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Inhibitory Effects of Rifampicin On A Briggs-Rauscher Oscillating System

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Inhibitory effects of rifampicin on a novel Briggs-Rauscher oscillating system in which a macrocyclic nickel(II) complex ($[NiL](ClO_4)_2$) acts as the catalyst are studied. The ligand L is 5,7,7,12,14,14-hexemethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene. The experimental results indicate that, in the rifampicin concentration range of 2.6 to 22.5 μM, injection of rifampicin caused temporal ceasing of oscillations and then the oscillator resumed oscillations with obvious changes both in oscillation period and oscillating cycles. A mechanism on the effects of rifampicin is proposed based on Model NF.

Key Words: Inhibitory effects, Briggs-Rauscher oscillation, Macrocyclic nickel(II) complex, Rifampicin.

INTRODUCTION

Some properties in kinetics and thermodynamics of Briggs-Rauscher oscillation[1] present when a certain amount of iodate, organic substrate, metal redox couples and hydrogen peroxide were mixed in a beaker. In the literatures, the $Mn^{2+/3+}$ redox couples[2-4] were introduced to catalyze Briggs-Rauscher oscillating reactions. Also, a macrocyclic nickel(II) complex[5] can be used as catalyst in Briggs-Rauscher system (KIO_3-$[NiL](ClO_4)_2$-$CH_2(COOH)_2$-H_2O_2-H_2SO_4), where L = 5,7,7,12,14,14-hexemethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene. An interesting feature about this complex is that it has similar structure to some metalloenzymes which are functioned in biological oscillations processes such as heartbeat, breath and metabolism.

Rifampicin is a kind of broad-spectrum antibiotic. In this note, the effects of rifampicin on Briggs-Rauscher system are reported. It is attractive that the pH in this Briggs-Rauscher system is closing to that of gastric juice (pH ≈ 2), making this system an imitator for oscillations in biosystem.

EXPERIMENTAL

The $[NiL](ClO_4)_2$ was prepared by a known technique[6] and was identified by IR and elemental analysis. Solutions of 0.14 M KIO_3, 1.73×10^{-2} M $[NiL](ClO_4)_2$, 2 M $CH_2(COOH)_2$(malonic acid) and 4 M H_2O_2 were prepared from 0.025 M H_2SO_4 which was diluted by double-distilled H_2O. Rifampicin solution was prepared immediately prior to use. All reagents are analytical grade. The oscillating reaction experiments were conducted by the method described in the literature[7].

RESULTS AND DISCUSSION

Effects of rifampicin on a typical oscillation: Fig. 1a shows potentials *vs.* time for the typical Biggs-Rauscher oscillation at 0 ºC. Oscillator oscillates for *ca.* 45 times and average oscillation period is 30.175 s. This oscillating system has a low activity energy (46.844 KJ/mol). During the oscillations, the solution colour changes repeatedly between yellow and brown. Fig. 1b reveals evident inhibitory effects which were caused by injecting 1 mL 6.5×10^{-4} M rifampicin into the oscillating system on the fourth circle. Oscillatior was temporally inhibited in the presence of the rifampicin, but, after a time pause, oscillations were regenerated with different oscillation periods, amplitudes of oscillation and oscillating cycles.

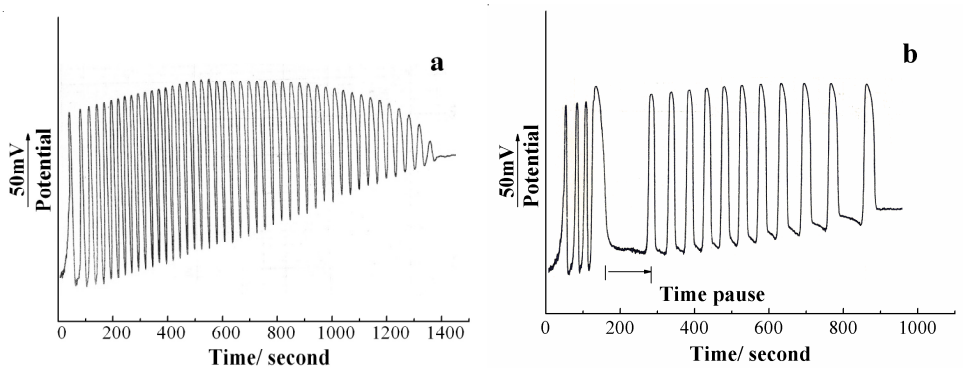

Fig. 1. Potentials *vs.* time for the proposed Biggs-Rauscher oscillating system (a) in the absence of rifampicin (b) in the presence of [rifampicin] = 1.625×10^{-5} M. Common conditions: $[KIO_3] = 2.1 \times 10^{-2}$ M, $[[NiL](ClO_4)_2] = 8.65 \times 10^{-4}$ M, [MA] = 0.15 M, $[H_2SO_4] = 2.5 \times 10^{-2}$ M, $[H_2O_2]$ = 1.4 M, temperature = 0 ºC

The dependence of time pause on the concentration of rifampicin is showed in Fig. 2. Time pause increased with the increasing concentration of rifampicin in 2.6-22.5 μM. The calibration data obey the following equation:

$$\text{Time Pause} = 0.00169*[\text{Rifampicin}]^{4.15982} \quad (R^2 = 0.99088,\ n = 15)$$

In present study on effects of rifampicin on the Biggs-Rauscher oscillation, it is found that injection of rifampicin caused obvious changes both in oscillation period and oscillating cycles. With the increase of rifampicin concentration, the change of oscillation period ($^{\Delta}t_p$) increased dramatically (Fig. 3a), and following equation was established:

$$^{\Delta}t_p/s = 2.45 + (-2.0131)*[\text{Rifampicin}] + 0.3241*[\text{Rifampicin}]^2 \quad (R^2 = 0.99522)$$

Oscillating cycles (n) decreased as the concentration of rifampicin increased (Fig. 3b). When the concentration of rifampicin is 22.5 μM, only two cycles of oscillation were regenerated.

