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Regioselective acetylation of 4-*t*-butylcyclohexanol in presence of β-cyclodextrin and its derivatives

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Abstract

Regioselective acetylation of 4-*t*-butylcyclohexanol (I) in the presence of β-CD, DMβ-CD, HPβ-CD and β-CD-polymer was carried out with 10–20 times excess acetic anhydride. At 1:10 ratio I and acetic anhydride, the control showed good amount of conversion (99.0%) to 4-*t*-butylcyclohexyl acetate (II) with a *trans*/*cis* ratio of 3.48 with very little unreacted alcohols present (*trans*/*cis* ratio 2.5). With increase in concentration of β-CD, although the ester yield was less than the control, the *trans*/*cis* ratio increased steadily from 3.46 for 1:0.1 (yield 57.7%) to 5.49 for 1:1 eq.(yield 74.4%) of I to β-CD. However, the *trans* ester yield was comparable to the control (76.9%) in the presence of 1 eq. of β-CD. The results indicated selectivity in esterification between the *trans* and *cis* alcohols due to inclusion inside β-CD cavity.

Keywords: β-Cyclodextrin; Regioselectivity; 4-*t*-Butylcyclohexanol; 4-*t*-Butylcyclohexyl acetate; *Trans*/*cis* ratio

1. Introduction

4-*t*-Butylcyclohexyl acetate (II) is in public use since 1950s as a fragrance compound in USA. It is used in soaps, detergents, creams, lotions, and perfumes [1]. 4-*t*-Butylcyclohexyl acetate is prepared by acetylation of I [2,3]. 4-*t*-Butylcyclohexanol (I) consists of *cis* and *trans* alcohols in the proportion 1:2.5 which corresponds to 28.5% *cis* and 71.5% *trans* [2]. It was found that the synthesis did not appreciably change the ratio of the isomers of acetates and alcohols. The proportions of *cis* and *trans* acetates prepared chemically were reported to be 22.0% *cis* and 78.0% *trans* [2]. Of the two, the *cis* isomer was found to exhibit a better fragrance note than the *trans* isomer [4].

β-Cyclodextrin and its derivatives have been reported to include cyclohexanols and cyclohexanediols with good amount of selectivity [5–7]. Earlier work in our laboratory, had reported selectivities in reaction of some monocyclic systems in the presence of β-CD and its derivatives. Hydrogenation of menthone and pulegone [8], sodium dithionite reduction of menthone and pulegone [9,10], sodium borohydride reduction of menthone and pulegone [11,12] and hydrogenation of thymol resulted in menthol and neomenthol in various proportions in the presence of β-CD and its derivatives [13].

Chemical esterification of I was undertaken in presence of β-CD and its derivatives to investigate whether any selectivity in esterification of *trans* and *cis* alcohol could be detected. The *cis* and *trans* isomers have slightly different flavour notes with the *trans* isomer having a rich woody odour and the odour of *cis* isomer being more intense and more flowery. These esters are also commercially important. No previous reports are

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available on regioselectivity in acetylation of I using β-CD and its derivatives.

2. Experimental

β-Cyclodextrin used was a gift from American Maize Products Company, USA. β-CD-polymer, DMβ-CD and HPβ-CD were prepared by the procedures of Shaw and Buslig [15], Szejtli et al. [16] and Pitha et al. [17], respectively and were used in reactions. Dimethyl sulfate and resorcinol procured from SD Fine Chemicals Ltd., India, chloroform, diethyl ether, potassium hydroxide, sodium sulfate, acetic anhydride, pyridine and butanol obtained from Qualigens India Ltd., and sodium bicarbonate from Ranbaxy Laboratories India were used. 4-*t*-Butylcyclohexanol was procured from Aldrich, USA.

The reaction was carried out in a round bottomed flask by taking 0.78 g (0.005 mol) I in 5 ml pyridine and 2.55 g (0.025 mol) of acetic anhydride (in case of 1:10 eq.) and 5.1 g (0.05 mol) acetic anhydride (in case of 1:20 eq.) with appropriate quantities of β-CD, DMβ-CD, HPβ-CD and β-CD-polymer. The reaction mixture was refluxed for 4 h at 115 °C and poured into 100 ml cold water. Upper ester layer was extracted with ether and washed with $NaHCO_3$ to neutralize the acid and dried with sodium sulfate. The ether layer was then evaporated to get the reaction mixture.

The reaction mixture was monitored by gas chromatography using a 10% Carbowax of CW 60/80 column at 120 °C, FID detector at 240 °C and injector at 240 °C with N_2 as the carrier gas at a flow rate of 40 ml/min.

