and, in some cases, tested.

Here we present a catalog of the known pH oscillators, divide them into mechanistically based categories based on whether they involve a single oxidant and reductant or an oxidant and a pair of reductants, and describe general mechanisms for these two major classes of systems. We also describe in detail the chemistry of one example from each class, hydrogen peroxide−sulfide and ferricyanide−iodate−sulfite. Finally, we consider actual and potential applications. These include using pH oscillators to induce oscillation in species that would otherwise be nonoscillatory, creating novel spatial patterns, generating periodic transitions between vesicle and micelle states, stimulating switching between folded and random coil states of DNA, building molecular motors, and designing pulsating drug delivery systems. We point out the importance for future applications of finding a batch pH oscillator, one that oscillates in a closed system for an extended period of time, and comment on the progress that has been made toward that goal.
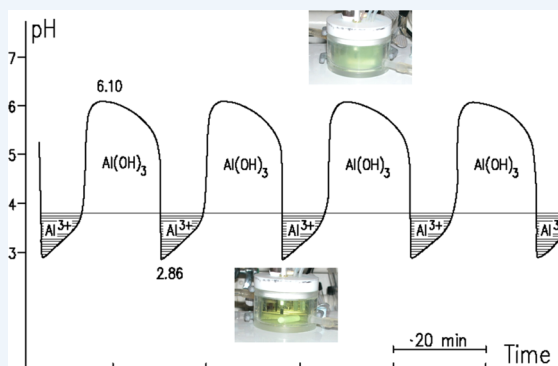
INTRODUCTION

Half a century ago, chemical oscillation was a rare and poorly appreciated phenomenon, with only two examples known, both having been discovered serendipitously and neither understood at a mechanistic level. With growing realization of the implications of far-from-equilibrium thermodynamics and the careful characterization and mechanistic analysis of the prototype Belousov−Zhabotinsky (BZ) reaction, oscillating chemical reactions began to attract increasing attention in the late 1970s. The development of an algorithm for the systematic design of new chemical oscillators in the early 1980s spurred a blossoming of activity in the field. Today, there are nearly 200 variants of chemical oscillators known.

The earliest oscillating reactions, whether discovered accidentally or designed deliberately, all exploited the easy accessibility of multiple oxidation states of oxyhalogen species. More recent work has expanded "the periodic table of chemical oscillation" to include additional families of reactions: bromate, chlorite, bromite, oxygen, sulfur, Cu(II)-catalyzed, manganese-based, and pH oscillators. Among these, the pH oscillators, along with the bromate and chlorite families, show the widest range of composition and have been most frequently employed to generate novel nonlinear temporal and spatial phenomena. Because of the ubiquity of the hydrogen ion in chemical and biological processes, it is also this group that offers the greatest promise for practical applications.

Periodic changes in pH occur in all chemical oscillators that operate in unbuffered aqueous solution, even in those that require strongly acidic media, like the Bray−Liebhafsky or Belousov−Zhabotinsky reactions. We define pH oscillators as systems in which the hydrogen ion plays the most important kinetic role in bringing about the oscillatory behavior. In such systems, the variation in pH, which can be as large as 6 pH-units, is neither a consequence nor an indicator but rather the driving force of the oscillations. If the pH oscillations are buffered, all oscillatory responses are suppressed, and the reaction becomes monotonic. The pH oscillators found to date all contain two major composite reactions that alternate in dominating the chemistry. One reaction produces H^+ in an autocatalytic fashion, while the other consumes H^+ in a slow process that produces an appropriate time lag.

In 1990, two of us published an Account[1] that described what was then the newly designed family of nearly a dozen pH oscillators. In the ensuing quarter century, there has been enormous progress in the discovery of additional systems (the number has more than doubled), in mechanistic understanding of how these oscillators function, and in identifying potential

applications for pH oscillators. This Account describes these developments.

SOME EARLY HISTORY

The discovery of the first pH oscillators was partly serendipitous. By the mid-1980s, we had finished our project aimed at designing more bromate- and chlorite-based oscillators, and our intention was to extend the realm of known oscillatory reactions. The method we had successfully used for producing new BrO_3^- and ClO_2^- oscillators was a semiempirical approach based on the theoretical work of Boissonade and De Kepper.[2] The key to the approach is to identify a delayed negative feedback that can be used to perturb an autocatalytic reaction that exhibits bistability in a flow reactor (CSTR).

In searching the literature for candidate autocatalytic reactions, we found a paper by Sorum et al.,[3] who had studied several such reactions, $IO_3^- - SO_3^{2-}$ (Landolt system), $MnO_4^- - SO_3^{2-}$, $IO_3^- - I^-$, and $IO_3^- - S_2O_3^{2-}$, by recording changes in pH. Inspired by Sorum's work, we ran the Landolt reaction in a CSTR using a glass electrode to monitor the reaction. Previously, oscillatory responses had been recorded with sensors like Pt redox electrodes, ion-specific electrodes, or spectroscopic absorbance measurements, but the possibility of monitoring oscillatory changes in pH had been neglected. As anticipated, we found a wide range of bistability between a high pH and a low pH steady state. Among many compounds tested as potential negative feedback species, the ferrocyanide ion proved the most effective. We soon saw large amplitude pH oscillations in the $IO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$ system.[4]

In parallel with our investigations on the Landolt reaction, we carried out CSTR experiments using the autocatalytic $H_2O_2 - S^{2-}$ reaction. This reaction had been the subject of a number of careful studies because it offers a cheap and convenient route to eliminate the malodorous, corrosive, and poisonous H_2S generated in sewage systems, by converting the hydrogen sulfide to harmless sulfate. Hoffmann[5] determined the stoichiometry of the reaction, found H^+-autocatalysis, and established the H^+-consuming and H^+-producing composite reactions in the system. Under CSTR conditions, we found bistability between high and low pH steady states, and to our great surprise, we observed high amplitude pH oscillations without having to introduce a third component.[6]

TAXONOMY OF pH OSCILLATORS

The compilation presented in Table 1 lists the known pH oscillators in chronological order of their discovery. We note that 21 of the 25 systems were developed by researchers who have been working in fruitful cooperation since 1980 at Brandeis University in the U.S. and at two Hungarian institutions, Eötvös University and the University of Debrecen.

