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Kinetic determination of calcium pantothenate by a $[CuL](ClO_4)_2$-catalyzed oscillating system

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The paper reported a new quantitative method for the determination of calcium pantothenate, basing on its perturbation effects on the new Belousov–Zhabotinskii oscillating system.

Oscillating chemical systems have been widely used to determine various analytes since the first application of chemical oscillators in 1978 by Tichonova *et. al.*[1] The great interest in oscillating chemical reactions is that they show a lot of non-monotonic behaviours in theoretical and experimental chemical kinetics. The well-known oscillating chemical reaction is the Belousov–Zhabotinskii (B–Z) reaction.[2,3] The reaction involves the oxidation of an organic species in an acidified bromate solution in the presence of a metal ion catalyst.[4,5] The catalysts in B–Z oscillating reactions are only limited to Ce^{3+}, Mn^{2+}, $Ru(bipy)_3^{2+}$ and $Fe(phen)_3^{2+}$; we refer to these oscillation reactions as classical. Tetraazamacrocyclic complex, however, was first reported as an alternative catalyst for the B–Z system in 1982.[6] Oscillating chemical reaction catalyzed by tetaazamacrocyclic complexes of Cu^{II} or Ni^{II} shows unusual kinetic features that are different from those of the classical oscillating reaction. Such features of these B–Z systems include having a low activation energy, being more vulnerable to the external perturbations, and having higher oscillating frequencies.[7] This unique feature is the presence of the extended π system in the macrocyclic ligand L, which ensures a high rate for reactions involving electron transfer at individual steps of the oscillating process.[8]

For the B–Z oscillating system in which a macrocyclic complex was used as a catalyst, the organic substrates include malonic acid,[9] pyruvic acid[10] or lactic acid.[11,12] Recently, a new B–Z oscillating system was reported: $NaBrO_3$–malic acid–$[CuL](ClO_4)_2$–H_2SO_4. The ligand L in the complex $[CuL](ClO_4)_2$ is 5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene.[13] Owing to the unique kinetic features of tetraazamacrocyclic complex-catalyzed oscillating reactions, the $[CuL](ClO_4)_2$-catalyzed oscillating system was used to survey the effect of the perturbation of calcium pantothenate as the analytical purpose.

Calcium pantothenate and pantothenic acid are usually considered to be vitamin B5. Calcium pantothenate is stable in aqueous solution and used as a supplement to treat, for examples, acne, osteoarthritis, rheumatoid arthritis, wounds, and to support the immune system.[14] It is also used in cosmetics and pharmaceuticals for skin emollient, regeneration and hair conditioning purposes.

The analytical methods for determination of calcium pantothenate include titration,[15,16] high-performance liquid chromatography,[17] reversed-phase liquid chromatographic methods,[18,19] and potentiometric titration.[20] In this article, a new method for determination of calcium pantothenate based on the $[CuL](ClO_4)_2$-catalyzed oscillating system is presented.

The experiment assembly was described elsewhere.[21,22] Sodium bromate, sulfuric acid and malic acid were of analytical grade. Commercial calcium pantothenate (≥ 98%, Sigma–Aldrich) was used. The catalyst $[CuL](ClO_4)_2$ was prepared according to a published procedure.[23] Solutions of 0.5 M $NaBrO_3$, 2 M malic acid and 0.0184 M $[CuL](ClO_4)_2$ were separately prepared with 0.9 M sulfuric acid. Aqueous solution of 0.1 M calcium pantothenate was freshly prepared by dissolving 1.1914 g calcium pantothenate in water to a final volume of 25 ml before the experiment. Solutions with lower concentrations were prepared just prior to use. Double-distilled water was used throughout.

Solutions of sulfuric acid (28 ml), malic acid (4 ml), $NaBrO_3$ (1.8 ml) and $[CuL](ClO_4)_2$ (6.2 ml) were added to a 50 ml glass beaker, which was thermostated at 16±0.5 °C. The platinum electrode and reference electrode were placed into the beaker. Then, the mixture was homogenized by continuous magnetic stirring at a rate of 500 rpm and the oscillating curve was recorded by a Y-t recorder. After a short induction period, the oscillating system got to steady cycles. The aqueous solution samples containing variable amounts of calcium pantothenate were injected into the reaction system at the bottom of the potentiometric cycle. The oscillation amplitude and period were all changed and then the oscillation cycle became another steady state again. Changes in the oscillation amplitude cycle $\Delta A = A - A_0$, where A_0 and A are the oscillation amplitude before and after the injection, respectively, and the changes in oscillation period cycle $\Delta T = T - T_0$, where T_0 and T are the oscillation period before and after the injection, respectively, were used as measurement signals to construct the calibration plot. Each of the potentiometric oscillating curves was recorded.

