Electron Transfer between *N*-Substituted Phenothiazines and the 1-Oxopiperidinium Ion in the Presence of β-Cyclodextrin

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The electron-transfer reactions between *N*-substituted phenothiazines and 4-acetoxy-2,2,6,6-tetramethyl-1-oxopiperidinium hexachloroantimonate (ATPO) in the presence of β-cyclodextrin (β-CD) in an aqueous solution have been studied. *N*-phenylphenothiazine (PPT) and *N*-phenethylphenothiazine (PEPT), included by β-CD, can transfer an electron to the β-CD·ATPO complex. However, no electron-transfer reaction between the β-CD·*N*-benzylphenothiazine (β-CD·BPT) complex and the β-CD·ATPO complex was observed under the same conditions. It has been suggested that the electron-transfer reactions were controlled by the conformations of the *N*-substituted phenothiazines in the cavity of β-CD.

Phenothiazine derivatives are widely used as tranquiling drugs owing to their sedative and antipsychotic activities.[1,2] Due to their relatively low ionization potentials, they can be easily oxidized to the corresponding radical cation intermediates.[3] It has been reported that the radical cations, themselves, are also pharmacologically active.[4] Ruperz[5] reported that phenothiazine drugs could act as electron donors in an electron-transfer reaction on the drug receptor site. Recent studies have focused on the formation of phenothiazine radical cations by different means.[6]

Oxopiperidinium ions are common one-electron oxidants, which can efficiently and selectively oxidize some kinds of organic compounds,[7,8] such as phenothiazine derivatives, by an electron-transfer mechanism.[9] Although the electron transfer between phenothiazines and 4-acetoxy-2,2,6,6-tetramethyl-1-oxopiperidinium haxachloroantimonate (ATPO) in organic solvents has been reported,[9] electron-transfer in an aqueous solution is still unknown, since both of the reactants are insoluble in water, and the resulting radical cations are unstable in water.

Cyclodextrin (CD), naturally occurring cyclic oligosaccharide, mostly consist of six, seven and eight D-glucose units for α-, β-, and γ-CD, respectively. CD plays an important role in including various organic molecules due to its hydrophobic cavity in aqueous solution. Owing to this property, it has been used in molecular vessels for chemical reactions, recognition sites of enzyme models, dissolving water-insoluble chemicals and stabilizing unstable substances.[10—14] CD and derivatives have also been used as building blocks of molecular devices,[15] especially in switching on and off the chemical and biochemical activities by chemical means.[16]

Recently, much attention has been paid to electron-transfer reactions in supramolecular systems.[17,18] In a previous communication[19] we reported on the *N*-benzylphenothiazine radical cation generated in the β-CD cavity by one-electron oxidation with nitric acid. In the present study, we demonstrated electron-transfer reactions between ATPO and *N*-phenylphenothiazine (PPT), *N*-benzylphenothiazine (BPT), and *N*-phenethylphenothiazine (PEPT) in the presence of β-CD in aqueous solution (Chart 1). The electron-transfer process was influenced by the microenvironment.

Results and Discussion

Electron transfer between *N*-substituted phenothiazines and ATPO occurred rapidly upon mixing the electron donor and acceptor in an acetonitrile solution. The characteristic absorption bands at around 515 nm were recorded for the *N*-substituted phenothiazine radical cations (Fig. 1) (Chart 2).

As Fig. 1 shows, no absorption at 400—550 nm was observed for both PPT and ATPO. A new absorption band at

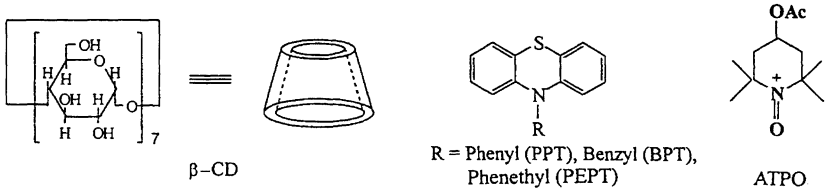


Chart 1.

