based on one-electron transfer quenching, but such conclusions should be reached with care. For example, in a dimeric system like $(trpy)(bpy)Ru(L)Ru(bpy)(trpy)^{4+}$ (L = 4,4′-bipyridine) the intermolecular ligands are weakly coupled electronically. Following one-electron reduction, the equilibrium,

$$2[LRu\text{-}RuL]^{3+} \rightleftharpoons [LRu\text{-}RuL]^{2+} + [LRu\text{-}RuL]^{4+}$$

for which $K \sim 1/4$,[17] would be quickly established giving rapid access to a two-electron reduced product.

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Design of Reaction Systems Exhibiting Overshoot-Undershoot Kinetics

Sir:

As a result of intensive research in the last decade, a number of systems showing oscillatory behavior have been found.[1] However, there is no clear-cut experimental example of a chemical reaction in which the concentration of an intermediate shows a few extrema in time as equilibrium is approached.[2] This kinetic phenomenon has been termed by Higgins[3] as "overshoot-undershoot" kinetics. We conjectured that such a phenomenon would occur upon addition of an appropriate reagent to a clock reaction system.

In such a system a halogenate ion oxidizes a substrate. If the halogenate is in excess, free halogen is formed suddenly after a long time lag. The appearance of free halogen corresponds to consumption of the substrate. The concentration of halogen changes according to a saturation curve, while the concentration of halide ion shows a maximum. We surmised that, upon perturbation of this system by a reactant which enters into a substitution reaction with the halogen, the concentration of the halide ion might exhibit two maxima and that of the halogen one maximum. We found that malonic acid is a suitable perturbing reactant.

In our experiments the reaction was followed by spectrophotometric determination of halogen and by monitoring the halide ion concentration using halide-selective electrodes.[4] As it appears from Figure 1, the addition of malonic acid to different clock systems resulted in the appearance of three extrema in the halide ion concentration vs. time curves.[5] The bromate-ascorbic acid-malonic acid system was studied in detail. The original clock reaction can be quantitatively described by the following three equations:[6]

$$BrO_3^- + 3H_2A \rightarrow Br^- + 3A + 3H_2O \qquad (1)$$

$$5Br^- + BrO_3^- + 6H^+ \rightarrow 3Br_2 + 3H_2O \qquad (2)$$

$$H_2A + Br_2 \rightarrow A + 2Br^- + 2H^+ \qquad (3)$$

(where H_2A stands for ascorbic acid and A for dehydroascorbic acid). For these reactions the following rate equations have been determined:

$$v_1 = -d[BrO_3^-]/dt = k_1[BrO_3^-][H_2A] \qquad (1')$$

$$v_2 = -d[BrO_3^-]/dt = k_2[BrO_3^-][Br^-][H^+]^2 \qquad (2')$$

$$v_3 = -d[Br_2]/dt = k_3[Br_2][H_2A] \qquad (3')$$

Reaction 1 can not be studied separately and, assuming the second-order rate equation (1′), Bognar[6] could give only a maximum value for k_1 ($k_1 < 3.3 \times 10^{-3}\ M^{-1}\ s^{-1}$). Reaction 2 has been thoroughly studied,[7] and the values for k_2 given by the different authors are in good agreement considering the different experimental conditions. According to our experiments the value of k_2 at 25 °C and at $I = 1.0$ ionic strength is $3.6\ M^{-3}\ s^{-1}$.[8] The bromine oxidation of ascorbic acid is a very fast reaction. No rate data are available in the literature. According to our stopped-flow experiments, when the concentration of both bromine and ascorbic acid is 0.06 M, the reaction is complete within 10 ms. It follows that $k_3 \gg 2 \times 10^3\ M^{-1}\ s^{-1}$. In the presence of malonic acid, only its bromination reaction should be considered. This has been extensively studied. There is general agreement that the rate-determining step is slow enolization of malonic acid which is followed by the fast addition of bromine to the enol:

$$(H_2M)_{keto} \rightleftharpoons (H_2M)_{enol} \qquad (4)$$

$$(H_2M)_{enol} + Br_2 \rightarrow HBrM + Br^- + H^+ \qquad (5)$$

Accordingly the rate of the bromination of malonic acid is given by the following equation:

$$v_4 = -\frac{d[Br_2]}{dt} = \frac{k_4 k_5 [Br_2][H_2M]}{k_{-4} + k_5[Br_2]} \qquad (4')$$

At higher bromine concentrations the rate is independent of bromine concentration, and the pseudo-first-order rate constant is equal to k_4. According to Leopold and Haim[9] the value

