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# Effect of Cyclodextrins on Electrophilic Aromatic Bromination in Aqueous Solution*

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Cyclodextrins act as molecular reactors to change the ratios of the products of reactions of anisole, acetanilide, 3-methylanisole, and 3-methylacetanilide with pyridinium dichlorobromate. With anisole and acetanilide, bromination at the *para* position is favoured over *ortho* substitution, and the effect is greatest with α-cyclodextrin. In the reactions of the methylanisole and methylacetanilide, the cyclodextrins afford higher yields of monobrominated products and less of the di- and tribromides, and β-cyclodextrin has the greatest effect. These outcomes can be attributed to inclusion of the substrates within the cyclodextrins restricting access of the reagent adjacent to the methoxy and acetamido groups. The yields of 4-bromoanisole, 4-bromoacetanilide, 4-bromo-3-methylanisole, and 4-bromo-3-methylacetanilide are thus increased from 73 to 94, 55 to 98, 37 to 86, and 39 to 72%, respectively. Perhaps more significantly, the quantities of the corresponding by-products are substantially reduced, from 27 to 6, 45 to 2, 63 to 14, and 61 to 28%. Since the reactions occur readily in water at ambient temperature, the cyclodextrins make them very efficient.

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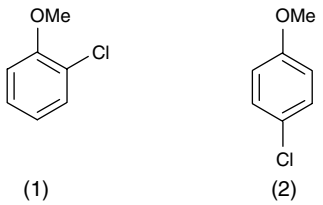
## Introduction

Cyclodextrins have attracted considerable attention as enzyme mimics, due to their ability to form inclusion complexes with small organic compounds in water and catalyze reactions of the included species.[1–5] They have also been exploited as molecular reactors, where they control the assembly of reactants to change the outcomes of chemical transformations.[6–16] Examples of the latter include the covalent attachment of dipolarophiles to cyclodextrins to reverse the regioselectivity of cycloadditions with nitrile oxides[6,7] and the development of a urea-linked cyclodextrin dimer to bias competing reactions to give indigoid dyes.[8]

Probably the most straightforward examples of cyclodextrin molecular reactors are those that involve a change in the regioselectivity of reaction as a result of a substrate being included in such a way as to restrict access of a reagent. Pioneering research in this area by Breslow et al.[9–11] showed that cyclodextrins alter the regioselectivity of aromatic substitution. Hypochlorous acid chlorination of anisole (3a) in the absence of a cyclodextrin gave the chlorides (1) and (2) (see Diagram 1), in a ratio of about 2 : 3. When the reactions were repeated in the presence of either α- or β-cyclodextrin, substantially more of the *para* isomer (2) was formed, particularly in the former case. Breslow et al.[9–11] reasoned that these chlorinations involve cyclodextrin hypochlorites and that, in the inclusion complexes with the cyclodextrins, the *ortho* positions of the anisole (3a) are shielded from chlorination while the *para* position is still accessible. A related study showed selective *para* chlorination of acetanilide (3b) in the presence of cyclodextrins[12] but cyclodextrin hypochlorites were not involved as intermediates in this case. The reactions discussed above were carried out in water, which has the added advantage of being an environmentally benign solvent. The cyclodextrins facilitate the use of this medium by increasing the solubility of organic substrates.




(1) (2)

**Diagram 1.**

Another example of the use of cyclodextrins to influence aromatic substitution was reported by Komiyama and Hirai,[13,14] where the regioselectivity of the Reimer–Tiemann reaction of phenol with chloroform was altered, again in favour of *para* substitution. Tee and Bennett[17] investigated the effects of cyclodextrins on the bromination of anisole (3a) with bromine/KBr in water, but in that system

* Dedicated to Professor John H. Bowie with best wishes on the occasion of his 65th birthday.