The B–Z oscillating chemical system exhibits a periodic change in the concentration of the reduced and oxidized forms of $[CuL]^{2+}$ and $[CuL]^{3+}$, accompanying periodic changes in colour between red and orange. This phenomenon indicates the following electron-transfer process:

$$[CuL]^{2+}\,(\text{red}) \underset{+\,e}{\overset{-\,e}{\rightleftharpoons}} [CuL]^{3+}\,(\text{orange}).$$

The spectrum of $[CuL]^{3+}$ is consistent with the spectrum reported in the literature.[24] The analyte causes changes in the oscillation amplitude and period, and after the perturbation, the system gradually regains the steady state. Because the above changes are linearly proportional to calcium pantothenate concentration, the analyte concentration in a desired range can be determined.

According to published data,[25] the category of this $[CuL](ClO_4)_2$-catalyzed oscillator belongs to oxidation spikes because there is a rapid excursion of the oxidized form in the course of the

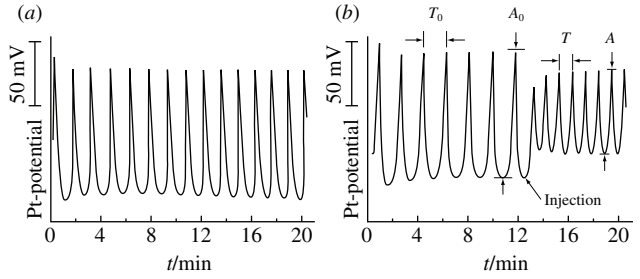


Figure 1 Typical oscillation profiles for the proposed oscillation system in the absence and presence of variable amounts of calcium pantothenate perturbation using Pt electrode: (*a*) without calcium pantothenate, (*b*) [calcium pantothenate] = 1.5×10^{-3} M. Common conditions: $[NaBrO_3] = 0.0225$ M; [malic acid] = 0.2 M; $[H_2SO_4] = 0.9$ M; $[CuL](ClO_4)_2 = 2.85\times10^{-3}$ M.

oscillation. Figure 1 shows typical oscillation profiles for the $[CuL](ClO_4)_2$-catalyzed oscillating system in the presence and absence of variable amounts of calcium pantothenate under the above experimental conditions. During a typical oscillation cycle, the potential dropped to a minimum and then increased gradually to the starting condition. In order to ensure accurate results, several injection points have been tested. When calcium pantothenate was injected at the maximum of the cycle, it had no effect on the oscillation system. However, after calcium pantothenate was injected at the minimum of the cycle, the oscillation system went into a new oscillatory state with the shorter period T and reduced amplitude. The system stayed in this state for a long time (> 2 h) before it finally run into a damped oscillation. The shorter period length observed here may be ascribed to an increased bromination reaction.[26–28] It was found that ΔA is linearly proportional to the calcium pantothenate concentration over the range of 5×10^{-6}–2.5×10^{-3} M (Figure 2). The linear regression equation is $\Delta A = (3.09\pm0.56) + (-23680.65\pm536.3)$[calcium pantothenate] ($r = -0.9982$, $n = 9$). The relative standard deviation (RSD) in five replicate determinations for 1.5×10^{-3} M calcium pantothenate was 2.6%. ΔT is second-order polynomial proportional to the concentration of calcium pantothenate over the range of 1.5×10^{-5}–2.5×10^{-3} M. The polynomial regression equation is $\Delta T = (-0.24\pm0.01) + (-520.44\pm32.51)$[calcium pantothenate] + $(71687.97\pm13120.55)\times$ ×[calcium pantothenate]^2 ($r = 0.9966$, $n = 8$). The RSD was 0.3%. The detection limit is 2.5×10^{-6} M.

In order to establish the suitability of the proposed method, known amounts of the standard calcium pantothenate were added to the analytical solution of the calcium pantothenate tablets and the same procedure was applied. The recovery experiments indicate that the accuracy of the proposed method is very good. From above experimental results, it is clear that this method is suitable for practical sample analysis (Table 1).

In order to obtain a maximum value of ΔA or ΔT, the influences of the experimental variables on the proposed oscillating reaction

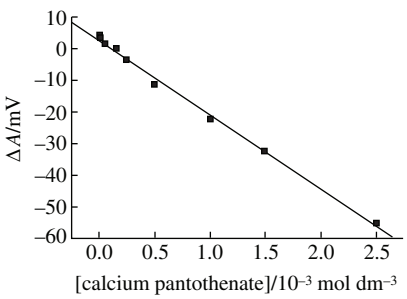


Figure 2 Calibration curve of the change of amplitude *versus* calcium pantothenate concentration in the range of 5×10^{-6}–2.5×10^{-3} M. Common conditions: $[NaBrO_3] = 0.0225$ M; [malic acid] = 0.2 M; $[H_2SO_4] = 0.9$ M; $[CuL](ClO_4)_2 = 2.85\times10^{-3}$ M.