Table 1 demonstrates the broad range of chemistry encompassed by the pH oscillators. Each system consists of an oxidant and either one or two other components. The second component is a reducing agent. We refer to systems composed of an oxidant and a single reductant as "one-substrate pH oscillators". In these systems, both the positive and negative feedback reactions are incorporated in the overall reaction that takes place between the oxidant and the reductant. In a few cases, a metal ion catalyst [Cu(II) or Mn(II), at concentrations 2−3 orders of magnitude lower than those of the main components] is required to tune the rates of the feedback reactions into a range that generates pH oscillations. In about half these systems, two

Table 1. Known pH Oscillators

(a) One-Substrate pH Oscillators			
no.	oxidant	reductant	pH range	ref
1	H_2O_2	S^{2-}	6.0–8.0	6
2	H_2O_2	$S_2O_3^{2-}$ (Cu^{2+})	4.9–8.5	7
3	IO_4^-	$S_2O_3^{2-}$	4.0–5.5	8
4	IO_4^-	NH_2OH	4.0–6.0	9
5	IO_3^-	NH_2OH	3.0–5.5	10
6	BrO_2^-	I^-	6.0–8.2	11
7	BrO_3^-	SO_3^{2-} (Mn^{2+})	3.5–7.2	12
8	H_2O_2	$S_2O_4^{2-}$	3.5–9.5	13
9	BrO_3^-	SO_3^{2-}	2.8–7.3	14

(b) Two-Substrate pH Oscillators				
no.	oxidant	reductant	second substrate	pH range	ref
10	IO_3^-	SO_3^{2-}	$Fe(CN)_6^{4-}$	3.0–7.3	4
11	IO_3^-	SO_3^{2-}	$CS(NH_2)_2$	3.5–7.0	16
12	IO_3^-	SO_3^{2-}	$S_2O_3^{2-}$	5.0–7.0	17
13	BrO_3^-	SO_3^{2-}	$Fe(CN)_6^{4-}$	2.7–6.2	15
14	H_2O_2	SO_3^{2-}	$Fe(CN)_6^{4-}$	4.8–7.8	18
15	BrO_2^-	NH_2OH	C_6H_5OH	4.5–7.5	19
16	BrO_2^-	$S_2O_3^{2-}$	C_6H_5OH	4.5–7.5	20
17	BrO_3^-	SO_3^{2-}	Marble	5.5–7.5	21
18	H_2O_2	SO_3^{2-}	Na_2CO_3	5.0–7.0	22
19	H_2O_2	SO_3^{2-}	HCO_3^-	4.5–6.5	23
20	H_2O_2	SO_3^{2-}	$S_2O_3^{2-}$	5.0–7.0	24
21	H_2O_2	SO_3^{2-}	Hemin	6.5–7.5	25

| (c) Special Cases		
no.	composition	pH range	ref
22	H_2O_2, $Fe(CN)_6^{4-}$	5.0–7.0	26
23	ClO_2^-, SO_3^{2-}	5.9–7.9	27
24	$S_2O_4^{2-}$, H_2O	4.9–6.3	28
25	HCHO, SO_3^{2-}, gluconolactone	7.2–10.0	29

other components must be present in addition to the oxidant to generate oscillations in pH. In these "two-substrate pH oscillators", the positive and negative feedback reactions arise separately from the H^+-producing autocatalytic oxidation of the first substrate and from a slow H^+-consuming reaction involving the second substrate. In most cases, the second substrate is also a reductant, but occasionally conjugate acid−base pairs (CO_3^{2-}, HCO_3^-) or organic species (hemin, phenol) can serve this function. There are four systems whose identity as "true pH oscillators" may be questioned, because no H^+ autocatalysis has been identified in the mechanisms of these reactions. We categorize these examples as "special cases".

HOW DO pH OSCILLATORS WORK?

In the one-substrate systems, the substrate is oxidized to two different extents depending on the initial pH and the initial ratio of oxidant to reductant (substrate). One pathway is a *partial oxidation*, which leads to formation of a relatively stable intermediate. This reaction consumes H^+; consequently, the pH rises when this stoichiometry prevails. This step is thus self-inhibitory. As the H^+ concentration falls, the partial oxidation gradually slows and then essentially shuts off when the pH becomes high enough. The high pH favors an alternative route. In this step, intermediate and substrate react to undergo *total oxidation*, accompanied by autocatalytic production of H^+. When this step is completed, the pH has been restored to its original low value, and the cycle can start again if fresh reactants have flowed into the reactor at an appropriate rate. The H^+-consuming and

Scheme 1. Positive (+) and Negative (−) Feedback Processes in a One-Substrate pH Oscillator[a]
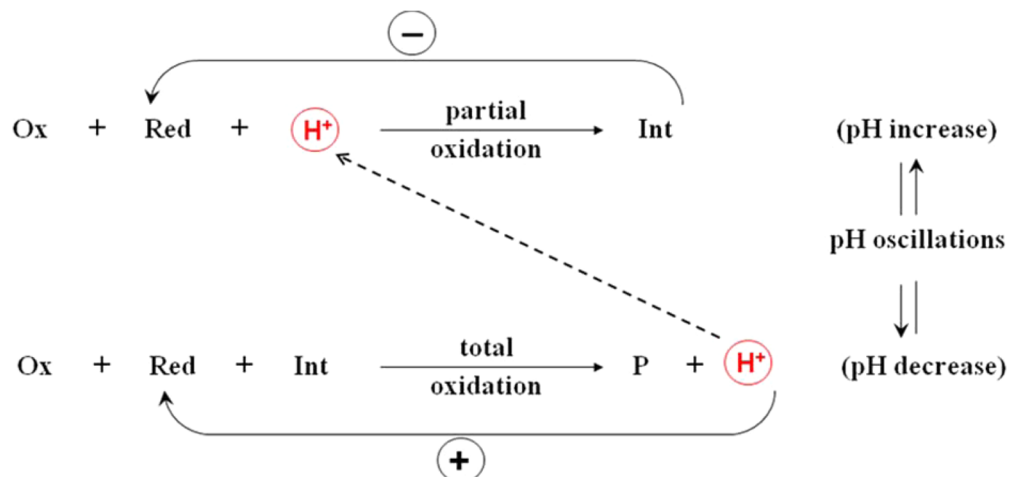
[a]Ox, oxidant; Red, reductant; Int, intermediate; P, end product; ⊖ in step 1 and ⊕ in step 2 denote autoinhibition and autocatalysis, respectively.