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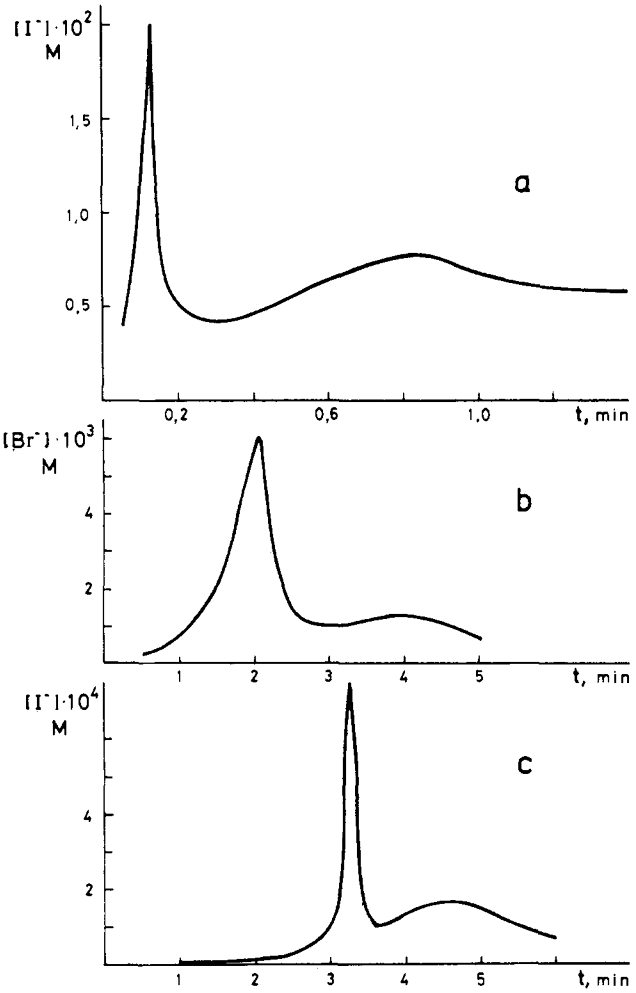

Figure 1. The overshoot–undershoot-type kinetic curves found in the following systems: (a) 0.04 M$[IO_3^-]_0$, 0.08 M $[HSO_3^-]_0$, 0.08 M $[H_2M]_0$, pH 2.5 (adjusted with NaOH); (b) 0.01 M $[BrO_3^-]_0$, 0.03 M $[Fe(CN)_6{}^{4-}]_0$, 0.02 M $[H_2M]_0$, 1.0 M $[HClO_4]_0$; (c) 0.005 M $[IO_3^-]_0$, 0.02 M $[AsO_3{}^{3-}]_0$, 0.02 M $[H_2M]_0$, pH 1.75 (adjusted with $HClO_4$).

of k_4 is 2×10^{-3} s^{-1} (T = 25 °C, medium 1.0 M $NaClO_4$), while we obtained under the same concentrations a much higher value of 6×10^{-3} s^{-1}. We have no explanation of this discrepancy. On the other hand we agree that the rate is independent of the hydrogen ion concentration when pH is <2. However, according to the exploratory experiments of Field, Körös, and Noyes,[10] the rate is proportional to $[H^+]$. k_{-4} has not been directly measured. Leopold and Haim[9] estimated the maximum value of the keto $\rightleftharpoons$ enol equilibrium (4) constant from which they obtained a minimum value for k_{-4} of 20 s^{-1}. Using the value of k_4 determined by us, the minimum value of k_{-4} is 60 s^{-1}. Since the rate of the bromination of malonic acid is independent of the concentration of bromine when the bromine concentration is $>10^{-4}$ M, it follows then that k_5 is larger than 1×10^7 M^{-1} s^{-1}.

The system of differential equations (1′-4′) has been solved numerically by a fourth order Runge-Kutta method[11] using the following set of rate constants: $k_1 = 8.3 \times 10^{-3}$ M^{-1} s^{-1}; $k_2 = 3.6 \times 10^{-3}$ s^{-1}; $k_3 = 2 \times 10^3$ M^{-1} s^{-1}; $k_4 = 6 \times 10^{-3}$ s^{-1}; $k_{-4} = 1.7 \times 10^3$ s^{-1}; $k_5 = 1.7 \times 10^7$ M^{-1} s^{-1}.

