HYDROLYSIS OF *O*-ACETYLSALICYLIC ACID (ASPIRIN) IN RELATION TO THE ASPIRIN–BROMATE–ACID OSCILLATING SYSTEM

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The uncatalyzed BrO_3^-–*O*-acetylsalicylic acid (aspirin) reaction in aqueous H_2SO_4 exhibits oscillatory behavior. The induction period observed before the onset of oscillations depends on the extent of hydrolysis of aspirin. The rate constant of hydrolysis of aspirin was determined indirectly from the value of induction period. When aspirin undergoes hydrolysis, the degradation products are salicylic acid and acetic acid. Salicylic acid may play a role of "active" substrate responsible for the oscillations. Aspirin® (Bayer) generates also oscillations with bromate.

Keywords: Chemical oscillators; Uncatalyzed bromate oscillator; Bromate; Aspirin; Kinetics; Esters hydrolysis.

In its classic form, the oscillatory Belousov–Zhabotinsky reaction (BZ)[1] consists of the metal-ion-catalyzed (e.g. Ce(IV)/Ce(III), Mn(III)/Mn(II)) oxidation of easily brominated and oxidized malonic acid with bromate ion in aqueous media at pH ~ 0. Oscillations can be observed in the ratio of the oxidized to the reduced forms of the metal ion catalyst, bromide ion concentration, and color. Many organic compounds have been used in place of malonic acid in the BZ reaction. The systems may be classified in terms of the role of the organic compound in determining the source of negative feedback – bromide ion, bromine hydrolysis, or a radical of organic compound itself[2].

A remarkable sub-group of BZ systems is the uncatalyzed bromate oscillators (UBO) consisting of a mixture of bromate, sulfuric acid and a phenol or aniline derivative. No metal ion catalyst is added[3]. In these systems, the organic compounds are easily oxidized and play the role of the metal catalyst. The reaction of the aromatic compound with $BrO_2^\bullet$ leads to the formation of the related quinone. A skeleton mechanism was proposed by Orbán, Körös and Noyes[4]. Györgyi et al.[5] proposed a more detailed mechanistic

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model which simulated well the dynamic behavior of some UBOs. Some reduced models for the UBO have been proposed in which the quinone plays an active role[6]. The prototype of the UBO systems is the bromate-phenol reaction which exhibits an astonishing variety of types of dynamic behavior, including sequential oscillations in a closed stirred batch reactor[7,8] . Gupta and Srinivasulu[9] observed that the bromate–salicylic acid system exhibit a few temporal redox-potential oscillations under batch configuration in narrow concentration ranges of the reactants. A particular UBO system was proposed by Farage and Janjic[10] with cyclohexane-1,4-dione (CHD) as substrate. CHD in its reaction with acidic bromate undergoes aromatization and one of the main resulting products, benzene-1,4-diol (H_2Q), is further oxidized and brominated to 1,4-benzoquinone and bromoorganics. H_2Q plays a central role in the function of the oscillatory system. When during the reaction a considerable amount of H_2Q accumulates, a direct reaction between bromate and H_2Q takes its role[11].

In our previous paper[12] we have reported that chemical oscillations occur in the uncatalyzed oxidation of *O*-acetylsalicylic acid with bromate in acid solution. In the present communication we report on the role of hydrolysis of aspirin in relation to the studied oscillatory system.

EXPERIMENTAL

All chemicals were used without further purification. $NaBrO_3$ (Merck), sulfuric acid, *O*-acetylsalicylic acid, salicylic acid and ferroin (Slavus) were of analytical reagent grade. All solutions were prepared with doubly distilled water. Aspirin® (Bayer AG, Leverkusen) and Acylpyrin® tablets (Slovakofarma, Hlohovec) were of pharmaceutical purity. Composition of commercial Aspirin® (Bayer): each tablet contains *O*-acetylsalicylic acid (500 mg), and maize starch and cellulose as auxiliary substances. Each tablet of Acylpyrin® (Slovakofarma) contains: *O*-acetylsalicylic acid (500 mg), and talc (talcum) and potato starch (solani amylum) as auxiliary substances. We analyzed the Aspirin® (Bayer) by the secondary ions mass spectrometry (SIMS) and the results found agree with those reported by the producer. High purity of Aspirin® was confirmed and impurities were not found.