Scheme 2. H⁺-Producing and H⁺-Consuming Processes in a Two-Substrate pH Oscillator[a]

$$[Ox] > [S_1] + [S_2]$$
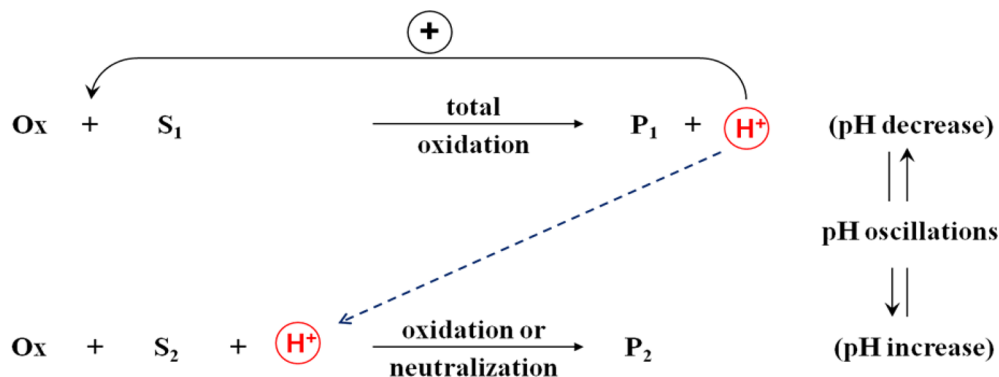
[a]Ox, oxidant; Red, reductant; S_1, reductant; S_2, reductant or H⁺-consuming reagent; ⊕ in step 1 denotes the autocatalysis.

H⁺-producing processes taking place in such one-substrate pH oscillators are illustrated in Scheme 1.

In the two-substrate pH oscillators, two consecutive reactions constitute the oscillatory process. In the first reaction, H⁺ is a product, but it serves as a reactant in the second reaction. Substrate 1 is always a reductant and undergoes total oxidation. This reaction is autocatalytic in H⁺, producing H⁺ until substrate 1 is used up. The resulting low pH environment initiates step 2, in which the H⁺ generated in the first reaction is largely consumed. Substrate 2 can also be a reductant that is oxidized only in the presence of acid, but sparingly soluble marble or even organic species can also be used.

■ CHEMISTRY OF THE pH OSCILLATORS

One of the attractive features of the pH oscillators is that their chemistry is relatively simple. The stoichiometry and the kinetics of the overall and composite reactions have been thoroughly studied, and both the positive and negative feedback processes can easily be identified. It is fair to state that the mechanisms of the pH oscillators are the best understood among all families of chemical oscillators.
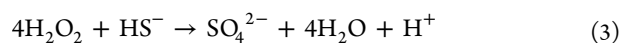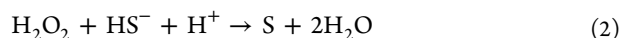
We discuss below some representative examples to illustrate the basic chemistry of the pH oscillators that we outlined in Schemes 1 and 2.

One-Substrate pH Oscillators

The oscillatory behavior in a one-substrate pH oscillator arises from the alternation of two distinct stoichiometries, which are governed by the composition and pH of the reaction mixture. Here we analyze the $H_2O_2-S^{2-}$ reaction as an example of this class.

In the $H_2O_2-S^{2-}$ oscillator, the primary input components are Na_2S and H_2O_2. A small amount of H_2SO_4 is also necessary for the reaction to proceed in an oscillatory manner. In addition to oscillation, one can observe high and low pH steady states or bistability between these states, depending on the initial ratio of the reactants and the flow rate. The pH oscillates between about 6.0 and 8.5, which can be monitored with a glass electrode. The oscillations can also be followed with a Pt redox electrode or visualized using an acid−base indicator, by periodic observation of a yellow color due to the appearance and disappearance of the S_4^{2-} intermediate, or by the turbidity associated with the formation and dissolution of elemental sulfur.

The oscillations in the responses listed above can be explained by the stoichiometries and kinetics established by Hoffmann for the H_2O_2 oxidation of sulfide ion.[5] According to Hoffmann, S^{2-} (its reactive form is HS^-) undergoes oxidation by the two routes shown in eqs 1−3:

$$S^{2-} + H^+ \leftrightarrow HS^- \tag{1}$$

$$H_2O_2 + HS^- + H^+ \rightarrow S + 2H_2O \tag{2}$$

$$4H_2O_2 + HS^- \rightarrow SO_4^{2-} + 4H_2O + H^+ \tag{3}$$

In an acidic environment with $[H_2O_2] \approx [S^{2-}]$, reaction 2 dominates, whereas at basic pH and when $[H_2O_2] \gg [S^{2-}]$, reaction 3 is the principal oxidation route. Reaction 2 consumes and reaction 3 produces protons. Starting at intermediate pH (∼7), if H_2O_2 is in stochiometric excess, reaction 3 is favored, and the pH decreases, which continues until nearly all the HS^- is consumed. This step starts slowly, but it becomes self-accelerating, because when H^+ is produced in eq 3, HS^-, which is more reactive than the unprotonated sulfide, is formed in eq 1. In the low pH environment, the stoichiometry switches from reaction 3 to reaction 2, white colloidal sulfur precipitates, and yellow S_4^{2-} appears in the solution. This turbid, low pH state is maintained until most of the H^+ produced in eq 3 is used up. When reaction 2, assisted by the strongly alkaline input S^{2-} solution, restores the original high pH, a new cycle can start once sufficient H_2O_2, Na_2S, and H_2SO_4 have accumulated in the CSTR. In this phase of the oscillatory process, the reaction mixture clears, because the sulfur is oxidized to SO_4^{2-} via eq 4:

$$S + 3H_2O_2 \rightarrow SO_4^{2-} + 2H_2O + 2H^+ \tag{4}$$
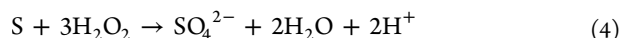
Typical pH oscillations measured in the $H_2O_2-S^{2-}$ system are shown in Figure 1.

