Spectrophotometric Determination of the Stability Constant of the Inclusion Complexes of Some Catechol Derivatives with β-Cyclodextrin Based on their Reaction with Iodate

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The effects of β-cyclodextrin (β-CD) inclusion on the kinetics of the oxidation of several cathechol derivatives, including 4-tert-butylcatechol, 3-methylcatechol and 3-methoxycatechol, with iodate was studied spectrophotometrically. The rate of the oxidation reactions decreased by increasing β-CD concentration as a result of inclusion. The stability constants for the inclusion complexes of the investigated compounds were determined based on the changes in the rate constants as a function of β-CD concentration at pH 3.0. The rate constants for the free and complexed forms and also the stability constants for the inclusion complexes were calculated. The role of the hydrophobic effect was evaluated by studying the influence of the presence of different amounts of ethanol on the β-CD: guest interaction. In a given H_2O-EtOH mixture the stability of β-CD complexes shows the order of 4-tert-butylcatechol ≈ 3-methylcatechol ≈ 3-methoxycatechol. Increasing ethanol content caused a decrease in the stability constant of the inclusion complexes and an increase in observed rate constants.

Keywords: Catechol derivatives; Inclusion complexes; Spectrophotometry; Stability constant.

INTRODUCTION

The unusual properties of cyclodextrins (CDs) originate in their unique structure. They are a group of cyclic oligosaccharides with six (α) seven (β) or eight (γ) glucose residues linked by α-[1-4] glycosidic bonds in a truncated cone shape structure. In general, cyclodextrins are fairly soluble in water. Despite a hydrophilic surface, cyclodextrins contain a hydrophobic cavity. It is the presence of this cavity that enables cyclodextrins to entrap hydrophobic molecules.[1] β-CD with an internal diameter of 0.78 nm can accommodate only relatively small and medium-sized organic molecules in which entrapment/inclusion occurs without the formation of formal chemical bonds.[2,3] The extent of complex formation, however, depends upon the polarity of the guest molecule. The stability of the inclusion complex may be increased by the presence of hydrophobic substitutents, such as the tert-butyl group, on the aromatic ring.[4]

Because of this inclusion, a change of the chemical or physical properties of the guest molecule is generally observed, opening a wide field of applications in areas such as organic and analytical chemistry. Their actual or potential uses in pharmaceuticals, foods, cosmetics, or chemicals have been summarized in some recent monographs.[5-14]

Inclusion of organic molecules in the CD cavity is confirmed by changes in spectroscopic parameters in aqueous solution subsequent to complexation. Parameters which have been monitored include UV-vis absorption spectrometry,[15] intensity of fluorescence,[16] and nuclear magnetic resonance.[17] In conjunction with spectrophotometric techniques, CDs have been widely used in fluorimetric analysis mainly to increase analyte sensitivity. Moreover, reports of the usage of CDs as analytical reagents in UV-vis spectrophotometry are scarce.[18] Chemical reactions pertaining to the included guest may take place, and the effects of inclusion on the reactivity vary widely depending on the guest, the CD, and the reaction examined.[19]

Among the first cyclodextrin inclusion complexes to be investigated were those containing substituted phenol and benzenediol molecules as guests.[3] The chemical or electrochemical oxidation of catechol derivatives and catecholamines has long been studied.[20] Catechol derivatives can be oxidized chemically to their corresponding *o*-quinones by proper oxidants such as iodate.

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β-CD inclusion of 4-tert-butylcatechol on the kinetics of its outer-sphere oxidation by transition metal complexes in acidic aqueous media.[4] They determined the magnitude of inclusion stability constants by ^{1}H and ^{13}C NMR spectroscopy.

In this paper, we report the results of the spectrophotometric investigation into the effects of the β-CD inclusion of 4-tert-butylcatechol, 3-methylcatechol and 3-methoxycatechol on the rate of their oxidation reaction with iodate. The role of the hydrophobic effect was evaluated by studying the influence of the presence of different constant amounts of an ethanol on the β-CD: guest interaction at 25 ± 0.1 °C. The stability constants of the β-CD inclusion complexes with investigated catechol derivatives have been determined based on the effect of β-CD on their oxidation reaction rate.

