Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **16:** 201–208, 1993.

Selective Hydroxymethylation of Guaiacol in the Presence of β-Cyclodextrin

RAMASWAMY RAVICHANDRAN and SOUNDAR DIVAKAR*
Organic Chemistry Section/Food Chemistry Department, Central Food Technological Research Institute, Mysore-570013, India.

(Received: 22 March 1993; in final form: 1 September 1993)

Abstract. Studies on the effect of β-cyclodextrin (BCD) and its derivatives on the selectivity in hydroxymethylation of guaiacol by formaldehyde was carried out. Fairly high selectivity with respect to isovanillyl alcohol formation was achieved. Significantly, the selectivity-enhancing effects of 2,6-di-*O*-methyl-BCD was much larger, giving rise to 22% more of isovanillyl alcohol formation than BCD and its polymer. UV, fluorescence, ^{1}H-NMR spectroscopic and potentiometric studies were also carried out to determine the orientation of guaiacol inside the BCD cavity.

Key words: Regioselectivity, hydroxymethylation, guaiacol-β-cyclodextrin complex.

1. Introduction

The design and synthesis of novel hosts and the study of their interaction with guests remain an active area of research in organic chemistry. In this regard, considerable interest has been focused on the role of BCD in organic synthesis [1]. The presence of BCD in reaction mixtures often leads to regio- and stereoselective organic reactions. This has been observed for the chlorination of anisole [2], formylation of phenols [3], hydroxymethylation of phenol [4] and in the synthesis of 4-hydroxybenzoic acid [5].

This paper reports the results of BCD-catalysed selective hydroxymethylation of guaiacol by formaldehyde.

2. Experimental

BCD was a gift from American Maize Products Company, USA, and was used without further purification. BCD-epichlorohydrin polymer and heptakis-(2,6-di-*O*-methyl)-BCD were prepared according to the procedure of Shaw *et al.* [6] and Szejtli *et al.* [7], respectively. Guaiacol, purchased from S.D. Fine Chemicals, India, was used after distillation once (110°C at 18 mm Hg).

A typical procedure employed for the reaction was as follows. Guaiacol/NaOH/HCHO in 1 : 3 : 10 molar proportions with the appropriate BCD catalyst (Table I) in 20 mL water was stirred at room temperature for three days. The reaction was

* Author for correspondence.

TABLE I. ^{1}H-NMR analysis of hydroxymethylation of guaiacol by formaldehyde.[a]

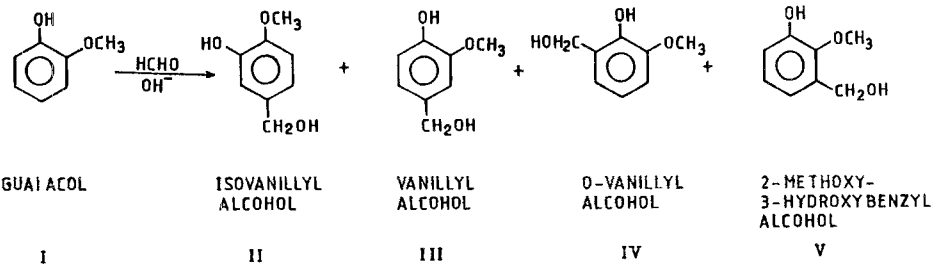
Sl No	Catalyst (molar ratio)	isovanillyl alcohol[b] (%)	Vanillyl alcohol[b] (%)	Yield of alcohols (%)
1	Uncatalysed	31.3	68.7	90
2	BCD(1)	34.0	66.0	>90
3	BCD(2)	40.0	60.0	>90
4	BCD(3)	43.7	56.3	71
5	BCD-Polymer(1)	35.3	64.7	88
6	Dimethyl-BCD(1)	53.2	46.8	74

[a] The results are an average of three experiments.

[b] The ratio of the signal areas of CH_2 protons of isovanillyl (4.75 ppm) and vanillyl alcohols (4.55 ppm) were employed to obtain the ratio of the alcohols formed. The yield was determined from peak areas of OCH_3 and CH_2 signals of the alcohols.

