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Regioselective monobromination of substituted phenols in the presence of β-cyclodextrin

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Abstract—Cyclodextrin acts as a restricting nanovessel to enhance regioselectivity in bromination of substituted phenols such as 3-nitrophenol, 2-chlorophenol, 3-chlorophenol, and 4-chlorophenol. In contrast to solution bromination, cyclodextrin facilitates regioselective monobromination and formation of polybrominated products are substantially reduced. Selectivities in brominations are also observed in water and in the solid state. The observed results are rationalized on the basis of specific modes of inclusion of substituted phenols inside the cyclodextrin cavity and find strong support from energy minimization studies and ^{1}H–^{1}H NOESY.

1. Introduction

The bromination of arenes is a reaction of immense synthetic and industrial importance, as the products are useful as pharmaceuticals, flame retardants, agrochemicals, speciality chemicals,[1] and synthetic intermediates capable of undergoing carbon–carbon bond formation via transmetalation reactions.[2] Brominated phenols, in particular, have broad applications in many synthetic organic transformations as starting precursors.[3] However, bromination of phenols is often unselective resulting in a mixture of mono- and polybrominated derivatives. Therefore, regioselective monobromination of phenols has evoked great contemporary interest. Although many reagents have been reported for selective brominations, they are not readily available and need to be freshly prepared. The reaction also requires harsh conditions. In this study, readily available, non-selective molecular bromine is used to achieve regioselective monobromination of some substituted phenols inside the cyclodextrin cavity both in organic as well as aqueous medium.

Cyclodextrins (CDs) are unique reaction nanovessels, forming inclusion complexes with many aromatic guest molecules and resulting in modified reactivities and remarkable selectivities.[4] These unique features have facilitated the use of CDs to mediate selective thermal[5] and photochemical[6] reactions. They also serve as enzyme models.[7,8] In general, CD functions by geometrically constraining the guest, stabilizing intermediates, and regulating the incoming reagents or reactive intermediates toward limited accessible sites thus improving the overall efficiency and selectivity.[9–13]

A pioneering work on the aromatic substitution reaction by Breslow and Campbell[14] has shown that CD alters the regioselectivity. Predominant *para*-chlorination of anisole[14] has been achieved in the presence of excess β-CD. Consequently, halogenation reactions inside the CD cavity have received extensive attention in recent years to achieve regio- and stereoselectivities.[15] Tee and Bennett[16] have made detailed and systematic studies on CD-mediated bromination of anisole and phenol and *para*-selectivity is achieved. Bromination of several simple aromatic substrates such as phenol,[16] anisole,[14,17] acetanilide,[17] phenyl acetate,[17] aniline, *N*-methylaniline, *N*,*N*-dimethylaniline, and *N*,*N*-diethylaniline[18] was studied inside CD cavity and appreciable regioselective brominations are observed. In most of the cases *ortho*/*para*-selectivity is altered and *para*-substituted products are predominant.

However, not much attention has been given to bromination of aromatic rings having more than one substituent. In an earlier report, iodination of *o*-chlorophenol, *o*-iodophenol, and *p*-iodophenol[19] and its kinetics were studied in the presence of β-CD. The rate of iodination of the CD-complexed substrate is faster than that of the free substrate and the *ortho*/*para* ratio decreases in the presence of CD. Recently, Easton et al.[17] have extended the bromination of anisole and acetanilide to derivatives having methyl groups in the 3-position. Both 3-methylanisole and 3-methylacetanilide are more reactive toward aromatic substitution. In bromination of 3-methylanisole and 3-methylacetanilide in the

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presence of α- and β-CD, the yield of monobromide increases. These results can be attributed to inclusion of the substrates within the CD cavity restricting access of the reagent to the adjacent methoxy and acetamido groups.

These interesting recent accounts prompted us to study the bromination of disubstituted phenols such as 3-nitrophenol **1**, 2-chlorophenol **2**, 3-chlorophenol **3**, and 4-chlorophenol **4** in the presence of β-CD. In these phenols, the phenolic hydroxy group strongly activates the aromatic ring while the nitro/chloro groups deactivate it. These substrates are chosen keeping in mind that an electron-releasing (–OH group) and electron-withdrawing groups are present in the same ring with their orientating influences opposing each other (**1**, **2**, and **4**). For comparison, the reactivity of 3-chlorophenol **3** is also studied (wherein the orientating influence of substituents reinforce each other).

