



Sodium Dithionite Reduction of 2S,5R-(–)-menthone and R-(+)-pulegone in the Presence of β -Cyclodextrin and Hydroxypropyl- β -cyclodextrin

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Abstract

Menthone on reduction with sodium dithionite, showed a good amount of menthol formation in the water/DMF system, with increasing β -cyclodextrin (β -CD) concentration from 47.0% for 0.1 equivalent of β -CD to 93.5% for 1 equivalent of β -CD. Increasing hydroxypropyl- β -cyclodextrin (HP β -CD) gave higher menthol/neomenthol (M/N) ratios from 2.8 to 3.5. In the case of pulegone, increasing β -CD showed an increase in the formation of menthols in the water/DMF system from 13.3% for 0.1 equivalent of β -CD to 78.1% for 1 equivalent of β -CD with greater proportions of neomenthol and neoisomenthol. However, HP β -CD which showed only marginal enhancement in the formation of menthol from menthone (32.1–41%), exhibited a greater proportion of menthol formation in the case of pulegone (55.1%). However, the phase-transfer capability of HP β -CD was not found to be significant.

Introduction

Pulegone [1–5] and menthone are most abundantly found in the plants of *Mentha spicata eromentha*, *Mentha piperita L.* and *Calatrintha incana*. Reduction of these essential oils enriched with menthone and pulegone using various catalysts and conditions results in the formation of menthols. Out of the eight possible optically active isomers, only (–)-menthol gives the persistent and pleasant peppermint-like odour and flavour [6].

Several chemical methods are available for the reduction of menthones and pulegones [7–13]. Among the other procedures, reaction in the presence of cyclodextrin often results in the alteration of well known chemical transformations [14]. A number of ketones and α , β -unsaturated aldehydes or carbonyl compounds have been reduced stereoselectively, using the chiral binding site, provided by complexation with β -CD [15–17].

In our earlier work, β -CD and its derivatives such as β -CD-polymer and heptakis-2,6-di-O-methyl- β -CD (DM β -CD) were used for the reduction of pulegone and menthone by sodium dithionite [18, 19]. In the present work further extension of the reduction of R-(+)-pulegone and (2S, 5R)-(–)-menthone were carried out in the presence of different concentrations of β -CD and hydroxypropyl- β -CD (HP β -CD) and the results are presented below.

Experimental

β -Cyclodextrin used was a gift from Sigma Chemical Company, USA. Hydroxypropyl- β -cyclodextrin prepared by the

procedure of Pitha *et al.* [20] was used in the reactions. CDCl₃ and DMSO-d₆ procured from Sigma Chemical Company, USA, DMF and sodium dithionite procured from SD Fine Chemicals Ltd. India were used. R-(+)-Pulegone was procured from Aldrich Chemical Company, USA. (2S,5R)-(–)-Menthone was prepared by the oxidation of menthol by chromic acid [21].

Reaction conditions

A typical procedure employed for the reduction of pulegone and menthone by sodium dithionite was as follows. Water or water-benzene (1 : 1, 25 mL) or water-DMF (1 : 1, 40 mL), containing NaHCO₃/Na₂S₂O₄/pulegone (1.85 mmole) or menthone (1.74 mmole) in the molar ratios 18 : 9 : 1 and the appropriate amount of the host (β -CD and its derivatives) was heated to boiling under nitrogen and stirred vigorously for 6 hours. The reaction mixture was cooled, acidified with dilute HCl, then extracted with ether which was then dried over Na₂SO₄ and concentrated. The reaction products obtained were analyzed by GLC.

GC analyses

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 and 240 °C respectively. The column was maintained at 110 °C. Clear separation of menthone (8.2 min), pulegone (9.0 min), isomenthone (9.3 min), neomenthol (13.4 min), neoisomenthol (15.4 min), and menthol (16.7 min) was achieved. The results are an average from three independent reactions.

