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# Temporal viscosity modulations driven by a pH sensitive polymer coupled to a pH-changing chemical reaction<sup>†</sup>

D. M. Escala,\*<sup>a</sup> A. P. Muñuzuri, 问 <sup>a</sup> A. De Wit <sup>b</sup> <sup>b</sup> and J. Carballido-Landeira<sup>b</sup>

The Formaldehyde-Sulfite (FS) and the Formaldehyde-Sulfite-Gluconolactone (FSG) systems are examples of complex chemical reactions accompanied by well-controlled variations in pH. While the FS system exhibits a clock behavior, in the FSG reaction, this mechanism is coupled with the hydrolysis of the gluconolactone which gives the possibility to show large temporal oscillations of pH in an open reactor. In this work, we show how these reactive systems, due to their organic nature, can be coupled with pH sensitive polymers, particularly with polyacrylic acid (PAA) to trigger temporal changes of viscosity. We characterize this coupled reactive system showing the effects of changes in the initial concentrations of the polymer and in the chemical reagents on the induction time, the magnitude of the pH variations and the temporal modifications of the viscosity.

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## Introduction

The development of new pH sensitive systems has recently attracted major interest due to their potential applications in many different fields. From a biomedical point of view, many cancer therapies are focused on delivering specific drugs *via* pH sensitive carriers into tumors where the pH is acid.<sup>1,2</sup> More generally, the study of pH sensitive materials and their interaction with different biological or chemical media can provide new horizons to treat many other diseases.<sup>3,4</sup> Towards that goal, a reliable methodology to couple a pH sensitive polymer to a pH clock reaction would be useful for testing new design drugs in an easy and cost effective way.

In parallel, controlling viscous fingering hydrodynamic instabilities by *in situ* chemically-driven viscosity changes<sup>5,6</sup> constitute another field of interest due to related applications in chemical and petroleum engineering.<sup>6,7</sup> Viscous fingering occurs when a less viscous fluid displaces a more viscous one, and gives rise to fingered deformation of the interface, which is detrimental to the displacement process. From an experimental point of view, chemical neutralization reactions coupled to pH sensitive polymers have been shown to modify<sup>7–9</sup> such fingering.

From a numerical point of view, several works have shown the efficiency of reactions to modulate the properties of this hydrodynamic instability.<sup>10–12</sup> In this context, the coupling here proposed between pH oscillators and viscosity changes opens a broad horizon for controlling viscosity-driven hydrodynamic instabilities.

The use of organic pH sensitive polymers is of interest in those applications to seek coupling with reactions presenting temporal modifications in the pH.<sup>13-15</sup> However, such pH changing reactions are typically inorganic and usually destructive towards pH sensitive polymers. Organic pH changing reactions have recently been introduced based on the Formaldehyde-Sulfite (FS) clock reaction,<sup>16,17</sup> and the Formaldehyde-Sulfite-Gluconolactone (FSG) reaction,<sup>18</sup> where the hydrolysis of a cyclic ester (gluconolactone) (and the subsequent pH decrease) is catalyzed by the basic environment of the clock generated after the consumption of the sulfite/bisulfite buffer by the formaldehyde dehydration.<sup>19</sup> Both systems feature rich and complex temporal behaviors, such as for example oscillations of pH when all the reagents are put together in an open continuously stirred tank reactor.<sup>19</sup> Although these systems have been extensively studied and characterized, in ref. 19 the possibility to find a coupling between these reactions and a pH sensitive polymer is opened.

In this context, we analyze here experimentally the dynamic coupling between a polyacrylic acid (PAA) polymer, the viscosity of which is sensitive to pH and the aforementioned FS and FSG pH clock reactions. PAA is a very well-studied acid polyelectrolyte capable to elongate its shape at high pH in aqueous solutions,<sup>8,20</sup> which produces an increase in the solution viscosity. Furthermore, PAA is one of the simplest pH sensitive polymers which can be

<sup>&</sup>lt;sup>a</sup> Group of Nonlinear Physics, Universidade de Santiago de Compostela,

Santiago de Compostela E-15782, Spain. E-mail: alberto.perez.munuzuri@usc.es <sup>b</sup> Université libre de Bruxelles (ULB), Nonlinear Physical Chemistry Unit, Service de Chimie Physique et Biologie Théorique, CP231, Campus Plaine,

<sup>1050,</sup> Brussels, Belgium

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<sup>‡</sup> Current address: Universidad de Oviedo, Campus de Llamaquique, Facultad de Ciencias, Departamento de Física, C/ Calvo Sotelo, s/n, 33007, Oviedo, Spain.