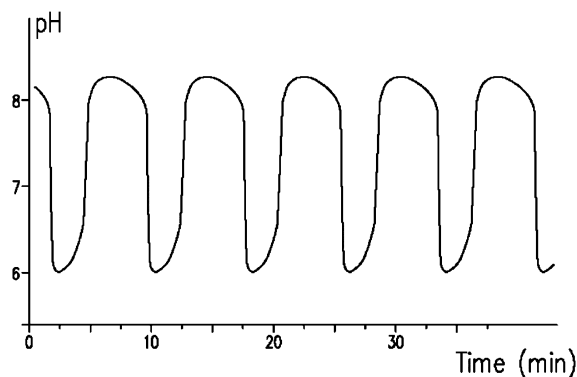**Figure 1.** pH-oscillations in the $H_2O_2-S^{2-}$ reaction in a CSTR. Input solutions: $[H_2O_2]$ = 0.4 M, $[Na_2S]$ = 0.0167 M, $[H_2SO_4]$ = 0.001 M. Flow rate: 6×10^{-4} s^{-1}. Adapted with permission from ref 6. Copyright 1985 American Chemical Society.
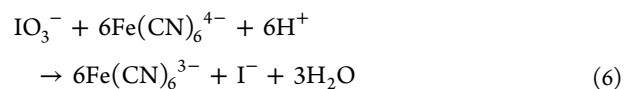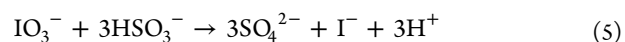
A quantitative model that includes six protonation equilibria and 12 redox reactions has been proposed by Rábai et al. and simulates the observed behavior quite well.[30]

Two-Substrate pH Oscillators

We take the $IO_3^--SO_3^{2-}-Fe(CN)_6^{4-}$ flow system as an example of a two-substrate pH oscillator. The input species are $NaIO_3$, Na_2SO_3, $K_4Fe(CN)_6$, and H_2SO_4. High amplitude pH oscillations (pH 3−7) and bistability appear in a wide range of experimental parameters. Besides the pH, oscillations in color

(yellow ↔ colorless) and in the potential of an I^--selective or a Pt electrode can be observed.

In a mixture of SO_3^{2-}, $Fe(CN)_6^{4-}$, and excess IO_3^-, two reactions separated in time, with the stoichiometries of eqs 5 and 6, comprise the key elements of the oscillatory cycle:

$$IO_3^- + 3HSO_3^- \rightarrow 3SO_4^{2-} + I^- + 3H^+ \tag{5}$$

$$IO_3^- + 6Fe(CN)_6^{4-} + 6H^+$$
$$\rightarrow 6Fe(CN)_6^{3-} + I^- + 3H_2O \tag{6}$$

Both reactions are essentially inactive above pH 7. However, if the initial pH in the reactor is around 7, eq 5, the Landolt reaction, begins slowly, gaining speed due to the autocatalytic multiplication of H^+, via formation of the highly reactive HSO_3^- and H_2SO_3 in the protonation of SO_3^{2-} driven by the H^+ formed in eq 5. This autocatalysis is terminated by the consumption of SO_3^{2-}. The acidic environment then allows reaction 6 to turn on. This step represents the major source of negative feedback. The drastic fall in pH during the autocatalytic stage also opens the way for the Dushman reaction to take place:

$$IO_3^- + 5I^- + 6H^+ \rightarrow 3I_2 + 3H_2O \tag{7}$$
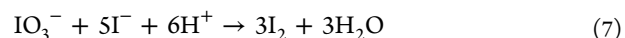
This reaction plays multiple roles in the oscillatory process: (a) it accounts for the transient appearance of the yellow color (I_2) in the reaction mixture; (b) a fast reaction between I_2 and the input sulfite delays the accumulation of this reagent in the reactor; (c) it contributes to the negative feedback by consuming H^+. Another important contributor to the time delay between the H^+-producing and H^+-consuming steps is the inflow of unprotonated, unreactive SO_3^{2-}, which rapidly removes H^+ through the protonation equilibria. A new autocatalytic pulse of H^+ starts to develop once the original pH is restored by the combined negative feedback process. A detailed mechanism that reproduces nearly quantitatively the dynamics observed in this system was formulated by Gaspar and Showalter.[31]

"Special" pH Oscillators

Four oscillators listed in Table 1 fall into a special category of pH oscillators. Each exhibits small amplitude pH oscillations (ΔpH ≤ 2). Hydrogen ion-producing and -consuming steps can be identified in their chemistry, but the way in which they function differs from that discussed in the examples above. In the "special" oscillators, no H^+ autocatalysis can be identified, which, one might argue, implies that they are not true pH-driven oscillators. In the $H_2O_2-Fe(CN)_6^{4-}$ system, the pH oscillates as a consequence of alternation of two stoichiometries in which H^+ participates. The overall process is the oscillatory decomposition of H_2O_2 to H_2O and O_2 catalyzed by the $Fe(CN)_6^{3-}/Fe(CN)_6^{4-}$ couple; the autocatalytic species are actually $OH^\bullet$ and $HO_2^\bullet$ radicals. The oscillatory thermal decomposition of dithionite is thought to be driven by HSO_3^- autocatalysis. No autocatalytic species has been characterized in the $ClO_2^--SO_3^{2-}$ oscillator. The special aspect of the $HCHO-HSO_3^-$−gluconolactone system is that the pH oscillation appears to involve only acid−base steps rather than redox reactions.