THEORETICAL BACKGROUND

By assuming the formation of a 1:1 complex the complexation equilibrium can be written as:

$$CD + C \rightleftarrows C(CD) \qquad K_f = [C(CD)]/[CD]\,[C] \qquad (1)$$

where C stands for the catechol derivative, CD for β-CD and C(CD) for the 1:1 complex between C and CD and [C], [CD] and [C(CD)] stand for the equilibrium concentrations of C, CD and C(CD), respectively. By considering:

$$C_t = [C(CD)] + [C] \qquad (2)$$

and

$$[CD] = C_{CD} - [C(CD)] \qquad (3)$$

where C_t and C_{CD} are analytical concentrations of C and CD, respectively, it can be written:

$$[C(CD)] = C_t - [C] \qquad (4)$$

and

$$[CD] = C_{CD} - C_t + [C] \qquad (5)$$

by substitution of Eq. 5 into Eq. 1

$$K_f = (C_t - [C])/(C_{CD} - C_t + [C])\,[C] \qquad (6)$$

By rearrangement of Eq. 6

$$K_f[C]^2 + (K_fC_{CD} - K_fC_t + 1)\,[C] - Ct = 0 \qquad (7)$$

$$[C] = \frac{-(K_fC_{CD} - K_fC_t + 1) + ((K_fC_{CD} - K_fC_t + 1)^2 + 4K_{f\,Ct})^{0.5}}{2K_f} \qquad (8)$$

If both the free and complexed forms of catechol derivative participate in a common reaction, and rate constants of complexed form are different from free form, at a constant excess concentration of iodate and constant pH we can write eq. (9)

$$k_{obs}\,C_t = k'\,[C] + k''\,[C(CD)] \qquad (9)$$

where k_{obs}, k' and k'' are observed rate constant for overall reaction, observed rate constant for free and complexed forms, respectively. Based on Eqs. 1 and 9, the ratio of [C] to [CD] varies for the solutions with constant concentrations of catechol derivatives and various concentrations of β-CD. The inclusion stability constants (K_f) and k'' were calculated from spectrophotometric data in various concentrations of β-CD.

EXPERIMENTAL

All experiments were performed with analytical reagent grade chemicals obtained from Aldrich. H_3PO_4, NaH_2PO_4, were of pro-analysis grade purchased from E. Merck. These chemicals were used without further purification. pH 3.0 phosphate buffer solution (0.15 mol L^{-1}) was prepared. The stock solutions of 3-methyl catechol, 3-methoxy catechol (5×10^{-3} mol L^{-1}), 1×10^{-3} mol L^{-1} 4-tert-butylcatechol, 4×10^{-2} mol L^{-1} β-CD and 1×10^{-2} mol L^{-1} IO_3^- were prepared by dissolving the compounds in distillated water. Sample dilutions were carried out by taking the appropriate aliquots from the stock solutions followed by dilution with phosphate buffer (pH = 3.0).

Absorption spectra were obtained with a Perkin Elmer Lambda 45 UV/Vis Spectrophotometer and in all experiments, samples were contained in a 1 cm path length quartz cells and the measurements were performed at (25 ± 0.1) °C.

RESULTS AND DISCUSSION

Iodate oxidizes catechol derivatives to their corresponding *o*-quinones. The rate of the reaction is very fast at low pH values and decreases by increasing the pH of the solution. We observed that at pH 3.0 the rate of the reaction was not very fast and the reaction could be monitored spectrophotometrically. Fig. 1 shows the absorption spectra of 4-tert-butylcatechol with time in the presence of iodate at pH 3.0. As Fig. 1 shows, the absorbance of the solution increased with time at 400 nm which shows oxidation of 4-tert-butylcatechol to its corresponding *o*-quinone. In order to monitor the oxidation reaction of 4-tert-butylcatechol with iodate, the absorbance changes at 400 nm were monitored. The absorbance-time plots for the oxidation reaction of 4-tert-butylcatechol with iodate at pH 3.0 in the presence of different concentrations of β-CD at 400 nm are shown in Fig. 2. As Fig. 2 shows, the reaction rate decreased by increasing β-CD concentration. Addition of β-CD to the 4-tert-butylcatechol causes formation of a 1:1 inclusion complex between them.[4] The decrease in the rate of the reaction by addition of β-CD indicates that the rate constant for the oxidation of the complexed form of 4-tert-butylcatechol is smaller than that of its free form. The amount of decrease in the reaction rate by the addition of a given amount of β-CD depends on the stability constant of the complex. Therefore, the change in the reaction rate as a function of β-CD concentration could be used for the determination of the stability constant of the produced inclusion complex.

