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Stereoselective Hydrogenation of Thymol over Rh/alumina in the Presence of β-cyclodextrin and its Derivatives

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Abstract

Stereoselective hydrogenation of thymol over Rh/alumina in the presence of various equivalents of β-cyclodextrin (β-CD) and its derivatives in the solid state was studied. Hydrogenation of thymol in the absence of β-CD gave 76.8% epimeric alcohols with a menthol/neomenthol (M/N) ratio of 5.6 and an alcohol/ketone ratio of 4.5, whereas the presence of 0.1 equivalent (to thymol) of β-CD gave rise to 94.6% of epimeric alcohols with a M/N ratio of 6.3 and an alcohol/ketone ratio of 45.4. The effect of β-cyclodextrin and its derivatives on the modification of the yield and the proportion of epimeric alcohols formed were found to be the salient features of this investigation. Inclusion complexation of thymol by β-CD studied by UV-Visible spectroscopy indicated a 2 : 1 stoichiometry of thymol: β-CD complex with a binding constant value of $480 \pm 40\ M^{-2}$.

Introduction

Thymol is present to the extent of about 49.6% in *Origanum tyttanthum* [1]. Other essential oils which contain thymol are from Thymus species such as *Thymus cilicum, Thymus revolutus, Thymus zygioides* [2], *Thymus serpyllum, Thymus borystenicum, Thymus marshallianus* [3], *Thymus pallidus, Thymus broussonetti, Thymus algeriensis, Thymus satureoldes* and *Thymus ciliatus* [4].

Hydrogenation of thymol rich essential oils under various conditions yield a mixture of menthones and menthols [5]. Several catalysts are available for the reduction of aromatic double bonds, which usually employ specialised catalysts at invariably high temperatures and pressures. The hydrogenation of thymol presents an interesting feature, since the complete reduction of all the aromatic double bonds leads to generation of 3 asymmetric centers, resulting in 8 epimeric alcohols being formed [6]. However, it is seldom that all the isomers are detected in the mixture. Invariably, the two most common isomers frequently encountered are menthol and neomenthol [7, 8].

The ratio of isomeric menthones and menthols varied with temperature, when thymol was hydrogenated over Rh/C and (Pd + Rh)/C [9] in the liquid phase at different temperatures. High yields of menthols were achieved by the hydrogenation of thymol over Ni—Cr_2O_3 in the temperature range of 140–174 °C at 2–10 MPa pressures [10]. The hydrogenation over Pt and Rh proceeded essentially via the ketone intermediate, whereas the direct conversion to menthol was observed with Ir [11]. Recently about 99.9% dl – menthol was obtained by the hydrogenation of thymol in the presence of oxides or hydroxides of Co, Mn and alkaline earth metals, whereas the reaction was carried out at 170 °C at a pressure of 0.3 MPa hydrogen [12]. Hydrogenation over Rh based catalysts followed the ketone intermediate path to result in epimeric menthols [13].

Solid state hydrogenation of thymol was also employed over various catalysts like Adams PtO_2, Raney Ni and Pt/C [14]. Hydrogenation of thymol in the solid state could be accomplished under mild conditions, using Rh/Al_2O_3 [15].

Hydrogenation with improved selectivity would be of practical importance, especially in the production of menthol, since hydrogenation of thymol or its essential oil sources gave rise to a mixture of menthols and menthones that are difficult to separate. Among other procedures, the presence of cyclodextrin in the reaction mixture often resulted in the regulation of well known chemical transformations [16] including several stereoselective transformations. Stereoselective hydrogenation of thymol with different catalysts at 22–130 °C resulted in a remarkable increase in menthol formation in the presence of β-CD-polymer at high pressures [17].

The present investigation describes the hydrogenation of thymol included inside β-CD and its derivatives such as water insoluble β-cyclodextrin-epichlorohydrin polymer (β-CD-polymer), heptakis-2,6-di-O-methyl-β-cyclodextrin (DMβ-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) in the production of menthol under mild reaction conditions.

