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# Selectivity in Bromination of Aniline and N-Substituted Anilines Encapsulated in β-Cyclodextrin

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***Abstract***: In contrast to the conventional bromination, aniline and N-methylaniline encapsulated in β-Cyclodextrin (β-CD) give ortho-bromoaniline and para-bromo-N-methylaniline respectively in larger yield. The results are explained on the basis of mode of complexation between β-CD and anilines.

## INTRODUCTION

A nonreducing cyclic oligosaccharide, β-cyclodextrin (β-CD) is a bottomless bucket shaped molecule composed of seven glucopyranose units, with a hollow hydrophobic cavity and peripheral hydroxyl groups that provide a chiral binding site capable of including selected organic guest molecules and in some cases catalyses the reactions of the included guest molecules.[1,2] Complexes of 1:1 stoichiometry are predominently formed. The interior of the torus of the CD molecule is moderately non-polar and the complexes are water soluble since all free hydroxyl groups of the glucose molecules are on the outside of the ring. The stability of the inclusion complexes and the selectivity in the reaction strongly depends on the size, shape and hydrophobicity of the guest molecules.[3]

The most interesting property of the CDs, which is of our current interest,[4] is that they can lead to the selectivity of organic reactions. In this respect, it has been reported that, in chlorination of anisole[5] by hypochlorous acid, addition of α-CD increases the para/ortho ratio. A very high selectivity for the para-position of phenol was observed in the carboxylation[6] and formylation[7] reactions when CD is used as the catalyst. Iodination of phenol and aniline[8] in the presence of β-CD decreases ortho/para ratio. Yet the examples of product specificities in CD bound substrates, are rather few. The selectivity achieved in the direct bromination of β-CD complexes of aniline (1), N-methylaniline, NMA (2), N,N-dimethylaniline, DMA (3) and N,N-diethylaniline, DEA (4) complexed with β-CD is discussed here. We found that in the bromination of β-CD complexes, monobromination can be carried out with moderately good yields without

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resorting to the customary blocking procedure. We also report here the complexation pattern of anilines (1 to 4) with ß-CD which helps to interpret the results obtained in the product studies.

## EXPERIMENTAL DETAILS

*Materials*

ß-CD (Sigma) and bromine (Merck) were used as received. Aniline (SD's), NMA (Sisco), DMA (Merck) and DEA (SRL) were purified by distillation under reduced pressure. Carbon tetrachloride (Qualigens, AR grade) and double distilled water were used throughout the study.

*Preparation of ß-CD complexes*

Reported procedure[9] was adopted for the preparation of ß-CD complexes of aniline and N-substituted anilines. To 10 mL of aqueous solution of ß-CD (600 mM) equimolar amount of guest molecule was added. After constant stirring for 24 hours at room temperature, the resultant white crystalline precipitate was filtered off, washed with diethyl ether to eliminate the guest molecule not included and dried in an air oven for 3 hours ($60^{o}C$). The dried white crystalline powder was used as such for further studies.

*Bromination of ß-CD-aniline complexes*

The ß-CD complex of aniline (2 g) or N-substituted aniline was dissolved in 5 mL of $CCl_4$ in dark at $0^{o}C$. About 6 mL of $Br_2$ in $CCl_4$ (various concentration of $Br_2$ in $CCl_4$; refer Table 4) was admitted dropwise for 20 min. and the reaction mixture was stirred constantly for 45 min. The reaction was arrested by pouring the mixture into 15-20 mL of ice cold water followed by the extraction with warm chloroform, dried over anhydrous sodium sulphate and solvent removed. The recovered product mixture was analysed by gas chromatography and confirmed by coinjection with the authentic samples prepared from known procedures.[10]

*Bromination of aniline in solution (without CD)*

To 10 mL of (160 mM) pure aniline or N-substituted aniline in $CCl_4$ kept at $0^{o}C$ was added 6 mL of $Br_2$ in $CCl_4$ (Table 4). The slow and careful addition was carried out with constant stirring for 45 min. in dark. The hydrobromic acid was removed by adding 20 mL of ice cold water into the reaction mixture. The product was extracted with diethyl ether, dried over anhydrous sodium sulphate, solvent removed and the product mixture analysed.