2. Results and discussion

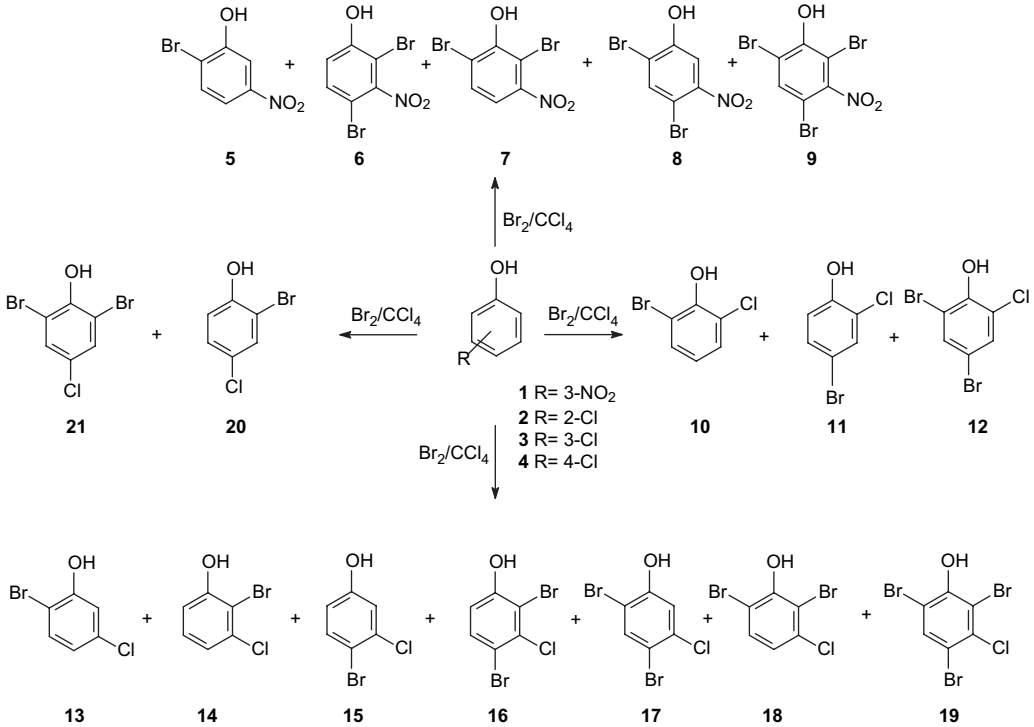
The structures of the various products obtained in the bromination of **1**–**4** using molecular bromine in different media are given in Scheme 1. The percentage conversion and yields of the various brominated products are presented in Tables 1–4.

Bromination of **1** in methanol was carried out with varying amounts of Br_2/CCl_4. The percentage conversion increases with an increase in bromine and polybrominated products like dibromides **6**–**8** and tribromide **9** are formed more significantly. In comparison, formation of monobromide **5** is less favored. With an increase in the reaction time as well as concentration of bromine, formation of tribromide **9** is more pronounced. Formation of di- and polybrominated products is rationalized due to the presence of the activating hydroxyl group. The observed results are in accordance with a previous report,[20] where NBS was used for bromination of **1**.

Table 1. Percentage conversion and product distribution in bromination of 3-nitrophenol **1** under various conditions[a]

Medium	Br_2/CCl_4	Time (h)	Conversion[b] (%)	Yield (%)		
				5	**6+7+8**	**9**
MeOH	1.0	12	19.8	12.7	44.4	42.9
MeOH	1.0	24	22.2	11.7	43.7	44.6
MeOH	2.0	24	40.5	11.1	34.9	54.0
MeOH	3.0	24	57.8	10.0	28.4	61.6
β-CD[c]	1.0	24	—	—	—	—
β-CD[c]	2.0	24	—	—	—	—
β-CD[d]	1.0	2	—	—	—	—
β-CD[d]	1.0	5	—	—	—	—
β-CD[e]	1.0	2	44.7	100	—	—
β-CD[e]	1.0	5	49.3	100	—	—
β-CD[e]	2.0	2	51.7	100	—	—
β-CD[e]	2.0	5	59.8	100	—	—
β-CD[e]	2.0	24	86.3	78.0	5.60	8.50
β-CD[f]	1.0	6	9.80	100	—	—
β-CD[f]	1.0	12	14.2	100	—	—
β-CD[f]	1.0	24	63.2	100	—	—
β-CD[f]	2.0	6	25.2	80.8	19.2	—
β-CD[f]	2.0	12	78.2	94.5	5.50	—
β-CD[f]	2.0	24	80.7	91.9	8.10	—
β-CD[f]	3.0	12	93.8	96.3	3.70	—
β-CD[f]	3.0	24	94.1	95.4	4.60	—

[a] Using Br_2/CCl_4 at room temperature. For structures of **5**–**9**, refer Scheme 1.
[b] Determined by GC; error limit ±3%.
[c] Reactions carried out in methanol.
[d] Reactions carried out in water.
[e] Reactions carried out in CCl_4.
[f] Reactions carried out in solid state.



Scheme 1. Products of bromination of 3-nitrophenol **1**, 2-chlorophenol **2**, 3-chlorophenol **3**, and 4-chlorophenol **4** using Br_2/CCl_4.

Table 2. Percentage conversion and product distribution in bromination of 2-chlorophenol **2** under various conditions[a]

Medium	Br_2/CCl_4	Time (h)	Conversion[b] (%)	Yield (%)		
				10	**11**	**12**
MeOH	1.0	5	98.7	16.4	61.8	21.6
MeOH	2.0	5	100	—	30.3	69.7
β-CD[c]	1.0	2	20.9	15.7	84.3	—
β-CD[c]	1.0	5	72.6	20.3	79.6	—
β-CD[c]	1.0	12	91.9	20.6	79.4	—
β-CD[d]	1.0	12	17.2	11.6	39.6	48.8
β-CD[d]	1.0	12	35.4	7.20	27.2	65.6
β-CD[e]	1.0	6	13.3	—	22.5	77.5
β-CD[e]	1.0	12	33.4	8.60	20.0	71.2
β-CD[e]	1.0	24	37.7	8.20	22.2	75.0

[a] Using Br_2/CCl_4 at room temperature. For structures of **10–12**, refer Scheme 1.
[b] Determined by GC; error limit ±3%.
[c] Reactions carried out in methanol.
[d] Reactions carried out in water.
[e] Reactions carried out in solid state.