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Materials and methods

β-CD purchased from Sigma Chemical Company (USA) was used throughout. β-CD polymer and DM-β-CD were prepared according to the procedures of Shaw and Buslig [18] and Szejtli *et al*. [19], respectively. HPβ-CD was prepared by reacting β-CD with propylene oxide which was isolated after repeated precipitation with acetone [20] and the degree of substitution was found by ^{1}H NMR to be 2.5. Thymol was purchased from Aldrich Chemical, USA. All the other reagents and solvents were of analytical grade. The solvents were distilled once before use. Rh/Al_2O_3 in powder form with a rhodium content of 5% was purchased from Aldrich Chemical Company, USA.

Thymol (0.25–0.75 mmole) and Rh/alumina (20–70 mg) and β-CD (depending upon equivalents to thymol) were ground to a fine powder (about 100 mesh) and transferred to a hydrogenation apparatus (of capacity 225 mL). The flask was filled with hydrogen gas after evacuation of air and set for hydrogenation at a pressure of 0.5–2.0 MPa for a period of about 4–12 h at room temperature with vigourous agitation. The product was recovered from the reaction mixture by filtering the Rh/alumina catalyst and β-CD after extracting with diethyl ether and evaporating the solvent to recover the product [21]. β-CD from the catalyst could be separated by adding water. In the case of β-CD-epichlorohydrin polymer, removal of rhodium catalyst after extracting reaction products was by the addition of dilute HCl which dissolved the catalyst. The product distribution of the reaction mixture was analyzed by GLC.

A Shimadzu GC-15A instrument fitted with a 20% Carbowax 20M, 3 m column with a 30 mL/min nitrogen flow rate was used. The injection and FID detection port temperatures were maintained at 200 °C and 240 °C, respectively. The column was maintained at 120 °C. Clear separation of menthone (6.35 min), isomenthone (7.28 min), neomenthol (10.29 min), neoisomenthol (11.93 min) and menthol (12.83 min) were achieved. Small amounts of isomenthol (13.8 min) were also observed. A few unidentified peaks probably arose from the partial hydrogenation products of thymol or its quinone.

^{1}H-NMR spectra for structural studies were recorded on a Brüker WH 270 instrument operating at 270 MHz at 20 °C. D_2O, containing a small amount of alkali (pH 10.5) was used as the solvent. The ^{1}H-NMR spectrum of a neat sample of thymol was obtained in $CDCl_3$ (20 mg of thymol in 0.5 mL of the solvent). The spectra of the complexes were recorded by adding increasing amounts of β-CD to a solution of 2.0 mg of thymol in 1 mL D_2O.

A Shimadzu UV-240 spectrophotometer at 20 °C was used for studying the binding equilibrium of thymol with β-CD. The spectra were recorded from 190 nm to 350 nm.

Results and discussion

Thymol was hydrogenated in the solid state over Rh/Al_2O_3. No solvent was employed and the reaction mixture was heterogeneous in nature. Three equivalents of hydrogen in the case of menthol formation as the major product and two equivalents of hydrogen in the case of menthone formation as the major product were consumed by the reaction mixture, indicating that all the three (or two) aromatic double bonds were reduced. The results of the reaction products are summarised in Table 1 and the hydrogenation profile is shown in Figure 1. Hydrogenation of thymol in the absence of β-CD gave 76.8% epimeric alcohols with a menthol/neomenthol (M/N) ratio of 5.6 and an alcohol/ketone ratio of 4.5. Hydrogenation in the presence of 0.1 equivalent (to thymol) β-CD gave rise to a 94.6% of epimeric alcohols with a M/N ratio of 6.3 and an alcohol/ketone ratio of 45.4 (Scheme 1). However, on increasing the concentration of β-CD from 0.1 to 0.7 equivalent, a gradual decrease in the total percentage of menthols to 70.0% and an increase in the amount of menthones to 22.9% (from 1.8%) was observed. The M/N ratio was however maintained at 4.7 to 6.0. When the concentration of β-CD was further increased to 1.0 equivalent the amount of menthols formed further increased to 83.6% with a minimum amount of menthones (1.0%) and some unidentified compounds (15%).