APPLICATIONS

The applications we discuss herein are based on coupling chemical, biochemical, and physical processes that are not normally oscillatory but are sensitive to a pH oscillator whose oscillations can stimulate repetitive responses in the target system. For this approach to work, it is essential that the oscillatory pH-stimulus
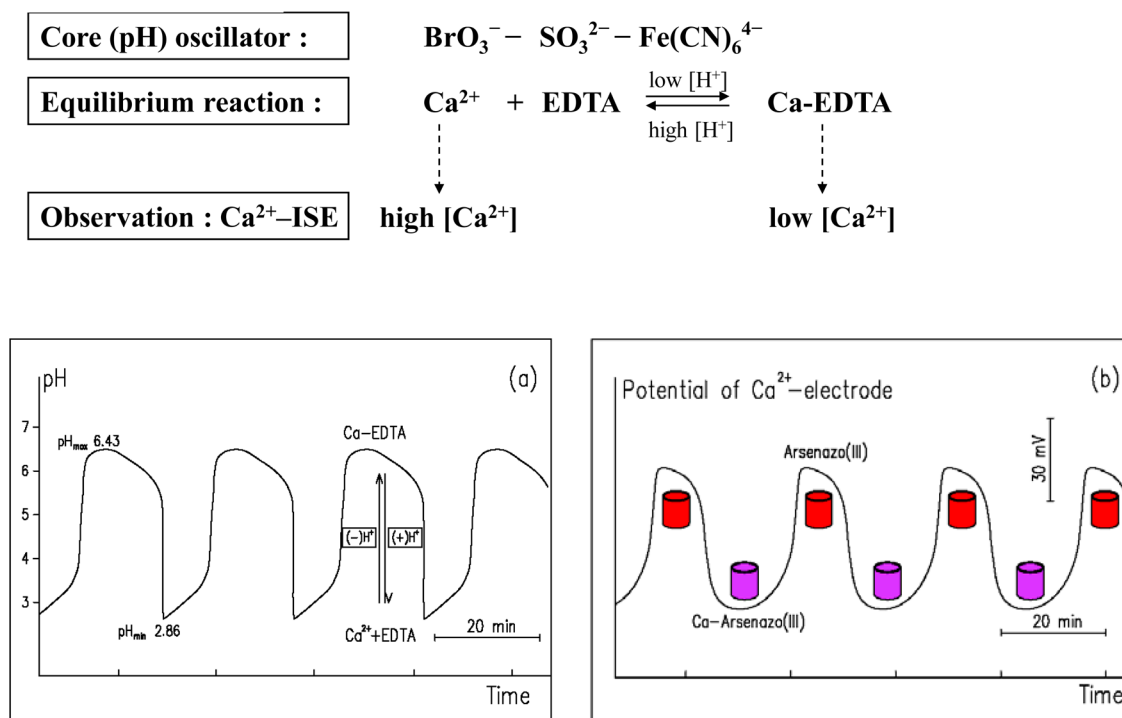
$$\text{Core (pH) oscillator :} \quad BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$$

$$\text{Equilibrium reaction :} \quad Ca^{2+} + EDTA \underset{\text{high [H}^+\text{]}}{\overset{\text{low [H}^+\text{]}}{\rightleftharpoons}} Ca\text{-}EDTA$$

$$\text{Observation : } Ca^{2+}\text{–ISE} \quad \text{high [Ca}^{2+}] \qquad\qquad \text{low [Ca}^{2+}]$$

Figure 2. Ca^{2+} concentration oscillations in the $BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$ + CaEDTA coupled system: (a) oscillation in the pH and in the position of the equilibrium; (b) oscillations in the potential of a Ca^{2+}–ISE.

be strong enough to alter the behavior of the target process but be minimally affected by changes in that pH-sensitive subsystem.

Nearly all known oscillatory reactions are based on redox chemistry, and this observation led many chemists to conclude that only ions that possess multiple oxidation states can participate in chemical oscillators. However, some non-redox ions, for example, Ca^{2+}, are involved in periodic processes in biological systems. We have developed a method by which such species can be incorporated in periodic reactions.[32] Since there is no way to build an oscillatory cycle around the chemistry of non-redox species, we used an indirect route to force them to oscillate.

We first sought acid−base equilibria (complex formation, hydrolysis, precipitation) in which the target ion participates and the equilibrium can be coupled to a pH oscillator. Under appropriate experimental conditions, the oscillatory pH changes shift the equilibrium between the unreacted and reacted states, producing periodic changes in the concentrations of all species involved in the equilibrium at the frequency of the pH oscillator. With this method we have generated oscillations in the concentrations of Ca^{2+}, Cd^{2+}, Al^{3+}, Zn^{2+}, Co^{2+}, Ni^{2+}, F^-, $(COO)_2^{2-}$, and $EDTA^{2-}$.

As an example, we show in Figure 2 oscillatory pulses in free Ca^{2+} measured in a CSTR containing the $BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$ oscillator with added CaEDTA.[32] At high pH, Ca^{2+} is bound in the Ca−EDTA complex; at low pH, it is free. The changes in Ca^{2+} concentration can be monitored with a Ca^{2+}-ion selective electrode (ISE) or visualized by adding a Ca^{2+}-sensitive indicator.

Oscillations in F^- concentration can be generated by coupling a precipitation and a complexation equilibrium to a pH oscillator. In the $BrO_3^- - SO_3^{2-} - Al(NO_3)_3 - NaF$ system (Figure 3), the core bromate−sulfite pH oscillator drives the first equilibrium to form $Al(OH)_3$ precipitate at high pH; the precipitate dissolves at low pH. If only the first equilibrium took place, the system would function as an Al^{3+} oscillator. However, if F^- ions are also present,

the first equilibrium drives the second, and the overall result is oscillation in F^- concentration.[33]

We suggest that similar processes may occur in biological systems to generate oscillatory pulses in the concentrations of some non-redox ions.

The spatial patterns that can develop in a thin solution or gel layer of an excitable or oscillatory mixture depend upon the relative diffusion rates of the activator and the inhibitor. When these are roughly equal, traveling waves are favored, while slower diffusion of the activator tends to result in stationary (Turing) structures.

pH oscillators are ideally suited for producing novel wave patterns and Turing structures, because (a) the effective diffusion rate of H^+, which often serves as activator, can be decreased by introducing large anions (e.g., polyacrylate) that bind protons and (b) any structures that develop can be visualized with acid−base indicators.

De Kepper and co-workers[34] worked out a design method to create Turing structures and other spatial patterns by running pH oscillators in a one-side-fed-reactor (OSFR). When the input concentrations and flow rate were varied in the $IO_3^- - SO_3^{2-} -$ thiourea pH oscillator, first spatial bistability and then spatiotemporal oscillations were observed in the disc-shaped reactor, which was composed of a 0.5−1.0 mm thick agarose gel. The traveling waves were slowed by introducing increasing amounts of sodium polyacrylate until the waves stopped and Turing structures appeared in the gel layer (see Figure 4).

