β-Cyclodextrin and Its Derivatives Mediate Selectivity in Reduction of (R)-(+)-Pulegone with Sodium Dithionite

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Abstract. Pulegone is reduced in two stages by sodium dithionite – first to menthone and later to epimeric menthols. The presence of β-cyclodextrin (BCD) and its derivatives resulted in more of the alcohols being formed. While the double bond was reduced predominantly in water, the ketone moiety was also reduced in a water–DMF mixture. A small percentage of menthone remained relatively unaffected in water–DMF even in the presence of BCD and its derivatives. Although no unreacted pulegone could be detected, exclusive alcohol formation was also not observed. Reduction of the double bond was found to be faster than that of the ketone.

Key words: (R)-(+)-pulegone, selectivity, 1 : 2 complex, menthone, menthol, neomenthol.

1. Introduction

The enzyme mimicking abilities of 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. 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. Such stereoselective reactions have been reported in the reduction of ketones [2], epoxidation of olefins [3] and cleavage of epoxides [4].

   In this communication we rehort the stereoselective effects of β-cyclodextrin (BCD) and its derivatives, in the sodium dithionite reduction of (R)-(+)-pulegone, and α,β-unsaturated carbonyl compound.

   Sodium dithionite is an inexpensive and readily available reducing agent, with a redox potential of −1.12 V, which is close to that of sodium borohydride (−1.24 V). Its lack of solubility in organic media has been overcome by the use of polar solvents or cosolvents or phase transfer catalysts [5]. In general, reduction of α,β-unsaturated ketones results in different types (viz. dihydroketones or saturated

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TABLE I. GC analyses of $Na_2S_2O_4$ reduction products of pulegone[a].

Solvent	Catalyst	Time (h)	Yield of ketone (%) (menthone)	Yield of alcohols (%)	Ratio of ketone/ alcohols	Ratio of menthol/ neomenthol
H_2O	uncatalysed	6	95.9	4.0	23.7	2.6
H_2O	BCD	6	83.6	16.4	5.1	4.7
H_2O	BCD-polymer	.6	88.6	11.4	7.8	2.4
H_2O	DM-BCD	6	62.4	37.6	1.7	2.9
H_2O : DMF	uncatalysed	6	47.4	52.5	0.9	2.7
H_2O : DMF	BCD	6	23.2	75.4	0.3	4.4
H_2O : DMF	BCD-polymer	6	36.2	63.6	0.6	2.8
H_2O : DMF	DM-BCD	6	10.3	89.4	0.1	3.2
H_2O : C_6H_6	DM-BCD	6	73.4	26.5	2.8	3.0
H_2O : C_6H_6	CTAB	6	14.3	84.0	0.2	18.6
H_2O : DMF	BCD	0.5	79.3	20.7	3.8	4.5
H_2O : DMF	BCD	1.0	73.2	26.7	2.7	4.5
H_2O : DMF	BCD	1.5	66.0	33.9	2.0	4.7
H_2O : DMF	BCD	2.0	59.6	40.1	1.5	4.8
H_2O : DMF	BCD	4.0	37.9	61.9	0.6	4.6
H_2O : DMF	BCD	6.0	23.2	75.4	0.3	4.4

[a]Unreacted pulegone was zero in all cases. Isomenthone, isomenthol and neoisomenthol were not detected.

alcohols) and yields of products, depending on the reaction conditions employed. The nature of the catalyst, reagent and the steric factors associated with the system decide the nature of the products formed. The competitive reduction of olefinic double bond and ketone function on one hand and olefinic double bond alone on the other, of (R)-(+)-pulegone in the presence and absence of BCD and its derivatives, with sodium dithionite in water, water–DMF and water–benzene was studied. The results obtained are summarised in Table I.

2. Experimental

The pulegone used was purchased from Aldrich Chemical Company, USA. Sodium dithionite from Merck (India) was of 80.4% purity (determined by titration of the iodine liberated from the reaction between known amount of $Na_2S_2O_4$ and iodate–iodide mixture against thiosulphate of known strength [6]). β-Cyclodextrins used were a gift from Amaizo Inc., USA. Heptakis-2,6-di-O-methyl-β-cyclodextrin (DM-BCD) and water-insoluble β-cyclodextrin–epichlorohydrin polymer were

prepared according to the procedure of Szejtli *et al.* [7] and Shaw *et al.* [8], respectively.