The observed pseudo-first-order rate constant for overall reaction (k_{obs}) was determined from the absorbance-time plots (Fig. 2), and the rate constants for the oxidation reaction of 4-tert-butylcatechol in the absence of cyclodextrin, k′ (eq. 10), was determined from the slope of the linear dependence of the observed pseudo-first-order rate constant for overall reaction (Fig. 3) on the concentration of 4-tert-butylcatechol.

$$IO_3^- + C \xrightarrow{k'} Q \qquad (10)$$

The plot of k_{obs} versus 4-tert-butylcatechol concentration remains linear with a positive *y*-intercept but decreases in both the slope and *y*-intercept were observed. The results showed that the observed pseudo-first-order rate constants for overall reaction for the oxidation of 4-tert-butylcatechol decreased by increasing β-CD concentration. At high concentrations of β-CD the rate becomes constant, indicative of saturation behavior.

This observation indicates that 4-tert-butylcatechol forms a very stable inclusion complex with β-CD in pH 3.0 aqueous solutions;[4] the complex is oxidized slower than the free form of 4-tert-butylcatechol.

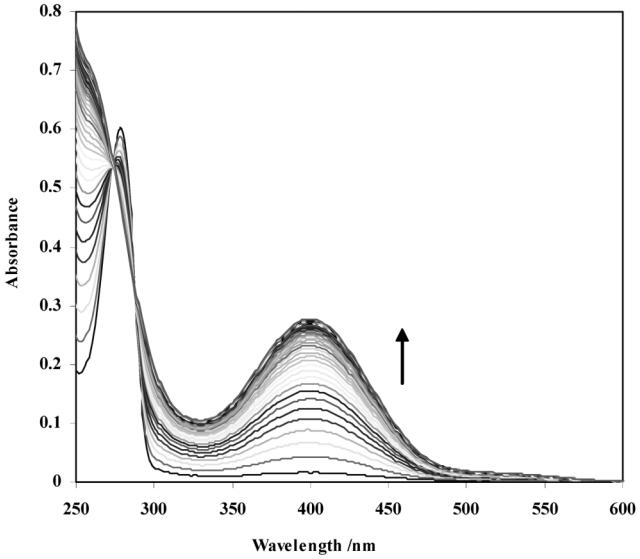

Fig. 1. The absorption spectra of 1.0×10^{-4} mol L^{-1} 4-tert-butylcatechol with time in the presence of iodate (5.0×10^{-3} mol L^{-1}) at pH 3.0. Time intervals 2 min.

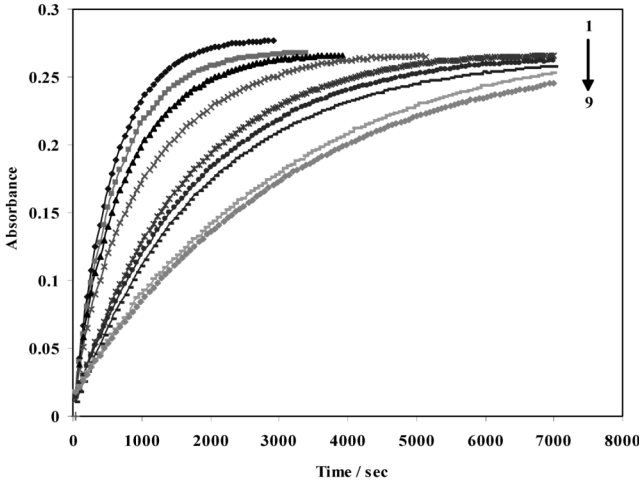

Fig. 2. The absorbance-time plots for the oxidation reaction of 4-tert-butylcatechol (1.0×10^{-4} mol L^{-1}) with iodate (5.0×10^{-3} mol L^{-1}) at pH 3.0 in the presence of (1) 0.0, (2) 2.5×10^{-5}, (3) 5.0×10^{-5}, (4) 7.5×10^{-5}, (5) 5.0×10^{-4}, (6) 7.0×10^{-4}, (7) 1.0×10^{-3}, (8) 3.0×10^{-3} and (9) 1.0×10^{-2} mol L^{-1} of β-CD at 400 nm.

$$IO_3^- + C(CD) \xrightarrow{k''} Q(CD) \quad (11)$$

Based on eq. 9 the observed pseudo-first-order rate constants for overall reaction decreased with increasing the ratio of the complex to the free form. At high concentrations of β-CD, complexed form is the predominate species in the solution and free catechol is negligible, and at low concentrations of β-CD the free catechol is predominate species in the solution and the complexed form is negligible. Therefore, the best region for calculations is the region between these two limiting regions so that the concentration of both complexed and free forms are strongly dependent on β-CD concentration.