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used with pH reactions. We show that, when PAA is mixed to the FS and FSG systems, chemically-driven temporal changes in the pH can induce a related temporal change in viscosity of the solution. We further demonstrate that the resulting system not only keeps the original features of the chemical reactions but that the viscosity changes are coupled to the kinetics of the chemistry. This introduces the FS–PAA and the FSG–PAA systems as potential candidates for controlling *in situ* the viscosity of a given environment depending on its pH.

## Materials and methods

The sodium sulfite stock solution was prepared from reagent grade Na<sub>2</sub>SO<sub>3</sub> (Sigma) diluting 25.21 g of reagent in 100 ml of double distilled water bubbled with argon to avoid oxidation. The PAA solution was prepared by diluting 1 g of the reagent grade polyacrylic acid with an average molecular weight of 4 000 000 g mol<sup>-1</sup> (Sigma), into 180 ml of double distilled water at 80 °C to facilitate solubility. After a complete solubilization, the mixture was cooled down to 23 °C and the final volume was kept at 200 ml obtaining a PAA stock solution of 0.5 wt%. The formaldehyde was used directly as a stock solution from commercial formalin solution (Sigma-Aldrich). The gluconolactone stock solution was freshly prepared for each experiment from reagent grade D-(+)-gluconic acid Delta-lactone (Sigma) diluting 0.356 g of gluconolactone in 10 ml of double distilled water. This solution has been used always fresh and in less than 300 seconds after being prepared in order to avoid hydrolysis effects.

For the Formaldehyde-Sulfite (FS–PAA) system, all the experiments were prepared mixing the sulfite and the PAA stock solutions and gently stirring to homogenize the polymer into the overall stock solution. Finally, a specific volume of formaldehyde was added to the previous mixture in order to start the reaction. To accurately account for the initial stages of the reaction the formaldehyde was always added 10 s after starting recording the dynamics. For the Formaldehyde-Sulfite-Gluconolactone (FSG–PAA) system, the gluconolactone (GLN) and the formaldehyde solutions where added simultaneously to the stock composed by the PAA and the sulfite mixture. All experiments were carried out in a 10 ml glass beaker using a magnetic stirrer at constant speed. Temperature was kept constant at 23 °C using a water thermostat. The chemical reactions describing the system are presented in the ESI.<sup>†</sup>

The temporal evolution of the pH has been recorded using an electronic pH-meter (Vernier) connected to a PC with a temporal resolution of 1 second. The viscosity was measured with a TA AR2000 rheometer using a 60 mm steel cone geometry with  $1^{\circ}$  angle in a cone-plate arrangement. The lower plate kept the temperature constant at 23 °C *via* a Peltier system. All measurements were done at a constant shear rate of 500 s<sup>-1</sup>.

In some experiments, temporal evolutions of viscosity and of pH were recorded simultaneously. For those cases, the solution was prepared in a beaker as stated above and the pH-meter was introduced in the solution to get the recordings. Some part of this solution was then taken into the rheometer. Thus, there is an intrinsic delay between the beginning of the pH recordings and those of viscosity due to the experimental procedure.

All the experiments presented in this work have been repeated at least three times and the error bars on experimental values have been calculated *via* their standard deviation.