monitored by TLC (hexane : ethylacetate = 10 : 1). After the disappearance of guaiacol, the reaction mixture was treated with about 1 g of sodium metabisulphite to destroy the excess unreacted formaldehyde, followed by neutralisation with $2N$ sulphuric acid. It was then extracted with n-butanol. The crude reaction product so obtained was analysed by ^{1}H-NMR in DMSO-d_6/$CDCl_3$ on a Varian EM-390 continuous wave 90 MHz NMR spectrometer, in order to determine the product distribution. The yield of the alcohols and their relative proportions were determined from the NMR spectra. Isovanillyl alcohol (**II**) (3-hydroxy-4-methoxybenzyl alcohol) δ = 3.83 (s, 3H, $-OCH_3$), 4.75 (s, 2H, $-CH_2OH$), 4.8 (s, br, 1H, $-OH$), 6.5–7.1 (m, 3H, Ar–H); vanillyl alcohol (**III**) (4-hydroxy-3-methoxybenzyl alcohol) δ = 3.83 (s, 3H, $-OCH_3$), 4.55 (s, 2H, $-CH_2OH$), 4.8 (s, br, 1H, $-OH$), 6.5–7.1 (m, 3H, Ar–H).

Ultraviolet spectra were recorded on a Varian Superscan 3 spectrophotometer, scanning the region between 600–200 nm. An Aminco-Bowman spectrophotofluorometer was used for measuring fluorescence spectra. Both UV and fluorescence measurements were carried out by adding BCD solutions (1 mM) in a 1 : 1 mixture of ethanol and water and 0.1M bicarbonate buffer at pH 10.5. BCD was added in increasing amounts to a known volume of the fluorophor (6-p-toluidinylnaphthalene-1-sulfonic acid, TNS) until the maximum fluorescence intensity was attained. Guaiacol was then gradually added and the decrease in fluorescence intensity was determined. Excitation was at 364 nm and emission at 464 nm. The values were corrected for dilution.



Scheme I.

Potentiometric studies were carried out using a Control Dynamics pH meter fitted with an Ingold combination electrode. Titrations were carried out using 0.1N HCl and NaOH solution with 10 mL of 0.01M guaiacol, the ionic strength of which was maintained constant by the addition of 0.2M NaCl. Titrations were carried out in both the free and complexed states. Log [salt]/[acid] was plotted against pH and the pH value corresponding to log[salt]/[acid] = 0 gave the pK value.

^{1}H-NMR spectra were recorded on a Bruker HFX 270 MHz NMR instrument fitted with a Spectrospin magnet operating at 20°C and an Aspect 3000 computer. About 100 scans were collected for each spectrum. BCD (0.6M) was added in gradual amounts to a solution of the guest molecule (0.1M) and spectra were recorded both in DMSO-d_6 and D_2O.

3. Results

Table I identifies the product distribution of the reaction, under various conditions. Theoretically, four products are expected as shown in Scheme I. However, only isovanillyl alcohol (**II**) and vanillyl alcohol (**III**) were obtained in all cases. In a typical reaction without any catalyst (BCD), the ratio of the alcohols **II/III** was 31.3/68.7, with an overall yield of 90%. The addition of BCD, however, modified this ratio (Table I). Besides its increase with an increase in BCD concentration, an enhancement in yield was also observed. The largest value (43.7/56.3) was observed with a three times molar excess of BCD to guaiacol. This corresponds to an increase of 12.4% of isovanillyl alcohol, in comparison with that of the uncatalysed reaction. However, a high concentration of BCD (> 3 molar equivalents) causes a decrease in the yield of alcohols. The effect of BCD/epichlorohydrin polymer (water insoluble) was almost identical with that of BCD (one equivalent), in both selectivity as well as yield of alcohols formed. The most remarkable was the catalytic effect of heptakis-(2,6-di-*O*-methyl)-BCD, which gave a fairly high ratio of **II/III** (53.2/46.8), exhibiting a total increase of 21.9% of isovanillyl alcohol, in comparison to that of the uncatalysed reaction. However, this selectivity was at the expense of the yield, which was nevertheless still found to be good (74%).

It was found that polymeric products were formed when the reaction was prolonged or when excess acid was added during work up.

Structural studies were carried out in order to understand the orientation of the guaiacol molecule inside the BCD cavity. UV spectra of guaiacol showed absorption maxima at 274 nm ($n - \pi^*$ transition of the phenol group, $\varepsilon = 3563$) and 226.5 nm ($\pi - \pi^*$ transition of the phenyl group, $\varepsilon = 5876$) in 1 : 1 ethanol-water and 279.5 nm ($\pi - \pi^*$ transition of the phenol group, $\varepsilon = 2567$), 236.5 nm ($\varepsilon = 5819$) and 225 nm ($\pi - \pi^*$ transition of the phenyl group, $\varepsilon = 4771$) in 0.1M bicarbonate buffer at pH 10.5. The addition of BCD solution caused no change in intensity or position of this absorption. This was observed in both 1 : 1 ethanol-water mixture as well as bicarbonate buffer at pH 10.5. Similar investigations, using fluorescence spectroscopy, did not reveal much change in the fluorescence emission of the BCD-TNS complex on adding guaiacol. Complexation of guest molecule in aqueous solution by BCD involves a change in environment for the guest molecule from polar to nonpolar. The absence of significant change in both UV and fluorescence spectroscopy may probably indicate the formation of a weak complex between BCD and guaiacol.