Nonlinear least-squares fits of the experimental rate constants to eqs. 8 and 9, using the measured values of k′ yielded the calculated values of k″ and K_f for the system; these are presented in Table 1. Fig. 4 shows sample fit data at the different concentrations of β-CD and a constant concentration of 4-tert-butylcatechol. The k″ and K_f values were obtained for several 4-tert-butylcatechol concentrations and the average values are reported in Table 1. The amount of K_f for 4-tert-butylcatechol obtained by the proposed method ($(8.61 \pm 0.9) \times 10^3$ L mol^{-1}) is in good agreement with the previously reported value ($(9.5 \pm 2.0) \times 10^3$ L mol^{-1}).[4] The absorbance-time plots for the oxidation reactions of 3-methylcatechol and 3-methoxycatechol with iodate in pH 3.0 aqueous solutions in the presence of different concentrations of β-CD were also obtained. The data were processed as described for 4-tert-butylcatechol and the values of k′, k″ and K_f were obtained (Table 1).

The decrease in the rate constants by formation of inclusion complexes is expected, because the rate constants for the electron transfer reactions decreases substantially upon inclusion of the reductant owing to steric hinderances to effective donor-acceptor orbital overlap.[4]

Comparison of the K_f values for the investigated catechol derivatives indicates that the complex of 4-tert-butylcatechol with β-CD is more stable than those of 3-methylcatecol and 3-methoxycatechol. This is not unexpected because for strong inclusion the guest molecule must fit tightly with the CD cavity and be hydrophobic in nature.[21] Crystallographic studies of the β-CD inclusion of several para-substituted tert-butylphenyl molecules reveal that orientation of the guest molecule depends on the nature of the para-substituent.[22] The hydrophobic tert-butyl substituent has a higher affinity than 3-methyl and 3-methoxy substituents for the cavity of β-CD.

In order to study the hydrophobic effect on the system, the effect of ethanol on the oxidation reaction of catechol derivatives with iodate in the presence of β-CD was also investigated. K_f, k′ and k″ values for 4-tert-butylcate-

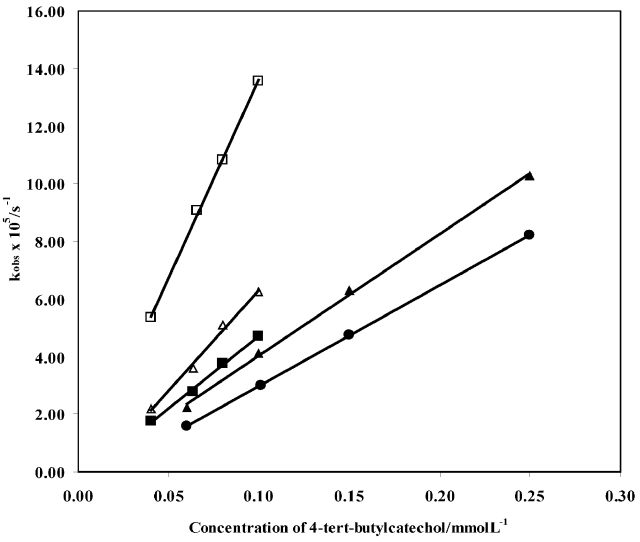

Fig. 3. Plots of k_{obs} as a function of 4-tert-butylcatechol concentration for the oxidation of 4-tert-butylcatechol (1.0×10^{-4} mol L^{-1}) by iodate (5.0×10^{-3} mol L^{-1}) in the presence of (□) 0.0, (Δ) 3.0×10^{-4}, (■) 6.0×10^{-4}, (▲) 1.2×10^{-3} and (●) 3.0×10^{-3} mol L^{-1} of β-CD at 25 ± 0.1 °C.