In contrast, monobromination is the predominant pathway when bromination was studied in CD medium. A remarkable selectivity is observed in solution and also in the solid state bromination of **1** in the presence of β-CD. When CCl_4 is used, a significant regioselectivity toward monobromination product **5** is observed. Polybrominated products **6–9** were totally suppressed and monobromide **5** was formed as the exclusive product. Bromination was also carried out in different time intervals and with excess bromine (Table 1). In contrast to solution bromination in the absence of CD, the rate of the reaction is fairly enhanced with an increase in the concentration of CD. Even in the presence of excess bromine, **5** is formed as the only product. In the solid state reaction, similar selectivities were observed and the percentage conversion also increases with an increase in the reaction time.

Bromination of β-CD complex of **1** was also studied in polar solvents such as methanol and water. To our surprise, there was no reaction even after 24 h. Actually in polar solvents such as methanol and water a stable product was observed by GC and we thought it was a monobromo derivative. In

Table 4. Percentage conversion and product distribution in bromination of 4-chlorophenol **4** under various conditions[a]

Medium	Br_2/CCl_4	Time (h)	Conversion[b] (%)	Yield (%)	
				20	**21**
MeOH	1.0	2	71.1	62.3	37.7
MeOH	1.0	5	58.7	22.7	77.3
MeOH	2.0	2	100	10.4	89.6
MeOH	2.0	5	100	—	100
β-CD[c]	1.0	2	27.9	100	—
β-CD[c]	1.0	5	47.9	100	—
β-CD[e]	2.0	2	85.7	94.0	6.00
β-CD[e]	2.0	5	100	80.3	5.70
β-CD[d]	1.0	2	60.3	97.3	2.60
β-CD[d]	1.0	5	63.1	97.1	2.80
β-CD[e]	1.0	6	53.6	100	—
β-CD[e]	1.0	12	82.0	94.1	5.90
β-CD[e]	2.0	6	42.4	75.6	21.9
β-CD[e]	2.0	12	89.5	89.6	9.30

[a] Using Br_2/CCl_4 at room temperature. For structures of **20** and **21**, refer Scheme 1.
[b] Determined by GC; error limit ±3%.
[c] Reactions carried out in methanol.
[d] Reactions carried out in water.
[e] Reactions carried out in solid state.

mass spectra, M and M+2 peaks are observed (equal intensities) at 217 and 219 *m/z* values. However, when the ^1H NMR spectrum was recorded, peaks corresponding to the four aromatic protons of **1** were observed, ruling out the absence of ring bromination. Very careful comparison showed that all four aromatic protons are slightly shielded ($\Delta\delta_H$ values for the H2, H4, H5, and H6 protons of **1** and its bromo derivative are only 0.013, 0.009, 0.010, and 0.016, respectively). These interesting observations have prompted us to propose that the hypobromide of **1** (Fig. 1) is formed as a stable isolable intermediate and this is much more significant in polar solvents.

The observed regioselectivity in the presence of β-CD is rationalized by proposing specific modes of inclusion of **1** inside the β-CD cavity. Schematic representation of various possible modes of inclusion of **1** in β-CD is given in Scheme 2 (modes **1a** and **1b**). In mode **1a** (which is more favored), the position *ortho* to the hydroxyl group is better

Table 3. Percentage conversion and product distribution in bromination of 3-chlorophenol 3 under various conditions[a]

Medium	Br_2/CCl_4	Time (h)	Conversion[b] (%)	Yield (%)						
				13	**14**	**15**	**16**	**17**	**18**	**19**
MeOH	1.0	2	62.1	32.2	10.9	56.2	—	—	—	—
MeOH	1.0	5	98.7	28.9	7.60	49.9	4.40	5.90	3.30	—
MeOH	2.0	2	100	22.1	2.70	41.9	11.8	11.2	6.40	3.90
MeOH	2.0	5	100	—	—	7.10	22.7	27.9	—	42.3
β-CD[c]	1.0	2	96.2	1.70	0.70	97.3	—	—	—	0.30
β-CD[c]	2.0	2	80.0	6.50	—	80.8	8.00	—	—	4.70
β-CD[d]	1.0	2	65.2	9.20	6.10	52.0	9.20	12.4	2.20	8.80
β-CD[d]	1.0	5	80.1	18.9	8.90	56.0	5.70	7.90	2.60	—
β-CD[e]	1.0	6	13.1	19.8	—	80.2	—	—	—	—
β-CD[e]	1.0	12	77.3	16.4	7.60	76.0	—	—	—	—
β-CD[e]	1.0	24	88.1	19.6	7.40	73.0	—	—	—	—
β-CD[e]	2.0	6	29.5	48.7	—	19.8	31.5	—	—	—
β-CD[e]	2.0	12	44.5	36.5	—	17.6	31.6	5.10	—	9.20

[a] Using Br_2/CCl_4 at room temperature. For structures of **13–19**, refer Scheme 1.
[b] Determined by GC; error limit ±3%.
[c] Reactions carried out in methanol.
[d] Reactions carried out in water.
[e] Reactions carried out in solid state.

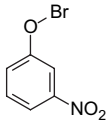
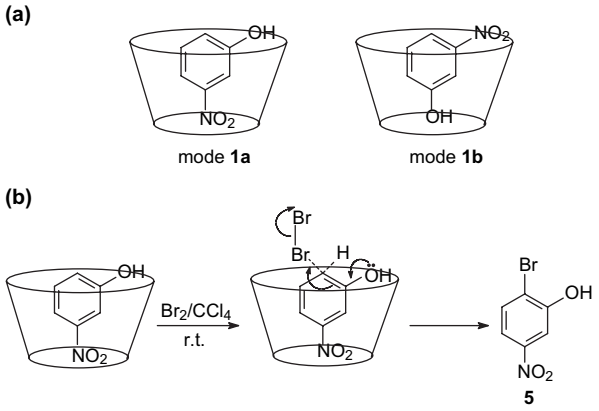


Figure 1. Hypobromite of 3-nitrophenol **1**.

exposed for bromination and approaches to other sites are sterically hindered by the CD cavity. The observed selectivity is also supported by molecular modeling data (Table 5), where **1a** has the minimum complexation energy than the other mode of inclusion, **1b**. This selectivity in bromination effectively illustrates the utility of β-CD, which limits polybromination, even in the presence of excess bromine.