However, pK values of the phenolic OH group of guaiacol in free and complexed states were found to be different. Guaiacol showed a decrease in pK value from 10.28 ± 0.1 (free) to 10.02 ± 0.1 in the presence of BCD. While organic acids exhibit an increase in pK value in the presence of BCD, phenols usually show a decrease in their pK values [1a]. The specific disposition of ionisable groups results in an increase or decrease of their pK values. Based on our studies with catechol, protocatechuic aldehyde, vanillin and eugenol (unpublished results) it can be surmised that an ionisable phenolic group exposed to the solvent gives rise to greater dissociation. This is also facilitated by the hydrogen bonding of the phenolate oxygen to the secondary hydroxyl groups of BCD. Hence the observed decrease in pK value.

^{1}H-NMR spectroscopy of the complex in DMSO-d_6 indicated a broadening of the OH group (as deduced from the ratio of the areas of OH to aromatic) of guaiacol on adding BCD, Table II. The chemical shift values of aromatic protons in general were not much affected. However, the signals did broaden, as evidenced from the observed reduced splitting. Among BCD protons, 2-OH and 3-OH, present at the wider end of the cavity, showed a slight upfield shift (0.02 ppm). Similarly, 6-OH, at the narrower end, showed a downfield shift (0.06 ppm). Other BCD protons were also affected to a lesser extent.

^{1}H-NMR spectra in D_2O were more informative (Figure 1 and Table II). The guaiacol H-5 signal showed a 0.06 ppm upfield shift on complexation. The methoxy group protons were little affected. Other aromatic protons (namely, H-3, H-4 and H-6) showed a 0.04 ppm upfield shift. However, the BCD protons showed significant shift. While H-5 showed 0.08 ppm upfield shift, H-2 and H-4 showed 0.03 and 0.04 ppm downfield shifts, respectively. Other protons (namely H-1 and H-6 a and b) showed very small (0.01–0.02 ppm) upfield shifts. An upfield shift of 0.04 ppm was observed for the H-3 protons. The ^{1}H-NMR data in D_2O clearly indicate that the phenyl ring of the guaiacol molecule is inserted almost into the middle of

TABLE II. ^{1}H-NMR data of the guaiacol-β-cyclodextrin system.[a]

	DMSO-d_6		D_2O	
	Free	Complex	Free	Complex
Guaiacol				
OH	8.90	8.94	—	—
OCH_3	3.75	3.74	3.84	3.83
H-3, H-4, H-6	6.77 (J = 9.8, 8.1, 8.9)	6.76 (J = 4.7, 6.9, 6.1)	6.94	6.90
H-5	6.90 (J = 5.5)	6.89 (J = 4.1)	7.03 (J = 3.1)	6.97 (J = 2.5)
BCD				
H-1	4.83	4.83	5.05 (J = 4.5)	5.04 (J = 3.1)
H-2	3.31	3.34 (J = 9.7, 9.0)	3.59 (J = 3.5, 10.02)	3.62 (J = 3.3, 10.02)
H-3	3.31	3.34	3.95 (J = 9.5)	3.91 (J = 9.4)
2-OH	5.80	5.78 (J = 6.7)	—	—
3-OH	5.74	5.72	—	—
H-4	3.60	3.63	3.57 (J = 10.06)	3.61 (J = 10.06)
H-5	3.60	3.63	3.85	3.77
H-6a&b	3.60	3.63	3.85	3.87
6-OH	4.45	4.53 (J = 5.3)	—	—

[a] Values for a 1 : 1 mixture of guaiacol and β-cyclodextrin.

the BCD cavity. Ring current effects of the phenyl ring on BCD protons confirm this. Substituents (namely, OH and OCH_3 groups) are present at the periphery, projecting outwards and exposed to the solvent.