^{1}H-NMR spectra were recorded with a Varian 390 continuous wave 90 MHz NMR spectrometer, in CCl_4 solvent. GLC analyses were performed with a Hewlett-Packard 5730 A instrument, fitted with a carbowax 20M, 6 ft (183 cm) column, maintained at 110°C, with a 30 mL/min nitrogen flow rate. Optical rotations were measured using a Perkin-Elmer 243 polarimeter ($c = 10$, C_2H_5OH). UV-visible spectroscopic studies were carried out using a Shimadzu UV-240 spectrophotometer at 20 ± 1°C.

2.1. Reduction Reaction

A typical procedure employed was as follows. Water or water–DMF (1 : 1) or water–benzene (1 : 1) mixtures (25 mL), containing $NaHCO_3/Na_2S_2O_4$/pulegone (3.1 mmol) in molar ratios 18 : 9 : 1 and the appropriate catalyst (1 mol for BCD and its derivatives, 0.3 mol for CTAB) was heated at 100°C under nitrogen atmosphere and stirred vigorously for 6 h. The mixture was cooled, acidified, then extracted with ether, dried over Na_2SO_4 and concentrated. The reaction products obtained were analysed by GLC: pulegone ($R_T = 9.68$ min), menthone ($R_T = 4.02$ min), menthol ($R_T = 8.22$ min) and neomenthol ($R_T = 6.74$ min). The reaction products were separated by column chromatography on silica gel, using hexane as the eluent and were characterised by comparing their m.p., specific rotation $[\alpha]_D^{20}$, IR, ^{1}H-NMR and GLC data with those of authentic samples. The products of the reduction reactions were found to be optically pure. The formation of isomenthone (through epimerization of menthone) or isomenthol/neoisomenthol (reduction products of isomenthone) were not detected by GLC.

3. Results and Discussion

The reduction of pulegone in water, without any catalyst, gave rise to menthone along with a very poor yield of a mixture of epimeric alcohols (4.0%). Insolubility of the substrate in water retards the reaction for the formation of epimeric alcohols. However, the presence of BCD or water insoluble BCD–epichlorohydrin polymer (BCD-polymer) increased the alcohol yield to 16.4 and 11.4%, respectively, with a high selectivity with respect to menthol formation (menthol/neomenthol (M/N) ratio = 4.7 and 2.4, respectively). The alcohol yield was further enhanced in the presence of heptakis-2,6-di-*O*-methyl-BCD (DM-BCD) to a maximum of 37.6%. Solubilisation of pulegone–BCD complex in water facilitated the reaction with the water-soluble dithionite reagent, resulting in an enhanced yield. Higher yields in the presence of DM-BCD were probably due to its greater solubilizing effect on menthone. Although the solubility of DM-BCD is poor at 100°C, its menthone complex may be more soluble at 100°C. In general, it was observed that olefinic

double bond reduction was more favoured over both ketone and olefinic double bond reduction in water as solvent.

However, the addition of DMF as a cosolvent to water (1 : 1) drastically increased the yield of alcohols to 52.5%, in the uncatalysed reaction, with a M/N ratio of 2.7. The presence of BCD enhanced the yield of alcohols further to 75.4%, with a M/N ratio of 4.4, indicating its stereoselective influence on the reduction. Addition of BCD-polymer led to a heterogeneous condition which gave an alcohol yield of 63.6% with a M/N ratio of 2.8. The highest yield of alcohols (89.4%) was achieved only in the presence of DM-BCD, with a M/N ratio of 3.2. While DM-BCD in water gave predominantly menthone (62.4%), alcohols were formed predominantly in water–DMF (89.4%).