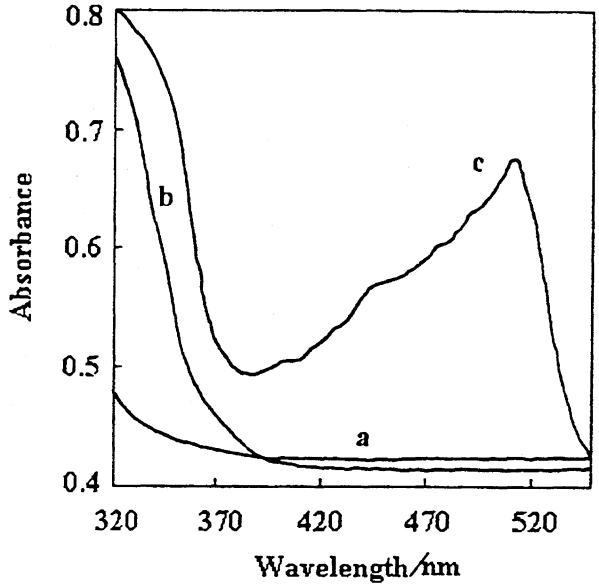


Fig. 1. Absorption spectra of ATPO (a), *N*-phenylphenothiazine (b), and *N*-phenylphenothiazine radical cation (c) generated upon mixing PPT (1.5×10^{-3} mol dm^{-3}) with ATPO (1.5×10^{-3} mol dm^{-3}) in acetonitrile.

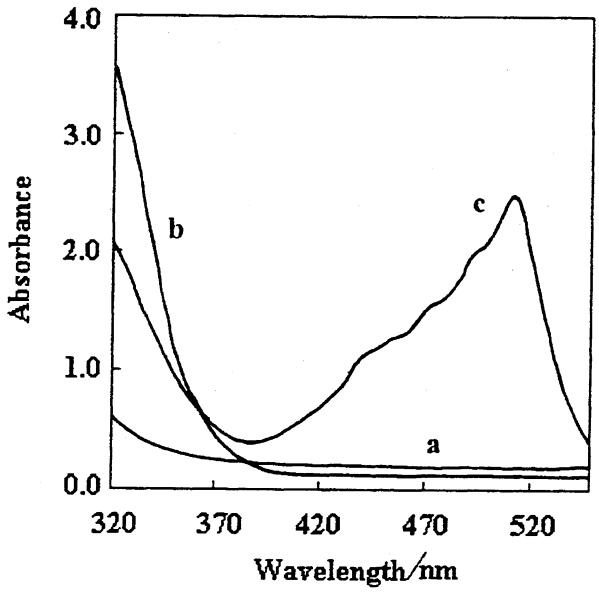


Fig. 2. Absorption spectra of *N*-phenylphenothiazine radical cation generated by one-electron oxidation of β-CD·PPT (1.5×10^{-3} mol dm^{-3}) with β-CD·ATPO (1.5×10^{-3} mol dm^{-3}) in aqueous solution.

515 nm appeared when ATPO was mixed with PPT in acetonitrile. It has been demonstrated that the absorption band at 515 nm is due to the radical cations of the phenothiazine derivatives.[20] An ESR measurement of the reaction solution gave a very strong triplet pattern (g = 2.0060, a(N) = 1.60 mT) due to the neutral nitroxide radical resulting from a one-electron reduction of ATPO by *N*-substituted phenothiazine. The ESR signal of the PPT radical cation was shielded by the strong triplet ESR spectrum of the nitroxide radical.

Interestingly, the same phenomena were observed upon mixing ATPO with PPT and PEPT in the β-CD aqueous solutions. When the β-CD·ATPO aqueous solution was added to the β-CD·PPT and β-CD·PEPT aqueous solutions, respectively, the resulting solutions became pink immediately after shaking. The characteristic absorption at 515 nm from *N*-substituted phenothiazine radical cations (Fig. 2) and a very strong triplet ESR spectrum of nitroxide radical were observed. Strangely, for β-CD·BPT, neither the characteristic absorption band of the BPT radical cation nor the triplet ESR spectrum of the nitroxide radical was observed upon mixing β-CD·BPT with β-CD·ATPO in an aqueous solution under the same conditions (Fig. 3).