The calculated curves agree qualitatively with the ones found experimentally. That is, three extrema in the concentration of bromide ion are obtained. Decreasing the value of k_4 to 3.3×10^{-3} s^{-1}, which is still larger than determined by Leopold and Haim,[9] produces rather good quantitative agreement as is shown in Figure 2.[12]

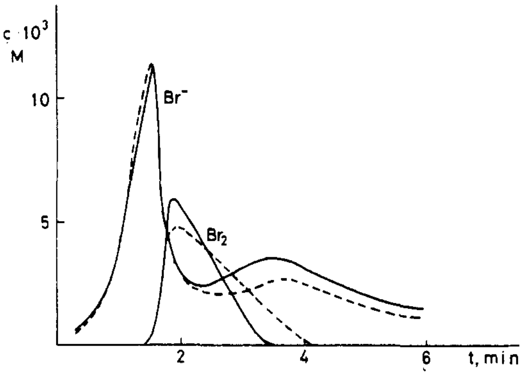

Figure 2. The change of concentration of bromide ion (Br^-) and bromine (Br_2) in time. Full lines show the experimentally measured values, while dashed lines are theoretically calculated. Initial concentrations: $[H_2A]_0$, 0.04 M; $[BrO_3^-]_0$, 0.02 M; $[H_2M]_0$, 0.04 M; $[HClO_4]_0$, 1.0 M.

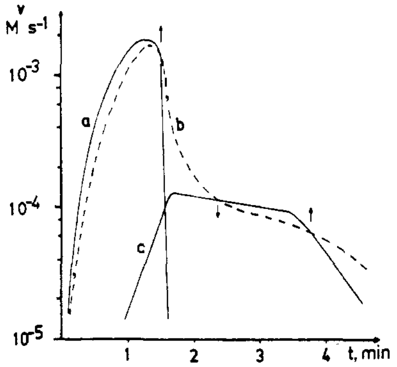

Figure 3. The computed rates of formation and consumption of bromide ion vs. time in the component reactions of the same system as in Figure 2: (a) formation of Br^- in reaction 3; (b) consumption of Br^- in reaction 2; (c) formation of Br^- in reaction 5. The rate of formation of Br^- in reaction 1 is always $<10^{-5}$ M s^{-1}.

This peculiar kinetic behavior was observed in this system when the following conditions for the initial concentrations of the reactants were maintained: $[H_2A]_0 < 3[BrO_3^-] < ([H_2A] + [H_2M])$. We can get a deeper insight into the mechanism of this system by plotting the rates of different reactions contributing to the formation and consumption of bromide ion as a function of time (Figure 3). The first maximum of the concentration of bromide ion occurs at the intersection of the curves a and b. (The contribution of reaction 1 is completely negligible and, as it appears from Figure 3, the contribution of reaction 5 is <5% at this point.) The appearance of the second and third extremum in the concentration of bromide ion is due to the interplay of reactions 2 and 5. Theoretical analysis and computer-simulated experiments are in progress to find the criteria for the perturbing substitution reaction leading to overshoot-undershoot kinetics. At present such a reactant can be selected only empirically.

Acknowledgment. The authors are grateful to Mr. György Póta for his help in the calculations.

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absorb at this wavelength. No explanation is given for the peculiar behavior.

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(11) The integration can be easily carried out if the step size is equal to 10^{-4}. For the calculation a Hewlett-Packard 9810 calculator was used.

(12) The calculated values of the concentrations of both bromine and bromide ion are rather insensitive to the value of k_3 if it is larger than the given limiting one.

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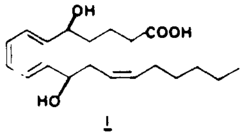
Total Synthesis of (±)-5,6-Oxido-7,9-*trans*,11,14-*cis*-eicosapentaenoic Acid, a Possible Precursor of SRSA

Sir:

Recent studies by Borgeat and Samuelsson[1] have shown that arachidonic acid is metabolized by rabbit or human peripheral polymorphonuclear leucocytes to a lipoxygenase type product, 5(*S*)-hydroxy-6,8,11,15-eicosatetraenoic acid, and to another substance demonstrated to be 5(*S*),12(*R*)-dihydroxy-6,8,10,14-eicosatetraenoic acid (**1** or double-bond stereoisomer). It was also found that **1** was formed from a labile precursor which could not be isolated but which could be intercepted chemically in various ways. For example, by quenching with methanol a mixture of products results which consists principally of the 12(*R*)- and 12(*S*)-methyl ethers of 5(*S*),12-dihydroxy-6,8,10,14-eicosatetraenoic acid.[2] During an informal discussion of the early results of this project with Professor Samuelsson in March of 1977, one of us proposed that the unstable precursor of **1** could be 5(*S*),6-oxido-7,9,11,14-eicosapentaenoic acid (**2** or Δ-7,9 stereoisomer) which might arise from the lipoxygenase-like intermediate 5(*S*)-hydroperoxy-6-*trans*,8,11,14-*cis*-eicosatetraenoic acid (**3**) by a pathway that has straightforward mechanistic precedent.[3,4] To test the correctness of this surmise, the synthesis of **2** and the Δ-7,9 stereoisomers has been undertaken. The synthesis of **2** has now been accomplished by the route described herein.[5] Very recently, Samuelsson and collaborators have proposed that the structure of the "slow-reacting substance of anaphylaxis" (SRSA)[6-8] involves the linkage of the sulfur of cysteine and C-5 of 5,6-oxido-7,9,11,14-eicosapentaenoic acid as exemplified by **4** (or Δ-7,9 stereoisomer), or a larger molecule having one or more additional amino acid units attached to cysteine.[9] Since there is abundant evidence which implicates SRSA in asthma and other diseases of the respiratory system (especially those involving hypersensitivity), the chemical synthesis of epoxy tetraene **2** and the Δ-7,9 stereoisomers assumes added significance and value for an ultimate proof of detailed structure.