Lagzi et al.[35] demonstrated that a pH oscillator coupled to a colloidal system can induce periodic interconversion between vesicle and micelle states. They added oleic acid, $pK_a \approx 8.3$, to the $HCHO - SO_3^{2-} -$ gluconolactone CSTR system, which oscillates between pH 7.0 and 9.5. Light scattering measurements showed that at high pH ($\sim$9.4), where the oleic acid is deprotonated, the negatively charged species repel each other, and micelles about 5 nm in size are formed; the mixture is transparent. The conversion
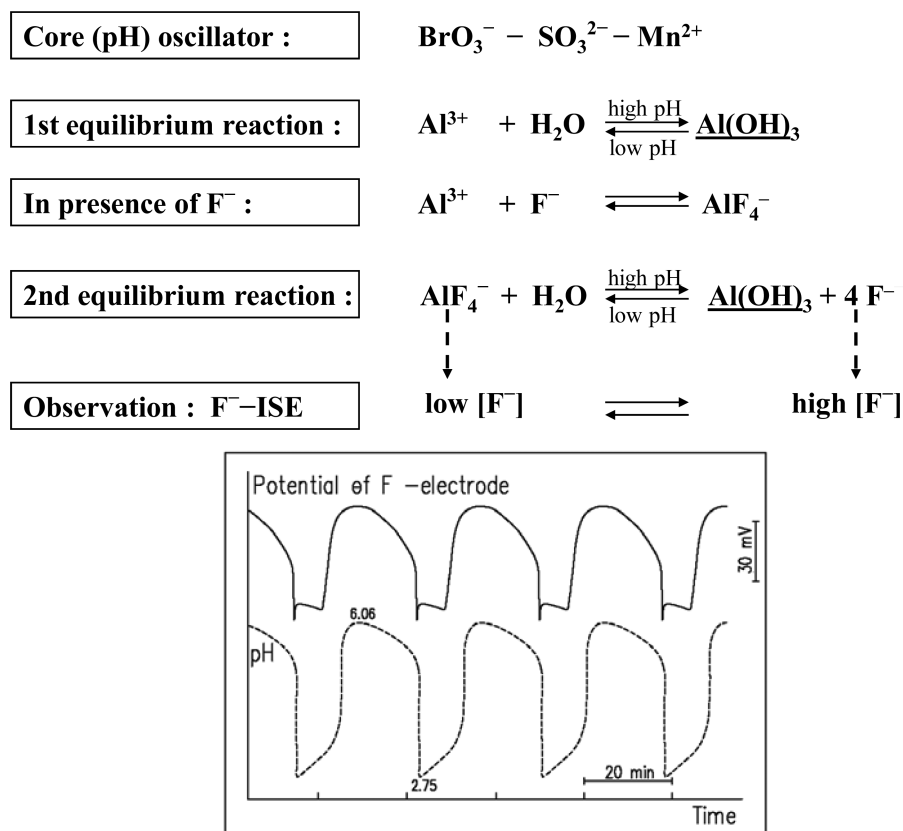
$$\text{Core (pH) oscillator :} \quad \text{BrO}_3^- - \text{SO}_3^{2-} - \text{Mn}^{2+}$$

$$\text{1st equilibrium reaction :} \quad \text{Al}^{3+} + \text{H}_2\text{O} \underset{\text{low pH}}{\overset{\text{high pH}}{\rightleftharpoons}} \text{Al(OH)}_3$$

$$\text{In presence of F}^- : \quad \text{Al}^{3+} + \text{F}^- \rightleftharpoons \text{AlF}_4^-$$

$$\text{2nd equilibrium reaction :} \quad \text{AlF}_4^- + \text{H}_2\text{O} \underset{\text{low pH}}{\overset{\text{high pH}}{\rightleftharpoons}} \text{Al(OH)}_3 + 4\,\text{F}^-$$

$$\text{Observation : F}^- - \text{ISE} \quad \text{low [F}^-\text{]} \rightleftharpoons \text{high [F}^-\text{]}$$

Figure 3. F^- concentration oscillations in the $\text{BrO}_3^- - \text{SO}_3^{2-} - \text{Mn}^{2+} + \text{Al(OH)}_3 + \text{NaF}$ flow system.
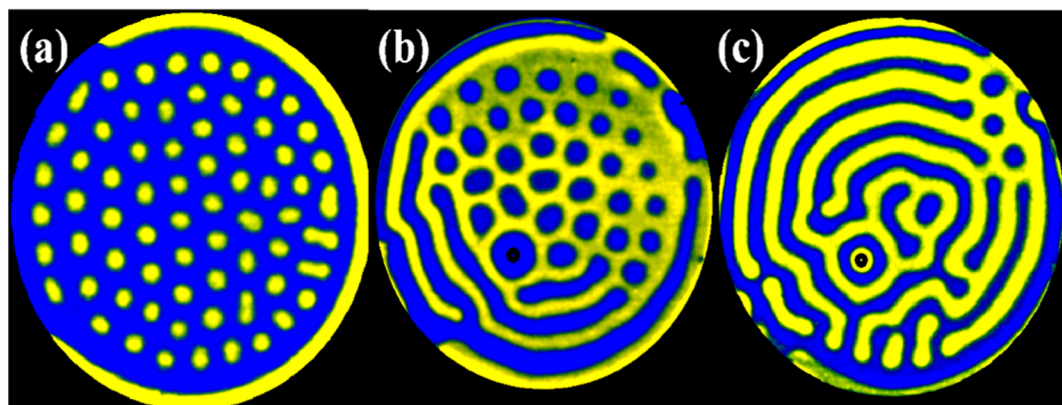

Figure 4. Hexagons (a), stripes (b), and a mixed Turing structure (c) observed in the gel disc of an OSFR fed with the $\text{IO}_3^- - \text{SO}_3^{2-} -$thiourea pH oscillator in the presence of polyacrylate. Reproduced with permission from ref 34. Copyright 2009 American Association for the Advancement of Science.

occurs around the pK value of the oleic acid. At low pH ($\sim$7), the oleic acid is mainly protonated, so the fatty acid molecules become neutral and undergo aggregation, forming bilayer membrane vesicles of about 100 nm radius; the solution becomes milky. This example illustrates that a molecular-scale subsystem, that is, a pH oscillator, can control the rhythmic aggregation–dispersion of macroscopic particles.