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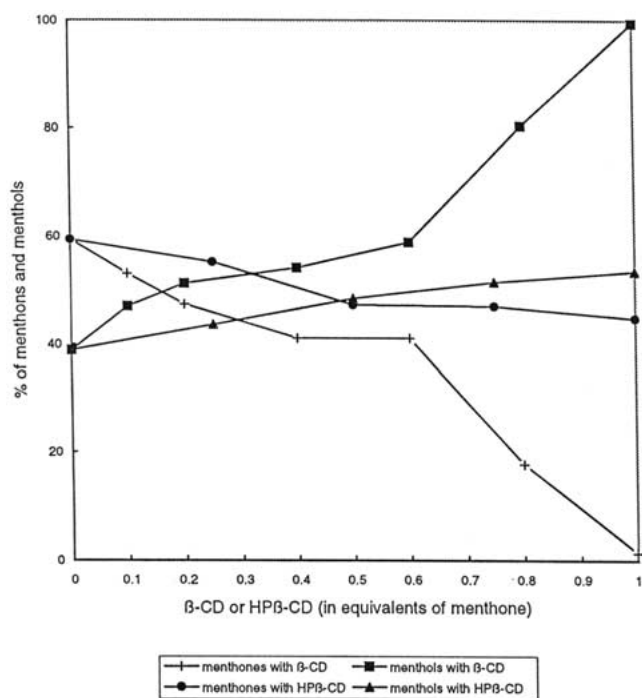


Figure 1. Effect of β -CD and HP β -CD on sodium dithionite reduction of menthone in a water : DMF mixture. Reaction conditions are given in the Experimental section.

Results and discussion

Reduction of (2*S*, 5*R*)-(-)-menthone

In the present work the effect of β -CD and HP β -CD was investigated in detail in the sodium dithionite reduction of (2*S*, 5*R*)-(-)-menthone and *R*(+)-pulegone. The results under various conditions are shown in Table 1 and Figure 1. Reduction of menthone by sodium dithionite carried out in water resulted in only 5.6% menthol. With increasing HP β -CD concentration, the percentage of alcohols increased from 4.0 (for 0.25 equivalent) to 19.0% (for 1 equivalent) with menthol/neomenthol (M/N) ratios of 40.0 and 26.1, respectively. Although the yield of alcohols were lower such high M/N values in water were not observed in the earlier studies.

The phase transfer abilities of HP β -CD were investigated in the benzene : water (1 : 1) system. Reduction in the presence of both HP β -CD and β -CD in water : benzene did not show as much conversion into alcohols (4.0%) as was observed with DM β -CD (82%) [18]. This low yield may be because in benzene : water, benzene may act as a highly competitive guest, especially when present in large molar excess, besides rendering the reagents insoluble. The use of an aqueous DMF (1 : 1) mixture as the solvent showed a slight enhancement in the yield of alcohols from 38.9% observed for the control to 53.5% for 1 equivalent of HP β -CD with M/N ratios of 2.8–3.5. However, increasing β -CD from 0.1 to 1 equivalent resulted in an increase of the epimeric alcohols from 47.0% to 93.5%.

In all the cases, with the exception of the reaction in water, the M/N ratios were found to be in the range 1.5–3.7, showing higher values than the control (2.9) at some ratios of

