



# Ester hydrolysis: Conditions for acid autocatalysis and a kinetic switch



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We dedicate this paper to Prof. Ben Feringa on the occasion of the award of the 2016 Tetrahedron Prize and the Nobel Prize in Chemistry.

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## ABSTRACT

Autocatalysis can be used to obtain a sharp switch in state after a programmable time lag. Here, autocatalysis driven by acid concentration during the dissolution and hydrolysis of solid esters was investigated. In a generic model of the process, conditions were identified for observation of a kinetic switch with the introduction of an inhibitor species, bicarbonate, to delay the onset of autocatalysis. The kinetic profiles from the hydrolysis of two esters, *D*-gluconic acid  $\delta$ -lactone and *DL*-lactide, were examined and evidence for dissolution-limited acid autocatalysis was obtained with lactide.

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## 1. Introduction

The term switch in chemistry is typically used to describe a molecule that responds to environmental stimuli, such as light or pH, with a change in conformational state.<sup>1</sup> Alternatively, a kinetic switch might be defined as one in which a chemical reaction sharply switches between a low and high concentration of product. This situation can arise in the presence of autocatalysis, when a product accelerates the rate of reaction.<sup>2</sup>

Autocatalysis plays an important role in diverse processes such as amplification of an enantiomeric species,<sup>3,4</sup> template-directed synthesis<sup>5</sup> and activation of trypsinogen by trypsin.<sup>6</sup> In a closed system, autocatalysis often manifests as an exponential increase in product after a time lag. Autocatalytic reactions also have the potential to be maintained in a low conversion state far-from-equilibrium and initiated on-demand. These kinetic switches may be useful when a rapid change in state is desired after a programmable length of time; for example, acid or base production can be coupled to material formation/degradation in coatings, adhesives or drug delivery devices.<sup>7,8</sup> New sources of autocatalysis generating changes in pH are being sought for such applications.<sup>9</sup>

One well known example of acid autocatalysis is ester hydrolysis. In this reaction, the formation of the carboxylic acid product can catalyse the hydrolysis resulting in an increase in reaction rate under non-buffered conditions. In fact, most (if not all) of the examples of autocatalysis by this mechanism take place in heterogeneous environments where other factors play an important role in the observed kinetics.<sup>10,11</sup> In the hydrolytic degradation of polyesters such as poly(lactic acid), the rate acceleration in loss of mass has been attributed to the increasing concentration of terminal carboxylic acid groups.<sup>12</sup> However, rate acceleration with liquid esters was demonstrated to arise by a physical mechanism whereby the product effectively aids in the solubilisation of the reactant.<sup>13</sup>

Here, evidence was examined for acid autocatalysis in the hydrolysis of two solid esters with differing dissolution rates: *D*-gluconic acid  $\delta$ -lactone and *DL*-lactide, the cyclic ester from which poly(lactic acid) can be synthesised. Although the kinetic constants for gluconolactone hydrolysis are well established,<sup>14</sup> surprisingly little exists in the literature on lactide hydrolysis. Hence we examined the conditions for a switch in a generic model designed to capture the main features of the reaction, rather than focussing on detailed, accurate models of the different cases presented experimentally. The addition of an inhibitor species, bicarbonate, that removes the acid, was included in order to delay the onset of autocatalysis. It was found that, experimentally, lactide displayed

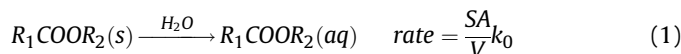
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features indicative of dissolution-limited acid autocatalysis whereas the acid catalysis was too weak in the case of gluconolactone for autocatalysis. A general strategy for obtaining kinetic switches in acid in ester hydrolysis is discussed.

## 2. Kinetic model

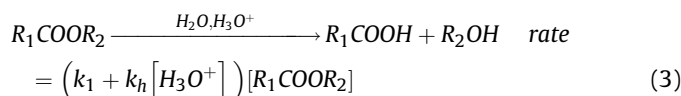
A dissolving sphere model was assumed for the increase in aqueous ester concentration  $[R_1COOR_2]$  when solid crystals were added to water:



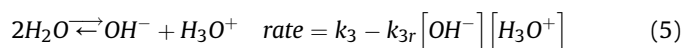
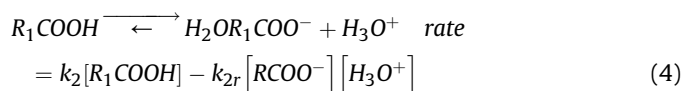
where  $SA$  is the total surface area of the crystals,  $V$  is the volume of water and  $k_0$  is the (constant) rate at which the ester is stripped from the solid surface ( $\text{mol dm}^{-2} \text{s}^{-1}$ ) which depends on a mass transfer coefficient (sensitive to stirring rate, units of  $\text{dm s}^{-1}$ ) and concentration of solid at the crystal surface (units of  $\text{mol dm}^{-3}$ ). The total surface area is determined from  $4\pi r^2 N$  where  $N$  is the number of crystals and  $r$  is the average crystal radius,  $r$ , which decreases linearly in time:

$$\frac{dr}{dt} = -\frac{M_r}{\rho}k_0 \quad (2)$$

with  $\rho$  = the density of the crystals and  $M_r$  = the molar mass of the ester. The hydrolysis reaction rate is given by:



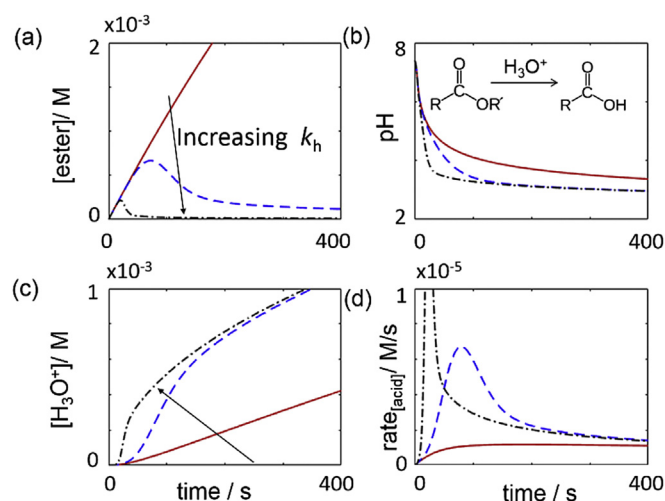
where  $k_1$  is the first order rate constant and  $k_h$  is the rate constant of the acid catalysed path. The reversibility of this reaction and base catalysis were ignored as they were found to play a negligible role in the kinetic profiles obtained here. The following reversible reactions were included for the dissociation of the carboxylic acid and water:



The values of the rate constants, unless otherwise stated, were:  $k_0 = 1 \times 10^{-5} \text{ mol dm}^{-2} \text{ s}^{-1}$ ,  $k_1 = 1 \times 10^{-3} \text{ s}^{-1}$ ,  $K_{a2} = k_2/k_{2r} = 1.4 \times 10^{-4}$  (lactic acid) and  $k_2 = 1 \times 10^3 \text{ s}^{-1}$ ,  $k_3 = 1 \times 10^{-3} \text{ M s}^{-1}$ ;  $k_{3r} = 1 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$ . The values for reactions (4) and (5) were taken from the literature<sup>15</sup> whereas the values for (3) were chosen in order to best illustrate the different cases discussed below. The density  $\rho = 1.2 \text{ g/ml}$ ,  $M_r = 144 \text{ g/mol}$  and average crystal radius  $r = 0.1 \text{ mm}$  (values for lactide). The volume of water was 20 ml and  $N$  was estimated from the initial mass/average crystal mass =  $m/(4/3\pi r^3 \rho)$ . All simulations had a starting pH of 7.4.

### 2.1. Case 1: dissolution-limited autocatalysis

With no acid catalysis, i.e.  $k_h = 0$ , the concentration of ester in solution increased as the crystals dissolved (Fig. 1(a), red curve). Complete conversion of solid ester to dissolved ester occurred at 8300 s or 2.3 h: only the first 400 s are shown here. The dissolved ester hydrolysed producing carboxylic acid and there was a decrease in pH and a corresponding increase in  $H_3O^+$  (Fig. 1 (b) and



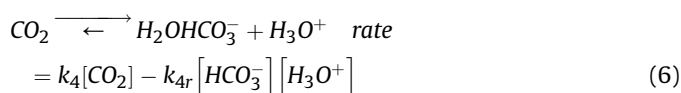
**Fig. 1.** Dissolution-limited autocatalysis in the simulations with mass of solid ester,  $m = 0.1 \text{ g}$ . The time profiles show the (a) concentration of dissolved ester (b) pH (c) concentration of  $H_3O^+$  and (d) rate of production of  $H_3O^+$ . The value of  $k_h$ , was increased (illustrated by the arrow) from 0 (red, solid line) to  $10 \text{ M}^{-1} \text{ s}^{-1}$  (blue dashed line) and  $20 \text{ M}^{-1} \text{ s}^{-1}$  (black, dash-dot).

(c)). The rate of production of  $H_3O^+$  increased to a constant value that depended strongly on the value of  $K_{a2}$  (Fig. 1(d), red curve).

When acid catalysis was included, a sharper drop in pH and rapid increase in the acid concentration was observed (Fig. 1 dashed lines). However, the dissolved ester concentration then rapidly decreased and the rate of acid production fell. Thus there were two processes evident in the acid profile: the first corresponded to a rapid growth from autocatalysis and the second a slow growth when the hydrolysis was limited by the rate of dissolution of ester.

### 2.2. Case 2: removal of inhibitor, no acid catalysis

In order to delay the onset of the acid ( $H_3O^+$ ) production, an inhibitor species can be introduced. A simple inhibitor that can be used in experiments with acid is bicarbonate. The rates of reactions and equilibria involving bicarbonate, carbonic acid and carbonate are well established.<sup>16</sup> For the pH range explored here, the behaviour can be accounted for by including the following reversible reaction in the model:



where  $[CO_2]$  is the dissolved carbon dioxide concentration,  $k_4 = 0.037 \text{ s}^{-1}$  and  $k_{4r} = 7.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ . The pKa of this equilibrium is 6.3.

The simulations in Fig. 2 show the ester dissolution and hydrolysis with inclusion of a  $HCO_3^-/CO_2$  buffer and no acid catalysis ( $k_h = 0$ ). The concentration of aqueous ester was unaffected by the buffer (Fig. 2(a), bold). The bicarbonate removed the acid produced from the ester hydrolysis until its level fell sufficiently (Fig. 2(a)) then there was a sharp drop in pH (Fig. 2(b)) and the concentration of acid ( $H_3O^+$ ) started to increase linearly in time (Fig. 2(c)). The rate of acid production jumped to a higher value after the time lag set by the initial strength of the buffer (Fig. 2(d)).

### 2.3. Case 3. combined autocatalysis and inhibition

With both acid catalysis and inhibition through  $HCO_3^-/CO_2$  included, the dissolution-limited autocatalysis occurred after a

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