The use of pH oscillators to drive pH-sensitive biochemical processes was demonstrated by Liedl and Simmel[36] who used the $\text{IO}_3^- - \text{SO}_3^{2-} - \text{S}_2\text{O}_3^{2-}$ pH oscillator to switch a pH-dependent DNA structure between two conformations, folded and random coil (Figure 5). The transition takes place at pH 5.5–6.5 and is associated with the protonation and deprotonation of cytosine residues in the DNA. At pH < 5.5, the cytosines are protonated,

and the DNA strands are folded. The molecule assumes a random coil conformation at pH > 6.5, when the cytosines are deprotonated. The iodate–sulfite–thiosulfate system oscillates between pH 5 and 7, an ideal range to induce structural transitions in the DNA, and iodate is a sufficiently weak oxidant that it does not cause degradation of the DNA. The authors suggest that the induced periodic conformation changes, if transformed to a cyclic stretching–contracting motion, might be used for construction of DNA-based nanodevices.

A "molecular motor" is a device that can convert chemical energy directly into mechanical work. The heart of one type of motor is a piece of pH-sensitive hydrogel that undergoes repetitive changes in its volume or length when it is connected to a pH oscillator. These movements may be transformed to
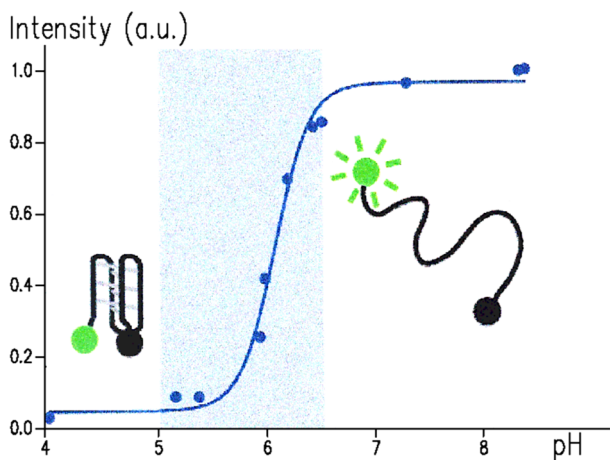
Figure 5. Switching of the conformation of DNA molecules between the folded and random coil states driven by the $IO_3^- - SO_3^{2-} - S_2O_3^{2-}$ pH oscillator. Reproduced with permission from ref 36. Copyright 2005 American Chemical Society.

mechanical work by attaching the gel to a weight or wall, against which it expands and contracts. Such a molecular machine could be fuelled by a pH oscillator. Research to date has focused on identifying the most appropriate responsive gels and finding experimental methods to characterize their mechanical and physical properties. An ideal gel would respond at least as fast as the frequency of the pH oscillator and would show large volume changes as the environmental pH is varied.

Experiments have been performed in which the gel to be tested is suspended in a CSTR, with a small weight glued to its lower end. The reactants of a pH oscillator are continuously supplied into the reactor, and changes in the pH and the gel dimensions are recorded. To date, $H_2O_2 - SO_3^{2-} - Fe(CN)_6^{4-}$, $BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$, and $BrO_3^- - SO_3^{2-} - Mn^{2+}$ have been utilized

as the pH oscillators. Such an experimental arrangement is shown in Figure 6.

A recent advance was reported by Okay and co-workers,[38] who prepared a poly(acrylic acid) cryogel, which seems to be the most promising candidate as a gel to use in molecular motors. When this gel was coupled to the $BrO_3^- - SO_3^{2-} - Fe(CN)_6^{4-}$ oscillator, 3-fold changes in the gel volume were observed, with swelling and shrinking response times of just seconds. The system functioned with macroscopic gel samples (1 cm length, 0.5 cm diameter), and its macroporous gel structure was resistant to the repetitive swelling−shrinking cycles.

One of the more practical applications suggested for pH oscillators is the development of a periodic drug delivery system.[39] The ionization state of a drug that has a protonatable group can be periodically switched by a pH oscillator if the pK_a of this group falls within the pH range of the oscillator. Because only uncharged species penetrate the cell membrane, the drug will appear in pulses on the other side of this barrier. Misra and Siegel[40] carried out a proof-of-principle experiment, in which they assembled and tested a device consisting of a CSTR and a side-by-side diffusion cell in which the donor and receptor sides were separated by a membrane. They used the $BrO_3^- - SO_3^{2-} -$ marble pH oscillator, with benzoic acid as the "drug" and an ethylene-vinyl copolymer as the membrane. When a mixture of benzoic acid and the components of the pH oscillator was circulated in the donor side of the cell, periodic accumulation of benzoic acid was detected on the receptor side. Figure 7 shows the experimental setup and the results. More recently, Bhalla and Siegel[41] developed a hormone delivery system constructed from biocompatible reagents and a hydrogel that was able to produce rhythmic pulses of gonadotropin releasing hormone as well as pH for a week.