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**Table 1. Products of bromination of compounds (3a)–(3c), (7a), and (7b)[A]**

| Entry | Substrate | Cyclodextrin (CD) | Reagent (mol equiv.) | Product ratios [%] (3) | (4) | (5) | (6) | | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (3a) | — | 1.1 | 0 | 12 | 73 | 15 | | |
| 2 | | α-CD | 1.1 | 0 | 2 | 94 | 4 | | |
| 3 | | β-CD | 1.1 | 0 | 6 | 86 | 8 | | |
| 4 | (3b) | — | 1.1 | 0 | 42 | 55 | 3 | | |
| 5 | | α-CD | 1.1 | 0 | 0 | 98 | 2 | | |
| 6 | | β-CD | 1.1 | 0 | 21 | 79 | 0 | | |
| 7 | (3c) | — | 1.1 | 41 | 2 | 57 | 0 | | |
| 8 | | α-CD | 1.1 | 40 | 2 | 58 | 0 | | |
| 9 | | β-CD | 1.1 | 77 | 1 | 22 | 0 | | |
| | | | | (7) | (9) | (11) | (13) | (14) | |
| 10 | (7a) | — | 0.6 | 50 | 23 | 12 | 14 | 1 | |
| 11 | | α-CD | 0.6 | 40 | 42 | 8 | 9 | 1 | |
| 12 | | β-CD | 0.6 | 36 | 59 | 3 | 2 | 0 | |
| 13 | (7a) | — | 1.1 | 23 | 37 | 19 | 20 | 1 | |
| 14 | | α-CD | 1.1 | 12 | 46 | 18 | 21 | 1 | |
| 15 | | β-CD | 1.1 | 4 | 86 | 5 | 5 | 0 | |
| 16 | (7a) | — | 2.2 | 0 | 30 | 29 | 34 | 7 | |
| | | | | (7) | (9) | (11) | (13) | (14) | (X) |
| 17 | (7b) | — | 0.6 | 51 | 36 | 8 | 5 | 0 | 0 |
| 18 | | α-CD | 0.6 | 43 | 48 | 6 | 3 | 0 | 0 |
| 19 | | β-CD | 0.6 | 44 | 48 | 5 | 3 | 0 | 0 |
| 20 | (7b) | — | 1.1 | 12 | 39 | 9 | 7 | 20 | 13 |
| 21 | | α-CD | 1.1 | 5 | 64 | 9 | 6 | 13 | 3 |
| 22 | | β-CD | 1.1 | 3 | 72 | 7 | 4 | 1 | 13 |

[A] Reaction with pyridinium dichlorobromate in water at room temperature. Reaction time was 1 h for (3a), (3b), (7a), and (7b), and 16 h for (3c).

the oligosaccharides did not alter the regioselectivity. Instead, they retarded the reaction rate, due to inclusion of both the substrate and the brominating agent. In light of the lack of regiocontrol in this system, the recent account of the use of pyridinium dichlorobromate for aromatic bromination in aqueous methanol[18] prompted us to investigate the effect of employing cyclodextrins with this reagent. As reactants for the study, we chose anisole (3a) and acetanilide (3b), in order to make direct comparisons with the chlorination of those compounds. Phenyl acetate (3c), and the methyl-substituted anisole (7a) and acetanilide (7b) were also selected as substrates, on the basis that the ester (3c) is less reactive, and the ether (7a) and amide (7b) more reactive, towards aromatic substitution.

## Results and Discussion

Each of the substrates (3a)–(3c), (7a), and (7b) (1.3 mM) was treated with pyridinium dichlorobromate (0.6, 1.1, and/or 2.2 mol equiv.), in water containing methanol (1% v/v). The reactions were carried out at room temperature, for either 1 or 16 h, in the absence of a cyclodextrin and in the presence of either α- or β-cyclodextrin (10 mol equiv.). After work-up, the crude product mixtures were analyzed using $^1$H NMR spectroscopy. The ratios of the components present are shown in Table 1. These were determined through integration of key resonances (Table 2) that were assigned based on comparison with the spectra of authentic samples in the cases of compounds (3a)–(3c), (4a), (5a), (5b), (7a), (7b), (11a), (13a), and (14a), and on data from the literature[19–25] for the bromides (4b), (4c), (5c), (6a), (6b), (9a), and (9b). Resonances were assigned to the methylacetanilides (11b), (13b), and (14b) by analogy with the spectra of the corresponding methylanisoles (11a), (13a), and (14a), and by comparison of observed chemical shifts and coupling constants with calculated values.[26] An unidentified compound (X) was also observed in reactions of the methylacetanilide (7b). It seems likely that this is the product of a secondary process, since it was not seen during the initial stages of reaction.