3. Results and discussion

3.1. Regioselective synthesis of 4-t-butylcyclohexyl acetate

Based on the inferences from the earlier studies on the orientation of monocyclic ring systems inside β-CD cavity, the orientation of the axial and equatorial hydroxyl groups of I was expected to be different when included inside the β-CD cavity. Consequently, the proportionality of esterification between axial and equatorial alcohols would be expected to be different. This aspect was taken up in the present work by carrying out the esterification reaction of 4-*t*-butylcyclohexanol in the presence of β-CD, DMβ-CD, HPβ-CD and β-CD-polymer.

β-Cyclodextrin and its derivatives possess varying numbers of –OH groups, which would also react with acetic anhydride. Hence, two sets of experiments were carried out for the esterification of I with 1:10 I:acetic anhydride and 1:20 I:acetic anhydride. The reaction was carried out with pyridine as the solvent at 115 °C and it contained appropriate quantities of β-CD and its derivatives and acetic anhydride. The reaction products were monitored by gas chromatography (Fig. 1). The proportion of *cis* and *trans* 4-*t*-butylcyclohexanols in the starting material was found to be 28.8% *cis* and

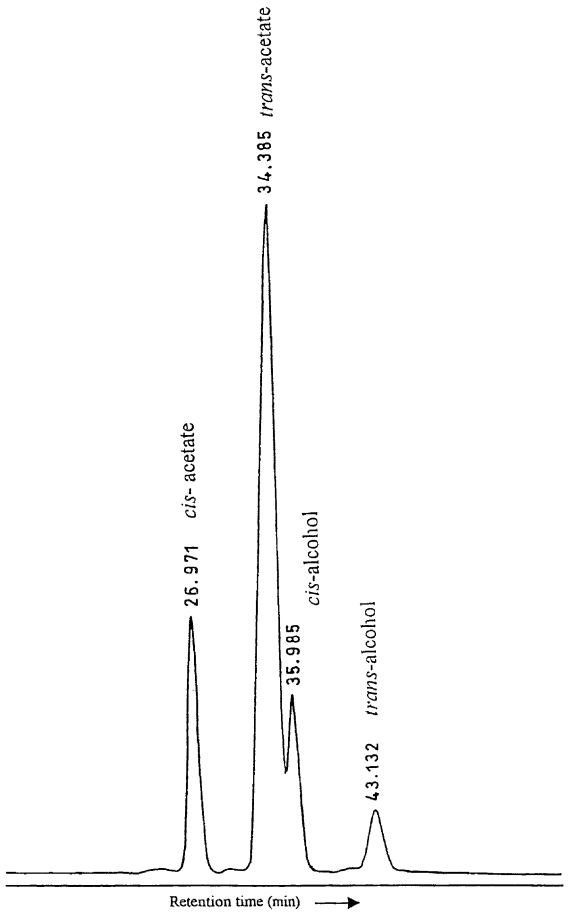
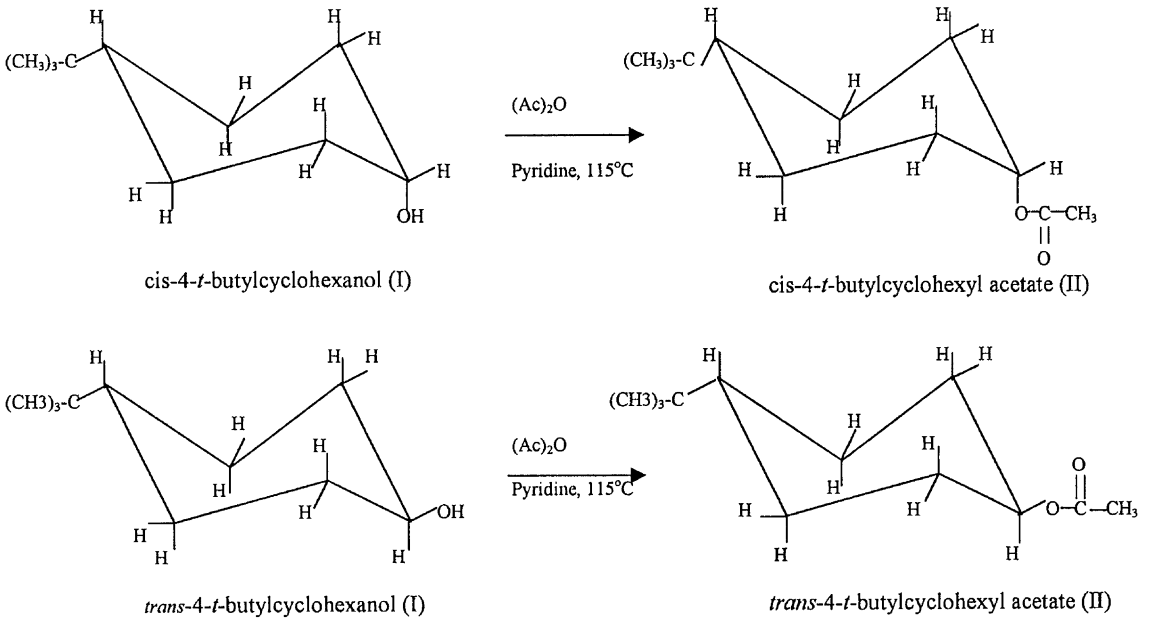


Fig. 1. Gas chromatographic profile of the reaction mixture from 0.5 eq. β-CD to 4-*t*-butylcyclohexanol in case of 1:10 4-*t*-butylcyclohexanol to acetic anhydride.