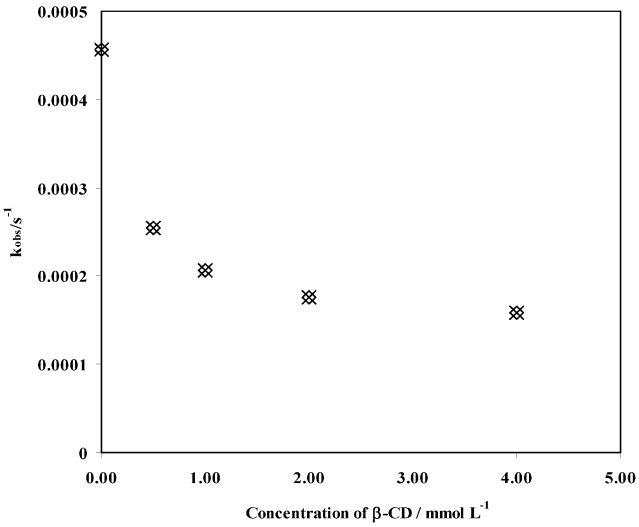

Fig. 4. A sample data fit obtained for different concentration of β-CD and 1.0×10^{-4} mol L^{-1} of 4-tert-butylcatechol. (×) experimental and calculated (□) points.

Table 1. Stability constants for inclusion complexes of catechol derivatives with β-CD and the observed pseudo first order rate constants for the oxidation of their free and complexed forms in different H_2O-EtOH mixtures at 25 ± 0.1 °C

Compound	Solvent composition / % EtOH (w/w)	K_f /L mol^{-1} (n = 3)[a]	k″ /s^{-1} (n = 3)	k′/s^{-1} (n = 3)
4-tert-butylcatechol	0	$(8.61 \pm 0.90) \times 10^3$	$(9.79 \pm 0.75) \times 10^{-5}$	$(5.34 \pm 0.53) \times 10^{-4}$
	4	$(6.05 \pm 0.62) \times 10^3$	$(1.35 \pm 0.12) \times 10^{-4}$	$(5.08 \pm 0.41) \times 10^{-4}$
	8	$(4.10 \pm 0.60) \times 10^3$	$(1.39 \pm 0.07) \times 10^{-4}$	$(4.56 \pm 0.37) \times 10^{-4}$
	16	$(2.12 \pm 0.41) \times 10^3$	$(2.07 \pm 0.12) \times 10^{-4}$	$(4.29 \pm 0.23) \times 10^{-4}$
3-methyl catechol	0	62.46 ± 6.75	$(8.76 \pm 0.32) \times 10^{-4}$	$(2.89 \pm 0.78) \times 10^{-3}$
	4	51.60 ± 5.80	$(1.41 \pm 0.07) \times 10^{-3}$	$(2.84 \pm 0.09) \times 10^{-3}$
	8	44.80 ± 3.50	-	-
	16	38.40 ± 3.71	$(1.63 \pm 0.10) \times 10^{-3}$	$(2.79 \pm 0.10) \times 10^{-3}$
3-methoxy catechol	0	61.91 ± 8.52	$(1.59 \pm 0.25) \times 10^{-4}$	$(3.26 \pm 0.10) \times 10^{-3}$
	4	48.20 ± 4.50	$(1.81 \pm 0.32) \times 10^{-3}$	$(3.11 \pm 0.38) \times 10^{-3}$
	8	39.60 ± 5.71	$(1.94 \pm 0.29) \times 10^{-3}$	$(2.96 \pm 0.44) \times 10^{-3}$
	16	33.30 ± 4.80	$(1.98 \pm 0.36) \times 10^{-3}$	$(2.87 \pm 0.41) \times 10^{-3}$

[a] Number of independent determinations

chol, 3-methylcatechol and 3-methoxycatechol were obtained as described above. The results are shown in Table 1. In general, complex stability decreased with increasing amounts of EtOH in the solvent mixture while it showed no significant effect on the k′ and k″ values. Increasing EtOH concentration caused a small decrease in k′ and a small increase in k″.