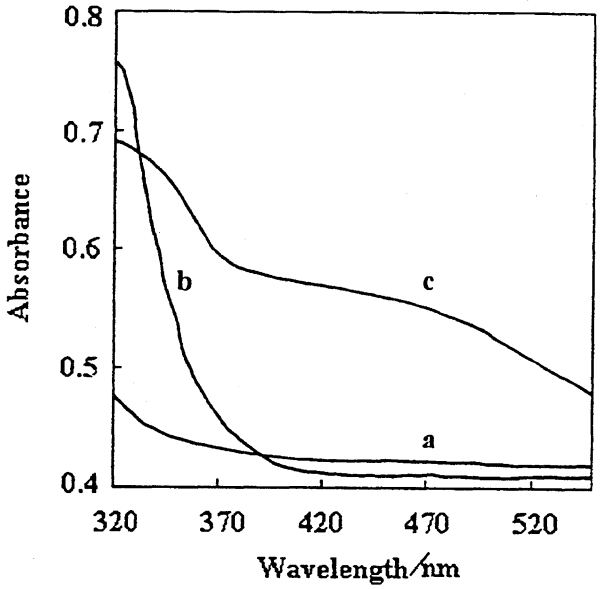


Fig. 3. Absorption spectra recorded upon mixing β-CD·BPT complex and β-CD·ATPO complex in aqueous solution under the same conditions as in Fig. 2.

It is worth noting that the phenothiazine derivatives can be included by β-CD. The binding constants (K_a)[21] for the inclusion of β-CD with PPT, BPT, and PEPT were determined to be 126, 312, and 211 dm^3 mol^{-1}, respectively. This indicated that the 1 : 1 complexes of phenothiazines and β-CD were formed, and that the β-CD·BPT is the most stable among the three complexes.

Otagiri[22] reported that the phenothiazine moiety was

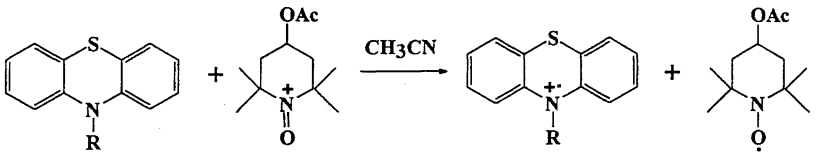
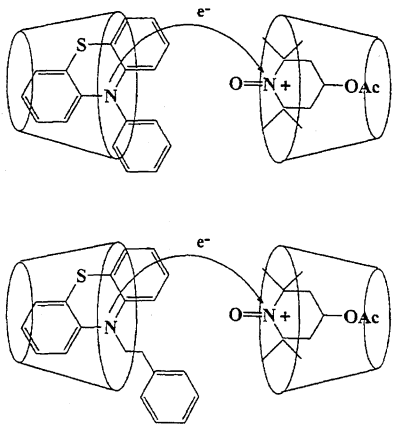


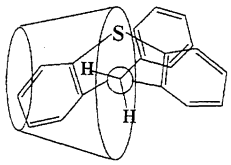
Chart 2.



Scheme 1.

partly included in the β-CD cavity and the *N*-substituent located outside of the β-CD cavity for the β-CD·*N*-alkylphenothiazine complexes. A molecular-dynamics calculation[21] showed that half of phenothiazine was embedded in the β-CD cavity, and the other half with a substituent was located outside. In this work, the β-CD·phenothiazine derivatives are electron donors, and β-CD·ATPO is an electron acceptor. It is expected that the donor complex transfers one electron to the acceptor complex by face-to-face association,[23] which is favorable for an interaction between the donor and the acceptor (Scheme 1). Other association forms, such as tail-to-tail and shoulder-by-shoulder, are unfavorable to the electron-transfer process, because of the steric hindrance of the β-CD wall.

For the β-CD·PPT complex, there is only one conformation in which the phenyl group points to outside the β-CD cavity. When the β-CD·PPT complex approached the β-CD·ATPO complex via face-to-face, the electron-transfer reaction occurred readily. In the β-CD·PEPT complex, because of the rotation of the CH_2–CH_2 bond of the phenethyl group and the N–CH_2 bond, one possible conformation of PEPT in the β-CD·PEPT complex is that the phenyl group is stretching out into the solvent. This conformation is also favorable for electron-transfer between β-CD·PEPT and β-CD·ATPO by face-to-face association. While in the β-CD·BPT complex the rotation of the N–CH_2Ph bond is restricted by the β-CD wall, the heterocycle of phenothiazine, the oxidation center, is just under the shielding of the benzyl group and the β-CD wall; thus, the electron-transfer pathway is blocked. The conformation of BPT in the β-CD cavity is illustrated in Newman projection (Scheme 2). The results obtained from a molecular-dynamics calculation[21] with GROMOS87 on the β-CD·PPT, β-CD·PEPT, and β-CD·BPT complexes are in agreement with the analysis mentioned above.