### Results and discussion

The coupling of a polymeric compound with a chemical pH oscillator is far from trivial, especially if we want the temporal characteristic features of the reaction to prevail. Not only important changes in pH are required but also sufficiently large resulting viscosity changes must be obtained. For this purpose, we introduce the following modifications to the original pH clock reactions.<sup>16,18,19</sup> In the original FS reaction,<sup>21</sup> the pH switch ("clock" behavior) is due to the consumption of the sulfite/bisulfite buffer during the dehydration of the formaldehyde. We modify the original recipe by adding PAA and removing the bisulfite as a stock reagent (see ESI<sup>+</sup> for details). The reason for this is that the bisulfite needed is generated by a pH equilibrium displacement between the sulfite already present and the acidic environment provided by the dissociation of PAA.<sup>22</sup> The bisulfite can be used in the coupling with the polymer, but in such a case, the presence of sulfite in the chemical system has to be guaranteed. Because of this, the simplest way to obtain sulfite from bisulfite and PAA would be to displace the pH equilibrium by adding sodium hydroxide into the medium. Although this method could be used as an alternative route to obtain the "clock" behavior (see ESI<sup>+</sup>), it would increase the complexity of the coupling by adding NaOH as one more reagent (additionally, see ESI,† the viscosity jumps obtained were remarkably smaller).

Fig. 1 presents the evolution of pH and viscosity for both systems, i.e., FS-PAA and FSG-PAA. Note that the viscosity evolves in a similar way as the pH curve in both cases. In the case of a FS-PAA system (Fig. 1a), the increase of viscosity correlates to the change in pH such that both show the characteristic "clock" shape. In a more complicated scenario, such as in the FSG-PAA system (Fig. 1b), the "peak" shape exhibited by the pH is simultaneously reproduced by the viscosity. Therefore, the temporal evolution of the viscosity is driven by the reaction kinetics and follows the same temporal signature as the modifications presented by the pH. To understand this pH/viscosity coupling we present in the forthcoming sections the effects of variations in each reagent concentration on the pH dynamics, in the reaction features and consequently, on their viscosity effects. We will first show the coupling between the PAA polymer and the FS clock reaction and next with the FSG chemical system.

#### (A) FS-PAA system

Fig. 2 is a summary of the different behaviors observed by varying the initial chemical concentrations in the FS–PAA system. For each experiment we recorded the temporal evolution of the pH (column a), the difference between the initial and final pH ( $\Delta$ pH) and viscosity ( $\Delta$  $\eta$ ) (column b) and the induction time as the time needed for the system to exhibit the clock (column c). Row 1 in Fig. 2 analyzes the effect of increasing the initial



**Fig. 1** Temporal evolution of pH and viscosity for (a) FS–PAA and (b) FSG–PAA systems. In both cases  $[SO_3^{2-}]_0 = 0.0684 \text{ M}$ ,  $[PAA]_0 = 0.4386 \text{ wt\%}$  and  $[formaldehyde]_0 = 0.0653 \text{ M}$ . In (b)  $[GL]_0 = 0.0070 \text{ M}$ . The shear rate and the temperature were fixed at 500 s<sup>-1</sup> and 23 °C, respectively.



**Fig. 2** Characterization of the FS–PAA system: pH temporal evolution (column a), viscosity and pH jumps (measured as the difference between the final and initial values) (column b), and induction time variation (column c). Row 1: PAA was varied for constant  $[SO_3^{2-}]_0 = 0.0684$  M and [formaldehyde]\_0 = 0.0933 M. Row 2: sulfite was varied for constant [formaldehyde]\_0 = 0.0933 M and [PAA]\_0 = 0.4386 wt%. Row 3: [formaldehyde] was varied for constant  $[SO_3^{2-}]_0 = 0.0684$  M and [PAA]\_0 = 0.4386 wt%. All viscosity measurements were made using a shear rate of 500 s<sup>-1</sup>.

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concentration of PAA while keeping all other initial concentrations constant (namely, the formaldehyde and sulfite initial concentrations). Several effects can be observed when the PAA concentration is increased (Fig. 2, row 1). The initial pH drastically reduces from 9.3 down to values around 7 due to the acidity of the polymer solution. The final value of the clock is also lowered down by 2 pH units. The global  $\Delta$ pH difference (Fig. 2b1) does not reflect measurable changes with the polymer concentration (even though it slightly reduces for [PAA]<sub>0</sub> > 0.25 wt%) but it is, in any case, significantly larger compared to the case without PAA. This is in contrast with the viscosity jump  $\Delta\eta$ , which presents a sudden sharp increase when the PAA concentration increases above 0.35 wt%. Note that experiments were conducted for concentrations well below the overlap concentration<sup>23,24</sup> (see ESI† for details) so we did not take into account those effects.