*Analysis*

Netel gas chromatograph (G.C) equipped with flame ionization detector and a 2 feet length i.d. 0.5 mm stainless steel column with SE-30 (10%) stationary phase was used for G.C. To confirm the formation of ß-CD complex-aniline, $^{1}H$- and $^{13}C$-NMR spectra of ß-CD complex were recorded in $D_2O$ and DMSO respectively with a JOEL GCX-400

NMR spectrometer. The IR spectra of anilines and their ß-CD complexes were recorded in KBr/neat, between 200-4000 $cm^{-1}$ using a Perkin-Elmer 577 IR spectrometer. UV-absorption spectra were recorded with a UV/VIS JASCO 7800 spectrophotometer. Optical densities were monitored at various wavelengths ranging from 200-300 nm (using spectroscopic grade methanol as the solvent at 25°C) and using the Benesi-Hildebrand method,[11] the dissociation constant, $K_D$, was obtained from the plot of $a_o b_o/\Delta$ OD vs $a_o+b_o$, where $a_o$ and $b_o$ being concentration of ß-CD and aniline respectively. Emission spectra were recorded with a JASCO FP 770 spectrofluorometer and intensities were monitored in the wavelength region 300-600 nm. Employing the modified Benesi-Hildebrand method[12] the dissociation constant ($K_D = 1/K_f$) was calculated from the ratio of the slope ($1/aK_f$) and intercept ($1/a$) from the linear plot of $b_o/\Delta I$ vs $1/a_o$ where 'a' is the proportionality constant. The absorption and emission spectra show slight hyperchromic and bathochromic shifts respectively, providing additional evidence for complex formation. The concentration of ß-CD was varied from 1-50 times as that of aniline.

The bromo derivatives formed on bromination of anilines (**1** to **4**) in free and complexed form with ß-CD were identified with their $^1$H-NMR and IR spectral data and also using GC by coinjection of authentic samples synthesised separately.[10] $^1$H-NMR measurements were obtained from a Perkin-Elmer (R32) (90 MHz) spectrometer (in $CDCl_3$/Acetone-$d_6$) with TMS as internal standard reference.

## RESULTS AND DISCUSSION

### Characterisation of ß-CD inclusion complexes

The spectral properties of the complexed guest molecule are often markedly different from the non-complexed species. Hence spectral measurements are frequently used to characterize CD complexes.[13] The orientation of the guest molecules in the CD cavity is governed by the molecular shape of the guest molecule and also by the interaction between the guest and CD.

*$^1$H-NMR spectra.* Complex formation is evidenced from 400 MHz $^1$H-NMR spectral studies of ß-CD complexes of anilines (**1** to **4**). The CD protons are identified on the basis of their specific coupling pattern.[14] In all the four complexes, the shielding effect is more pronounced on $H_3$ of ß-CD proton which is oriented towards the interior of the cavity (Table 1) and less pronounced on the $H_6$ proton which is on the narrow opening of the CD molecule and directing towards the outside of the cavity. The other protons $H_1$, $H_2$ and $H_4$, all located on the exterior wall have only small upfield shift. It is interesting to note that, the shifts are quite strong compared to other substrates.[4,14] The unusually stronger shifts arise due to the aromatic anisotropic effect of induced magnetic field of aryl ring and the nitrogen atom. These observations are consistent with the notion that complexes are formed between ß-CD and anilines (**1** to **4**).