DM-BCD was also used in water–benzene (1 : 1), where it is soluble in both the solvents to different extents. This facilitates both complexation and reduction, occurring mainly in or near the organic phase, and also minimises the formation of sulfinites, products of a major side-reaction of dithionite in water [5]. Reduction was very slow, the alcohol yield being 26.5% with a M/N ratio of 3.0. A high yield of menthone (73.4%) was due to olefinic reduction being more favoured by DM-BCD than reduction of double bond and ketone functions, implying regioselective influence by DM-BCD. However, no unreacted pulegone could be detected by GC, the substrate conversion being 100%. However, an exceptionally high value for the M/N ratio of 18.6 was achieved with 84% yield of alcohols with cetyltrimethylammonium bromide (CTAB) which was employed as a phase transfer catalyst.

A water–benzene mixture was chosen because of the solubility of both DM-BCD and CTAB in the two solvents. Benzene was not employed as a replacement for DMF since the compounds exhibit different behaviour with cyclodextrins. While DMF is known to form ternary complexes with cyclodextrins and other guest molecules, benzene forms an insoluble and stable complex. Also DM-BCD cannot be compared with CTAB as a phase transfer catalyst. While CTAB distributes itself between two phases, being present at the interface, DM-BCD can be present in either of the solvents.

The time course of the reaction was studied in water–DMF in the presence of BCD, in order to find the selectivity and yield variations with time. It can be seen from Table I that menthone formation was very high in the initial stages of the reaction (regioselective). With progress in time, there was an increase in the yield of alcohols, with a corresponding decrease in the menthone formed. The M/N ratio of the alcohols formed was very high (stereoselective) and was found to remain constant throughout.

In essence, it could be inferred from the ketone/alcohols ratio (Table I), that pulegone is reduced in two steps. First it is reduced to menthone, which is further reduced to alcohols (Scheme 1). These two steps could be distinctly differentiated from each other, under appropriate experimental conditions (Table I). The presence of BCD and its derivatives resulted in more of the alcohols being formed. While the double bond was reduced in water, predominantly by dithionite, the ketone

Scheme 1.
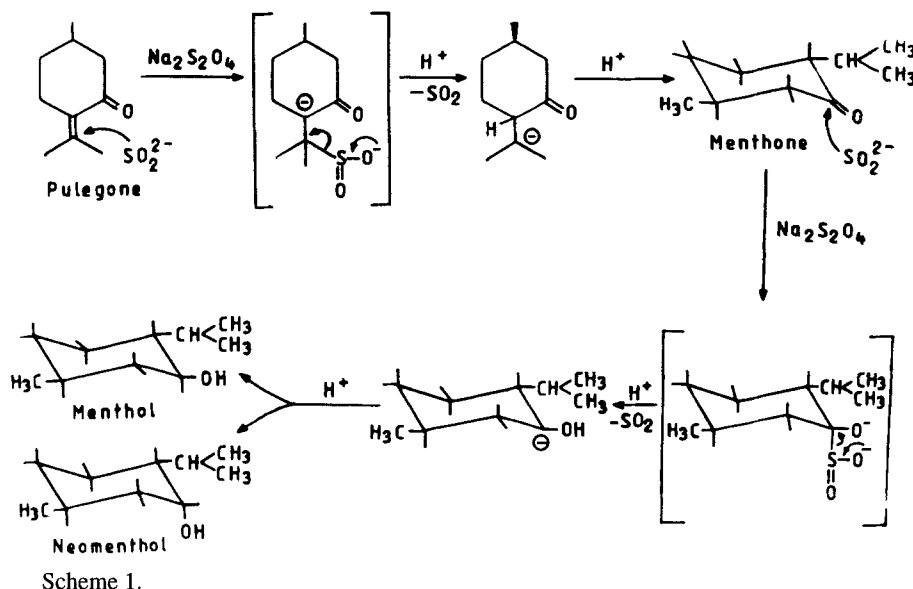
function was also simultaneously reduced in water–DMF mixture. However, a small percentage of menthone remained relatively unaffected in the latter solvent mixture even in the presence of BCD and its derivatives. Although no unreacted pulegone could be detected in all the cases studied, exclusive alcohol formation was also not observed. Also, while the reduction of the double bond appeared to be relatively fast, that of the ketone was slower. The reduction was also not completely chemoselective. The better yield of alcohols obtained in the presence of BCD and its derivatives, is probably due to the solubilization of pulegone/menthone in water, through the formation of an inclusion complex, in conformity with the steric requirement for inclusion.