Scheme 2.

In order to clarify the electron-transfer reaction mechanism, an inhibition experiment has been carried out. Adamantanone was added as an inhibitor to the β-CD·*N*-substituted phenothiazine solutions. Since the binding constant for the inclusion of β-CD with adamantanone (5×10^5 $dm^3\ mol^{-1}$)[21] is much larger than the K_a values for the β-CD·phenothiazine derivatives complexes, the adamantanone preferentially binds with β-CD in the competition, and the phenothiazine derivatives are ruled out the β-CD cavities (Chart 3). In this case, no characteristic absorption of the radical cations of phenothiazine derivatives was observed. This finding indicates that the electron-transfer reactions occurred between the β-CD complexed donor and acceptor in an aqueous solution, not between the free donor and acceptor as the behavior in an organic solution. In fact, *N*-substituted phenothiazines and ATPO are not soluble in water.

It is clear that the electron-transfer reaction between β-CD·BPT and β-CD·ATPO is controlled by the conformation of BPT in the β-CD cavity in which the oxidation center is surrounded by a β-CD wall and covered by a benzyl group. If this is true, we may predict that the electron-transfer reaction will take place if the strong restriction to BPT in the complex is removed or the β-CD·ATPO is replaced by a small oxidant which can squeeze in the β-CD·BPT complex. According to this idea, two more experiments were designed.

Firstly, β-CD was replaced by γ-CD, which has a bigger cavity (8.3 Å) than that of β-CD (6.5 Å).[11] The K_a value for the inclusion of γ-CD with BPT is ca. 620 $dm^3\ mol^{-1}$. Interestingly, when a γ-CD·BPT aqueous solution was mixed with a β-CD·ATPO aqueous solution, the color turned to pink after shaking, and the absorption band at 515 nm showed that the BPT radical cation was generated. Electron-transfer certainly occurred. Since in the γ-CD·BPT complex, the big cyclodextrin cavity makes the rotation of the N–CH_2Ph bond to occur freely, the oxidation center consequently opens to the acceptor; thus, the steric hindrance was reduced when γ-CD·BPT was attacked by β-CD·ATPO (Scheme 3).

Secondly, β-CD·ATPO was replaced by nitric acid, a small oxidant. When the concentrated nitric acid (65%) was added into the β-CD·BPT aqueous solution with shaking, the solution turned pink, and then slowly became darker, the absorption band at 515 nm was observed. In addition, the ESR

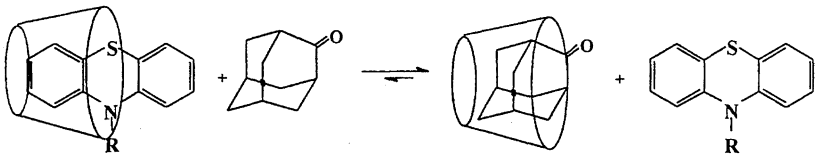
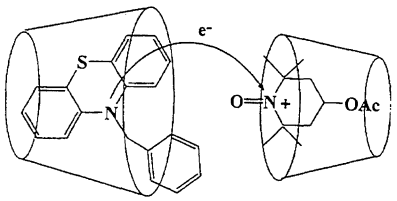


Chart 3.



γ-CD·BPT β-CD·ATPO

Scheme 3.

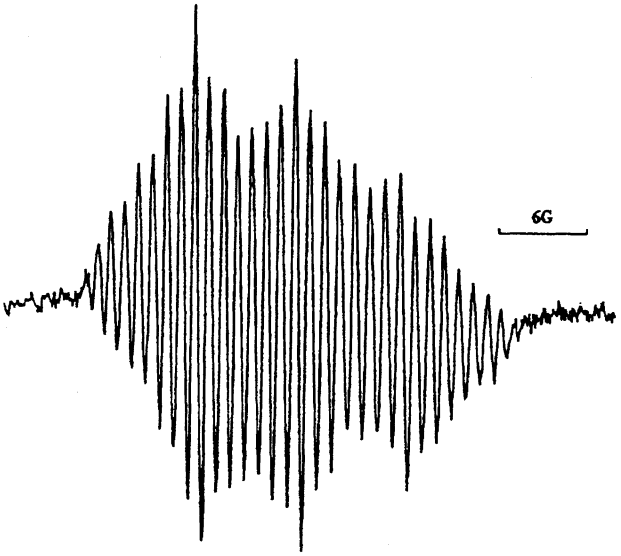
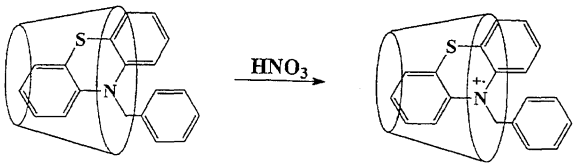