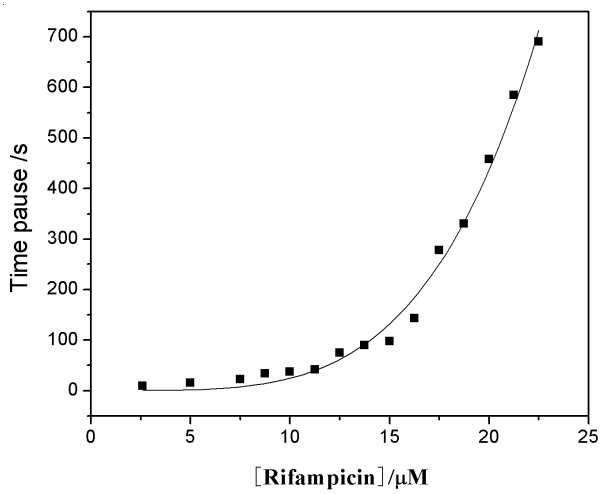

Fig. 2. Dependence of time pause on [Rifampicin] from 2.6 μM to 22.5 μM. (Other conditions are the same as those in Fig. 1)

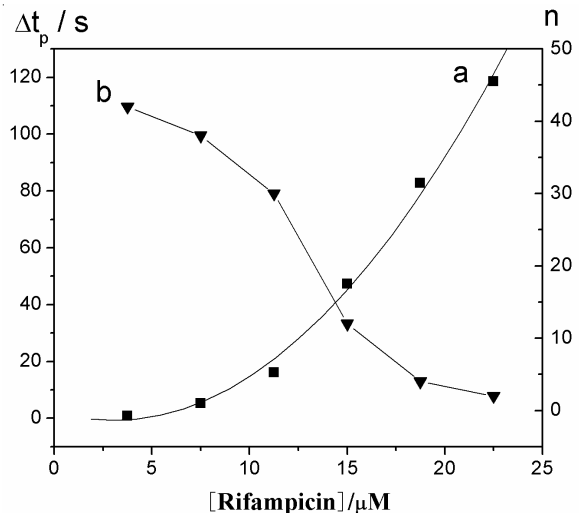

Fig. 3. Curve of the changes in oscillation period ($^{\Delta}t_p$) (a) and the decrease in oscillating cycles (n) (b) *vs.* the [Rifampicin] in the range of 2.6 - 22.5 μM. (Other conditions are the same as shown in Fig. 1)

Mechanism interpretation: A probable mechanism interpretation for the inhibitory effects of rifampicin on the system is proposed based on model NF[3]. Briggs-Rauscher reaction is considered an iodide ion-driven oscillator with repeating consumption and generation of I^- that can be monitored by iodide-selective electrode. Formation of oxygen and iodine complies with the following reaction in stoichiometry[3]:

$$2IO_3^- + 5H_2O_2 + 2H^+ \longrightarrow I_2 + 5O_2 + 6H_2O$$

The above reaction is induced probably by following six steps and some other reactions:

$$HOI + I^- + H^+ \rightleftharpoons I_2 + 2H_2O$$
$$I^- + IO_3^- + 2H^+ \rightleftharpoons HOI + HOIO$$
$$IO_3^- + HOIO + H^+ \rightleftharpoons 2IO_2^{\cdot} + H_2O$$
$$IO_2^{\cdot} + [NiL]^{2+} + H^+ \rightleftharpoons HOIO + [NiL]^{3+}$$
$$[NiL]^{3+} + H_2O_2 \longrightarrow [NiL]^{2+} + H^+ + HOO^{\cdot}$$
$$H^+ + IO_3^- + HOO^{\cdot} \longrightarrow IO_2^{\cdot} + H_2O + O_2$$

The solution colour shows obviously changes from yellow to brown repeatedly, indicating the oscillations between $[NiL]^{2+}$ and $[NiL]^{3+}$. $[NiL]^{2+}$ is yellow. $[NiL]^{3+}$ itself is green, while the solution presents brown because of dissolved iodine which was generated during the course of the oscillation. The manners of reactions involving the catalyst can be explained as follows[5]:

$$H_2O_2 + [NiL]^{2+} + H^+ \longrightarrow [NiL]^{3+} + H_2O + OH^{\cdot}$$
$$OH^{\cdot} + [NiL]^{2+} + H^+ \longrightarrow [NiL]^{3+} + H_2O$$
$$OH^{\cdot} + H_2O_2 \longrightarrow H_2O + HOO^{\cdot}$$

In Biggs-Rauscher system, the organic substrate malonic acid reacts with I_2 and releases I^-:

$$CH_2(COOH)_2 \longrightarrow (HOOC)CH{=}C(OH)_2 \text{ (enol)}$$
$$(HOOC)CH{=}C(OH)_2 \text{ (enol)} + I_2 \longrightarrow IHC(COOH)_2 + I^- + H^+$$

$HOO^{\bullet}$ plays an important role in the system. Inhibition effects of rifampicin on the Biggs-Rauscher system are similar to that of superoxide on the Biggs-Rauscher system and hence it is reasonable to believe that crifampicin eliminated $HOO^{\bullet}$ radical during the oscillation:

$$\text{rifampin} + HOO^{\cdot} \longrightarrow \text{radical of rifampin} + H_2O_2$$

It is assumed that radical of rifampin was oxidized into a steady substance, *i.e.* 3-formyl rifamycin SV[8] during the oscillations. Then oscillations regenerate when rifampicin decayed completely.

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