UV-visible spectroscopic investigation of the interaction between pulegone and BCD showed that the addition of BCD to a water–ethanol (60 : 40) solution of pulegone $(1.9 \times 10^{-4}$ M) produced an increase in absorbance (hyperchromic) in the $\lambda_{\max}$ 257.5 nm $(\varepsilon = 7477, \pi-\pi^*$ transition of the conjugated α,β-unsaturated ketone) indicating formation of an inclusion complex. A plot of ΔA (difference in absorbance between free and complexed pulegone) against [BCD]/[pulegone] resulted in an asymptotic curve which did not show any change in absorbance beyond a ratio of 0.4–0.5 (Figure 1A and B) indicating that $\simeq 0.5$ equivalent of BCD to pulegone causes maximum change in A, the change being less thereafter. This also indicates that a 1 : 2 complex is formed between BCD and pulegone.

Evaluation of the binding constant value for the 1 : 2 complex was carried out using Scatchard analysis [9], Figure 1B. A plot of $\Delta A/(\Delta A_{\max} - \Delta A)$ [pulegone] (corresponding to $\bar{\nu}/S_f$) was plotted against $\Delta A/\Delta A_{\max}\rho$ (corresponding to $\bar{\nu}$) when a curve as shown in Figure 1B is obtained ($\Delta A_{\max}$ = maximum value for ΔA obtained from a plot of ΔA versus ρ = [BCD]/[pulegone]; $\bar{\nu}/S_f$ = fraction
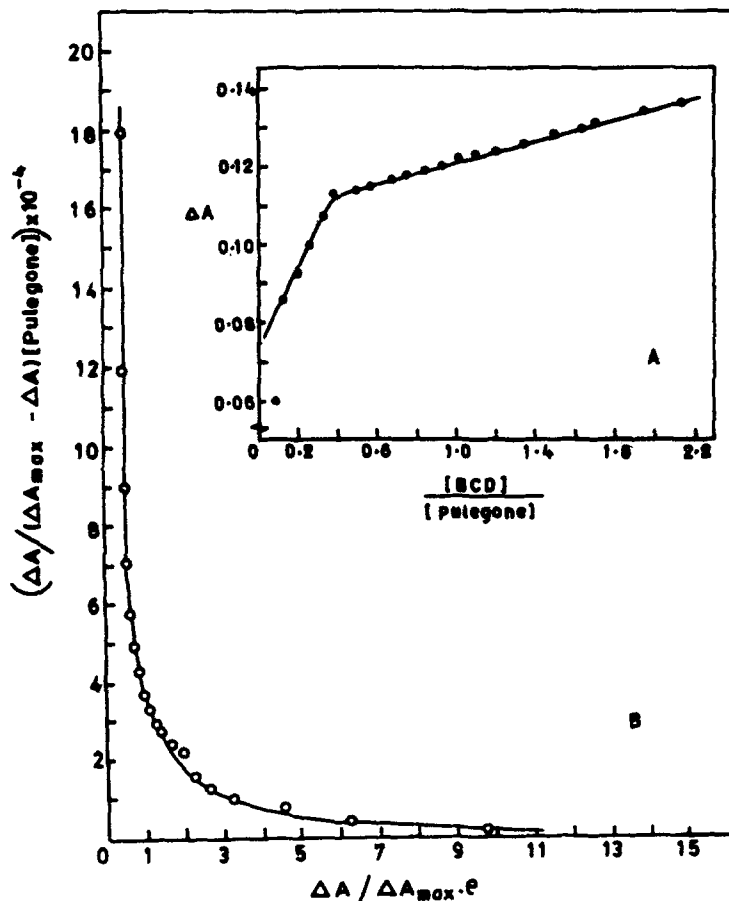
Fig. 1.   Determination of binding constant value for the 1 : 2 complex of BCD and pulegone.
[BCD] = 1.94×10^{-3} M; [pulegone] = 1.907×10^{-4} M. (A) Determination of stoichiometry of
the 1 : 2 complex (BCD : pulegone). (B) Evaluation of binding constant value from Scatchard
analysis. A plot of $\Delta A/(\Delta A_{max} - \Delta A)$ [pulegone] versus $\Delta A/\Delta A_{max} \cdot \rho$ was plotted where
the slope = $-1/K_D$ gave the binding constant value of $(1.5 \pm 0.3) \times 10^3$ M^{-1}.