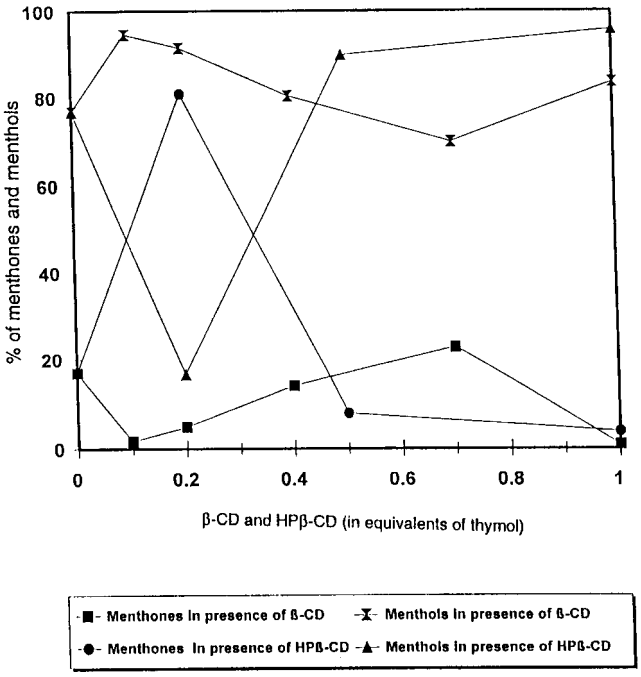
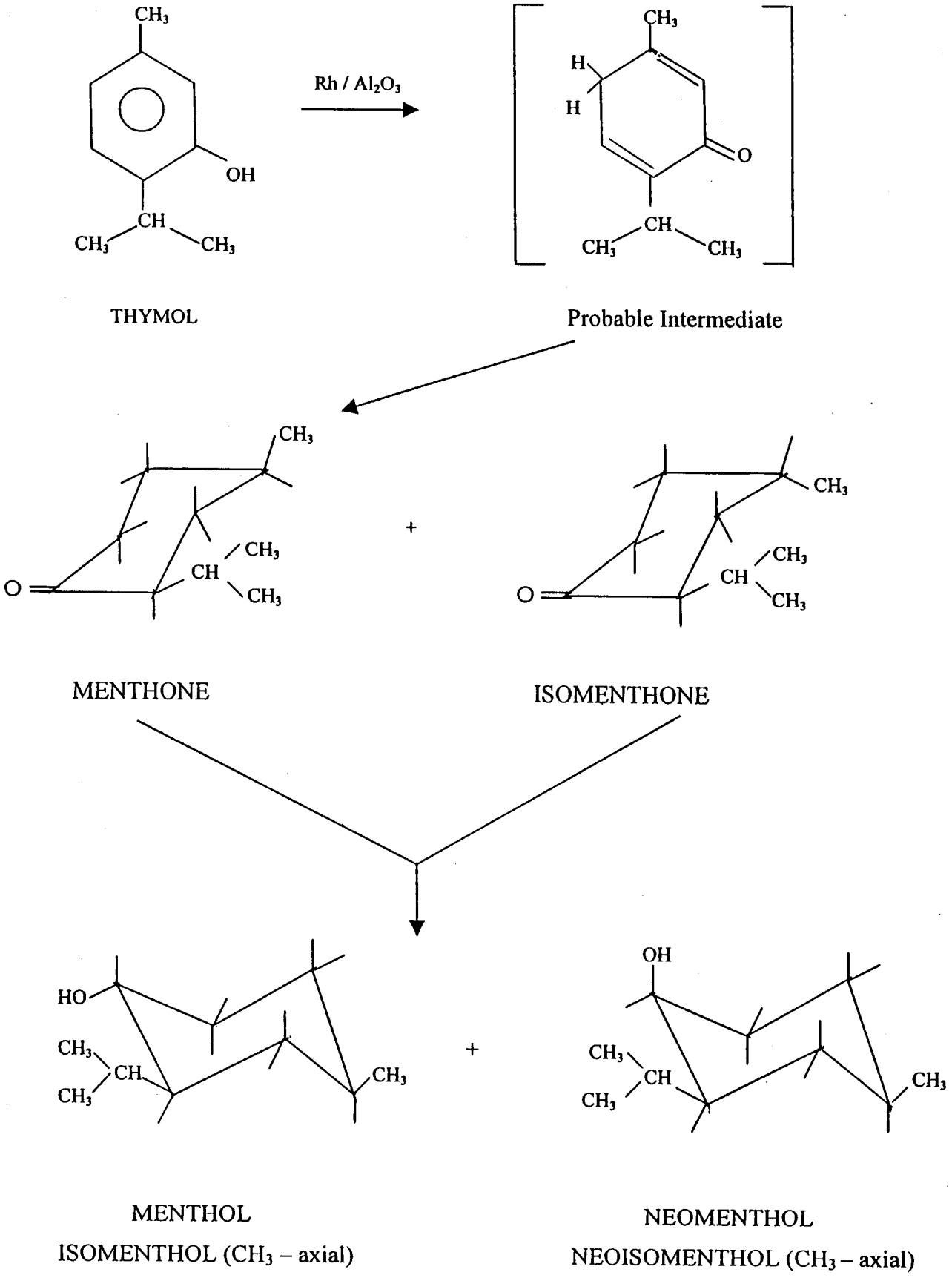