Scheme 1. Esterification of 4-*t*-butylcyclohexanol.

71.1% *trans*. The reaction is depicted in Scheme 1. The results are shown in Table 1 (1:10 I:acetic anhydride).

In case of 1:10 I:acetic anhydride, the reaction showed 70–99% completion. While in the control, the reaction showed 99% completion, in the presence of β-CD and its derivatives, a large proportion of about 20–30% unreacted I was detected. The control showed with very little of unreacted alcohols present (0.97%) with a *trans*/*cis* ratio of 3.48. With increase in the concentration of β-CD, the proportion of *trans* ester increased, while the proportion of *cis* ester decreased. In the presence of increasing amounts of β-CD the proportions of the *trans* isomers were always less

Table 1
Gas chromatographic data of the reaction products of 4-*t*-butylcyclohexanol reaction with acetic anhydride (1:10 eq. of 4-*t*-butylcyclohexanol: acetic anhydride)[a]

Reaction condition	4-*t*-Butylcyclohexyl acetate			Unreacted alcohol (%)	*Trans*/*cis* esters
	Cis (%)	*Trans* (%)	Total ester (%)		
Control	22.1	76.9	99.0	1.0	3.48
1:0.1 β-CD	16.7	57.7	74.4	25.6	3.46
1:0.2 β-CD	21.2	67.9	89.0	11.0	3.20
1:0.4 β-CD	13.2	58.4	71.6	28.4	4.42
1:0.6 β-CD	12.2	56.1	68.3	31.7	4.59
1:0.8 β-CD	10.9	55.4	66.3	33.7	5.06
1:1 β-CD	13.5	74.4	87.9	12.1	5.49
1:0.1 DMβ-CD	24.4	67.2	91.5	8.5	2.74
1:0.1 HPβ-CD	20.7	57.2	77.9	22.1	2.75
1:0.1 β-CD-polymer	25.3	73.3	98.6	1.4	2.89

[a] Error in GC measurements will be ±5%. Retention time (min): *cis* acetate, 26.9; *trans* acetate, 34.4; *cis* alcohol, 36.0; *trans* alcohol, 43.1.

than those of the control. At 0.1 eq. of β-CD, it was 57.7%. It increased to 74.4% with 1 eq. of β-CD. Although the proportions of *trans* isomers were less than the control, the *trans*/*cis* ratio increased steadily from 3.46 for 0.1 to 5.49 for 1 eq. of β-CD. From 0.4 β-CD equivalent onwards the proportion of *trans*/*cis* ratio increased from 4.42–5.49. However, in the presence of β-CD derivatives like DMβ-CD, HPβ-CD and β-CD-polymer the *trans*/*cis* ratio showed a value of around 2.7–2.9. In the presence of β-CD derivatives, the *cis* ester proportions were higher than those observed in the presence of various equivalents of β-CD. Also in these cases, the extent of unreacted alcohols were found to be lesser than those observed in the presence of various equivalents of β-CD.

In the presence of 1:20 I:acetic anhydride (Table 2), the control showed larger conversion (98.0%) than the reactions carried out in the presence of β-CD and its derivatives. Here also the esterification behaviour by β-CD and its derivatives were similar to those observed with 1:10 I:acetic anhydride. With increase in β-CD from 0.1 to 1 eq., the yields of the *trans* ester varied from 55 to 75%. However the *trans*/*cis* ratio increased steadily from 2.39 for 0.1 eq. β-CD to 5.2 for 1 eq. of β-CD. The control showed a *trans*/*cis* ratio of only 3.4. Here also, 0.1 eq. of DMβ-CD, HPβ-CD and β-CD-polymer gave *trans* ester yield of around 70.0% with a *trans*/*cis* ratio of 2 to 3. Again the proportion of the unreacted I was around 30% at higher β-CD equivalents and the proportion of the *cis* ester was higher, when the β-CD derivatives were employed.