In addition, by increasing the polymer concentration, the FS–PAA system shows longer induction times (*i.e.* longer interval of time required to jump to the final stable pH value), which is particularly noticeable for PAA concentrations larger than 0.35 wt% (see Fig. 2c1). Therefore, the addition of PAA to the pH clock reaction has two antagonistic behaviors: it enhances the viscosity difference while it slightly decreases the pH difference. In the forthcoming analysis we will use a PAA initial concentration of 0.4386 wt%, which provides the best balance between pH jumps and viscosity jumps.

The first row in Fig. 2 shows that the polymer is the key ingredient to couple the clock reaction and the viscosity changes. The PAA affects the system in a similar way as the bisulfite from the original recipe.<sup>18</sup> In this sense, the acidic environment generated by the dissociation of the PAA solution provides a pool of protons that generates bisulfite by equilibrium displacement from the sulfite already present in the system. By this process, the consumption of the sulfite/bisulfite buffer by the formaldehyde dehydration is the step responsible for the clock behavior, improved with the additional gain of a large viscosity change. A polymer with shorter length chain (PAA-4.5 × 10<sup>5</sup> g mol<sup>-1</sup>) was also tested. The results (shown in the ESI†) demonstrate that the coupling is robust and occurs regardless of the polymer size.

By tuning the initial sulfite concentrations (Fig. 2, row 2) we have also observed differences in the clock behavior. An increase in the sulfite concentration produces an increase in both the initial and final pH values (the former particularly noticeable for  $[SO_3^{2-}]_0 > 0.0614$  M and the later for larger concentrations of  $[SO_3^{2-}]_0$  and a decrease in the induction time (column c). The maximum viscosity difference does not match with the maximum difference in pH (Fig. 2b2). The reason of this disagreement is because for concentrations of sulfite below 0.0614 M, the viscosity increases due to the basic character of the solution. Above this concentration, the ionic strength becomes stronger and inhibits the repulsive effects of the polymer chains preventing a full elongation which produces a limitation in the viscosity change.<sup>21</sup> The negative viscosity differences observed for low sulfite concentrations are produced by the acidic character of the formaldehyde solution. A low sulfite concentration is not enough to buffer this effect and, as a consequence, the final viscosity is smaller compared to the initial one.

In Fig. 2, row 3, the effect of varying the formaldehyde initial concentration is analyzed. In the temporal pH evolution (column a), we observe two distinct behaviors: increasing the formaldehyde initial concentration up to 0.0840 M is accompanied by a drastic increase of the final pH value and a decrease of the induction time (column c). Experiments performed with [formaldehyde]<sub>0</sub> > 0.0840 M do not reflect significant changes in these features. Both viscosity and pH curves have a steep increment for formaldehyde concentrations below 0.065 M (see Fig. 2b3). Above 0.065 M the differences between the final and the initial pH values remain almost constant. In the case of viscosity the curve has a similar shape compared with the pH curve, however, the variation decreases by increasing the formaldehyde concentration.

#### (B) FSG-PAA system

Next, the effect of changing initial concentrations of reagents is analyzed for the full FSG–PAA system with the goal to understand whether the addition of gluconolactone can help to reset the clock and, thus, achieve a viscosity peak in the system.