Figure 1. Effect of β-CD and HPβ-CD on the hydrogenation of thymol over Rh/alumina.

Hydrogenation in the presence of 1.0 equivalent β-CD-polymer resulted in 83.6% menthols with a M/N ratio of 6.2. However, reduction in the presence of 0.2 equivalent of HPβ-CD gave the highest amount of menthones (80.9%) and about 16.7% of menthols. With an increase in the HPβ-CD concentration, a drastic increase in the proportion of menthols was detected, i.e., 89.9% at 0.5 equivalent and 95.8% at 1.0 equivalent with an increase in the alcohol/ketone ratio to 11.2 and 24.0, respectively. The M/N ratio however decreased to 2.3 at both concentrations of HPβ-CD. However, reaction in the presence of DMβ-CD gave 80.7% of neoisomenthol with 12.8% of unknown compounds and 6.5% of methone and isomenthone.


CH3
OH
CH
CH3
CH3
Rh / Al2O3
H
H
O
THYMOL
Probable Intermediate
MENTHONE
ISOMENTHONE
HO
OH
MENTHOL
ISOMENTHOL (CH3 – axial)
NEOMENTHOL
NEOISOMENTHOL (CH3 – axial)

Scheme 1.

Table 1. Hydrogenation of thymol over Rhodium/alumina in the presence of β-cyclodextrin and its derivatives[a]

Catalyst	Equivalent	Menthone (%)	Isomenthone (%)	Total	Neomenthol (N) (%)	Menthol (M) (%)	Total	Alcohol/ ketone ratio	M/N ratio	Unknown (%)
Control	–	1.2	15.7	16.9	11.6	65.2	76.8	4.5	5.6	6.1
β-CD	0.1	0.3	1.5	1.8	12.9	81.7	94.6	45.4	6.3	3.7
β-CD	0.2	0.9	4.1	5.0	13.0	78.5	91.5	18.3	6.0	3.6
β-CD	0.4	1.2	12.9	14.1	12.4	68.0	80.4	5.0	5.5	5.3
β-CD	0.7	11.1	11.8	22.9	12.2	57.8	70.0	3.1	4.7	7.0
β-CD	1.0	0.5	0.5	1.0	12.6	71.0	83.6	83.6	5.6	15.0
β-CD-polym	1.0	2.2	10.7	12.7	11.6	72.0	83.6	6.5	6.2	3.7
HPβ-CD	0.2	30.0	50.3	80.9	4.2	2.5	16.7	0.06	5.5	2.4
HPβ-CD	0.5	4.1	3.9	8.0	27.3	62.6	89.9	11.2	2.3	2.1
HPβ-CD	1.0	1.6	2.4	4.0	28.8	67.0	95.8	24.0	2.3	2.1
DMβ-CD	0.5	2.4	4.1	6.5	0.0	80.7[b]	80.7	12.0	∞	12.8

[a]By GC analysis.
[b]Neoisomenthol.

