Short communication

Stereoselective hydrogenation of (2S,5R)-(−)-menthone in presence of β-cyclodextrin

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Abstract

In the presence of β-cyclodextrin and its derivatives, the hydrogenation reaction of (2S,5R)-(−)-menthone proceeded smoothly with high stereoselectivity for the formation of (1R,2S,5R)-menthol.
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The enzyme mimicking abilities of β-cyclodextrins arise mainly as a result of their capacity to include guest molecules in their cavity [1]. The orientation and extent of inclusion is not only governed by the nature of groups, but also their steric disposition [2]. During the course of certain reactions involving included guest molecules, products evolve with specific stereochemistry around reaction centres. This occurs due to geometric restriction dictated by the asymmetric cyclodextrin cavity around the reaction centre of the included guest molecules [3]. Such stereoselective reactions have been reported in the reduction of ketones, epoxidation of olefins and cleavage of epoxides [4]. (2S,5R)-(−)-menthone is present in many essential oils (46.8% menthone in Minthostachys verticillata oil, 35–74% menthone in the essential oils of peppermint, geranium and other mint oils [5]). Reduction by various reducing agents of this ketone yields epimeric menthols. In this communication we report the stereoselective and enantioselective effects of β-cyclodextrin (BCD) and its derivatives, in the hydrogenation of (2S,5R)-(−)-menthone (Scheme 1).

The results obtained in this study on menthone are shown in Table 1. The rates of hydrogen consumption under alkaline conditions by methone in the presence of BCD, BCD-polymer, DMBCD and CTAB are shown in Fig. 1. Except for the reaction in the presence of DMBCD and BCD-polymer, the rates of reduction in the presence of BCD, CTAB and control reactions showed sigmoidal behaviour. It can be seen that slightly less than

one equivalent of hydrogen was consumed. The rates of hydrogen consumption in the initial stages were higher for reactions in the presence of BCD, BCD-polymer, CTAB and DMBCD than that of the control reaction. Even after 8 h, DMBCD showed only about one-third equivalent of hydrogen consumption.

It was difficult to reduce ketones in the absence of alkali with Raney nickel. It can be seen from Table 1 that, hydrogenation in the absence of alkali, resulted in very low yields of alcohols (10.1%) in the control reaction. However, addition of BCD caused an increase in the yields of alcohols formed, with an increase in BCD concentration. An alcohol yield of 56.7% was observed for the reaction mediated by one molar equivalent of BCD. While the presence of BCD-polymer showed 17.7% formation of alcohols, presence of DMBCD did not show any effect at all. Surprisingly, the addition of CTAB gave the highest yield of alcohols (91.3%), along with a high menthol/neomenthol ratio (2.2). In contrast, other reactions showed more neomenthol formation as observed from fractional values obtained for the menthol/neomenthol ratios.

However, presence of small amount of alkali increased the yields of alcohols formed. The control reaction gave a yield of 55.3% of alcohols with the menthol/neomenthol ratio of 1.1. Presence of CTAB, BCD and its derivatives gave yields of alcohols greater than 90%. The only exception being DMBCD mediated reaction, which gave a yield of only 35.5% of alcohols. However, all these reactions gave menthol/neomenthol ratios greater than 2.0, with the highest value of 4.8 observed for the reaction in the presence of BCD. Presence of 0.1 M equivalent of BCD resulted in a yield of 88.1% alcohols, which increased to

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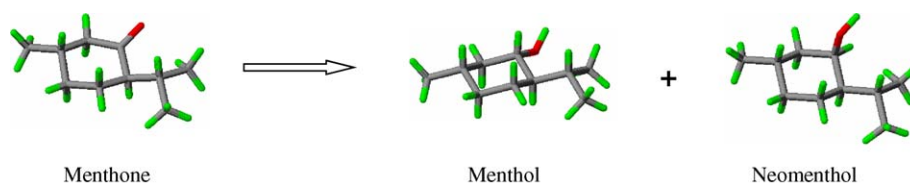
Scheme 1.

Table 1
GC analyses of (2S,5R)-(−)-menthone hydrogenation products over a Raney Ni catalyst

Conditions (molar equivalents to ketone)	Unreacted menthone (%)	Yield of menthol (%)	Yield of neomenthol (%)	Yield of alcohols (%)	Menthol/neomenthol (ratio)
Without alkali					
Control	89.9	3.4	6.7	10.1	0.5
BCD (0.1)	87.4	4.2	8.4	12.6	0.5
BCD (0.5)	77.0	9.6	13.4	23.0	0.7
BCD (1.0)	43.3	24.0	32.7	56.7	0.7
BCD-polymer (1.0)	82.3	6.0	11.7	17.7	0.5
DMBCD (1.0)	100.0	0.0	0.0	0.0	–
CTAB (0.5)	8.6	62.8	28.6	91.3	2.2
With alkali					
Control	44.7	28.7	26.6	55.3	1.1
BCD (0.1)	11.9	58.8	29.3	88.1	2.0
BCD (0.5)	3.9	64.8	31.3	96.1	2.1
BCD (1.0)	0.3	82.6	17.1	99.7	4.8
BCD-polymer (1.0)	8.2	64.3	27.5	91.8	2.3
DMBCD (1.0)	64.5	25.0	10.5	35.5	2.4
CTAB (0.5)	2.7	69.6	27.7	97.3	2.5

99.7% in the presence of 1 equiv. of BCD. Presence of CTAB was found to be affected very little by alkali, the yield of alcohols in the presence of alkali being 97.3% with the menthol/neomenthol ratio of 2.5.