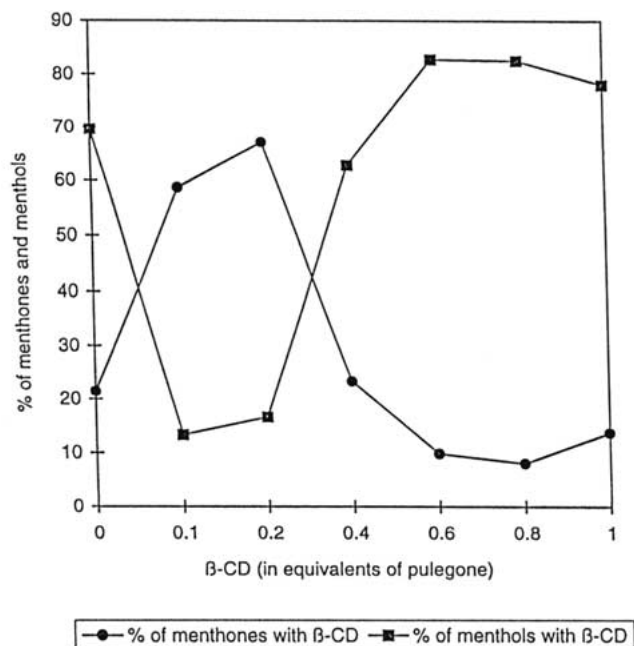


Figure 2. Effect of β -CD on sodium dithionite reduction of pulugone in a water : DMF mixture. Reaction conditions are given in the Experimental section.

β -CD and HP β -CD. The reduction in the presence of β -CD gave better yields of alcohols but the reaction in the presence of HP β -CD gave better M/N ratios. Between HP β -CD and β -CD, HP β -CD is known to be a better solubilising agent than β -CD. Also the binding constant values of menthone in water for the menthone- β -CD complex was reported to be 546 M^{-1} whereas with HP β -CD it was 980 M^{-1} [22]. However, HP β -CD did not lead to better conversion, probably because of greater steric hindrance of the reagent by the long arms of HP β -CD to the included menthone inside the HP β -CD cavity. But the better conversion selectivities in the case of HP β -CD shows that besides the inclusion phenomenon, the rim-hydroxyl groups may also play a role in the observed effects. While DM β -CD (earlier study) was found to be a better phase transfer agent, HP β -CD was not found to be so because of its greater hydrophilic nature. Although the exact mechanism of reduction is not known [23, 24], the preference of the attacking SO_2 dianion for the axial position (less hindered side) probably resulted in equatorial formation of alcohol in a marginally higher amount especially in the case of β -CD. From this study β -CD was found to be a better host in bestowing greater stereoselectivity in the reduction when compared to DM β -CD, HP β -CD, β -CD-polymer and the control.

Reduction of *R*(+)-pulegone

The effect of β -CD and HP β -CD on the reduction of pulugone was also investigated in detail. In most cases, the reduction of pulugone gave rise to menthones and menthols, indicating that the initial reduction was that of the olefinic double bond followed by that of the keto group (Table 2 and Figure 2).

Table 1. GC data on sodium dithionite reduction of menthone in presence of β -CD and HP β -CD

Solvent	Catalyst in equivalents	Menthone	Iso-menthone	Total	Neo-menthol	Menthol	Total	M/N	Unknown
Water ^a	Control	70.6	21.6	92.2	0.0	5.6	5.6	∞	2.1
Water	HP β -CD								
	0.25	57.6	40.0	97.6	0.1	4.0	4.1	40.0	0.0
Water	0.50	57.6	38.5	90.1	0.6	7.2	7.8	12.0	2.5
Water	0.75	41.6	34.0	75.6	1.4	16.0	17.4	11.4	6.4
Water	1.00	40.9	40.1	81.0	0.7	18.3	19.0	26.1	0.0
H ₂ O : C ₆ H ₆ ^a	Control	78.8	15.8	94.6	0.0	3.4	3.4	∞	2.0
H ₂ O : C ₆ H ₆	B								
	HP β -CD								
	0.25	77.7	16.3	94.0	0.0	3.0	3.0	∞	3.0
H ₂ O : C ₆ H ₆	0.50	79.7	15.5	95.2	0.0	3.1	3.1	∞	3.0
H ₂ O : C ₆ H ₆	0.75	77.9	17.2	95.1	0.0	3.6	3.6	∞	1.3
H ₂ O : C ₆ H ₆	1.00	77.7	15.5	93.2	0.0	4.1	4.1	∞	2.5
H ₂ O : C ₆ H ₆	β -CD 1.0	88.4	5.9	94.3	0.1	3.9	4.0	39.0	1.7
H ₂ O : DMF ^a	Control	31.8	27.9	59.3	10.2	29.6	38.9	2.9	0.5
H ₂ O : DMF	HP β -CD 0.25	29.8	25.3	55.1	11.5	32.1	43.6	2.8	1.3
H ₂ O : DMF	0.50	23.0	24.3	47.3	11.5	37.0	48.5	3.2	3.8
H ₂ O : DMF	0.75	26.6	20.5	47.1	11.4	40.0	51.5	3.5	1.4
H ₂ O : DMF	1.00	23.3	21.6	44.9	12.5	41.0	53.5	3.3	1.8
H ₂ O : DMF	β -CD 0.1	30.2	22.8	53.0	13.4	33.6	47.0	2.5	1.8
H ₂ O : DMF	0.2	25.2	22.2	47.4	13.0	38.2	51.2	1.5	2.9
H ₂ O : DMF	0.4	21.0	20.1	41.1	13.9	43.4	54.1	3.1	0.0
H ₂ O : DMF	0.6	23.1	18.0	41.1	19.4	39.5	58.9	2.0	0.0
H ₂ O : DMF	0.8	7.5	10.2	17.7	17.2	63.2	80.4	3.7	0.0
H ₂ O : DMF	1.0	0.8	0.5	1.3	32.1	61.4	93.5	2.9	5.2