Scheme 2. (a) Possible modes of inclusion of **1** inside β-CD cavity. (b) Mechanism of bromination of **1** in the presence of β-CD.

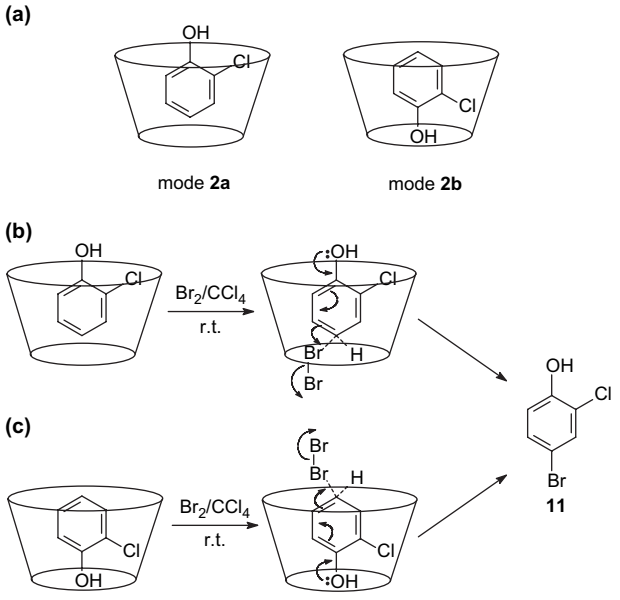
The above observed selectivity in the bromination of **1** prompted us to extend the studies to other substituted phenols, namely 2-, 3-, and 4-chlorophenols. Solution bromination of 2-chlorophenol **2** was carried out in methanol medium at various time intervals and with excess bromine. A mixture of monobromides **10** and **11** along with dibromide **12** were obtained. With an increase in reaction time, monobromides undergo further bromination and consequently the yield of dibromide increases. In fact, dibromide **12** was formed as the only product in the presence of excess bromine. However, bromination of **2** in the presence of β-CD in methanol resulted in selective bromination and **11** was obtained as the major product (Table 2) along with a small amount of **10** and formation of **12** was totally suppressed. When the same bromination was carried out in water, a dramatic change in selectivity was observed. In contrast to methanol, formation of monobromides **10** and **11** decreased in the presence of CD, and dibromide **12** was the major product even with an equimolar amount of bromine. When bromination was carried out in the solid state, the selectivity was totally altered and dibromide **12** was formed as the major product even in an equimolar concentration of bromine and the yield of monobromides **10** and **11** decreased. This may be attributed to the increase in the local concentration of bromine around the β-CD complex of **2** in the solid state.

Table 5. Complexation energies (ΔE) in kcal/mol for 1:1 complexes of **1**–**4** obtained from energy minimization studies

Substrate	Energy[a]	
	Mode **a**	Mode **b**
β-CD/**1**	−26.53	−22.96
β-CD/**2**	−23.87	−22.34
β-CD/**3**	−20.79	−19.10
β-CD/**4**	−25.27	−20.22

[a] $\Delta E_{complex}-\Delta E_{host}-\Delta E_{guest}$ obtained by CVFF force field. RMS derivative for each substrate of 0.001 is achieved.

The observed selectivity of bromination of **2** in the presence of β-CD was also explained by the specific modes of inclusion of **2** inside the β-CD cavity (modes **2a** and **2b**, Scheme 3). Molecular modeling studies indicate that both modes are probable with the former slightly more stable (Table 5). In both modes of inclusion the *para*-position of the hydroxyl group of **2** is readily available to bromine attack. The *ortho*-position is hindered by the CD cavity and this causes predominant formation of **11** along with a small amount of **10**.



Scheme 3. (a) Possible modes of inclusion of **2** inside β-CD cavity. (b) Mechanism of bromination of **2** in the presence of β-CD via mode **2a**. (c) Mechanism of bromination of **2** in the presence of β-CD via mode **2b**.

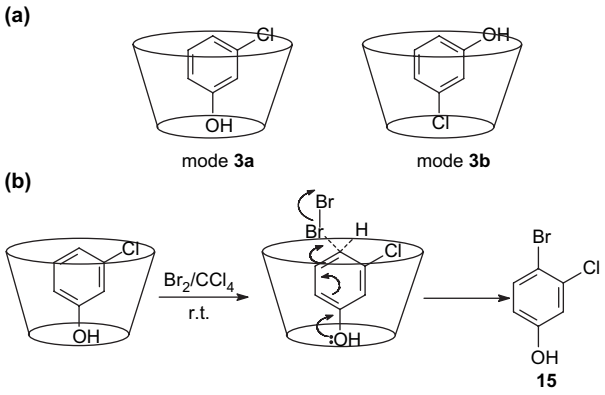
In bromination of **2**, carried out in water and also in the solid state, an improved yield of dibromide **12** was observed. This may be attributed to (a) the poor electron-withdrawing ability of the chloro group (compared to the nitro group of **1**) with consequent increase in reactivity and (b) the increase in local concentration of bromine near the substrate in the solid state bromination. Thus, the results demonstrate that, with substrate **2**, the orientation and reactivity of the hydroxyl group dominate and the chloro substituent has little effect.

