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An Organic-Based pH Oscillator

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In a recent paper, we suggested that the acid- or base-catalyzed dehydration of a hydrated carbonyl compound provides a suitable foundation for an organic-based pH oscillator. Here we present the first experimental example of such an oscillator in a flow reactor, utilizing the base-catalyzed dehydration of methylene glycol as a source of positive feedback (OH^- autocatalysis) coupled with the base-catalyzed hydrolysis of gluconolactone for negative feedback (H^+ production). The large amplitude oscillations (between pH 7 and 10) are reproduced in a kinetic model of the reaction. Such experiments present new possibilities in the design of pH oscillators.

Introduction

Chemical oscillations occur widely in biology, as a natural consequence of the feedback processes that occur in living systems.[1] There is considerable interest in the development of simple chemical oscillators that mimic certain features of these biological systems to provide insight into these nonlinear processes.[2,3] Recently, Kurin-Csorgei et al. utilized a pH oscillating chemical reaction to drive a complexation process, as a means of investigating the periodic pulsing of metal ions such as calcium.[4,5] It has also been suggested that pH oscillators may be coupled with a chemo-sensitive polymer to directly convert chemical energy into mechanical energy.[6] Such devices may find applications in periodic drug delivery, or as actuators, micropumps or switches.[7,8] There is a need for the development of less aggressive, biocompatible pH oscillators as, to date, pH oscillating reactions are limited to redox reactions involving halogens, sulfur and a few transition metals in an open reactor.[9,10]

In a recent paper, we suggested that the base-catalyzed dehydration of a carbonyl compound may provide a suitable source of positive feedback for the development of an organic-based pH oscillator.[11] The minimal model we proposed was based on the methylene glycol−sulfite reaction, which displays complex behavior in a flow reactor.[12] Large amplitude oscillations were observed in this model upon addition of a base consuming step. Here we present experimental results with the methylene glycol−sulfite reaction coupled to the hydrolysis of gluconolactone. The latter is a base-catalyzed, acid producing, reaction that provides the necessary delayed negative feedback required for the observation of oscillations. Moreover, gluconolactone is produced during the enzymatic oxidation of glucose, a reaction which is exploited in devices for the detection of glucose.[13] Thus our experiments present new possibilities in the design of biocompatible pH oscillators. The oscillations are reproduced in a kinetic model of the system.

Experimental Section

Three stock solutions were prepared in doubly distilled deionized water: methylene glycol, sulfite/bisulfite buffer and gluconolactone. The solution of methylene glycol was prepared by diluting 37% formalin solution (Aldrich) 1 day in advance to allow complete de-polimerization. The solution of sodium sulfite and metabisulfite was freshly prepared daily from reagent grade Na_2SO_3 and $Na_2S_2O_5$ (Aldrich) and bubbled with nitrogen. The gluconolactone solution was also prepared freshly from reagent grade D-gluconic acid-lactone (Aldrich). This stock solution was used for a maximum of up to 40 min as the hydrolysis of gluconolactone begins upon dissolution.

The reactor used in batch and continuous flow experiments is a 50 mL water-jacketed cylindrical-shaped glass reactor. The pH was measured by a calibrated combination pH electrode (Mettler Toledo) and a Hanna pH meter connected to a computer. The electrode potential measurements were carried out with a combination redox electrode and Keithley 2000 multimeter also connected to a PC. The temperature was kept constant at 20 °C with a Haake thermostat. The reactor was stirred by an Ika magnetic stirrer and the stirring rate was kept at 400 rpm in all experiments. The batch experiments were started by simultaneously adding the gluconolactone and methylene glycol solution to the sodium sulfite and bisulfite solution. In the continuous stirred tank reactor (CSTR) experiments, the three stock solutions were pumped into the reactor by a Gilson peristaltic pump.

Results and Discussion

Previously, we studied the methylene glycol−sulfite reaction:[12]

$$CH_2(OH)_2 + SO_3^{2-} \rightleftharpoons CH_2(OH)SO_3^- + OH^- \qquad (A)$$

This reaction shows clock behavior in a batch reactor, with an induction period followed by a rapid transition from pH ∼ 6 to pH ∼ 10. Bistability and small amplitude, irregular, oscillations in pH were obtained when the reaction was performed in a continuous stirred tank reactor (CSTR). Further investigation led us to suspect that the primary source of feedback in this system is the base-catalyzed rate determining step: the dehydration of methylene glycol (step 1 in Table 1). In a simplified model of the reaction, we demonstrated that coupling this reaction with a suitable OH^- consuming step would lead to large-amplitude, periodic oscillations in a flow reactor.[11]