An *O*-acetylsalicylic acid solution was stored in laboratory at 22 °C. Measurement have been carried out in a thermostatted cylindrical glass reactor (diameter 3.5 cm, height 7.5 cm) at a constant temperature of 40 ± 0.1 °C. The total volume of the reaction mixture was 20 ml. The reactor was closed with a rubber stopper through which a commercial indication platinum electrode (0.5 × 0.8 cm) and reference mercury(I) sulfate electrode were inserted into the reaction mixture. Potentiometric measurements have been carried out using a digital multimeter Metex-4660A and processed by a PC. The solution was stirred magnetically with a Teflon-coated stirrer (length 2.0 cm, diameter 0.8 cm). The reactants were introduced into the reactor in the order: aqueous solution of H_2SO_4, *O*-acetylsalicylic acid and bromate.

RESULTS AND DISCUSSION

Figure 1 (curve *1*) presents the potentiometric curves measured in the uncatalyzed *O*-acetylsalicylic acid (aspirin)–bromate system at reaction conditions $[BrO_3^-]_0$ = 50 mmol dm^{-3}, [aspirin]$_0$ = 7.6 mmol dm^{-3}, $[H_2SO_4]_0$ = 1.0 mol dm^{-3}, temperature 40 °C and stirring 100 rpm. Only a freshly prepared solution of aspirin generates such type of the reaction course. There exists an induction time, IP ~ 120 min, i.e., the preoscillatory period defined as the time interval between mixing of all the reagents and the first maximum of the electrode potential.

Figure 1 (curve *2*) shows the same system with identical initial concentrations but the experimental was performed with 13-day old stock solution of aspirin. In this case the IP was eliminated. IP drops with aging of water stock solution of aspirin. Hydrolysis of the aspirin seems to be a major reason for the instability of aspirin solutions. Esters such as aspirin are subject to hydrolysis. The hydrolysis of aspirin was studied in detail by Edwards[13]. The process may be catalyzed with acid or base or may be uncatalyzed ("spontaneous"). The carboxylic group of aspirin may be either protonated or deprotonated (COO^-) depending on the solution pH. The pH of freshly

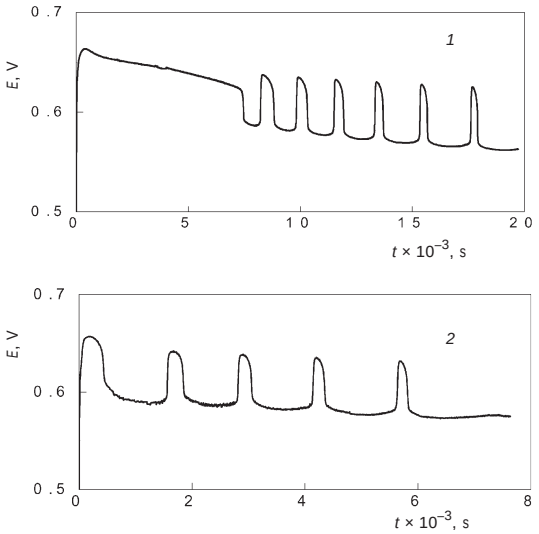
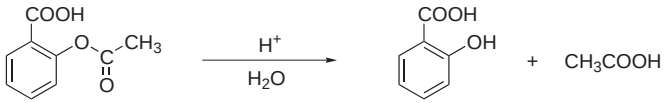


FIG. 1
Time dependence of the Pt redox potential in the BrO_3^-–aspirin–H_2SO_4 system at 40 °C and at stirring rate 100 rpm. Initial concentrations: $[BrO_3^-]_0$ = 50 mmol dm^{-3}, $[H_2SO_4]_0$ = 1 mol dm^{-3}, [aspirin]$_0$ = 7.6 mmol dm^{-3}. *1* Freshly prepared solution of aspirin, *2* 13-day old stock solution of aspirin

prepared solution of aspirin with doubly distilled water is 2.76 under our conditions and this value slowly drops with time. pH of an 8-day old solution of aspirin is 2.56. Above pH 2.4, the specific acid-catalyzed mechanism becomes less important with decreasing proton concentration. However, at this pH, it would be reasonable to expect that a fraction of aspirin would be present in the carboxylate form. The aspirin present as carboxylate would then be able to react by the intramolecular general base-assisted nucleophilic-attack mechanism[14]. Marrs[14] found the rate constant of hydrolysis of aspirin $k = 10^{-5}$ s^{-1} at 60 °C and at pH 2.8. Converting to day^{-1} and reducing to 22 °C, $k = 0.08$ day^{-1}. The reaction products of hydrolysis of aspirin are salicylic acid (SA) and acetic acid (AA) (Scheme 1).