Methanol-mediated bromination of **3** leads to mixtures of monobromides **13**, **14**, and **15**, dibromides **16**–**18**, and tribromide **19**. When carried out with an equimolar amount of bromine, monobromides **13**–**15** were formed with a small amount of a mixture of dibromides **16**–**18**. At higher concentration of bromine, dibromides **16** and **17** and tribromide **19** were formed as major products (Table 4).

An impressive regioselectivity is also observed in solution as well as in the solid state bromination of **3** in the presence of β-CD. In the bromination of **3** in methanol in the presence of β-CD, monobromide **15** was formed as the exclusive product

along with trace amounts of monobromides **13** and **14**. Compared to solution bromination, the formation of dibromides was totally suppressed. Compound **15** is the exclusive product, even at higher concentration of bromine (Table 3). In aqueous medium, the same selectivity was maintained and monobromide **15** was formed as the major product and polybromides were totally suppressed. The same trend is also observed when the bromination was carried out in the solid state. However, the percentage conversion was lower in the solid state. With excess bromine, formation of dibromide **16** increased along with monobromides **13** and **14**.

Regioselectivities observed in **3** are also rationalized by specific modes of complexation of **3** inside the β-CD cavity. As in other cases, here also two types of inclusion are possible (modes **3a** and **3b**, Scheme 4). Molecular modeling studies (Table 5) support that mode **3a** is slightly more favored as it has the lower complexation energy than mode **3b**. In mode **3a** the hydroxyl group is penetrating into the β-CD cavity and the position *ortho* to chlorine is more exposed in the wider secondary hydroxyl side of CD. Bromination at this position (Scheme 4) leads to the predominant formation of **15**, which is also in accordance with the mesomeric electron release by chloro and hydroxyl groups.

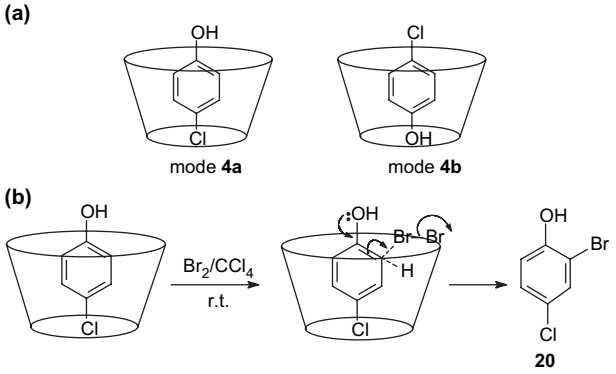


Scheme 4. (a) Possible modes of inclusion of **3** inside β-CD cavity. (b) Mechanism of bromination of **3** in the presence of β-CD.

Bromination is also extended to **4**, in which the functional groups are *para* to each other and their orientating influences oppose each other, which limit the number of possible products. Methanol-mediated solution bromination gives monobromide **20** and dibromide **21**.

Dibromide **21** was formed as the only product at higher bromine concentration. A significant selectivity was observed in the presence of β-CD/methanol-mediated bromination. Monobromide **20** was formed as the exclusive product. Even at higher concentration of bromine, **20** was formed as the major product (Table 4). When the reactions were carried out in water as well as in the solid state, the selectivities were maintained. Thus, compared to solution bromination, in the CD-mediated reaction, formation of **20** is increased and **21** is totally suppressed.

This observed selectivity is rationalized by specific modes of complexation of **4** inside the β-CD cavity. Molecular modeling studies show that mode **4a** is energetically preferred than mode **4b** (Scheme 5 and Table 5). Energy-minimized values for two possible modes with substrates **1**–**4** in the presence of CD are given in Table 5. From the energy minimization values, modes **a** (**1**–**4**) are more favorable, which also rationalize the observed regioselectivities in all the cases. The corresponding energy-minimized modeling structures for modes **a** (**1**–**4**) are given in Figure 2.



Scheme 5. (a) Possible modes of inclusion of **4** inside β-CD cavity. (b) Mechanism of bromination of **4** in the presence of β-CD.

To gain insight into the strength of binding of the brominated products, complexation energies of their 1:1 β-CD complex are also calculated and the values are presented in Table 6. A comparison of the values with that of the starting phenols **1**–**4** reveals that when the bromo group enters into the *ortho*-position to hydroxyl group (which is the predominant product with substrates **1** and **4** yielding **5** and **20**, respectively), the complexation energies are higher in the product. This may be rationalized by proposing that intramolecular hydrogen bonding now occurs between bromo and hydroxyl groups in the products, which weaken the intermolecular hydrogen bonding between the phenolic hydroxyl group and cyclodextrin hydroxyl groups.

When bromine enters into *para*-position (which is the major product with **2** and **3** yielding **11** and **15**, respectively), complexation energies of products are either comparable (with **11**) or lower (with **15**). Hence it is likely that in these cases both hydroxyl and bromo groups may enter into intermolecular hydrogen bonding with both rims of the cyclodextrin. With dibromo derivatives, lower complexation energies are obtained, reflecting their greater stability inside the cyclodextrin cavity, which may be due to their increased acidity upon bromination with a concomitant increase in hydrogen bonding.