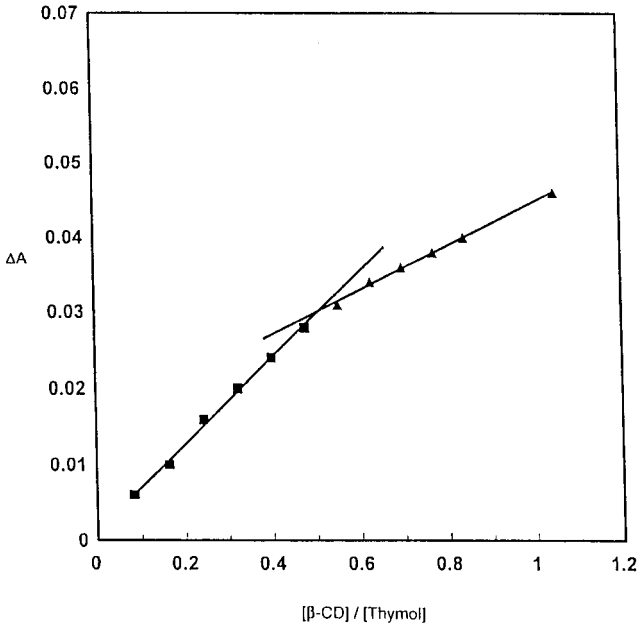


Figure 2. Determination of the stoichiometry for the β-CD-thymol 1 : 2 inclusion complex from UV-Visible spectroscopy. [β-CD] = 1.33303 $\times$ 10^{-2} M; [Thymol] = 1.3314 $\times$ 10^{-3} M.

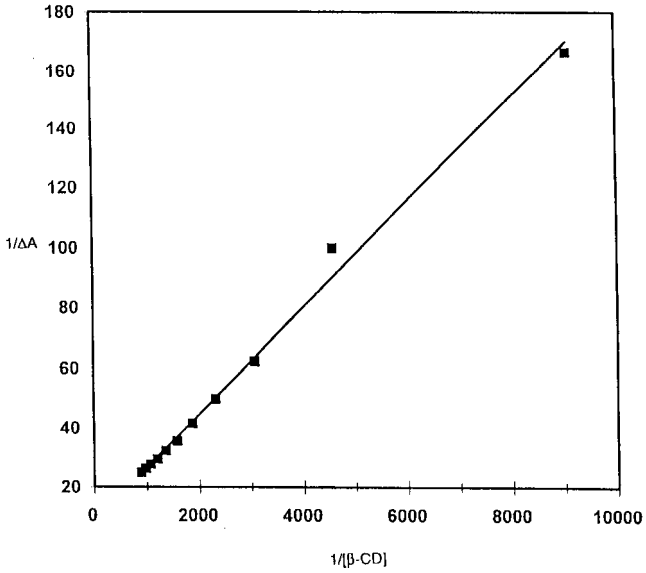


Figure 3. Determination of the binding constant value by the double reciprocal method in aqueous ethanol (90 : 0). [β-CD] = 1.33303 $\times$ 10^{-2} M; [Thymol] = 1.3314 $\times$ 10^{-3} M.

Some of the salient features of hydrogenation are:
Conversion to alcohols was good in the presence of 0.1 equivalent β-CD, β-CDpolymer, HPβ-CD and DMβ-CD. Although the M/N ratios obtained with β-CD and its derivatives were comparable to those of the control, excellent alcohol/ketone ratio values were obtained in the presence of 0.1, 0.2 and 1.0 equivalents of β-CD and 0.5 equivalent and 1.0 equivalent of HPβ-CD and 1.0 equivalent of DMβ-CD. The workup procedure was quite easy and the recovery of β-CD could also be carried out quite efficiently. Since HPβCD was slightly hygroscopic, obtaining reasonable homogeneous reaction conditions was not possible although the conversion was good. Nevertheless, the reaction took place efficiently under heterogeneous reaction conditions.