SCHEME 1

In our previous paper we have examined the uncatalyzed bromate–aspirin–acid oscillator and have accepted the assumption that the product of aspirin hydrolysis, salicylic acid, may play the role of an "active" substrate. The activity of aspirin decreases if the solution is stored for few days and, on the contrary, the activity of hydrolysis product, salicylic acid, increases. We assume that the IP of the oscillating reaction reflects the time period for which aspirin was stored in water at room temperature (22 °C) or, in other words, the IP is the time necessary for accumulating a sufficient amount of salicylic acid to induce oscillations. During the induction period, concentrations of various reactants and intermediates assume quasi-steady-state values. We are inclined to claim that some kind of analogy exists between this system and the BrO_3^-–CHD one[11]. In the latter one an active substrate (H_2Q) is continuously generated during the redox reaction of CHD and bromate, and it seems that in the former one an active substrate SA is produced during the aspirin hydrolysis – bromate reaction.

We prepared our oscillatory systems with variously aged stock solutions of aspirin. The IP decreased nearly exponentially with the time of storing aspirin in water solution. Thus one may assume pseudo-first-order kinetics with respect to the concentration of aspirin, according to the equation

$$-\mathrm{d[aspirin]}/\mathrm{d}t = k_{\mathrm{exp}}\,[\mathrm{aspirin}]$$

where k_{exp} is the experimental rate constant of aspirin hydrolysis.

A linear least-squares fit of the ln IP versus time dependence gives k_{exp} = 0.149 day^{-1} at 22 °C.

Though the present value is higher in comparison with the rate constants of hydrolysis obtained by Marrs[14] and Edwards[13], it is not unexpected. This discrepancy could be attributed to the difference in the temperature and in pH because the hydrolysis of aspirin proceeded in distilled water and at 22 °C while the oscillating reaction proceeded at 40 °C and in 1 M H_2SO_4. The substitution of water with 1 M H_2SO_4 results in a variation of 10% in the value of rate constant of hydrolysis. Our indirect measurement of the rate constant of hydrolysis agrees reasonably well with direct spectrophotometric kinetic measurement of Marrs[14] and Edwards[13], giving 0.08 day^{-1} (22 °C).

This result can be considered to be indirect corfirmation of our working hypothesis that the product of hydrolysis, salicylic acid, which is oxidized and brominated to benzoquinone and bromoorganics, may be a substrate responsible for the oscillations. We have tested salicylic acid to see whether it can act as oscillatory substrate in their reaction with bromate. We were able to find concentration conditions that gave regular oscillations in the system BrO_3^-–salicylic acid–H_2SO_4 at temperature 40 °C (Fig. 2, curve *1*).

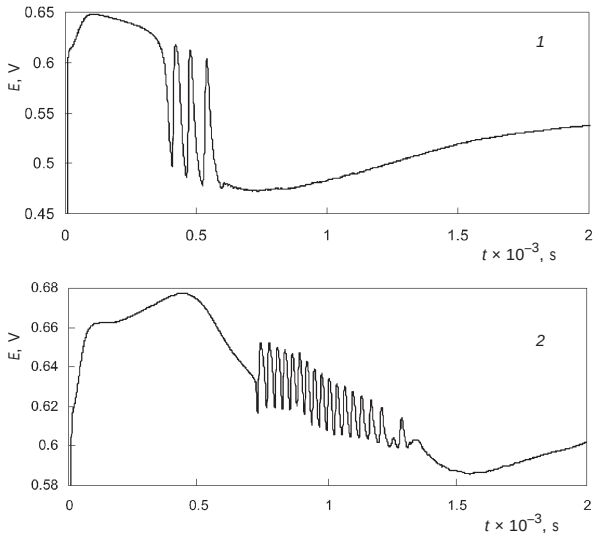


FIG. 2

Time dependence of the Pt redox potential in the BrO_3^-–salicylic acid–H_2SO_4 system at 40 °C and 100 rpm. Initial concentrations: $[BrO_3^-]_0$ = 40 mmol dm^{-3}, $[H_2SO_4]_0$ = 1.5 mol dm^{-3}, [salicylic acid]$_0$ = 10 mmol dm^{-3}. *1* Uncatalyzed course, *2* catalyzed course with [ferroin]$_0$ = 0.025 mmol dm^{-3}