^a Values in percentage; Volume of reaction mixture : water = 25 ml; water : benzene (1 : 1) = 25 ml; water : DMF (1 : 1) = 40 ml; Error in GC measurements = \pm 5%.

Table 2. GC data on sodium dithionite reduction of pulegone^a

Solvent	Catalyst in equivalents	Menthone	Iso-menthone	Total	Neo-menthol	Neo-isomenthol	Menthol	Total	Pulegone	Unknown	M/N
H ₂ O ^b	Control	41.2	25.3	66.5	11.0	0.0	12.5	23.5	1.0	10.0	1.1
H ₂ O	HP β -CD (0.5)	43.0	32.0	75.0	8.0	0.0	9.9	17.9	0.8	6.3	1.6
H ₂ O	1.0	43.4	32.9	76.3	3.5	0.0	5.5	9.0	1.7	13.0	1.2
H ₂ O : C ₆ H ₆ ^b	Control	0.8	0.5	1.3	0.0	0.0	0.0	0.0	95.0	3.7	0.0
H ₂ O : C ₆ H ₆	HP β -CD (0.5)	1.1	0.8	1.9	3.3	0.0	0.0	3.3	93.0	1.8	0.0
H ₂ O : C ₆ H ₆	β -CD 1.0	3.5	2.3	5.8	0.0	0.0	0.0	0.0	89.0	5.2	0.0
H ₂ O : DMF ^b	Control	11.1	10.3	21.4	20.6	7.0	42.0	67.6	2.0	7.0	2.0
H ₂ O : DMF	β -CD (0.1)	38.9	19.7	58.6	5.6	2.6	5.1	13.3	2.9	25.0	2.4
H ₂ O : DMF	0.2	43.6	23.5	67.1	12.8	0.0	3.8	16.6	2.0	14.3	1.3
H ₂ O : DMF	0.4	12.7	10.6	23.3	20.7	5.3	42.0	62.8	0.0	13.9	2.0
H ₂ O : DMF	0.6	5.9	3.9	9.8	27.6	5.5	49.7	82.8	0.0	7.4	1.8
H ₂ O : DMF	0.8	4.8	3.2	8.0	27.1	2.7	52.8	82.6	0.0	8.2	2.0
H ₂ O : DMF	1.0	8.0	5.7	13.7	24.3	4.1	49.7	78.1	0.0	8.2	2.0
H ₂ O : DMF	HP β -CD (0.5)	2.3	6.7	9.0	21.0	5.4	55.1	81.4	5.3	4.2	2.6
H ₂ O : DMF	1.0	2.3	1.5	3.8	25.7	9.5	50.7	85.9	6.3	4.0	2.0

^a GC Values are in percentage; Error in GC measurements = \pm 5%.

^b Volume of reaction mixture : water = 25 ml; water : benzene (1 : 1) = 25 ml; water : DMF (1 : 1) = 40 ml.