Structural studies

Ultraviolet-visible spectroscopy

The orientation of thymol inside the β-CD cavity determines the observed product formation. Hence, an attempt was made to elucidate the orientation of thymol inside the β-CD cavity by UV and ^{1}H-NMR spectroscopy. Since thymol was not soluble in water the UV-Visible spectroscopic study was carried out in aqueous ethanol (water : ethanol 90 : 10). The thymol solution was prepared in aqueous ethanol (1.33 $\times$ 10^{-3} M). The β-CD solution in ethanol (1.33 $\times$ 10^{-2} M) prepared in the above mentioned thymol solution, was gradually added to the thymol solution and the UV-Visible spectra of the mixture were monitored. Thymol exhibited a strong absorption at 271 nm corresponding to the $\pi - \pi^*$ transition of the phenol ($\epsilon = 2320$ in 10% aqueous ethanol) group. With the addition of increasing amounts of β-CD,

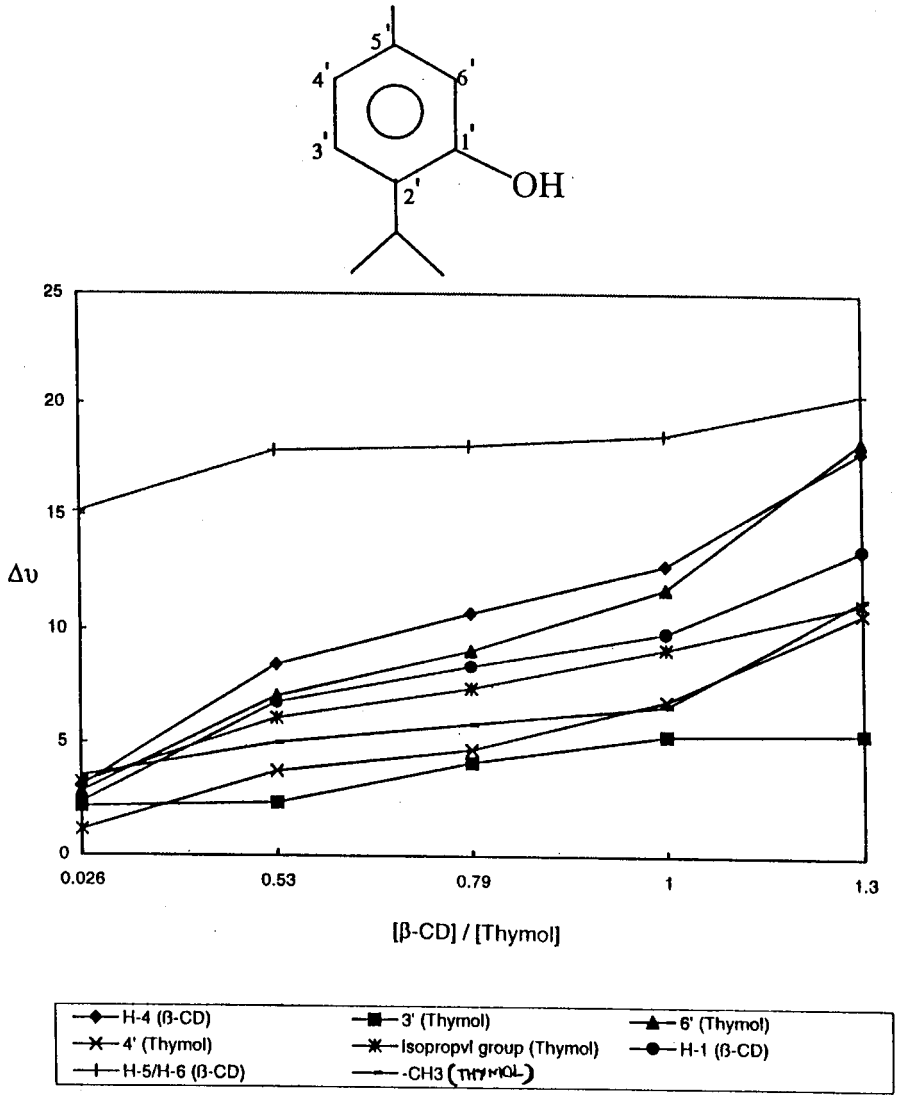


Figure 4. Effect of inclusion of thymol on proton NMR signals of β-CD and thymol groups. Solvent = D_2O, pH = 10.5. Thymol = 0.013M. Spectra were recorded by adding increasing amounts of β-CD in D_2O at pH 10.5. β-CD protons: ♦, H-4 (3.56 ppm); ●, H-1 (5.06 ppm); H-5/H-6 (3.83 ppm). Thymol protons: ■, 3′ (7.01 ppm, d, 6.9 Hz); ▲, 6′ (6.45 ppm, s); ×, 4′ (6.35 ppm, d, 6.9 Hz); ——, CH_3 (2.14 ppm, s); ∗, isopropyl CH (3.16 ppm, sept, 6.3 Hz).

hyperchromicity was observed along with a bathochromic shift of 5 nm (271 nm → 276 nm). Both hyperchromicity as well as bathochromicity indicated the formation of an inclusion compound of thymol with β-CD. A titration plot of ΔA (the difference in absorbance between thymol and that at a certain concentration of β-CD) versus [β-CD]/[Thymol] exhibited an asymptotic