The results observed from molecular modeling studies find strong support from the ^{1}H–^{1}H NOESY results. Two-dimensional NMR spectroscopy has recently become an important method for the investigation of the interaction between host CDs and guest molecules. In these aspects, the mode of inclusion of substrate **1**–**4** inside the CD is unequivocally assigned based on NOESY. The β-CD complex of 3-nitrophenol **1** shows a cross peak ‘a’, due to the interaction of H5 proton of β-CD with H5 and H6 protons of **1** (Fig. 3(i)). This confirms the polar nitro group is deeply penetrated inside the hydrophobic cavity shown in Scheme 2. Figure 3 (ii) shows NOE spectra of β-CD complex of 2-chlorophenol **2**, in which the cross peaks ‘b’ and ‘c’ show the interaction between H3, H5, and H6 of **2** with CD’s H3 and H5 protons. A clear cross peak ‘d’ is observed in

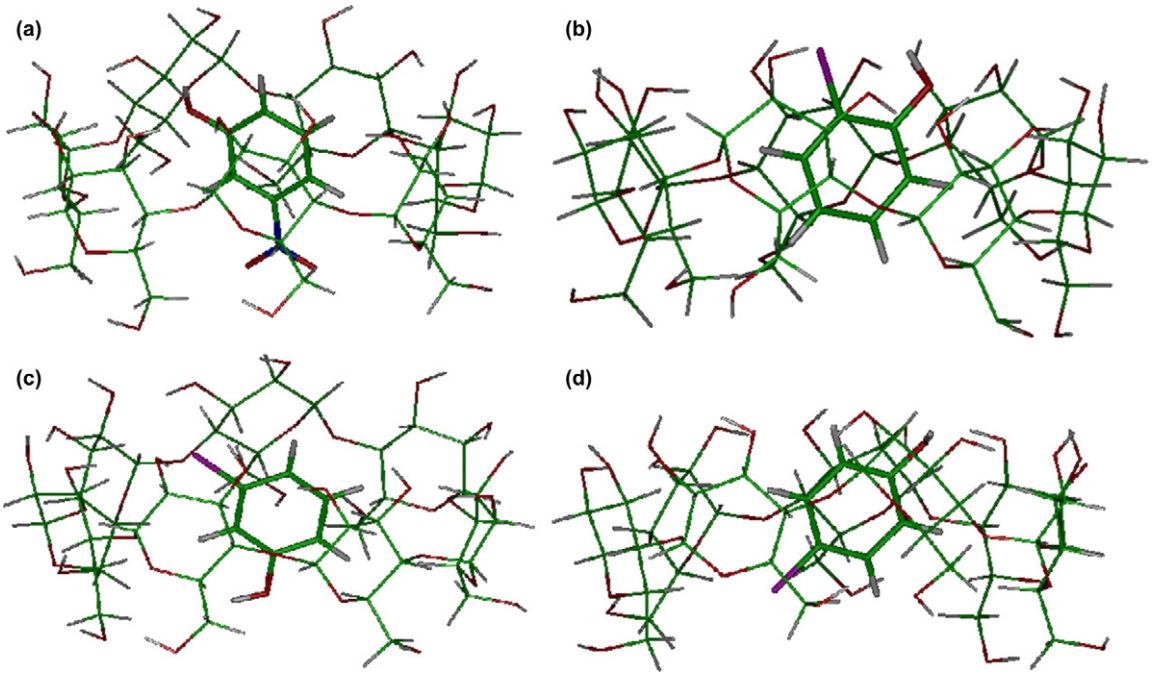


Figure 2. CVFF-optimized β-CD inclusion complexes: (a) 3-nitrophenol (mode **1a**), (b) 2-chlorophenol (mode **1b**), (c) 3-chlorophenol (mode **1c**), and (d) 4-chlorophenol (mode **1d**).

Table 6. Complexation energies (ΔE) in kcal/mol for 1:1 β-CD complex of **1**–**4** and their brominated products **5**–**21**[a] obtained from energy minimization studies

Monobromide	Energy[b]	Dibromide	Energy[b]	Tribromide	Energy[b]
5	−24.28	**6**	−28.53	**9**	−30.49
		7	−27.72		
		8	−27.09		
10	−22.84	**12**	−24.22		
11	−22.03				
13	−22.85	**16**	−22.19		
14	−21.59	**17**	−22.75		
15	−23.10	**18**	−22.85		
20	−24.62	**21**	−24.49		

[a] For structures of **1**–**21**, refer Scheme 1.
[b] $\Delta E_{complex}-\Delta E_{host}-\Delta E_{guest}$ obtained by CVFF force field. RMS derivative for each substrate of 0.001 is achieved.

3-chlorophenol **3** with CD, indicates the strong correlation between CD's H3 and H5 with H2 of **3** and cross peak 'e' H5 of CD's with H5, H6, and H2 of **3** (Fig. 3 (iii)). These cross peaks confirm hydroxyl group of **3** is included inside the cavity and chloro group is focusing in the secondary side. Similarly cross peaks 'f' and 'g' are observed due to the interaction of CD's H3 and H5 protons with H2 and H3 protons of **4**, respectively (Fig. 3(iv)).

3. Conclusions

A mild and efficient protocol for the regioselective bromination of substituted phenols **1**–**4** has been achieved by employing CD as a reaction vessel (even with the non-selective brominating agent Br_2/CCl_4) both in aqueous and organic media. The CD cavity provides an effective protection to the guest controlling the approach of bromine toward the accessible sites in substrates. In addition, β-CD complexation has also resulted in regioselective monobromination unaffected by di- and tribromo derivatives in all these substituted phenols even in the presence of excess bromine. It is also interesting to note that electronic effects, which are usually dominant in phenol bromination, play a less significant role when the substrates **1**–**4** are included inside the β-CD cavity.