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TABLE 1: Mechanism for the Methlyene Glycol−Sulfite Reaction with Gluconolactone Where GL = Gluconolactone, GA = Gluconic Acid and G^- = Gluconate Anion

reaction	rate	rate constant
(1) $CH_2(OH)_2 \rightleftharpoons CH_2O + H_2O$	$R_1 = (k_1 + k_{OH}[OH^-])[CH_2(OH)_2]$	5.5×10^{-3} s^{-1}, $k_{OH} = 2100$ M^{-1} s^{-1}
	$R_{-1} = k_{-1}[CH_2O]$	10 s^{-1}
(2) $HSO_3^- \rightleftharpoons SO_3^{2-} + H^+$	$R_2 = k_2[HSO_3^-]$	3.1×10^3 s^{-1}
	$R_{-2} = k_{-2}[SO_3^{2-}][H^+]$	5×10^{10} M^{-1} s^{-1}
(3) $CH_2O + SO_3^{2-} \rightarrow CH_2(O^-)SO_3^-$	$R_3 = k_3[CH_2O][H^+]$	5.4×10^6 M^{-1} s^{-1}
(4) $CH_2(O^-)SO_3^- + H^+ \rightleftharpoons CH_2(OH)SO_3^-$	$R_4 = k_3[CH_2(O^-)SO_3^-][H^+]$	1×10^{10} M^{-1} s^{-1}
	$R_{-4} = k_{-4}[CH_2(OH)SO_3^-]$	2×10^{-3} s^{-1}
(5) $H_2O \rightleftharpoons H^+ + OH^-$	$R_5 = k_5$	1×10^{-3} M s^{-1}
	$R_{-5} = k_{-5}[H^+][OH^-]$	1×10^{11} M^{-1} s^{-1}
(6) GL $\rightleftharpoons$ GA	$R_6 = (k_6 + k_{OH}[OH^-])[GL]$	8×10^{-4} s^{-1}, $k_{OH} = 2000$ M^{-1} s^{-1}
	$R_{-6} = k_{-6}[GA]$	1.6×10^{-4} s^{-1}
(7) GA $\rightleftharpoons G^- + H^+$	$R_7 = k_7[GA]$	2.5×10^2 s^{-1}
	$R_{-7} = k_{-7}[G^-][H^+]$	1×10^6 M^{-1} s^{-1}

The hydrolysis of gluconolactone produces gluconic acid and is base-catalyzed:[14]

$$C_6H_{10}O_6 + H_2O \rightleftharpoons C_6H_9O_7^- + H^+ \qquad \text{(B)}$$

Upon addition of appropriate concentrations of gluconolactone (GL) to a methylene glycol−sulfite clock reaction in a batch reactor, we observed a single peak indicative of positive feedback (rapid transition to high pH) coupled with delayed negative feedback (decay to low pH) (Figure 1a).

Oscillations were observed in the methlyene glycol−sulfite reaction in a CSTR upon addition of gluconolactone. The behavior was monitored with a platinum electrode and with a pH electrode. The oscillations in potential were small (of the order of 1 mV), demonstrating that unlike other pH oscillatory systems, this reaction is not based on redox processes (Figure 1b). Large amplitude pH oscillations were observed, typically between pH 7 and 10 (Figure 1c). Despite the rapid aging of the GL stock solution, we observed little dampening in the oscillations with stock solutions up to around an hour old.

An experimental bifurcation diagram is plotted in Figure 2a. Upon increasing the flow rate (k_0) in a CSTR, there is a transition from a high pH steady state to oscillations. The maxima and minima of the oscillations are marked in this diagram. The period and amplitude of the oscillations increases with increasing flow rate. The phase diagram in Figure 2b indicates the parameter values necessary for oscillatory behavior (closed circles). Oscillations were observed for a reasonable range of inflow concentrations of gluconolactone, $[GL]_0$, and flow rates.

The essential features of this system are captured in a simple model (Table 1). The methlyene glycol−sulfite reaction model has been previously investigated.[12] The main reactions are steps 1−5 in Table 1. To these reactions, we add steps 6 and 7 with previously reported rate constants.[14] Reactions 1 and 6 are base or acid-catalyzed depending on the conditions. The acid catalysis channel is not significant at the pH in this work and so is omitted for simplicity. Inclusion of the acid catalysis in the rate law makes no difference to the simulated behavior. Numerical integration of the eleven resulting kinetic equations gives rise to a single oscillation in pH under appropriate batch conditions (Figure 3 a). Oscillations are obtained in the open system when the rate laws are augmented with flow terms $k_0([X]_0 - [X])$ where k_0 is the flow rate and the concentration $[X]_0$ is the inflow concentration of species X. Numerical integration of the rate equations was performed using package XPPAUT.[15] The method of integration was CVODE with, typically, $dt = 0.01$ and ATOL (tolerance) $= 1 \times 10^{-8}$. Bifurcation and phase diagrams were calculated using the AUTO interface of XPPAUT. The time step was 1×10^{-5} and tolerances were set at 1×10^{-5}.