curve [22] with 1 : 2 stoichiometry (Figure 2), indicating the formation of a 1 : 2 complex between β-CD and thymol. The binding constant value as determined by plotting $1/\Delta A$ versus $1/[\beta\text{-CD}]$ (Figure 3) was $480 \pm 40\ M^{-2}$ for the 1 : 2 complex [22].

^{1}H-NMR spectroscopy

The presence of two thymol molecules for one molecule of β-CD as indicated by UV-Visible spectroscopy, may lead to several types of orientations for the two thymol molecules inside the β-CD cavity. Also, there may be differences in the extent of penetration of the guest inside the cavity. Hence, a ^{1}H-NMR investigation of the complexation was carried out in alkaline D_2O (the pH of the sample being 10.5), as thymol was insoluble in D_2O. ^{1}H-NMR spectra of the β-CD-thymol system showed upfield shifts of H-4′, H-6′, —CH_3 and —$CH(CH_3)_2$ of the thymol protons in the range 6.62 to 12.81 Hz on adding β-CD to thymol (Figure 4).

The β-CD protons also showed upfield shifts in the range 8–20.4 Hz. Among the thymol protons, H-6′ showed a maximum upfield shift of 18.3 Hz followed by isopropyl (11.4 Hz) > H-4′ (10.8 Hz) > —CH_3 (7.9 Hz) and H-3′ (5.4 Hz). Among the β-CD protons, the order of decreasing upfield shifts was

$$\text{H-4 (17.9 Hz)} > \text{H-1 (13.5 Hz)} > \text{H-2 (11.6 Hz)}$$

$$> \text{H-3 (8.6 Hz).}$$

While the UV-Visible spectroscopic studies indicated 1 : 2 stoichiometry of the β-CD-thymol complex, ^{1}H-NMR spectroscopy gave an indication of the orientation of the guest molecule. Both H-6′ and the isopropyl protons of thymol showed maximum upfield shifts indicating that the inclusion

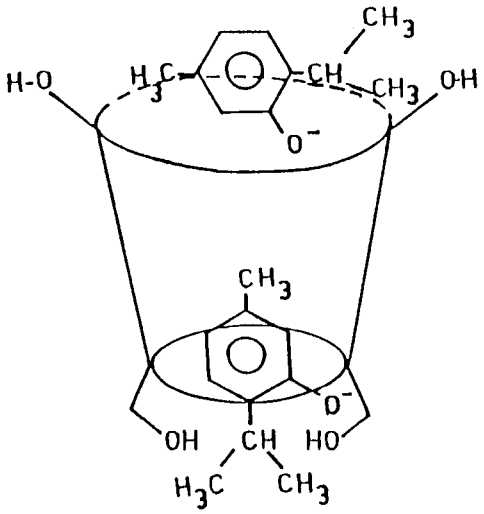


Figure 5. Proposed disposition of thymol molecules inside the cavity of β-CD.