Irrespective of the extent of acetic anhydride employed, both 1:10 and 1:20 I:acetic anhydride almost showed similar results. The extent of unreacted I increased with increase in concentration of β-CD reaching a value of 30.0%. However, the three β-CD derivatives employed namely, DMβ-CD, HPβ-CD and β-CD-polymer and the control showed greater conversions with very little unreacted alcohols, the exception being in the presence of HPβ-CD at 1:10 I:acetic anhydride. The conversion of *cis* alcohol also decreased with increase in β-CD concentration. But the control and the three derivatives of β-CD gave good conversion of *cis* alcohol. Hence, with increase in β-CD concentrations, the *trans*/*cis* ratios were higher than others.

The reaction mixtures other than control were largely heterogeneous with large amount of insoluble β-CD and its derivatives. However, upto 0.2 eq. of β-CD and 0.1 eq. of DMβ-CD and HPβ-CD dissolved in pyridine.

Inclusion of (I) inside β-CD cavity was studied by Siegel and Breslow [14] who determined binding constant value for the 1:1 complex of I with β-CD. However, the orientation of the alcohols inside β-CD cavity was not shown. The *trans*/*cis* ratio increased beyond 0.4 eq. of β-CD. This indicated selectivity in esterification between the *trans* and *cis* alcohols. The *trans* alcohol has the hydroxyl group on the equatorial position, while the *cis* alcohol has the hydroxyl group on the axial position. Compound I can be included inside the β-CD cavity either with the hydroxyl end

Table 2
Gas chromatographic data of reaction products of 4-*t*-butylcyclohexanol reaction with acetic anhydride (1:20 eq. of 4-*t*-butylcyclohexanol: acetic anhydride)[a]

Reaction condition	4-*t*-Butylcyclohexyl acetate			Unreacted alcohol (%)	*Trans*/*cis* esters
	Cis (%)	*Trans* (%)	Total ester (%)		
Control	22.3	75.8	98.0	2.0	3.4
1:0.1 β-CD	29.1	69.6	98.7	1.3	2.39
1:0.2 β-CD	26.7	71.4	98.1	1.9	2.67
1:0.4 β-CD	20.8	68.4	89.2	10.8	3.29
1:0.6 β-CD	13.8	54.8	68.6	31.4	3.97
1:0.8 β-CD	13.0	55.9	68.9	31.1	4.3
1:1 β-CD	13.7	75.3	89.0	11.0	5.2
1:0.1 DMβ-CD	24.2	74.2	98.3	1.7	3.02
1:0.1 HPβ-CD	29.0	69.6	98.7	1.3	2.39
1:0.1 β-CD-polymer	31.4	66.6	98.0	2.0	2.11

[a] Error in GC measurements will be ±5%. Retention time (min): *cis* acetate, 26.9; *trans* acetate, 34.4; *cis* alcohol, 36.0; *trans* alcohol, 43.1.

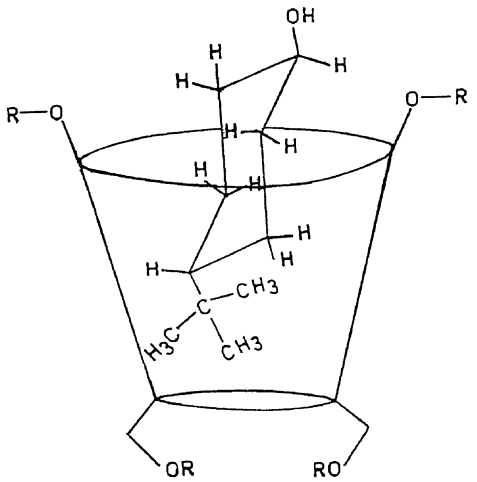


Fig. 2. Orientation of 4-*t*-butylcyclohexanol molecule in side the β-cyclodextrin cavity. R = H, –CO–CH_3.

inside the cavity or with the 4-*t*-butyl group inside the β-CD cavity. It is the second orientation, which is most probable (Fig. 2) as it explains the formation of the *trans* ester in predominant amount compared to *cis*. Presence of 4-*t*-butyl group inside the β-CD cavity puts the equatorial hydroxyl group of the *trans* alcohol to project outside, thereby facilitating reaction to take place with the equatorial hydroxyl group. In this disposition, the reaction with the axial group would be sterically hindered by the hydroxyl groups of β-CD molecule and its derivatives, thereby relatively decreasing the formation of the *cis* ester. This reaction also involves esterification of the hydroxyl groups on carbon atom 2 of β-CD and its derivatives where such groups are free. This will impose further steric restriction on the reaction with the axial hydroxyl groups of I. On this count also, reduction in *cis* esterification leads to larger *trans*/*cis* ratio of the ester than the control and β-CD derivatives. In the case of β-CD derivatives, substitution on the carbon 2 of β-CD probably imposes steric restriction for inclusion as well as reaction if I included in their cavities. This probably explains their comparable conversion yields and *tans*/*cis* ratios to the control reaction.

Acknowledgements

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