The oscillations take place between pH values of 7 and 10 and are of the same form as those observed in the experiment, with a slow evolution of OH^-, followed by a more rapid production of that species (Figure 3b). We note that an important feature of the methylene glycol−sulfite reaction is the sulfite−bisulfite buffer (step 2) with a pK_a of 7.2. The buffer damps any changes in pH up to around pH 8 at which point all sulfite has been consumed in step (4), and there is a rapid, autocatalytic, evolution of OH^-. With high $[OH^-]$, the catalyzed hydrolysis of gluconolactone becomes significant, returning the pH to neutral.

Oscillations occur via a supercritical Hopf bifurcation at $k_0 = 4.5 \times 10^{-3}$ s^{-1} and disappear via a saddle node infinite period (SNIPER) bifurcation at $k_0 = 5.3 \times 10^{-3}$ s^{-1} (Figure 3c). Thus

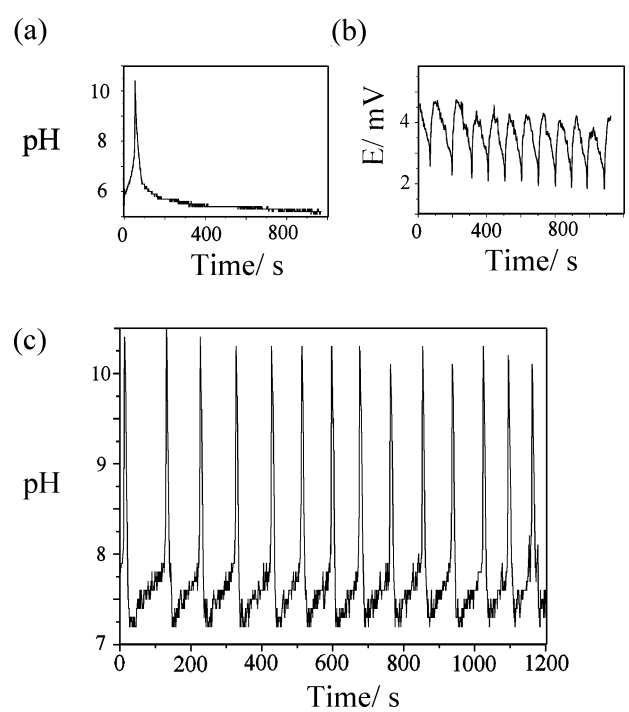

Figure 1. Methylene glycol−sulfite−gluconolactone reaction with $[CH_2(OH)_2]_0 = 0.10$ M, $[SO_3^{2-}]_0 = 5 \times 10^{-3}$ M, $[HSO_3^-]_0 = 0.05$ M, and $[GL]_0 = 6.7 \times 10^{-3}$ M unless otherwise stated. (a) pH changes versus time in a batch reactor. (b) Pt potential oscillatory changes in a flow reactor with $k_0 = 5.22 \times 10^{-3}$ s^{-1}. (c) Large amplitude pH oscillations in a flow reactor with $[GL]_0 = 8 \times 10^{-3}$ M and $k_0 = 5.76 \times 10^{-3}$ s^{-1}.