The number of oscillations increases if a catalyst (Mn(II), Ce(IV) or ferroin) is present in the system (Fig. 2, curve *2*). For example, the mixture of composition 10 mM SA, 40 mM $NaBrO_3$ and 1.5 M H_2SO_4 shows 3 oscillations after an induction period of ~7 min in closed stirred batch reactor and initial addition of 0.025 mM ferroin increases the number of oscillations to 18 and IP to 12 min. Similar results have been reported by Gupta et al.[9]

We performed experiments where initial composition of the UBO was varied to mimic the hydrolysis process of aspirin and measured the length of the IP. Table I shows dependence of the IP on the initial salicylic and acetic acids concentrations which are products of aspirin hydrolysis. Induction period drops with the increasing concentrations of salicylic and acetic acids. It can be seen that if 5.6 mM SA and the same amount of acetic acid are added to the system the induction period is suppressed.

Acetylsalicylic acid can be replaced by medicin aspirin, used from two different producers. Figure 3 shows two time dependences obtained with Aspirin® tablets (*1*) and Acylpyrin® tablets (*2*). Both Aspirin® and Acylpyrin® tablets were weighed and dissolved in redistilled water and were prepared freshly. Reaction conditions were 1 M H_2SO_4, 50 mM $NaBrO_3$,

TABLE I
Dependence of the induction period on the initial *O*-acetylsalicylic, salicylic (SA) and acetic (AA) acids concentrations

$[aspirin]_0$ mmol dm^{-3}	$[SA]_0$ mmol dm^{-3}	$[AA]_0$ mmol dm^{-3}	IP min
7.6	5.3	5.3	0
7.6	3.8	3.8	22
7.6	2.85	2.85	31
7.6	1.9	1.9	64
7.6	0.95	0.95	83
7.6	0	0	120
5.3	1.9	1.9	21
0	7.6	0	no oscillations
0	5.3	0	no oscillations
7.6	5.3	0	0
0	5.3	5.3	no oscillations

Initial concentrations: $[H_2SO_4]_0$ = 1 mmol dm^{-3}, $[BrO_3^-]_0$ = 50 mmol dm^{-3}, 40 °C, 100 rpm, aspirin was prepared freshly.

7.6 mM aspirin, 40 °C and 100 rpm. The agreement between the time courses of the oscillating reactions (*1*) and (*2*) is good. Also in this case, the IP decreases with the time of contact of aspirin with water. The efficiency of any drug depends on its chemical stability. While there are numerous beneficial physiological responses in vivo, such as anticlotting and analgesic reactions, once the aspirin is ingested, it is being hydrolyzed or degraded, before it is consumed.

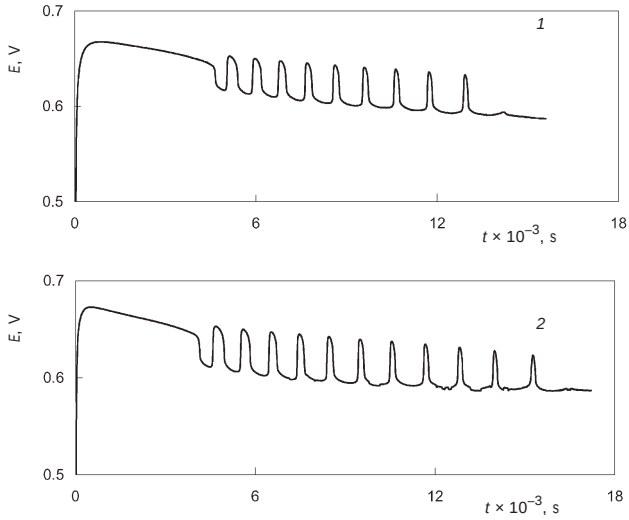


FIG. 3
Redox potential versus time plot showing oscillations with medicin aspirin as a substrate. Aspirin tablets were weighed and dissolved in redistilled water. *1* Aspirin® tablets, *2* Acylpyrin® tablets. The same initial concentrations of aspirin, BrO_3^- and H_2SO_4 as in Fig. 1

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