Hydrogenation involved reduction in heterogenous conditions with BCD and Raney nickel being immiscible in the solvent alcohol employed. This heterogeneity did not affect the observed selectivity under certain conditions. BCD, DMBCD and CTAB mediated hydrogenation exhibited remarkable effects on yields of ketones and alcohols and M/N ratios both in the absence as well as in the presence of alkali. In all these cases, the role of

Fig. 1. Rates of hydrogen consumption by menthone.

DMBCD was found to be complementary to that of BCD. In menthone hydrogenation, it exhibited a pattern different from that of CTAB. While the reduction did not occur in the absence of alkali, it yielded only 35.5% alcohols in the presence of alkali, whereas CTAB gave 90% yield of alcohols in both the cases. Presence of BCD especially with alkali showed remarkable selectivity with menthone, unlike DMBCD. The reaction containing DMBCD was heterogenous in the case of hydrogenation where Raney nickel remained as an insoluble component.

Metals (Ni, Cu, Mn, Cr), triethylamine, amino acids, base, catalyst support, additives or impurities, in many cases, act as promotors and increase the efficiency of the Raney nickel catalyst. In a similar way, BCD and its derivatives also seem to act as promoters.

In the hydrogenation of (2S,5R)-(−)-menthone, besides the orientation of guest molecules inside BCD cavity, it is the orientation of the inclusion complex as a whole with respect to the catalytic Ni surface that enhances the selectivity. β-Cyclodextrin or DMBCD probably provides a molecular anchor for the included guest molecules to be brought closer to the nickel surface which may not be so fascile in the control reaction. This molecular anchoring also sidesteps the short comings that may arise due to heterogenous nature of reaction in case of BCD and its polymer. Similar type of caging may also help in the case of CTAB which encloses the ketones by either miscellar or reverse miscellar formation in alcohol anchoring the enclosed ketone on the nickel surface for fascile reduction. The probable mode of encapsulation may be through miscellar formation in alcohol, since only in that disposition, CTAB can replace alkali by cleaning
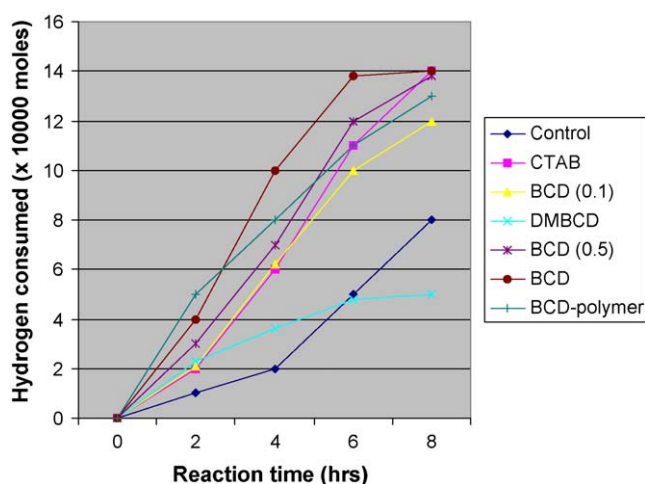
the metal surface by interaction between the positively charged quarternaryammonium head group of the amphiphile and the metal surface. It is not clear whether ionisation of BCD hydroxyl groups due to presence of alkali also plays a supporting role in reduction besides activation of metal surface.

In summary, the hydrogenation data presented in this work, provide a viable method for the reduction of essential oils into desired alcohols, by varying the conditions like use or non-use of alkali and CTAB, BCD and its derivatives, especially DMBCD. The catalyst is very cheap and the work up procedure is very simple. The BCD used can be recovered and reused.

1. Experimental

1.1. Hydrogenation over Raney nickel

A typical procedure employed for the hydrogenation reaction was as follows. (2S,5R)-(−)-menthone was taken in alcohol along with Raney nickel suspension and with or without alkali and hydrogenated. After hydrogenation, the Raney nickel catalyst was filtered off, and the filtrate acidified and extracted with ether, dried and concentrated. The product distribution of the reaction mixture was analysed by GLC. The rates of consumption of hydrogen by (2S,5R)-(−)-menthone was determined by monitoring the decrease in hydrogen pressure in the container with time. The relation, $P_2V_2T_1/T_2P_1$ 22,400, gave the initial and final hydrogen concentration, in moles, the difference of which showed the amount of hydrogen consumed by the compound. P_2 is the initial pressure and pressure after time t (h), V_2 the volume of the container, T_1 and P_1 are standard temperature and pressure.

1.2. GC analyses

A Shimadzu GC-15A instrument fitted with 20% carbowax 20 M, 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 250 °C, respectively. The column was maintained at 130 °C. Clear separation of menthone (4.0 min); menthol (6.2 min) and neomenthol (6.9 min) were achieved. The reaction products were separated by silica gel column chromatography using hexane as eluant and were characterized by comparison with authentic samples.

1.3. Optical purity

The optical purity of the isolated compounds were measured on a Perkin-Elmer 243 polarimeter in ethanol solvent ($C = 1$) at 20 ± 1 °C.

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