**Table 1.** 400 MHz $^1$H-NMR chemical shifts of cyclodextrin protons[a,b]

| | ß-CD | ß-CD-Aniline complex | ß-CD-NMA complex | ß-CD-DMA complex | ß-CD-DEA complex |
|---|---|---|---|---|---|
| $H_1$ | 2065.7 | 1963.8 | 2036.0 | 1961.8 | 1963.1 |
| $H_2$ | 1502.9 | 1400.0 | 1468.0 | 1400.0 | 1401.5 |
| $H_3$ | 1628.6 | 1485.0 | 1548.0 | 1489.1 | 1483.1 |
| $H_4$ | 1471.4 | 1367.5 | 1436.0 | 1367.3 | 1369.2 |
| $H_5$ | 1582.9 | 1482.9 | 1548.0 | 1483.6 | 1481.5 |
| $H_6$ | 1591.4 | 1517.5 | 1586.4 | 1516.4 | 1513.9 |

[a] Chemical shifts are expressed in Hz; solvent $D_2O$.
[b] Abbreviations: NMA = N-Methylaniline;
DMA = N,N-Dimethylaniline;
DEA = N,N-Diethylaniline.

*$^{13}$C-NMR spectra*. An advantage of $^{13}$C-NMR over the $^1$H-NMR spectrum is that it can provide direct and useful information of the position of all the carbon atoms of the guest and thus on the degree of penetration of the guest molecule in the cavity. However, only the position of the aromatic ring of the guest in the cavity can be determined by the use of $^1$H-NMR method. The $^{13}$C-NMR chemical shifts for the various carbon atoms of ß-CD, anilines (**1** to **4**) and their ß-CD-aniline complexes are summarized in Table 2. The possible conformation of the complex between cyclodextrin and anilines (**1** to **4**) is shown in Figure 1.

As a result of complexation, all the carbon atoms of ß-CD undergo considerable downfield shift (deshielded). It is clearly noticed that $C_3$ and $C_5$ carbon atoms which are residing inside the cavity are deshielded largely compared to other carbon atoms of ß-CD.

As the aryl ring of the guest molecule is deeply included into the cavity, the chemical shift values of carbon atoms of the complexed anilines are different from the uncomplexed one.[15,16] The carbon atoms of anilines (**1** to **4**) in their ß-CD complex exhibit a significant shielding effect which is significant in the case of $C_4$, in all the complexes, providing a clear idea that $C_4$ atom of anilines (**1** to **4**) penetrates deeply into the cavity. It is also inferred that all other carbon atoms of the phenyl ring are also encircled by the CD moiety. Only the $C_1$ carbon atom of aniline in its ß-CD complex is deshielded which results in the exposure of that $C_1$ carbon atom outside the CD cavity (Scheme 1). Though the large chemical shift observed $C_7$ and $C_8$ atoms of ß-CD complex of DMA requires further analysis, there is a possibility that the phenyl and dimethylamino groups in the complex may not be in the same plane. Furthermore, the $C_9$ and $C_{10}$ carbon atoms of DEA in its ß-CD complex show only marginal shift towards upfield. This observation reveals that the two methyl groups of DEA are away from the CD cavity. All the above results indicate complex fromation between ß-CD and anilines (**1** to **4**).

**Table 2.** 400 MHz $^{13}$C-NMR chemical shifts (Hz) of β-CD, anilines (**1** to **4**) and β-CD-aniline complexes[a,b]

| β-CD | | β-CD-Aniline complex | β-CD-NMA complex | β-CD-DMA complex | β-CD-DEA complex |
|---|---|---|---|---|---|
| Carbon atoms | (δ) | (Δδ)[c] | (Δδ) | (Δδ) | (Δδ) |
| 1[d] | 102.018 | +0.011 | -0.111 | -0.065 | -0.095 |
| 2 | 72.419 | -0.063 | -0.126 | -0.095 | -0.126 |
| 3 | 72.905 | -0.232 | -0.201 | -0.186 | -0.308 |
| 4 | 81.648 | +0.011 | -0.095 | -0.065 | -0.065 |
| 5 | 71.933 | -0.187 | -0.187 | -0.156 | -0.265 |
| 6 | 59.912 | -0.095 | -0.140 | -0.110 | -0.171 |