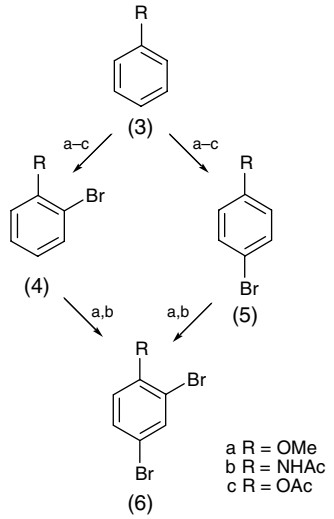
The reactions of anisole (3a) and acetanilide (3b) with 1.1 equiv. of the brominating agent gave small amounts of the dibromides (6a) and (6b), respectively, presumably by way of the corresponding monobromides (4a), (4b), (5a), and (5b) (Scheme 1). Phenyl acetate (3c) reacted to a much lesser extent, even after a much longer reaction time, and only the monobromides (4c) and (5c) were produced, i.e., there was no evidence of formation of the dibromide (6c). In the reactions of the methylanisole (7a) and methylacetanilide (7b), unreacted starting materials and the corresponding monobromides (9a) and (9b), dibromides (11a), (11b), (13a), and (13b), and tribromides (14a), (14b), and the unidentified product (X) in the case of the acetanilide (7b), accounted for at least 95 mol-% of the product mixtures. This was determined by analysis of $^1$H NMR spectra and particularly through comparison of the integrations of all the methyl proton resonances relative to those of the aromatic protons. While it is conceivable that the monobromides (8a), (8b), (10a), and (10b), and the dibromides (12a) and (12b) could also have been produced (Scheme 2), they were each detected at most in only trace quantities ($\leq$3%).

In the reactions carried out in the absence of a cyclodextrin, the formation of only small amounts of the dibromides (6a) and (6b) from anisole (3a) and acetanilide (3b), respectively, relative to the yields of the corresponding monobromides (4a), (4b), (5a), and (5b) (Table 1, entries 1 and 4), indicates that the bromo substituents of (4a), (4b), (5a), and (5b) reduce the reactivity of these systems towards further aromatic substitution. This deactivation is typical of halogens and is greatest with the acetanilides (3b)–(5b). By contrast, the yields of the dibromides (11a), (11b), (13a), and (13b) from the methylanisole (7a) and methylacetanilide (7b) are more substantial (Table 1, entries 10, 13, 16, 17, and 20), particularly with the anisole (7a), where monobromination appears to activate the system to further reaction. Presumably, the combination of methoxy and methyl substituents perturbs the balance of resonance and inductive effects normally seen with a bromo group. Significant quantities of (8a), (8b), (10a), (10b), (12a), and (12b) do not build up in the reactions of (7a) and (7b). This is probably due largely to the selectivity of bromination *para* to a methoxy or acetamido group, but another contributing factor may be that, like (9a) and (9b), the bromides (8a), (8b), (10a), (10b), (12a), and (12b) are unusually reactive, and once formed react further to give (11a), (11b), (13a), (13b), (14a), and (14b), respectively.