It is well known that solvating stability of the solvent plays a key role in different complexation reactions. The addition of ethanol lowers the relative permittivity of aqueous medium: hydrophilic interactions between the hydroxyl groups of ethanol and the external ones of the dextrin are enhanced. Since the medium is a hydroalcoholic solution, the possible encapsulation of the alcohol molecule by the cyclodextrin in competition with the β-CD:catechol derivatives complexed formation must be considered. However the constants reported in the literature for the binding of β-CD and/or its derivatives to the shortest alcohols indicate that it is negligibly small.[23] As a consequence most of the effects observed in the presence of alcohols can be attributed to a change in the solvophobic characteristics of the medium. If other molecules with apolar portions are added to the medium, as in the case with alcohols, the apolar part of the guest molecule will then, in part, be surrounded by these alcohol molecules. This large variability could be an indication of conformational changes experienced by the macrocycle induced by the different solvent media.

CONCLUSION

This paper reports spectrophotometric study of the effects of β-CD inclusion on the rate of the oxidation reaction of several catechol derivatives with iodate. The effect of β-CD concentration on the rate of the oxidation reaction of catechol derivatives with iodate was used for the determination of stability constants. The reactions were monitored by measuring the absorbance change of the solution at λ_{max} for the oxidation product with time. Inclusion caused a decrease in rate of the oxidation reaction. This method is suitable for spectrophotometric determination of the stability constants of inclusion complexes of β-CD with compounds where their absorption spectra are exactly the same as for their complexes or even for nonabsorbing compounds. As was expected, due to more hydrophobicity of 4-tert-butylcatechol, its complex with β-CD is more stable than those of 3-methylcatechol and 3-methoxycatechol. For an association process where the hydrophobic effect plays an important role, an increase in the apolar character of the medium results in a clear decrease in the affinity of binding. Thus, the higher hydrophobic character of the medium due to an increase of the amount of ethanol cosolvent causes less stability of inclusion complexes.

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REFERENCES

1. Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325.
2. Szejtli, J. *Cyclodextrins and their Inclusion Complexes: Akadema*; Kiado: Budapest, 1982; p 25.
3. VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242.
4. Imonigie, J. A.; Macartney, D. H. *Inorg. Chem.* **1993**, *32*, 1007.
5. Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743.
6. Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457.
7. Liu, J.; Wu, B.; Zhang, B. *J. Chin. Chem. Soc.* **2005**, *52*, 1165.
8. Chen, C.-Y.; Lin, C.-H.; Yang, J.-H. *J. Chin. Chem. Soc.* **2005**, *52*, 753.
9. Chen, S. *J. Chin. Chem. Soc.* **1996**, *43*, 45.
10. Lin, S.-Y.; Kao, Y.-H. *J. Chin. Chem. Soc.* **1988**, *35*, 173.
11. Chen, S. *J. Chin. Chem. Soc*. **1996**, *43*, 503.
12. Wu, H.-L.; Wu, S.-M.; Chen, S.-H. *J. Chin. Chem. Soc.* **1997**, *44*, 141.
13. Chen, S. *J. Chin. Chem. Soc.* **1999**, *46*, 239.
14. Afkhami, A.; Khalafi, L. *J. Chin. Chem. Soc.* **2007**, *54*, 431.
15. Benesi, H.; Hildebrand, J. H. *J. Am. Chem. Soc*. **1949**, *71*, 2703.
16. Hamai, S.; Ikeda, T.; Nakamura, A.; Ikeda, H.; Ueno, A.; Toda, F. *J. Am. Chem. Soc.* **1992**, *114*, 6012.
17. Paton, R. M.; Kaisers, E. T. *J. Am. Chem. Soc*. **1970**, *92*, 4723.
18. Szente, L.; Szejtli, J. *Analyst* **1998**, *123*, 735.
19. Guernelli, S.; Lagana, M. F.; Spinelli, D.; Meo, P. L.; Noto, R.; Riela, S. *J. Org .Chem.* **2002**, *67*, 2948.
20. Afkhami, A.; Nematollahi, D.; Khalafi, L.; Rafiee, M. *Int. J. Chem. Kinet.* **2005**, *37*, 17.
21. Johnson, M. D.; Reinsborough**,** V. C.; Ward, S. *Inorg .Chem.* **1992**, *31*, 1085.
22. Hamilton, J. A.; Savesan, M. N.; Steinrauf, L. K. *Carbohydr. Res.* **1981**, *89*, 33.
23. Tee, O. S.; Gadosy, T. A.; Giorgi, J. B. *J. Chem. Soc., Perkin Trans 2,* **1993**, 1705.