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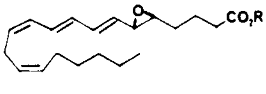
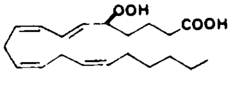


2 R : H
14 R : CH_3



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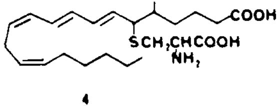

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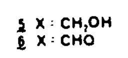
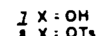
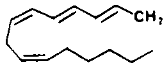


5 X : CH_2OH
6 X : CHO



7 X : OH
8 X : OTs
9 X : $\overset{+}{P}Ph_3$



10 X : OSi
11 X : OH
12 X : OSO_2CH_3
13 X : $(CH_3)_2S^+$

The mono-*tert*-butyldimethylsilyl ether (**5**)[10] of *trans*-2,4-hexadiene-1,6-diol[11] was converted into the aldehyde **6** (70% yield) by oxidation with 1.1 equiv or pyridinium dichromate[12] in methylene chloride at 25 °C for 4.5 h.[13] The phosphonium salt **9**, mp 89–90 °C, was prepared by the sequence (1) reaction of amylmagnesium bromide and cuprous bromide–dimethyl sulfide complex in ether with excess acetylene followed by treatment of the adduct with 1-lithio-1-pentyne and hexamethylphosphoric amide (to form the mixed Gilman reagent) at −70 °C and subsequent exposure to excess ethylene oxide at −78 to −20 °C over 1 h to give, after quenching with aqueous ammonium chloride–ammonia buffer and extractive isolation, *cis*-3-nonen-1-ol (**7**);[14] (2) reaction of **7** with *p*-toluenesulfonyl chloride (1.3 equiv) and pyridine (4 equiv) at 0 °C for 9 h to form tosylate **8** (76%); (3) displacement of tosylate by iodide using sodium iodide in acetone at 25 °C for 16 h (90%); and (4) reaction of the iodide with triphenylphosphine in benzene at reflux for 18 h to afford **9** (83%).

The phosphonium iodide **9** was converted into the corresponding ylide by reaction in tetrahydrofuran at −78 °C for 10 min with *n*-butyllithium (1 equiv) and then treated sequentially and without delay with 16 equiv of hexamethylphosphoric amide and the aldehyde **6** (1 equiv). After stirring at −78 °C for 10 min, the reaction mixture was brought gradually to 0 °C, stirred at that temperature for an additional 30 min, and quenched with pH 7 phosphate buffer. Extractive isolation afforded the tetraene ether **10** which was cleaved with tetra-*n*-butylammonium fluoride (1.05 equiv)[10] in tetrahydrofuran at 0 °C for 30 min to give, after chromatographic purification on silica gel, the hydroxy tetraene **11** (90% overall yield from **6** and **9**). The tetraene ether **10** showed ultraviolet λ_{max} (ethanol) at 263, 271.5, and 283 nm (ϵ 38 400, 49 100, 36 600).

The hydroxy tetraene **11** was converted into the epoxy ester by the following procedure. A solution of **11** in tetrahydrofuran at −25 °C was treated with 1.25 equiv of triethylamine and 1.2 equiv of methanesulfonyl chloride with stirring for 1 h to form the mesylate **12** and this solution was treated with 20 equiv of dimethyl sulfide, first at −20 °C and then at 0 °C for 18 h. The resulting solution of sulfonium salt **13** was then cooled to −78 °C and treated dropwise with a tetrahydrofuran solution of lithium diisopropylamide (~1.5 equiv) until a dark color persisted, at which point an additional 1.2 equiv of lithium diisopropylamide was added followed after 30 s by 2 equiv of methyl 4-formylbutyrate.[15] After stirring at −78 °C for 15 min

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