| Anilines | Anil -ine | β-CD-Ani. complex | NMA | β-CD-NMA complex | DMA | β-CD-DMA complex | DEA | β-CD-DEA complex |
|---|---|---|---|---|---|---|---|---|
| Carbon atoms | (δ)[e] | (Δδ) | (δ) | (Δδ) | (δ) | (Δδ) | (δ) | (Δδ) |
| $C_1$[d] | 146.6 | -1.654 | 150.2 | +0.611 | 150.2 | +0.019 | 147.8 | +0.225 |
| $C_2$, $C_6$ | 115.0 | +1.264 | 112.3 | +0.962 | 112.3 | +0.203 | 112.0 | +0.309 |
| $C_3$, $C_5$ | 128.7 | +0.088 | 129.2 | +0.603 | 129.2 | +0.588 | 129.1 | +0.074 |
| $C_4$ | 117.9 | +2.212 | 116.7 | +1.491 | 116.7 | +0.869 | 115.5 | +1.500 |
| $C_7$, $C_8$ | - | - | 30.2 | +0.738 | 30.2 | +8.264 | 44.2 | +0.465 |
| $C_9$,$C_{10}$ | - | - | - | - | - | - | 12.5 | +0.057 |

[a] Abbrevations are the same as in Table 1.
[b] Chemical shift values are assigned with DMSO signals as the base in both the complexes and the free substrates at room temperature.
[c] + and - signs indicate shielding and deshielding respectively.
[d] Numbering of carbon atoms of β-CD and anilines (**1** to **4**) are given in Figure 1.
[e] Chemical shift values of anilines (**1** to **4**) are collected from literature; Ref. 16.

The orientation given in Scheme 1 for the substrates (**1** to **4**) seems to be consistent with the $^1$H- and $^{13}$C-NMR spectral results.

*Dissociation constants.* The dissociation constants of the four complexes were determined by employing absorption or fluorescence spectral data and the Benesi-Hilderbrand methods.[11,12] From the data given in Table 3, it is concluded that the formation constant ($1/K_D$) decreases in the order NMA ≃ Aniline > DEA >> DMA. The inclusion of DMA in the β-CD cavity is not very favourable than others because of the steric hindrance offered by the two methyl groups.

**Table 3.** Dissociation constants obtained with absorption and fluorescence spectral methods[a]

| Anilines | $\lambda_{ex}$ (nm) | $K_D$[b] (M) | $\lambda_{em}$ (nm) | $K_D$[c] (M) |
|---|---|---|---|---|
| Aniline | 277 | $1.5 \times 10^{-3}$ | 342.0 - 350.5 | $1.4 \times 10^{-3}$ |
| NMA | 284 | $1.4 \times 10^{-3}$ | 355.5 - 360.0 | $0.8 \times 10^{-3}$ |
| DMA | 271 | $22.9 \times 10^{-3}$ | 356.0 - 364.5 | $21.2 \times 10^{-3}$ |
| DEA | 256 | $2.2 \times 10^{-3}$ | 363.0 - 364.5 | $3.5 \times 10^{-3}$ |

[a] Abbreviations are the same as in Table 1.
[b] Value obtained with absorption spectral method.
[c] Value obtained with fluorescence spectral method.

*IR spectra.* In ß-CD complexes of anilines (1 to 4), the observed peaks are relatively so weak. The intensity of aromatic C-H bending vibration for the monosubstituted aryl ring (having 5 adjacent hydrogen atoms, in the region 770-730 $cm^{-1}$ is decreased as in the case of ß-CD-chalcone complex.[4] This clearly indicates that the aryl rings of anilines (1 to 4) are hidden inside the CD cavity.

In the case of aniline and NMA, $\gamma$ N-H bending is shifted from 1590 to 1580 $cm^{-1}$ (sharp) upon complexation. The $\gamma$ C-H stretching frequency of $N-CH_3$ observed at 2830 $cm^{-1}$ in the free NMA was found shifted with reduced intensity to 2880 $cm^{-1}$ in its ß-CD complex. In ß-CD complexes of DMA and DEA, the peaks for the methyl groups are clearly noticed at 2860-2880 $cm^{-1}$ (broad). This shows the presence of alkyl groups in the exterior of the CD moiety.