Fig. 4. ESR spectrum of BPT radical cation generated by one-electron oxidation of BPT with nitric acid in β-CD aqueous solution at room temperature. The ESR parameters were assigned as: g = 2.0052; a = 0.710 (N), 0.384 (β-H), 0.093 (H-1, H-2), 0.201 (H-3) mT, which is in agreement with the literature.[9]



Scheme 4.

spectrum was recorded for the BPT radical cation (Fig. 4). As expected, electron transfer occurred between β-CD·BPT and nitric acid. It is rationalized that nitric acid with a small volume can enter into the β-CD cavity of the β-CD·BPT complex to oxidize BPT to the corresponding radical cation (Scheme 4). This idea was also supported by an inhibition experiment. When the inhibitor adamantanone was added into a β-CD·BPT aqueous solution, no absorption at 515 nm and ESR signals of the BPT radical cation were observed upon mixing with nitric acid under the same conditions.

Conclusions

In summary, the electron-transfer reactions between the β-CD·N-substituted phenothiazine derivatives and β-CD·ATPO were significantly influenced by the conformations of the phenothiazine derivatives restricted by the β-CD cavity. No electron-transfer reaction occurred between β-CD·BPT and β-CD·ATPO for the special conformation of BPT in the β-CD·BPT complex in which the oxidation center was shielded by the β-CD wall and the substituent. However, the electron-transfer reactions between γ-CD·BPT and β-CD·ATPO as well as between β-CD·BPT and nitric acid occurred. In the inclusion complexes of β-CD with *N*-substituted phenothiazine, in which the substituent is $Ph(CH_2)_n$, when n is 0 electron-transfer reaction takes place, when n is 1 the electron transfer-reaction cannot take place, however, when n is 2 the electron-transfer reaction takes place again. Thus, we wish that knowledge concerning this interesting electron-transfer reaction would have further applications to molecular devices, such as molecular switchers.

Experimental

Instrumentation. The absorption spectra were recorded on a Shimadzu UV-2100 spectrophotometer. Elemental analyses were performed on a PE240-C instrument. Melting points were taken on an X_4 melting-point apparatus, and the temperature was uncorrected. The ^{1}H NMR spectra were taken with a Bruker DMX-500 spectrometer. ESR spectra were recorded with a Bruker ER-200 spectrometer at room temperature.

Chemicals. β-CD was commercially obtained and recrystallized twice from distilled water, and was desiccated in *vacuum* at 90 °C for 24 h before use. γ-CD was purchased from Sigma, and was used directly. The phenothiazine used for synthesis of its derivatives was obtained from a commercial source without further purification. *N*-Phenylphenothiazine, *N*-benzylphenothiazine, and *N*-phenethylphenothiazine were synthesized according to a literature procedure.[24] 4-Acetoxy-2,2,6,6-tetramethyl-1-oxopiperidinium hexachloroantimonate was synthesized according to a previous report.[25]

***N*-phenylphenothiazine.** Mp 94—94.5 °C (Lit,[26] 94.5 °C). Found: C, 78.32; H, 4.77; N, 5.10%. Cacld for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09%. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 6.61—6.80 (m, 8H), 7.45 (m, 5H).

***N*-Benzylphenothiazine.** Mp 90—91 °C (Lit,[24] 90—91 °C). Found: C, 78.63; H, 5.23; N, 4.82%. Cacld for $C_{19}H_{15}NS$: C, 78.85; H, 5.22; N, 4.84%. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 5.06 (s, 2H), 6.40—7.12 (m, 8H), 7.30 (s, 5H).

***N*-Phenethylphenothiazine.** Mp 72—73 °C (Lit,[24] 72—73 °C). Found: C, 79.40; H, 5.67; N, 4.63%. Cacld for $C_{20}H_{17}NS$: C, 79.16; H, 5.65; N, 4.62%. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.14 (t, 2H), 4.12 (t, 2H), 6.96—7.26 (m, 8H), 7.36 (m, 5H).