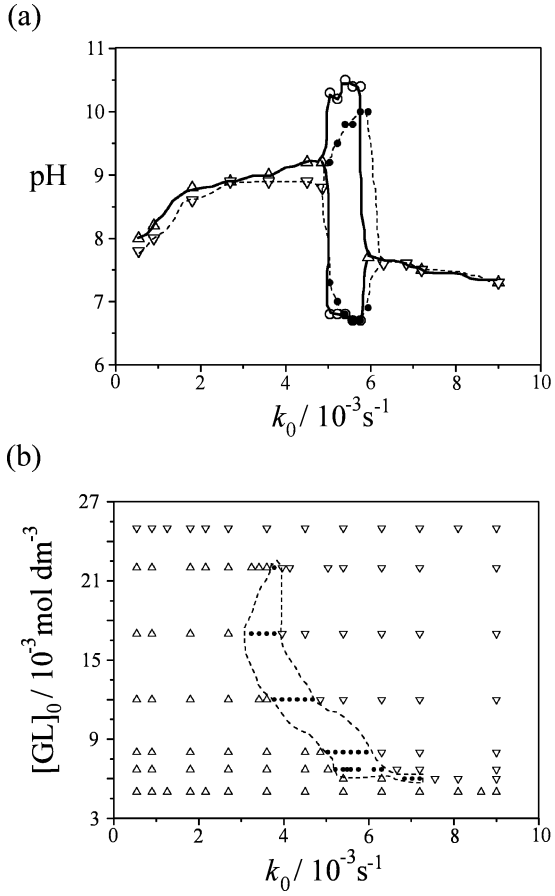

Figure 2. (a) Bifurcation diagram showing the evolution of pH oscillations with flow rate in a CSTR. Experimental conditions: $[CH_2(OH)_2]_0 = 0.10$ M, $[SO_3^{2-}]_0 = 5 \times 10^{-3}$ M, $[HSO_3^-]_0 = 0.05$ M, $[GL]_0 = 8 \times 10^{-3}$ M. ○ = oscillatory state with increasing flow rate, ● = oscillatory state with decreasing flow rate, △ = pH steady state with increasing flow rate, ▽ = pH steady state with decreasing flow rate. (b) Phase diagram of methylene glycol−sulfite−gluconolactone flow system in the gluconolactone concentration−flow rate plane. Fixed parameters: $[CH_2(OH)_2]_0 = 0.10$ M, $[SO_3^{2-}]_0 = 5 \times 10^{-3}$ M, $[HSO_3^-]_0 = 0.05$ M. ● = oscillatory state, △ = high pH steady state, ▽ = lower pH steady state.

there is an increase in the period and amplitude of oscillations with increasing flow rate. The region of oscillations as a function of GL inflow concentration is shown in Figure 3d and has the conventional cross-shape.[16] Preliminary results indicate that bistability is observed in experiments with $[GL]_0 \leq 3 \times 10^{-3}$ M. We also note that the region of oscillations in the state diagram is sensitive to the stirring rate. These results will be discussed further in a more detailed paper.

In conclusion, we have demonstrated how the base catalysis of methylene glycol can be coupled with hydrolysis of gluconolactone to create an organic-based pH oscillator. The reaction displays large amplitude oscillations in OH^- when performed in a CSTR. Our simple model of the reaction is in excellent agreement with the experimentally observed behavior. More quantitative agreement might be obtained upon inclusion of additional steps which may be important such as the Cannizzaro reaction, or the decay of GL in the stock solution.

As many hydrolysis and dehydration processes are acid or base-catalyzed, we believe these experiments present new possibilities in the design of pH oscillators. Methylene glycol can be replaced by a number of organic species with a carbonyl group, which have a stable hydrated form and undergo base-catalyzed dehydration. Additionally, the gluconolactone may be replaced with the glucose−glucose oxidase enzyme (GOX) reaction, which also produces gluconolactone, thereby creating an enzymatic negative feedback loop.[17,18] A biocompatible pH oscillator may eventually be used as a probe or sensor in biological systems or provide a source of chemical energy for chemo-sensitive polymeric devices.

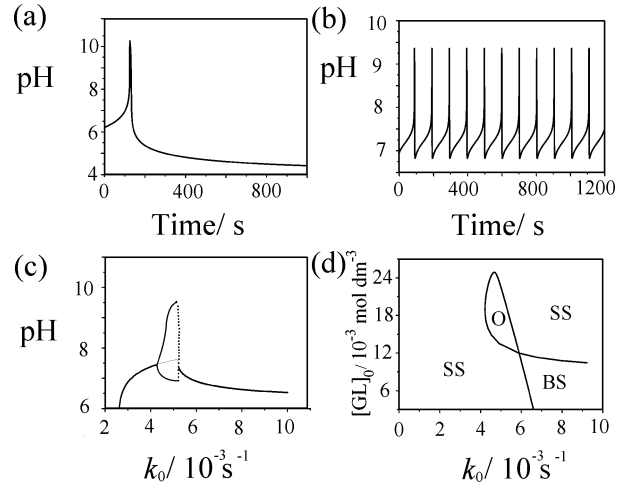

Figure 3. Model (Table 1) calculations with $[CH_2(OH)_2]_0 = 0.10$ M, $[SO_3^{2-}]_0 = 5 \times 10^{-3}$ M, $[HSO_3]_0 = 0.05$ M, $[GL]_0 = 0.02$ M unless otherwise stated. (a) pH time trace in closed system with $[GL]_0 = 6.7 \times 10^{-3}$ M. (b) pH oscillations in an open system with flow rate $k_0 = 5 \times 10^{-3}$ s^{-1}. (c) Bifurcation diagram with oscillations for $k_0 = (4.3-5.3) \times 10^{-3}$ s^{-1}. (d) Phase diagram where O = region of oscillations, SS = steady state and BS = bistability.

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