A pulsating drug delivery device might be more effective than conventional approaches, particularly in diseases that show strong circadian dependency. However, significant obstacles must be overcome to construct a usable drug delivery system of this type. One cannot use a CSTR; any buffering effect of the
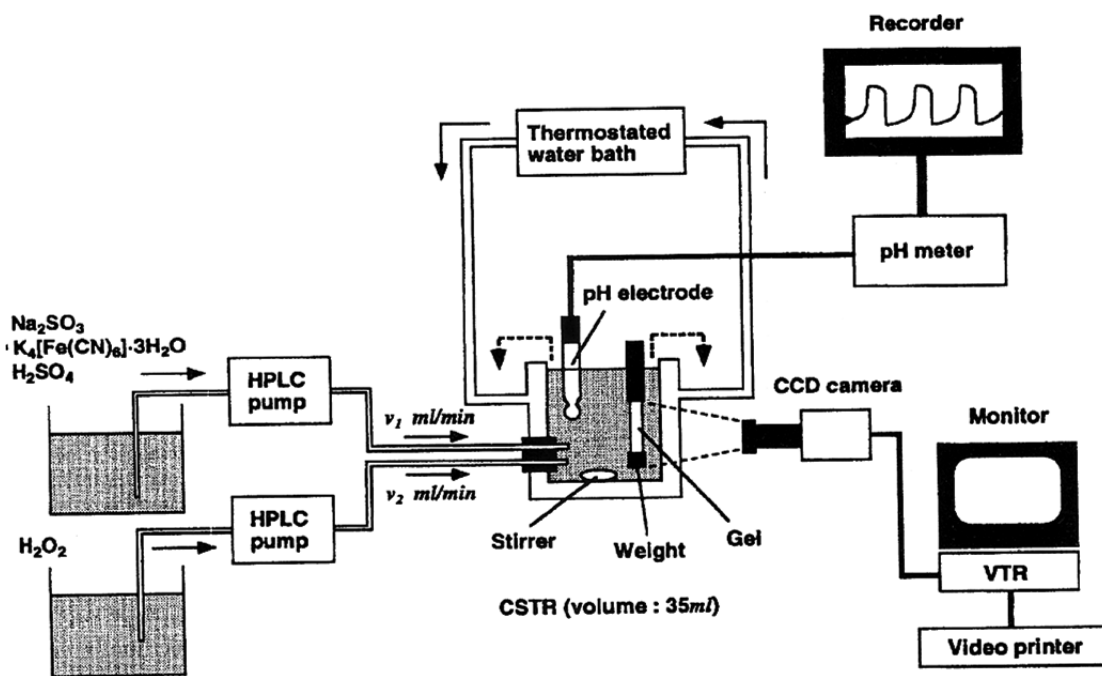

Figure 6. Experimental arrangement to measure the gel size in the $H_2O_2 - SO_3^{2-} - Fe(CN)_6^{4-}$ pH oscillator. Reproduced with permission from ref 37. Copyright 1996 Elsevier B.V.
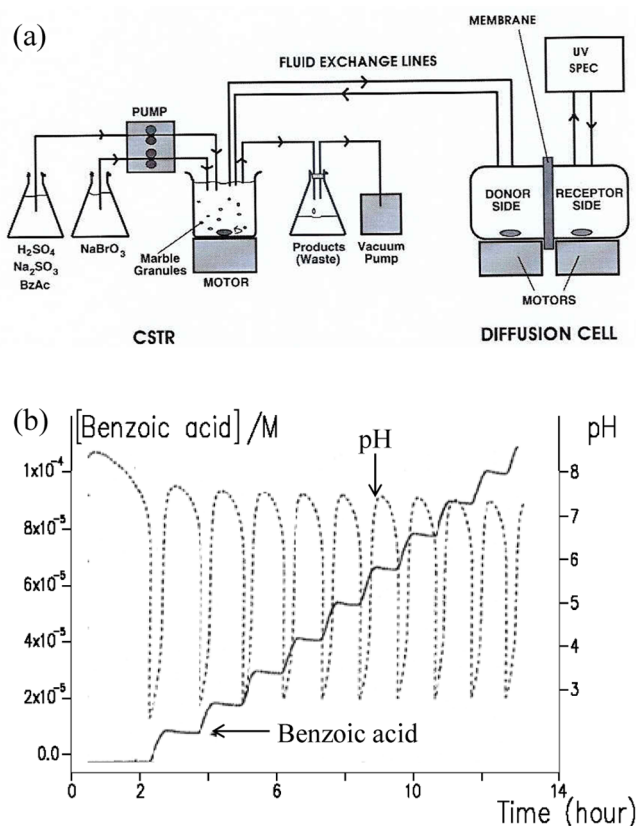
Figure 7. Experimental model of a drug delivery device based on a pH oscillator: (a) setup; (b) pH oscillation in donor cell and accumulation of benzoic acid in receptor cell. Reproduced with permission from ref 40. Copyright 2002 Elsevier B.V.

drug may destroy the pH oscillations; the oxidant of the oscillator may oxidize the drug; diffusion through the membrane may be too slow with respect to the period of the oscillator. Nonetheless, the idea appears worth pursuing.

CONCLUDING REMARKS

Clearly, the study of pH oscillators has come a long way during the past quarter century. What can we expect in the next 25 years? Our expectation is that future work will focus less on expanding the roster of systems than on fulfilling the potential of the applications described here and of others yet to be imagined. A key to carrying out this program is to develop batch pH oscillators, systems that, like the classic BZ reaction, oscillate for an extended period of time in a closed system without the need for a flow of fresh reactants. By focusing on the need to regenerate the component that is consumed most rapidly, we have succeeded[42] in generating oscillations in a closed *two-phase* system in the following CSTR pH oscillators: $BrO_3^- - HSO_3^- - Mn^{2+}$, $BrO_3^- - HSO_3^- - Fe(CN)_6^{4-}$, and $IO_3^- - HSO_3^- - Fe(CN)_6^{4-}$. The key component was supplied by slow dissolution from a gel layer at the bottom of reaction vessel containing a high concentration of the reagent in question. In each case, we used silica gel loaded with Na_2SO_3, the most common reductant in the pH oscillators. Silica gel can hold high concentrations of SO_3^{2-} (>2 M), is inert to its environment, is rigid and resistant to the intense stirring, and releases the loaded species at a nearly constant rate for many oscillatory periods. The fact that a number of pH oscillators have ranges that encompass pH 7 makes them better candidates for applications that require biocompatibility

than their halogen-based counterparts, which tend to oscillate at much more acidic pHs.

Although we have not discussed them in detail here, we note also that several general models for pH oscillators have been proposed,[43] which can be easily adapted to describe the detailed behavior of new systems or to characterize new configurations such as the closed two-phase system described above, semi-batch reactors,[44] or more complex arrangements involving membranes for drug delivery.[40] The possibility of covalently linking one or more components of a pH oscillator to a polymer whose volume changes with pH, much as has been done with the BZ reaction and redox-sensitive polymers,[45] is also worth exploring.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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