4-Acetoxy-2,2,6,6-tetramethyl-1-oxopiperidinium Hexachloroantimonate. Mp 144—145 °C (Lit,[27] 144— 145 °C). Found: C, 23.98; H, 3.64; N, 2.57%. Cacld for $C_{11}H_{20}Cl_6NO_3Sb$: C, 24.07; H, 3.63; N, 2.55%.

Preparation of β-CD·ATPO Complex Solution. ATPO (41.3 mg, 7.5×10^{-2} mmol) was dissolved in dichloromethane, and then mixed with 50 ml of β-CD aqueous solution (2.0×10^{-3} mol dm^{-3}). The resulting solution was stirred until the dichloromethane evaporated completely. A clear β-CD·ATPO complex solution containing ATPO 1.5×10^{-3} mol dm^{-3} was obtained.

Preparation of Cyclodextrin·Phenothiazine Derivatives Solutions. As described above, aqueous solutions of phenothiazine derivatives (1.5×10^{-3} mol dm^{-3}) containing β-CD (2.0×10^{-3} mol dm^{-3}) and 1.5×10^{-3} mol dm^{-3} of γ-CD·BPT aqueous solutions were prepared, respectively. The resulting solutions were

stirred for 3 h.

All of the solutions were degassed with argon by bubbling before measurements.

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References

1) M. Gordon, P. N. Craig, and C. L. Zirkle, "Molecular Modification in Drug Design Adv. Chem. Ser.," ACS, Washington D. C. (1964), Vol. 45, p. 40.

2) P. Mitchell, *Austral. New Zealand J. Psych.*, **27**, 370 (1993).

3) E. Bosch and J. K. Kochi, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1057; M. C. Hovey, *J. Am. Chem. Soc.*, **104**, 4916 (1982); H. Y. Cheng, P. H. Sachet, and R. L. McCreery, *J. Am. Chem. Soc.*, **100**, 962 (1978); B. C. Gilbert, P. Hanson, R. O. C. Norman, and B. T. Sutclffe, *Chem. Commun.*, **1996**, 161; J. P. Billon, G. Gouquis, and J. Combrison, *Bull. Soc. Chim. Fr.*, **1962**, 2062.

4) C. M. Gooley, H. Keyzer, and F. Setshell, *Nature*, **232**, 81 (1969); G. Testylier, D. Daveloose, F. Leterrier, O. Buchman, and M. Shimoni, *Photochem. Photobiol.*, **39**, 2739 (1984); S. Ohnishi and H. M. McConnell, *J. Am. Chem. Soc.*, **87**, 2293 (1965).

5) F. Ruperz, J. C. Conesa, and J. Soria, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 391.

6) D. C. Borg and G.. C. Otzias, *Proc. Natl. Acad. Sci. U.S.A.*, **48**, 623 (1962); L. Levy, T. N. Tozer, L. D. Tuc, and D. B. Loveland, *J. Med. Chem.*, **15**, 898 (1972); P. H. Sackett, J. S. Mayausky, T. Smith, S. Kalus, and R. L. McCreery, *J. Med. Chem.*, **24**, 1342 (1981); P. P. Kelder, N. J. de Mol, and L. H. M. Janssen, *Biochem. Pharmacol.*, **42**, 1551(1991); A. Vasquez, J. Tudela, R. Varon, and F. A. Garcia-Canovas, *Biochem. Pharmacol.*, **44**, 889 (1992); H.-M. Zhang, X.-Q. Ruan, Q. -X. Guo, and Y.-C. Liu, *Res. Chem. Intermed.*, **24**, 687 (1998).

7) J. M. Bobbit and M. C. L. Flores, *Heterocycles*, **27**, 509 (1988); M. Yamaguchi, T. Miyazawa, T. Takata, and T. Endo, *Pure Appl. Chem.*, **62**, 217 (1990).

8) T. Ren, Y. -C. Liu, and Q.-X. Guo, *Bull. Chem. Soc. Jpn.*, **69**, 2935 (1996).

9) Q.-X. Guo, B. Liu, and Y. -C. Liu, *Chem. Res. Chin Univ.*, **11**, 195 (1995); Y.-C. Liu, Z.-L. Liu, L.-M. Wu, and P. Chen, *Tetrahedron Lett.*, **26**, 4201 (1985).