Reduction of pulegone in water resulted in 66.5% (control) menthones along with a 23.5% mixture of the epimeric alcohols. However, the presence of 0.5 equivalent of HP β -CD decreased the yield of alcohols to 17.9% and increased that of ketones to 75.0%. Increasing the HP β -CD to 1.0 equivalent yielded 9% alcohols and 76.3% ketones. In the present study, HP β -CD was found to protect the menthone formed from reduction to menthol.

The reduction of pulegone in water : benzene (1 : 1) was practically difficult in both control reactions as well as in presence of β -CD and HP β -CD. The control reaction gave 95.0% of unreacted pulegone with poor yield of ketones (1.3%). Reaction in the presence of 0.5 equivalent of HP β -CD resulted in 1.9% of menthones, 93.0% pulegone and 3.3% of menthols. Addition of 1 equivalent of β -CD gave rise to 5.8% of menthones with 89.0% unreacted pulegone. The very low conversion in the water-benzene system was probably due to the same reasons arising out of using benzene as in the reduction of menthone.

However, as observed earlier, addition of DMF as a co-solvent to water (1 : 1) drastically increased the yield of alcohols with a greater yield of menthols than the control reaction (67.6%). Increasing the amount of β -CD resulted in an increase in the amount of alcohols formed from 13.3% for 0.1 equivalent to 78.1% for 1 equivalent β -CD. The presence of β -CD initially retarded the reduction of menthone as observed by the increase of menthones from 58.6% (0.1 equivalent of β -CD) to 67.1% (0.2 equivalent of β -CD), which later decreased to 13.7% (1.0 equivalent β -CD). Addition of 0.5 equivalent of HP β -CD yielded about 81.4% and 9.0% of alcohols and ketones respectively. The highest amount of menthol was detected for the reaction in the presence of 0.5 equivalent HP β -CD (55.1%). A further increase in HP β -CD to 1.0 equivalent, yielded 85.9% of menthols and 3.8% of ketones.

There was no significant change in the M/N ratios, which were in the range 1.1 to 2.6 for the control and β -CD and HP β -CD catalyzed reactions. A small amount of neo-isomenthol was observed in the water-DMF mixture from 2.6 to 4.1% with increasing β -CD equivalents from 0.1 to 1.0. The control also showed 7.0% of neo-isomenthol. Apart from the reaction in the water : benzene system all the reactions showed very small amounts of unreacted pulegone and some unknown compounds.

The percentage of unknown compounds varied from 1.8 to 25.0%. With increasing β -CD equivalents, the proportion of unknown compounds decreased. Reaction in the presence of HP β -CD resulted in a minimum amount of unknown compounds. The presence of β -CD and HP β -CD enhanced the yield of alcohols.

Differences in the reduction of menthone and pulegone were found in the reaction in the presence of HP β -CD. The reduction of menthone in a 1 : 1 water : DMF mixture in the presence of HP β -CD resulted in marginally higher selectivity (M/N ratios in the order 2.8–3.5), whereas the selectivity was low in the case of pulegone (M/N ratios 2–2.6). Higher yields of menthols were obtained from menthone reduction in the presence of β -CD (93.5%). In the case of menthone,

the presence of HP β -CD (in 1 : 1 water : DMF) gave a higher yield of alcohols (53.5%) than the control (39.8%) and in the case of pulegone, the yield of alcohols was high (85.9%) compared to the control (67.6%) under identical reaction conditions. However, β -CD exhibited better conversion of menthone in the water : DMF mixture (Table 2) than HP β -CD. Although the conversion efficiency in water : DMF was the same in both β -CD and HP β -CD in the case of pulegone, the only difference being the formation of neo-isomenthol (in case of pulegone), which probably might have arisen from isomenthone. The difference in complexation between menthone and isomenthone by β -CD and HP β -CD besides steric factors arising out of the presence of the long arms of the hydroxypropyl groups in HP β -CD are responsible for the observed differences.

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