Fig. 3 presents a summary of the different results observed. In this case, the analysis is centered on analyzing the effects of the presence of gluconolactone on both the chemical features and the viscosity variations. Hence, all these experiments were carried out with  $[formaldehyde]_0 = 0.0933 \text{ M}, [SO_3^{2-}]_0 = 0.0684 \text{ M}$ and  $[PAA]_0 = 0.4386$  wt% and only varying the initial concentration of gluconolactone (GL) stock solution (see Fig. 3). For low initial concentrations of gluconolactone, we observe a clock behavior with a jump in pH of around 4 units (the smaller the GL concentration, the larger the final pH value and, consequently, the larger the pH difference). By smoothly increasing the concentration of gluconolactone, we observe a transition (around  $[GL]_0 =$ 0.01 M) from the clock shape to the characteristic "peak" behavior of the FSG reaction (Fig. 3a), where the pH reaches a maximum value and then decays to a new stable value (typically larger compared to the initial one). As observed in Fig. 3c, the induction time does not show significant changes with the GL concentration, as it remains around  $(14 \pm 4)$  seconds.

In Fig. 3b, we measure two different pH variations ( $\Delta pH$ ) defined as the differences between the maximum pH value (at the "peak") and the initial pH value (so-called Max pH), and between the final and the initial values (so-called Final pH). Both curves are similar for low values of GL while they differ once the "peak" behavior is manifested in the reaction. Note that the error bars of the results increase in those experiments where the peak is shown, which indicates the complexity of adding a time dependent reagent into the system (please note that the gluconolactone hydrolysis varies with time). Even with the presence of PAA, the hydrolysis of the gluconolactone produces the delayed negative feedback needed to generate the pH pulse.<sup>16</sup> As the difference in viscosity between the peak value and the final value is almost negligible (a few mPa s in the case shown in Fig. 1b), we compute the viscosity gap between the final stable state and the initial value  $(\Delta \eta)$ . We find that  $\Delta \eta$  does not show significant variations with the concentration of GL. Even if there is an increment in the final pH value, the presence of gluconolactone produces a dampening in the viscosity change via its soft acidic features.<sup>19</sup>



**Fig. 3** FSG–PAA system characterization for different concentrations of  $[GL]_0$ . (a) pH vs. time curves. (b) Maximum pH difference, final pH and viscosity. (c) Variations of the induction time with  $[GL]_0$ . The maximum (final) pH gap was measured as the difference between the maximum (final) pH value and the initial pH value. The experimental conditions were kept constant and equal to:  $[SO_3^{2-}] = 0.0684$  M,  $[PAA]_0 = 0.4386$  wt% and  $[formaldehyde]_0 = 0.0933$  M.

## Conclusions

We have here proposed a route to couple a pH responsive polymer with pH clock reactions (FS and FSG chemical reactions) in order to obtain viscosity variations linked to changes in pH.

In particular, we have studied the role of the initial reagents concentrations on the chemical features and the viscosity modifications. On the one hand, the addition of the polymer modifies the chemical FS system, by introducing longer induction times for the clock behavior, and also enhancing the viscosity gap differences between the initial and final states. On the other hand, the concentrations of sulfite and formaldehyde on the chemistry of both pH reactions (similar to those reported in the original recipe by Kovacs et al.<sup>18</sup>) also modify the viscosity jumps in the clock behavior. In the case of the FSG-PAA system we have noticed that an increase of the gluconolactone initial concentration is the main responsible of a transition from a clock to a peak shape in both the pH and dynamic viscosity temporal changes. Although this work was exclusively centered in the use of PAA polymers, (with two different length chains) the same protocol can be extended in order to couple another pH sensitive polymer with a chemical system. Different variations of the system presented along the main text were analyzed in the ESI,† adding robustness to the mechanism as variations on the viscosity were still observed. This broadens the range of possible applications. It is worth mentioning that changes in the viscosity can also be induced controlling the temperature of the solution, nevertheless this is not always an option especially in the cases considered as possible applications in the introduction. In any case, the changes reported here are significantly larger than those expected by temperature variations.

The presence of positive and negative feedbacks in the FSG polymer-modified system opens the possibility to obtain pH and viscosity temporal oscillations when the reaction is run in an open continuously stirred tank reactor (CSTR) as observed without polymer.<sup>16–19</sup> The presence of oscillatory viscosity solutions linked to pH temporal modulations would be of particular interest in a variety of fields ranging from nonlinear chemistry to more applied fields, such as testing *in vitro* drug delivery in a controlled way.

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