of molecules bound to concentration of free ligand molecules). The curve can be
resolved into two components. The initial portion close to the ordinate corresponds
to a 1 : 2 (BCD : pulegone) complex formed at lower concentrations of BCD, and
the final portion close to the Y-axis probably represents a mixture of 1 : 1 and 1 : 2
complexes at higher BCD concentrations. The negative slope of the initial portion
is equal to $-1/K_D$, where K_D is the binding constant value for the 1 : 2 complex.
The calculated value was found to be $(1.5 \pm 0.3) \times 10^3$ M^{-1}.

An increase in the proportion of menthol in reactions catalysed by BCD and
its derivatives is due to the latters' capacity to provide a stereoselective binding
site. The normally hindered equatorial attack is made further difficult in the inclu-
sion complex, due to specific orientation of pulegone in the BCD cavity which

imparts hindrance to the attack of the reagent. It is proposed that an adduct formed (Scheme 1) due to the preference of the SO_2 dianion [5, 11] for the axial position (less hindered side) results in equatorial alcohol (menthol) being formed in a predominant amount. The stepwise electron transfer mechanism will not give rise to this observed stereoselectivity [10].

The best selective reduction of an olefinic double bond of conjugated enones [12], so far reported, involved the use of complex Li–Cu hydrides, iron carbonyls or $NaBH_4$ with prolonged reaction times, and that for the complete reductions [13] of the double bond and ketone function required difficult and more complex systems like borohydride associated with cryptands or ammonium species and Li–Cu hydride or iron carbonyls, that are not easy to prepare or handle.

In summary, sodium dithionite, if used under proper experimental conditions (solvent and catalyst), as described in this communication, is a versatile reducing agent for near selective double bond reduction of unsaturated conjugated carbonyl compounds like pulegone and can compete advantageously with other methods reported in the literature.

Acknowledgements

References

1. R. Fornasier, F. Reniero, P. Scrimin and U. Tonellato: *Macromol. Chem. Rapid. Commun.* **6**, 1 (1985).
2. S. Divakar, M. S. Narayan and A. K. Shaw: *Indian J. Chem.* **32B**, 387 (1993).
3. Y. Hu, A. Harada and S. Takahashi: *Synth. Commun.* **18**, 1607 (1988).
4. Y. Hu, M. Uno, A. Harada and S. Takahashi: *Chem. Lett.*, 797 (1990).
5. F. Camps, J. Coll and J. Guitart: *Tetrahedron* **42**, 4603 (1986).
6. A. I. Vogel: *A Text Book of Qualitative Inorganic Analysis*, 4th Edition, Longman, London, p. 382 (1979).
7. T. Szejtli, A. Liptak, I. Jodal, P. Gugedi, P. Nanasi and A. Narsmely: *Starch/Starke* **32**, 165 (1980).
8. P. E. Shaw and B. S. Buslig: *J. Agric. Food Chem.* **34**, 834 (1986).
9. S. Divakar and K. R. K. Easwaran: *Biophys. Chem.* **27**, 139 (1987).
10. A. V. Veglia and R. H. de Rossi: *J. Org. Chem.* **53**, 5281 (1988).
11. P. G. Gassman, O. M. Rasmy, T. O. Murdock and K. Saito: *J. Org. Chem.* **46**, 5457 (1981).
12. R. H. Mueller and J. G. Gillick: *J. Org. Chem.* **24**, 4647 (1978).
13. O. Louis-Andre and G. Gelbard: *Tetrahedron Lett.* **26**, 831 (1985).