affected the phenol group (phenoxide) of thymol drastically in such a way as to disturb H-6′ and the isopropyl in their microenvironment. Even for β-CD, protons H-4 and H-1, which are in the middle of the cavity showed maximum shifts, indicating that inclusion of the aromatic ring of thymol affected the middle of the interior part of the β-CD cavity.

The inclusion of the isopropyl group inside the cavity may not be possible, as there may be significant steric hindrance to the rotating isopropyl group from the β-CD groups at the narrower and wider ends. This leaves only the inclusion of the methyl group at the 5-position through both the narrower and wider ends of β-CD as another distinct possibility. It has been shown that in the case of *o*-substituted aromatic phenols, the end which goes into the β-CD molecule is largely dependent on the substituent characteristics, namely, their polarity and bulkiness [22]. For this reason also, inclusion of the methyl group, as a hydrophobic group, into one of the ends of β-CD is a distinct possibility. The orientation of the second thymol molecule leaves only two possibilities. The first one involves inclusion of the methyl group. But, in this orientation, the microenvironment of the phenoxide group may not be affected much. The other possibility is that the thymol molecule is placed perpendicular to the axis of the β-CD cavity. This may involve stabilization through hydrogen bonding interaction between the secondary hydroxyl groups of β-CD and the phenoxide ion. While this may be the disposition for one thymol molecule, the other molecule may be included through the narrower end with the methyl group at the 5-position projecting into it (Figure 5). This structure observed in solution may not be the same as that in the solid-state. The admixture containing thymol and β-CD molecule will experience weak intermolecular interactions only, like H-bonding, but will not exhibit inclusion of thymol into the β-CD cavity. Hence, the solution structure is only an approximate one which may partially explain the product generation.

The results of the studies reported here have clearly shown that under similar experimental conditions in all the cases, a diverse set of products could be formed, depending upon the stoichiometries and nature of the β-CD and its derivatives. Thus, while menthols were higher in some cases, menthones were found to be higher in other cases and in one instance even neo-isomenthol was formed. Since a heterogeneous reaction mixture was employed, the mode of catalysis of Rh/Al_2O_3 was found to be altered by the presence of β-CD and its derivatives in various proportions. Although Rh/Al_2O_3 has been shown to produce menthone from thymol under solid state conditions [15] the amount of menthone formed was only to the extent of 17% (control) in the present studies. However, 0.2 equivalent of HPβ-CD produced 81% of menthone. The presence of 0.1 equivalent of β-CD produced 95% of menthol with only 1.8% menthone, implying that the mode of hydrogenation, i.e., the catalytic pathway for the reduction has been altered. One probable reason for this is that the orientation of thymol, the stoichiometry and the binding constant values of the complexes between thymol and β-CD and its derivatives may be slightly different leading to the observed product distribution.

Although hydrogenation is expected to reduce aromatic double bonds, the exact mode of formation of menthone is less understood. Hydrogenation occurs through *in situ* oxidation to quinone and reduction of the same may give rise to menthone and isomenthone. The proximity of β-CD, containing partially and/or fully included thymol to the catalytic surface holds the key to the observed product distribution.

Both the proposed orientations for thymol can explain the selectivities observed, as the aromatic (planar) phenolic molecule is converted into the cyclohexyl derivative in the chair conformation. The steric requirements for formation in the sterically restricted reaction vessel of molecular β-cyclodextrin result in sterically divergent product formation. Menthol, neomenthol, neoisomenthol and isomenthol formation is an example of this ‘steric stress’ exerted by molecular β-cyclodextrin on the product generation which requires the methyl group at position 5 to occupy axial or equatorial positions. This reaction has brought out this feature clearly.

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