Table 1 Determination results and recovery of calcium pantothenate in water sample.

Sample	Determined result/ 10^{-3} mol dm^{-3}	Added/ 10^{-3} mol dm^{-3}	Found/ 10^{-3} mol dm^{-3}	Recovery (%)
1	1.017	0.25	1.243	98.11
2	0.961	0.25	1.201	99.17
3	1.735	0.25	1.989	100.2
4	1.679	0.25	1.946	100.88
5	1.510	0.50	2.045	101.74
6	1.538	0.50	2.059	101.03
7	1.228	1.00	2.298	103.14
8	1.257	1.00	2.256	99.9

were studied. The effect of H_2SO_4 concentration was studied in the range of 0.7–1.2 M. However, when the concentration of H_2SO_4 is lower than 0.7 M, no oscillating reaction after calcium pantothenate was injected. It was found that both ΔA and ΔT increased with the concentration of H_2SO_4 over the range of 0.75–1.2 M. In order to obtain optimal ΔA and ΔT, a 0.9 M sulfuric acid concentration was selected.

In the range of 0.17–0.28 M, the influence of malic acid was tested. As the concentration was increased, ΔA first increased to a maximum and then decreased. The changes of ΔT were similar to the changes of the effect of H_2SO_4 concentration. A concentration of 0.2 M was chosen as maximum sensitivity.

Changes in $NaBrO_3$ concentration were over the range of 0.0125–0.03 M. The result showed that, with increasing $NaBrO_3$ concentration, ΔA increased but ΔT decreased. According to the above three criteria, a concentration of 0.0225 M was finally adopted as optimal.

As the catalyst $[CuL](ClO_4)_2$ concentration was increased from 2.024×10^{-3} to 3.68×10^{-3} M, ΔA increased to a maximum and then decreased, after that it increased again and decreased lastly. ΔT was found to decrease with $[CuL](ClO_4)_2$ concentration. The value of 2.85×10^{-3} M was chosen for the optimum concentration.

The effect of temperature also was studied. Raising it from 5 to 35 °C, the oscillation period decreased in the absence of calcium pantothenate perturbation. Furthermore, the temperature scarcely affected the system response to the perturbation. However, it is a long time to inject calcium pantothenate when the temperature is too low. Contrarily, when the temperature is too high, it is difficult to ensure the same injection points on the determination of calcium pantothenate. Finally, a temperature of 16 °C was chosen as the most appropriate.

The influences of foreign species and ions in the reaction medium were also investigated. The oscillating system was perturbed with a sample, which contained calcium pantothenate and variable amounts of interferences. More than 15 foreign ions causing an error of less than 5% were studied in the determination of 5×10^{-5} M calcium pantothenate (Table 2). Large amounts of Ca^{2+} and most common ions have no effect on the determination, except for chloride and iodide. As can be seen in Table 2, the selectivity of the method is acceptable.

Table 2 Influence of foreign ions and species on the determination of 5×10^{-5} M calcium pantothenate.

Foreign ions and species	Tolerated ratio
Li^+, K^+	2000
Ni^{2+}, Al^{3+}, Mg^{2+}, NH_4^+, Ca^{2+}, Na^+, Mn^{2+}, $H_2PO_4^-$, Zn^{2+}	1000
F^-	100
Cu^{2+}	50
Fe^{3+}	20
Malonic acid, pyruvic acid	10
Oxalic acid	2
Ag^+	1
Cl^-, I^-	0.4
Fe^{2+}	0.02

The oscillating system often consists of many kinetic steps involving several independent variables,[29] so the mechanisms of oscillating reaction are usually rather complex. According to the well-known FKN mechanism[30] and published data,[13] the $[CuL]^{2+}$-catalyzed oscillating system can be described by the following reactions:

$$BrO_3^- + Br^- + 2H^+ \rightleftharpoons HOBr + HBrO_2 \quad (1)$$

$$HBrO_2 + Br^- + H^+ \rightleftharpoons 2HOBr \quad (2)$$

$$HOBr + Br^- + H^+ \rightleftharpoons Br_2 + H_2O \quad (3)$$

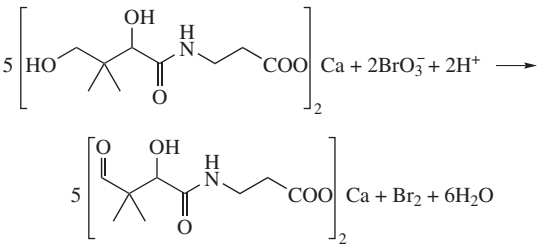
$$BrO_3^- + HBrO_2 + H^+ \rightleftharpoons 2BrO_2^{\cdot} + H_2O \quad (4)$$

