One-electron Oxidation of *N*-Benzylphenothiazine by Nitric Acid in the Presence of β-Cyclodextrin

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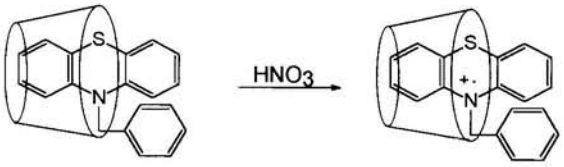
(Received January 12, 1998; CL-980029)

Oxidation of *N*-benzylphenothiazine with nitric acid in aqueous solution was investigated in the presence of β-cyclodextrin by means of UV-vis and ESR spectroscopy. The *N*-benzylphenothiazine radical cation generated in β-cyclodextrin cavity is much more stable than that outside of β-cyclodextrin cavity and that in organic solvent.

Phenothiazine derivatives are important drugs which have sedative and anti-psychotic functions.[1] The phenothiazine radical cations can be generated in metabolism of phenothiazine-based drugs.[2] It has been reported that the radical cations themselves are pharmacologically active.[3] Thus, formation and stabilization of phenothiazine radical cations in aqueous solution are compelling subjects[4] for studying biochemical processes. Knowledge of these processes has a potential application to biological systems as well as pharmacological studies.

Recently, Kochi *et al*[5] reported that various phenothiazines are oxidized to the corresponding sulfoxides in dichloromethane by the catalysis of nitric oxide and related nitrogen oxides, the reactive intermediates are the phenothiazine radical cations which are quickly transformed to the sulfoxides. Here, we report the results of one-electron oxidation of *N*-benzylphenothiazine (BPT) with nitric acid in aqueous solution in the presence of β-cyclodextrin (β-CD) and the UV-vis and ESR evidence for generation and stabilization of the corresponding radical cation.



Cyclodextrin (CD) is well known as a kind of enzyme model[6] which has widely been used in inclusion complexation studies.[7] Several authors have utilized CD to stabilize the radical intermediates.[8]

An aqueous solution containing 1.5×10^{-3} mol/dm^3 of BPT and 2×10^{-3} mol/dm^3 of β-CD and a dichloromethane solution containing 1.5×10^{-3} mol/dm^3 of BPT were degassed by bubbling with argon stream. When 80 μl of concentrated nitric acid (65%) was added into 3 ml of the BPT dichloromethane solution at room temperature, the colorless solution turned red immediately, but the color was bleached in a moment. While 80 μl of concentrated nitric acid was dropped into 3 ml of the β-CD-BPT aqueous solution with shaking under the same experimental conditions, the solution turned to pink and then slowly became darker to red, the red color was faded slowly. The absorption band at 515 nm and the ESR spectrum show the generation of the BPT radical cation in the solution (Figures 1 and 2).

As Figures 1 and 2 show, the oxidation reaction of BPT by nitric acid involves a radical cation intermediate. Owing to the

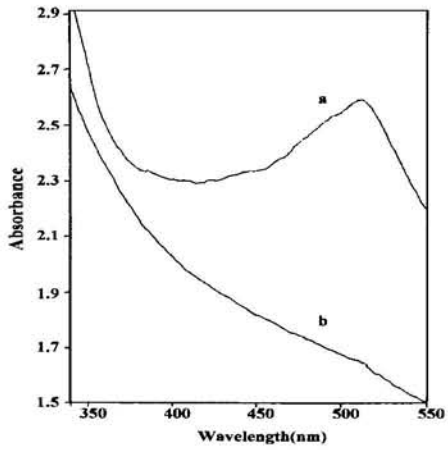


Figure 1. UV-vis spectra taken for the oxidation of BPT (a) and BPT + adamantanone (b) by nitric acid in the presence of β-CD in aqueous solutions at room temperature.

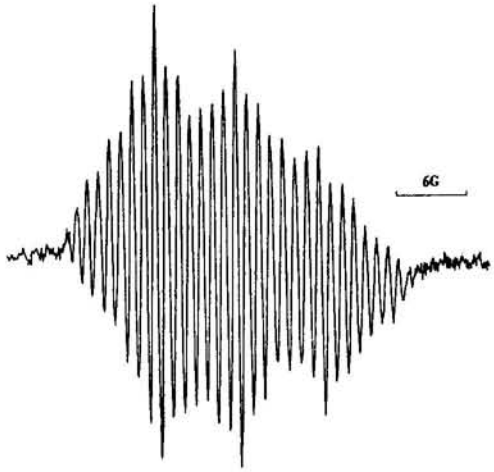


Figure 2. ESR spectrum of the BPT radical cation generated by one-electron oxidation of BPT with nitric acid in β-CD cavity in aqueous solution at room temperature.

strong oxidativity of nitric acid, the BPT radical cation was further oxidized rapidly to the sulfoxide in organic solvent. Therefore, it was difficult to take the absorption and ESR spectra of the radical cation. The association constant (K_a)[9] for complexation of β-CD with BPT in aqueous solution at room temperature was determined to be 312 dm^3/mol, which indicates that the stable inclusion complex of β-CD-BPT is formed. A Molecular Dynamics calculation[9] showed that the phenothiazine moiety of BPT is included into the β-CD cavity and the benzyl group locates outside the β-CD cavity, the phenothiazine heterocycle is just under the shield of the benzyl group and the β-CD wall, which protects BPT from the attack of the oxidant. However, HNO_3 is a strong oxidant with a relatively small size, it might enter into the β-CD cavity of the β-CD-BPT complex to oxidize BPT to $BPT^{+\cdot}$. The lifetime of $BPT^{+\cdot}$ in β-CD cavity was long enough due to the efficient protection (Figure 3).

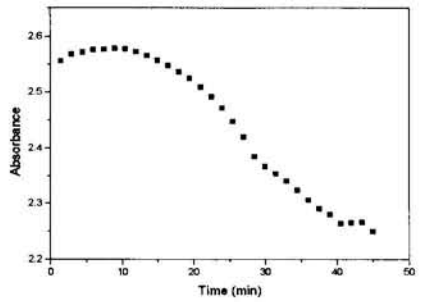


Figure 3. Relationship between the absorption intensity of BPT radical cation at 515 nm and time at room temperature.

As Figure 3 shows, the absorbance of BPT radical cation at 515 nm increased at the beginning of mixing the β-CD-BPT aqueous solution with nitric acid, and then decreased with time at room temperature. This finding indicates that the β-CD plays a significant role in stabilization of BPT radical cation in aqueous solution.

To clarify the one-electron oxidation of BPT occurred in β-CD cavity, an inhibition experiment has been carried out. Adamantanone was added into the β-CD-BPT complex as an inhibitor. Since the K_a value for complexation of β-CD with adamantanone ($ca.5\times10^5$ dm^3/mol)[9] is much larger than that with BPT (3.12×10^2 dm^3/mol), adamantanone is preferentially incorporated into the β-CD cavity. It is readily understood that BPT is excluded from the β-CD cavity. In this case, when nitric acid was added into this solution, no characteristic absorption (Figure 1(b)) and ESR spectra were measured. Since nitric acid rapidly oxidize free BPT to sulfoxide, the lifetime of the intermediate BPT radical cation in the conversion of BPT to sulfoxide was too short to be detected by UV-vis and ESR spectroscopies.

Based on the observation above, we can conclude that the one-electron oxidation of BPT by nitric acid occurs in aqueous β-CD solution and the BPT radical cation is stabilized by β-CD.

We thank the National Natural Science Foundation of China for the financial support (No.29572067).

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