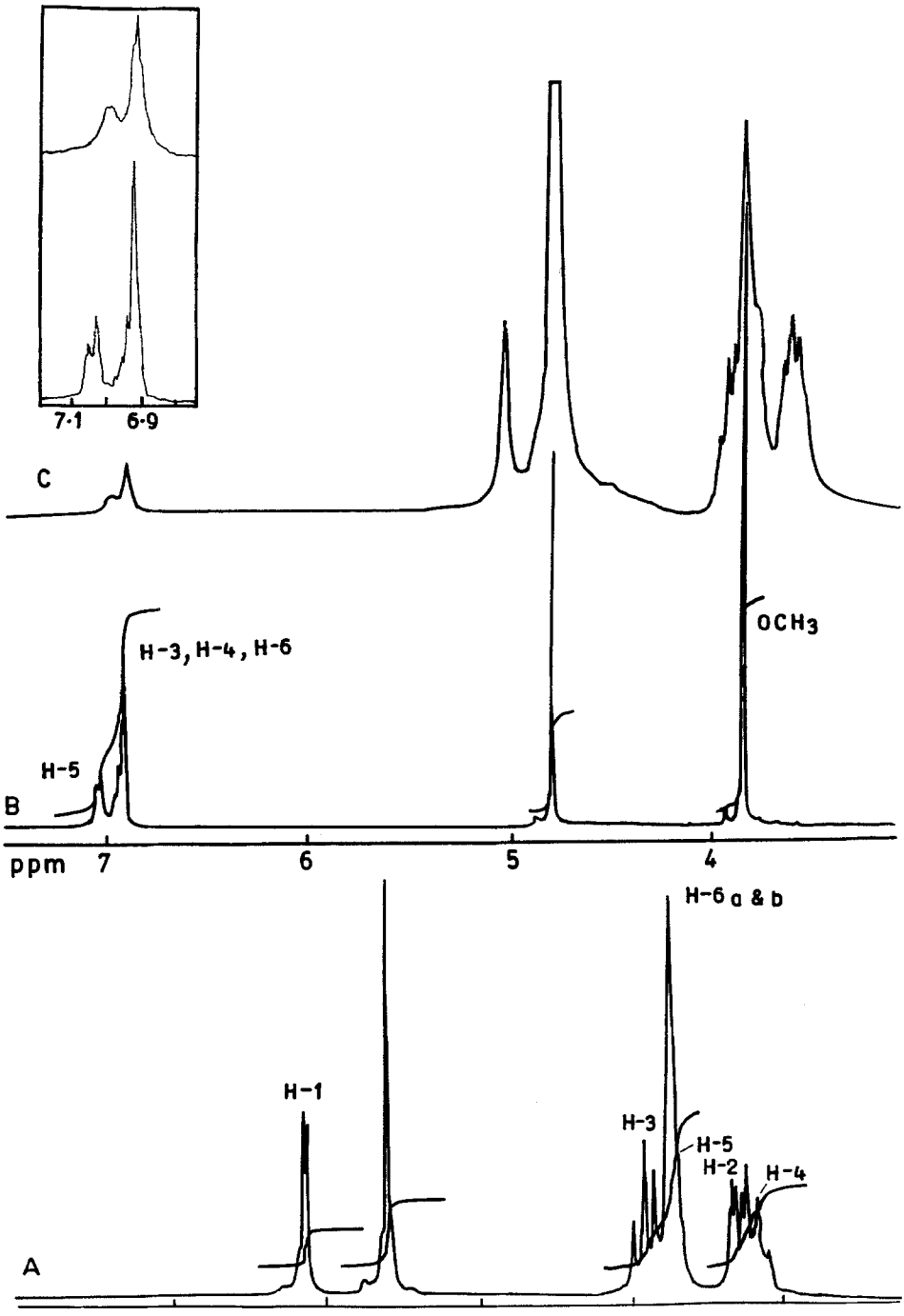


Fig. 1. ^{1}H-NMR spectra of guaiacol-BCD complex. A 1 : 1 complex of guaiacol and BCD (0.05M) was used. (A) BCD, (B) guaiacol; and (C) BCD-guaiacol complex. Inset – aromatic region expanded. (For instrumental conditions, see text.) Solvent – D_2O.