$$Br_2 + HOOCCH(OH)CH_2COOH \longrightarrow Br^- + H^+ + HOOCCH(OH)(Br)CHCOOH \quad (5)$$

$$BrO_2^{\cdot} + [CuL]^{2+} + H^+ \longrightarrow [CuL]^{3+} + HBrO_2 \quad (6)$$

$$HOOCCH(OH)(Br)CHCOOH + 6[CuL]^{3+} + 3H_2O \longrightarrow 6[CuL]^{2+} + Br^- + 2HCOOH + 2CO_2 + 7H^+ \quad (7)$$

As a part of the experiment, cyclic voltammetry was applied to clarify species, which reacted with calcium pantothenate in the oscillating system. The cyclic voltammograms of the acidic $NaBrO_3$ solution in the absence and in the presence of 1.5×10^{-3} M calcium pantothenate are shown in Figure 3. The reduction current of $NaBrO_3$ solution decreased with calcium pantothenate concentration. Considering the potential of BrO_3^-/Br_2 (1.51 V) is the highest among BrO_3^-/Br_2 (1.51 V), BrO_3^-/HOBr (1.49 V) and BrO_3^-/Br^- (1.44 V), Br_2 is the possible reduction product of BrO_3^- by calcium pantothenate. The reaction can be expressed as follows:



$$5\left[HO\text{–}CH(OH)\text{–}C(CH_3)_2\text{–}CH(NH)\text{–}CO\text{–}CH_2\text{–}CH_2\text{–}COO\right]_2Ca + 2BrO_3^- + 2H^+ \longrightarrow$$

$$5\left[O{=}CH\text{–}C(OH)(CH_3)_2\text{–}CH(NH)\text{–}CO\text{–}CH_2\text{–}CH_2\text{–}COO\right]_2Ca + Br_2 + 6H_2O \quad (8)$$

In the oscillation system, calcium pantothenate was injected at low level, so the concentration of bromine (Br_2) is also low.[31]

Reaction (8) consumed a lot of BrO_3^-, which is the reactant of reactions (1) and (4). Reactions (1)–(4) are reversible, so the concentration of $BrO_2^{\cdot}$ in the system decreases. With the decrease of free $BrO_2^{\cdot}$ concentration, $[CuL]^{3+}$ concentration decreased in reaction (6) and the value of ln $[CuL]^{3+}/[CuL]^{2+}$ changed. The result is shown in Figure 1. With reaction (8) occurs successively, the Br_2 will accumulate. When Br_2 concentration rises to a sufficient amount, reaction (3) occurs to the reverse direction and increases the concentration of HOBr and Br^-. As a product is a reactant of another reaction in equations (1)–(4), reactions (2), (1) and (4) take place respectively. Then reactions (1)–(4) resume to the original rate. With the increase of Br_2 and $BrO_2^{\cdot}$ concentrations, reactions (5) and (6) occur, respectively, and the products of HOOCCH(OH)(Br)CHCOOH and $[CuL]^{3+}$ make reaction (7) to proceed in succession.

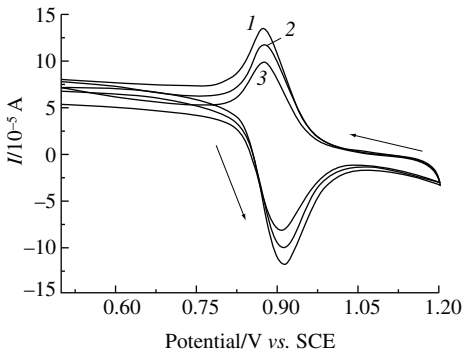


Figure 3 Cyclic voltammograms of the reactions in (*1*) $[NaBrO_3] = 0.05$ M, $[H_2SO_4] = 0.9$ M, [calcium pantothenate] = 0; (*2*) $[NaBrO_3] = 0.05$ M, $[H_2SO_4] = 0.9$ M; [calcium pantothenate] = 1.5×10^{-3} M; (*3*) $[NaBrO_3] = 0.05$ M, $[H_2SO_4] = 0.9$ M; [calcium pantothenate] = 2.5×10^{-3} M; scan rate, 100 mV s^{-1}.

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