4. Experimental

4.1. Materials

β-Cyclodextrin (Aldrich) is used as received. 3-Nitrophenol (Merck), 2-chlorophenol (Aldrich), 3-chlorophenol (Fluka), 4-chlorophenol (Merck), and bromine (Merck) were used as received without further purification. Stock solution of bromine (Merck) was prepared by dissolving 6.25 mL of bromine in 100 mL of CCl_4 and making up to 250 mL in a standard measuring flask. 1:1 CD complex is prepared by mixing an equimolar amount of phenols (**1**–**4**) and β-CD, stirred for 12 h, filtered, and washed with small amount of ether to remove any uncomplexed substrate. This complex was dried in an air oven at 50 °C for 6 h.

Complex formation of the substrates **1**–**4** with β-CD was inferred by calculating the formation constants (K_f) using Benasi–Hildebrand[22] method for **1**–**4**. The formation constant (K_f mol^{-1} dm^3) for **1**, **2**, **3**, and **4** are 386, 202, 139, and 106, respectively.

Proton magnetic resonance (^1H NMR) and NOESY spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$/DMSO-d_6 using TMS as an internal standard. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. The percentage conversion and relative yield of the final products are carried out by using gas chromatography (Shimadzu GC-17A model, ZB-5

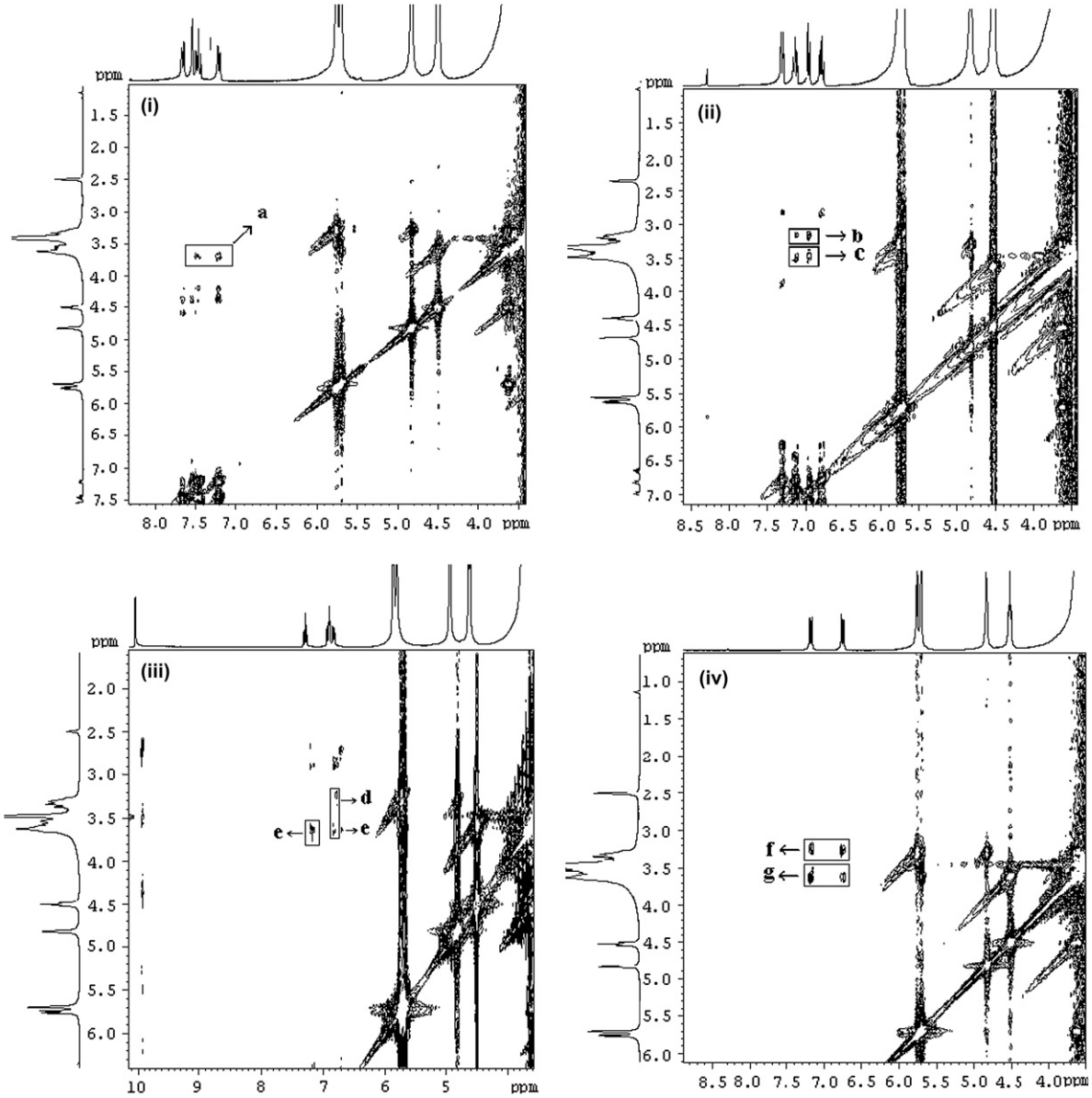


Figure 3. ^{1}H–^{1}H NOESY spectra (300 MHz, in DMSO-d_6) of β-CD complex of (i) 3-nitrophenol **1**, (ii) 2-chlorophenol **2**, (iii) 3-chlorophenol **3**, and (iv) 4-chlorophenol **4**.

(10%) capillary column with FID detector using high purity nitrogen as carrier gas). GC–MS were recorded on Finnigan GC–MS with RTX5-MS capillary column and high purity helium as carrier gas.