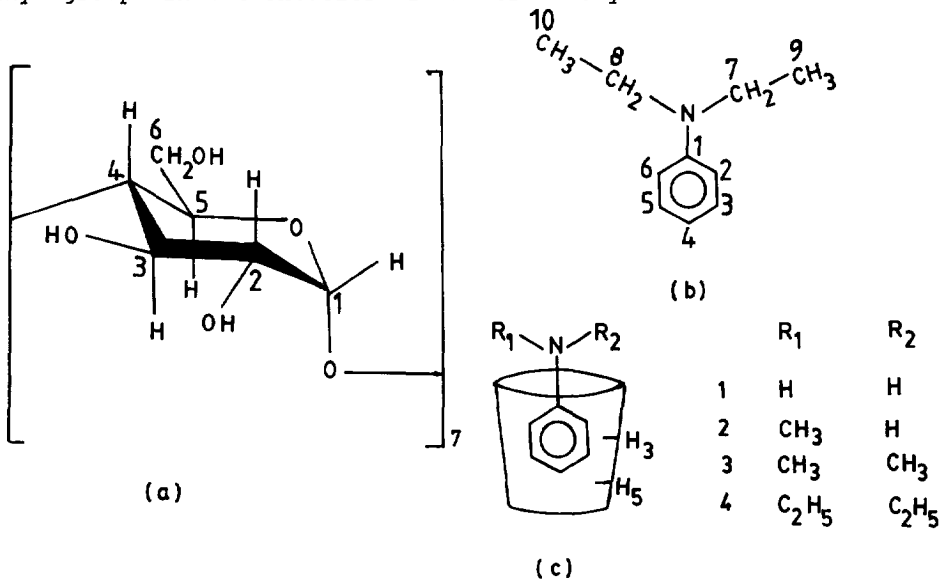



**Figure 1.** Structures of (a) ß-CD, (b) DEA and (c) postulated conformations of ß-CD-aniline complexes.

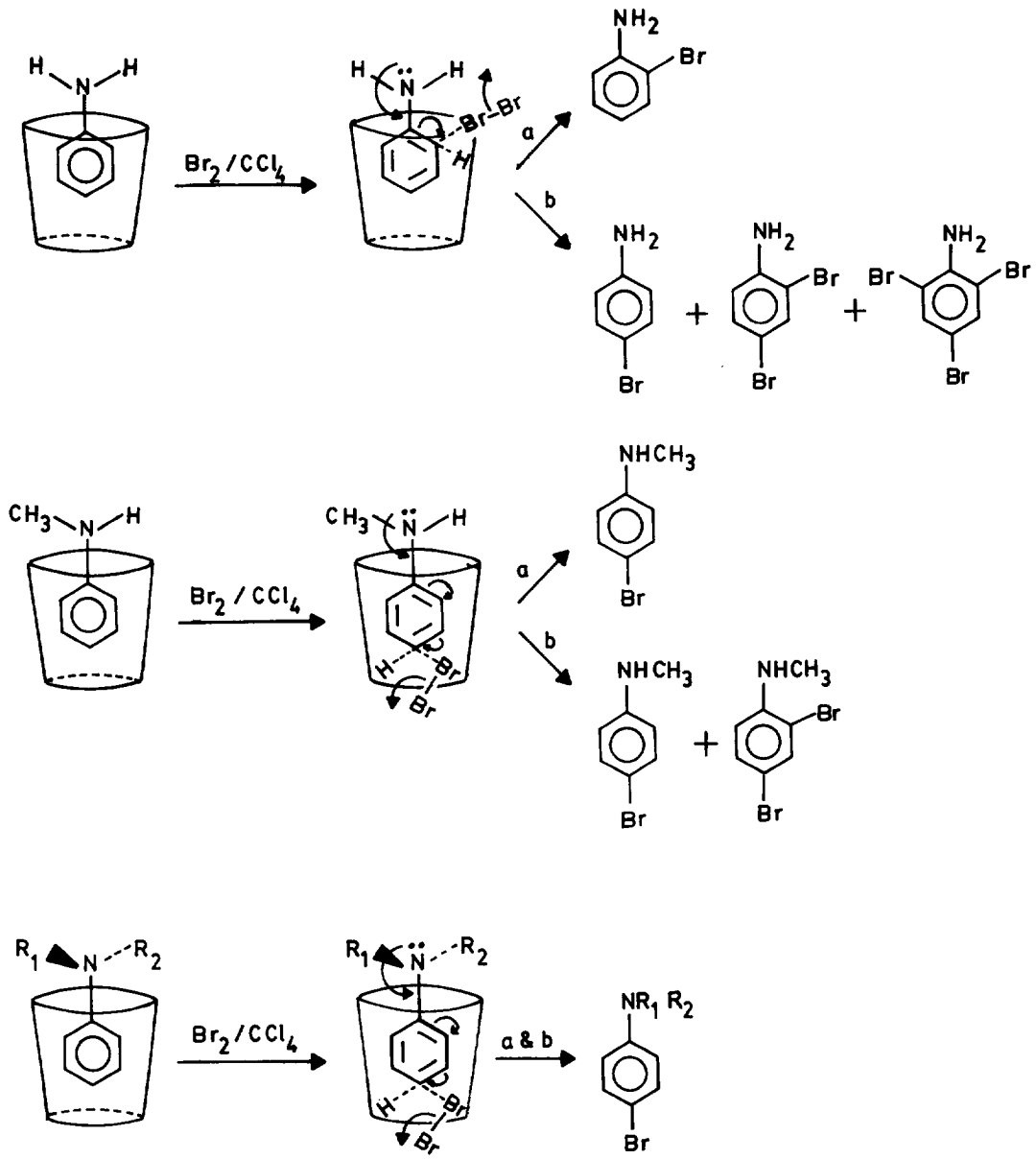
**Regioselective bromination of aniline and N-substituted anilines**

Aniline is known to undergo aromatic electrophilic substitution on bromination to yield para- as well as tri-bromoaniline with the product ratio depending on the reagent or reaction conditions.[17] In a recent paper[18] to interpret the results of the kinetics of bromination of substituted phenols and other aromatics (other than amines) catalysed by α-cyclodextrin in aqueous solution, Tee and Javed propose the mechanism involves the reaction between free substrate and the α-CD-$Br_2$ complex. However we have studied the bromination of amines encapsulated in β-CD. In the present investigation the direct bromination of anilines (**1** to **4**) with $Br_2$ in $CCl_4$ as well as β-CD complexes of amines has been extensively studied with the aim of determining the selectivity in the reactions. The product distribution depends on the molarity of bromine used. The results are summarized in Table 4.

**Table 4.** Reactions between various anilines (**1** to **4**) and bromine in $CCl_4$ in the presence and absence of β-CD[a,b,c]