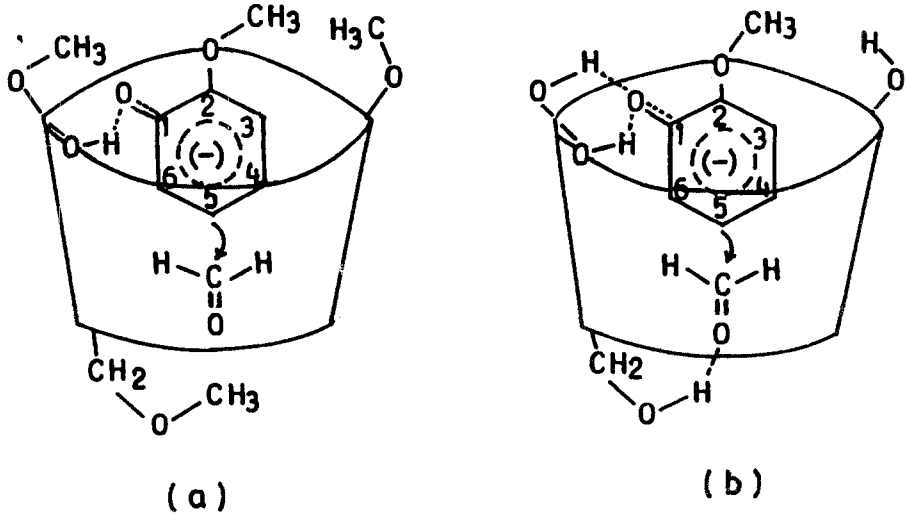


Fig. 2. Selectivity in hydroxymethylation of guaiacol. Orientation of guaiacol and formaldehyde in (a) heptakis-2,6-di-*O*-methyl-BCD and (b) BCD.

4. Discussion

The proposed mechanism for the present selective synthesis is depicted schematically in Figure 2. It has been well established that the rate constant for the formation of inclusion complexes with BCD is much greater for formaldehyde than for the phenolate ion [4]. At the same time, mechanistic studies carried out earlier [4], reveal that the BCD first forms a complex with formaldehyde, with subsequent inclusion of the phenolate ion.

β-Cyclodextrin is a macrocyclic compound consisting of seven α-1,4-linked D-glucopyranose units. It is also a very weak acid ($pK \simeq 12.1$, [1a]). Hence, in the presence of a three times molar excess of alkali, very few secondary hydroxyl groups (two out of fourteen on a statistical average) will be in the deprotonated state. Guaiacol, which is in the form of the phenolate ion, is oriented in such a manner inside the BCD cavity that only C-5 (*para* to $-OCH_3$) is exposed to attack by the already complexed formaldehyde molecule in preference to C-4. Structural studies carried out also point to solely such an orientation.

The positioning of guaiacol inside the BCD cavity is regulated by two factors: hydrogen bonding and steric interactions. Hydrogen bonding between the secondary hydroxyl protons of BCD and the quinone oxygen of guaiacol tilts the benzene ring such that C-5, which is *para* to $-OCH_3$, is exposed to attack by formaldehyde. This is once again aided by the steric interactions between the OCH_3 group of guaiacol and the OH groups at the rim of the BCD cavity (Figure 2b). This steric interaction is much more pronounced in the case of heptakis-2,6-di-*O*-methyl-BCD (Figure 2a) than in nonmethylated BCD molecules, including the polymer, and hence the greater selectivity observed in the methyl derivative.

Heptakis-2,6-di-*O*-methyl-BCD, which has a similar structure to hydroxypropyl-BCD, controls the orientation of formaldehyde inside the cavity and makes the attack more selective on the approaching C-4 or C-5 carbon atoms. The immobility of formaldehyde is more evident in the methyl derivative (where 6-OH is methylated along with 2-OH) than in BCD or its polymer, favouring attack at C-5 in preference to C-4. In the uncatalysed reaction the *para* position is more activated by the phenolate ion (also for steric reasons), which gives rise to more vanillyl alcohol, as expected.

Acknowledgements

The authors gratefully acknowledge the Director, CFTRI, for encouragement and facilities provided. RR thanks UGC for the award of his Junior Research Fellowship.

References

1. (a) M.L. Bender and M. Komiyama: *Cyclodextrin Chemistry*, Springer-Verlag, Berlin (1978). (b) J. Szejtli: *Cyclodextrins and Their Inclusion Complexes*, Akademia Kiado, Budapest (1982).
2. R. Breslow and P. Campbell: *J. Am. Chem. Soc.* **91**, 3085 (1969).
3. S. Divakar, M.M. Maheswaran and M.S. Narayan: *Indian J. Chem.* **31B**, 543 (1992) and references therein.
4. (a) M. Komiyama: *J. Chem. Soc. Chem. Commun.*, 651 (1988). (b) M. Komiyama: *J. Chem. Soc. Perkin Trans. I*, 2031 (1989).
5. M. Komiyama and H. Hirai: *J. Am. Chem. Soc.* **106**, 174 (1984).
6. P.E. Shaw and B.S. Buslig: *J. Agric. Food Chem.* **34**, 834 (1986).
7. J. Szejtli, A. Liptak, I. Jodal, P. Gugedi, P. Nanasi and A. Neszmelyi: *Starch/Stärke* **32**, 165 (1980).