10) M. L. Bender and M. Komiyama, "Cyclodextrin Chemistry," Springer-Verlag, Berlin (1978).

11) J. Szejtli, "Cyclodextrin Technology," Kluwer, Dordrecht (1988).

12) W. Saenger, *Angew. Chem., Int. Ed. Engl.*, **19**, 344 (1980); V. Schurig and H. P. Nowotony, *Angew. Chem., Int. Ed. Engl.*, **29**, 939 (1990); S. Li and W. C. Purdy, *Chem. Rev.*, **92**, 1457 (1992).

13) G. Wenz, *Angew. Chem., Int. Ed. Engl.*, **33**, 803 (1994).

14) K. A. Connors, *Chem. Rev.*, **97**, 1325 (1997).

15) D. Duchene, "New Trends in Cyclodextrins and Derivatives," de Sante, Paris (1991).

16) F. Vögtle, "Supramolecular Chemistry," Wiley, Chichester (1991); H. Morrison, "Bioorganic Photochemistry Vol 2: Biological Applications of Photochemical Switchers," Wiley, New York (1993); R. Arad-Yellin and B. S. Green, *Nature*, **371**, 320 (1994).

17) Y. Yamamoto, S. Shiraki, and Kawamura, *J. Chem. Soc., Perkin Trans. 2*, **1992**, 2241; M. R. Wasielewski, *Chem. Rev.*, **92**, 436 (1992); Y. Kuruda, M. Ito, T. Sera, and H. Ogoshi, *J. Am. Chem. Soc.*, **115**, 7003 (1993); T. Hayashi, T. Takimura, and H. Ogoshi, *J. Am. Chem. Soc.*, **117**, 16006 (1995); J. A. Roberts, J. P. Kirby, and D. G. Nocera, *J. Am. Chem. Soc.*, **117**, 8051 (1995); P. J. F. de Rege, S. A. Williams, and M. J. Therien, *Science*, **269**, 1409 (1995).

18) G. de Santis, L. Fabbrizzi, M. Licchcli, A. Poggi, and A. Taglietti, *Angew. Chem., Int. Ed. Engl.*, **35**, 202 (1996); C. A. Hunter and R. K. Hyde, *Angew. Chem., Int. Ed. Engl.*, **35**, 1936 (1996); T. Arimura, C. T. Brown, S. L. Spring, and J. L. Sessler, *Chem. Commun.*, **1996**, 2239; M. Kropf, E. Joselevich, H. Durr, and I. Willner, *J. Am. Chem. Soc.*, **118**, 655 (1996); M. P. Scannell, D. J. Fenick, S.-R. Yeh, and D. E. Falvey, *J. Am. Chem. Soc.*, **119**, 1971 (1997).

19) H.-M. Zhang, X.-Q. Ruan, Q.-X. Guo, and Y.-C. Liu, *Chem. Lett.*, **1998**, 449.

20) H. P. Rieder, *Med. Exptl.*, **3**, 353 (1960); J. P. Billon, *Bull. Soc. Chim. Fr.*, **1961**, 1923; E. R. Riehl, H. S. Chiou, J. Keepers, S. Kennard, and P. C. Reeves, *J. Heterocycl. Chem.*, **1975**, 397.

21) X.-Q. Ruan, M. S. Degree Thesis, Lanzhou University, 1997.

22) M. Otagiri, K. Kekama, and K. Ikeda, *Chem. Pharm. Bull.*, **23**, 183 (1975).

23) S. Hamai, *Bull. Chem. Soc. Jpn.*, **55**, 2721 (1982); J. S. Manka and D. S. Lawrence, *Tetrahedron Lett.*, **30**, 7341 (1989).

24) D. Clarke, B. C. Gilbert, P. Hanson, and C. M. Kirk, *J. Chem. Soc., Perkin Trans. 2*, **1978**, 1103.

25) R. I. Zhdanov, V. A. Golubev, V. M. Giba, and E. G. Rozantsev, *Proc. Acad. Sci. USSR*, **196**, 856 (1971).

26) H. Gilman, P. R. V. Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66**, 1214 (1944).

27) Y.-C. Liu, Y.-B. Ding, and Z.-L. Liu, *Huaxue Xuebao*, **48**, 1199 (1990).