| Substrate | Run No. | $Br_2$ in $CCl_4$ mM[d] | % Conversion | Product distribution (%) ortho- | para- | 2,4-di | 2,4,6-tri | X |
|---|---|---|---|---|---|---|---|---|
| Aniline | 1 | 10 | 74 (100)[f] | 57 (-) | - (90) | 10 (10) | 1 (-) | 6 (-) |
| 167 mM | 2 | 20 | 81 (100) | 65 (-) | - (79) | 13 (20) | 1 (1) | 2 (-) |
| | 3 | 50 | 94 (100) | 71 (-) | - (70) | 15 (26) | 3 (4) | 5 (-) |
| | 4 | 100 | 99 (100) | 74 (-) | - (60) | 16 (30) | 4 (10) | 5 (-) |
| | 5 | 200[e] | 100 (100) | - (-) | 24 (49) | 50 (39) | 18 (12) | 7 (-) |
| NMA | 6 | 10 | 14 (55) | - (-) | 14 (39) | - (16) | - (-) | - (-) |
| 161 mM | 7 | 20 | 44 (91) | - (-) | 33 (31) | - (60) | - (-) | 11 (-) |
| | 8 | 50 | 67 (98) | - (-) | 48 (16) | 12 (82) | - (-) | 7 (-) |
| | 9 | 100 | 88 (99) | - (-) | 63 (14) | 18 (85) | - (-) | 7 (-) |
| DMA | 10 | 50 | 47 (43) | - (-) | 27 (32) | - (-) | - (-) | 20 (11) |
| 159 mM | 11 | 100 | 55 (86) | - (-) | 30 (76) | - (-) | - (-) | 25 (10) |
| DEA | 12 | 100 | 33 (21) | - (-) | 19 (21) | - (-) | - (-) | 14 (-) |
| 156 mM | 13 | 200[e] | 58 (31) | - (-) | 16 (31) | - (-) | - (-) | 42 (-) |

[a] Abbreviations are the same as in Table 1.
[b] Stirred for 45 min.; dark; 0°C. Analysed by GC (error limit ± 5%).
[c] β-CD:Substrate = 1:1 complex.
[d] [Substrate]/[$Br_2$] = 1.6 to 16 times; > 1 (molar ratio).
[e] [Substrate]/[$Br_2$] = 0.8; < 1 (molar ratio).
[f] Numbers in the parentheses are results obtained in the bromination of anilines (**1** to **4**) carried out under exactly the same conditions but without β-CD.
**X** To be characterised.


Br2 / CCl4
a
b
NH2
Br
NHCH3
R1 N R2
a & b
NR1 R2
R1 = R2 = CH3 or C2H5
a = Lower [Br2]
b = Higher [Br2]

Scheme 1.

As it can be seen, ortho-bromoaniline is formed as the major product when bromination was carried out with ß-CD-aniline 1:1 complex at 100 mM $Br_2$ in contrast to the formation of para-bromoaniline in solution. In the conventional method para-isomer predominates as expected (Runs 1-4). This is because of the greater electron density at para-position.[19] Eventhough the para-position is electron rich, ortho-isomer is the major one in bromination of ß-CD complex and this indicates that, the aniline resides inside the cavity in such a way that the ortho-position is exposed to easier attack of the electrophile ($Br^+$). The ß-CD-aniline structure is likely to be as shown in Figure 1 and in Scheme 1 and thus accounts for selectivity.

When the substrate/$Br_2$ molar ratio is greater than unity the monosubstitution is favoured and when less than unity, di- and tri-bromoderivatives are formed in addition to monobrominated product (Run 5).

In the bromination of NMA (Runs 6-9), as the substrate/$Br_2$ molar ratio is decreased, formation of para-bromo derivative increased in bromination of ß-CD complex but it is just reverse in the conventional method. As the methyl group offers steric hindrance to the approach of bromine in NMA and also the complex is relatively weaker (Table 3), the electrophilic attack takes place in the para-position in this case. Because of steric hinderance for $Br^+$ in the 2- position, the yield of 2,4-dibromo derivative is lower in the complex. The protonation of amino group by the HBr formed also provides further steric hindrance to the attack at ortho-position.

Compared to aniline and NMA, DMA and DEA favour only para-bromination and the extent of reaction is less in complex when compared to conventional method (Runs 10-13). It is likely that in the complexation of DMA and DEA, the dimethylamino or diethylamino groups and the phenyl group may not be in the same plane (Scheme 1). This will result in considerable reduction in the electron density at the para-position due to reduced mesomeric interaction compared to uncomplexed DMA and therefore the yield is lower. It is reported that bromine reacts with amine to form some complex with the result that the normal reaction is greately retarded.[20] This may be the reason for the observation of unidentified products (X), in the bromination of ß-CD complexes of anilines (1 to 4) (Table 4).

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