4.2. Energy minimization studies

Energy minimization calculations[21] are carried out for all the substituted phenols **1–4** and their brominated products **5–21** in the presence of β-CD using Insight II Discover program in IRIX system. Calculations are done in a vacuum and structures are minimized using CVFF force field and RMS derivative 0.001 is achieved in each case.

4.3. General procedure for bromination of substrates 1–4 in solution

Bromine (0.5 mmol) in CCl_4 stock solution was added slowly by dropwise to the substrate (0.5 mmol) in 5 mL of methanol with stirring for the specified time as in Tables 1–4 at room temperature. After completion of the reaction, the excess of bromine is quenched completely by the addition of excess $NaHSO_3$, and the product was extracted by chloroform and analyzed by capillary GC. All brominations are carried out in bulk and products are separated by column chromatography (pet. ether/ethyl acetate 9:2) and analyzed using ^{1}H NMR spectroscopy and other products are identified by GC–MS.

4.4. General procedure for bromination of β-CD complexes of 1–4

One hundred milligrams of the solid 1:1 β-CD complex of **1–4** is dissolved in 5 mL of water/MeOH/CCl_4. An equimolar amount of bromine in CCl_4 stock solution was added dropwise with continuous stirring at room temperature for a period of time as in Tables 1–4. After completion of the reaction, excess of bromine was removed by addition of

excess $NaHSO_3$ and complex was dissolved in excess of water, the products extracted with hot $CHCl_3$, and products were analyzed by GC. In solid state bromination the procedure is followed in the absence of solvent.

4.4.1. 2-Bromo-5-nitrophenol (5). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* 8.7 Hz, 1H), 7.71 (dd, *J* 8.7 and 2.4 Hz, 1H), 7.87 (d, *J* 2.4 Hz, 1H); GC–MS *m*/*z* 216.9 (M), 218.9 (M+2).

4.4.2. 2,4-Dibromo-3-nitrophenol (6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* 8.7 Hz, 1H), 7.37 (d, *J* 8.7 Hz, 1H); GC–MS *m*/*z* 296.6 (M), 298.6 (M+2).

4.4.3. 2,6-Dibromo-3-nitrophenol (7). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* 8.1 Hz, 1H), 7.68 (d, *J* 8.1 Hz, 1H); GC–MS *m*/*z* 296.6 (M), 298.6 (M+2), 300.4 (M+4).

4.4.4. 2,4-Dibromo-5-nitrophenol (8). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.68 (s, 1H); GC–MS *m*/*z* 296.9 (M), 298.9 (M+2).

4.4.5. 2,4,6-Tribromo-3-nitrophenol (9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H); GC–MS *m*/*z* 375.0 (M), 377.0 (M+2).

4.4.6. 2-Bromo-6-chlorophenol (10).[23] GC–MS *m*/*z* 207.5 (M).

4.4.7. 4-Bromo-2-chlorophenol (11). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* 2.4 Hz, 1H), 7.27 (dd, *J* 8.7 and 2.4 Hz, 1H), 6.89 (d, *J* 8.7, 1H); GC–MS *m*/*z* 207.8 (M).

4.4.8. 2,4-Dibromo-6-chlorophenol (12). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* 2.4 Hz, 1H), 7.45 (d, *J* 2.4 Hz, 1H); GC–MS *m*/*z* 286.5 (M), 290.0 (M+4).

4.4.9. 2-Bromo-5-chlorophenol (13). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* 8.7 Hz, 1H), 6.81 (dd, *J* 8.7 and 2.4 Hz, 1H), 7.03 (d, *J* 2.4 Hz, 1H); GC–MS *m*/*z* 207.9 (M), 209.8 (M+2).

4.4.10. 2-Bromo-3-chlorophenol (14).[23] GC–MS *m*/*z* 207.9 (M), 209.8 (M+2).

4.4.11. 4-Bromo-3-chlorophenol (15). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, *J* 3 Hz, 1H), 7.41 (d, *J* 8.7 Hz, 1H), 6.65 (dd, *J* 8.7 and 2.7 Hz, 1H); GC–MS *m*/*z* 207.9 (M), 209.8 (M+2).

4.4.12. 2,4-Dibromo-3-chlorophenol (16). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* 8.7 Hz, 1H), 6.63 (d, *J* 8.7 Hz, 1H); GC–MS *m*/*z* 285.9 (M), 287.9 (M+2), 290.3 (M+4).

4.4.13. 2,4-Dibromo-5-chlorophenol (17). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.14 (s, 1H); GC–MS *m*/*z* 285.9 (M), 287.9 (M+2), 290.3 (M+4).

4.4.14. 2,6-Dibromo-3-chlorophenol (18). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* 8.7 Hz, 1H), 6.85 (d, *J* 8.7 Hz, 1H); GC–MS *m*/*z* 286.0 (M), 287.9 (M+2), 290.3 (M+4).

4.4.15. 2,4,6-Tribromo-3-chlorophenol (19). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 1H); GC–MS *m*/*z* 366.0 (M), 368.0 (M+2), 369.6 (M+4).

4.4.16. 2-Bromo-4-chlorophenol (20). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.18 (d, *J* 8.7 Hz, 1H), 6.94 (d, *J* 8.7 Hz, 1H); GC–MS *m*/*z* 207.9 (M), 209.7 (M+2).

4.4.17. 2,6-Dibromo-4-chlorophenol (21). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H); GC–MS *m*/*z* 285.9 (M), 287.9 (M+2), 290.3 (M+4).

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23. As these two brominated products (**10** and **14**) are formed in poor yield, they are identified from their mass values from GC–MS analysis.