**Table 2. NMR signals used for determining product ratios**

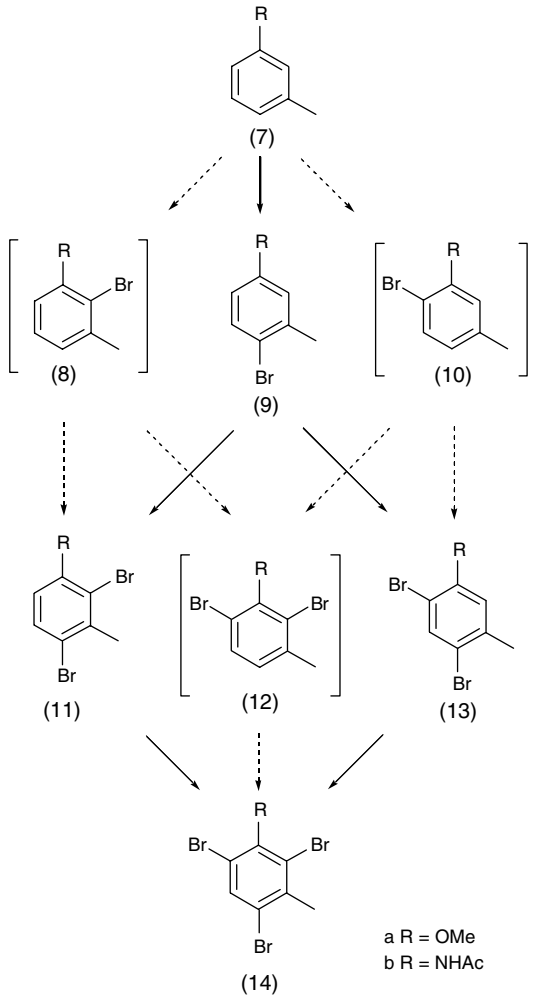
| Compound | Solvent | Spectroscopic data[A] | Reference |
|---|---|---|---|
| (3a) | $CDCl_3$ | 7.22 (2 H, m, H3, H5), 6.91–6.80 (3 H, m, H2, H4, H6), 3.77 (3 H, s, $OCH_3$) | [B] |
| (3b) | [$D_6$]DMSO | 7.54 (2 H, d, *J* 7.5, H2, H6), 7.26 (2 H, t, *J* 7.5, H3, H5), 7.00 (1 H, t, *J* 7.5, H4), 2.02 (3 H, s, $NHCOCH_3$) | [B] |
| (3c) | $CDCl_3$ | 7.38 (2 H, m, H3, H5), 7.24 (1 H, m, H4), 7.09 (2 H, m, H2, H6), 2.28 (3 H, s, $COCH_3$) | [B] |
| (4a) | $CDCl_3$ | 7.54 (1 H, dd, *J* 8.0 and 1.5, H6), 7.27 (1 H, ddd, *J* 8.0, 7.5 and 1.5, H5), 6.90 (1 H, dd, *J* 8.5 and 1.5, H3), 6.84 (1 H, ddd, *J* 8.5, 7.5 and 1.5, H4), 3.89 (3 H, s, $OCH_3$) | [B] |
| (4b) | [$D_6$]DMSO | 7.61 (1 H, d, *J* 7.5 and 1.5, H6), 7.33 (1 H, td, *J* 7.5 and 1.5, H5), 7.10 (1 H, td, *J* 7.5 and 1.5, H4), 2.06 (3 H, s, $NHCOCH_3$) | [19] |
| (4c) | $CDCl_3$ | 7.60 (1 H, dd, *J* 8.5 and 1.5, H6), 7.32 (1 H, ddd, *J* 8.0, 7.5 and 1.5, H5), 7.13 (1 H, m, H3), 7.12 (1 H, m, H4), 2.34 (3 H, s, $COCH_3$) | [20] |
| (5a) | $CDCl_3$ | 6.70 (2 H, d, *J* 9.0, H2, H6), 7.29 (2 H, d, *J* 9.0, H3, H5), 3.79 (3 H, s, $OCH_3$) | [B] |
| (5b) | [$D_6$]DMSO | 7.53 (2 H, d, *J* 9.0, H3, H5), 7.43 (2 H, d, *J* 9.0, H2, H6), 2.02 (3 H, s, $NHCOCH_3$) | [B] |
| (5c) | $CDCl_3$ | 7.46 (2 H, d, *J* 9.0, H3, H5), 6.96 (2 H, d, *J* 9.0, H2, H6), 2.27 (3 H, s, $COCH_3$) | [21] |
| (6a) | $CDCl_3$ | 7.65 (1 H, d, *J* 2.5, H3), 3.87 (3 H, s, $OCH_3$) | [22] |
| (6b) | [$D_6$]DMSO | 7.72 (1 H, d, *J* 2.1, H3), 2.11 (3 H, s, $NHCOCH_3$) | [23] |
| (7a) | $CD_3OD$ | 7.11 (1 H, t, *J* 8.0, H5), 6.71 (2 H, m, H4, H6), 6.66 (1 H, m, H2), 3.73 (3 H, s, $OCH_3$), 2.28 (3 H, s, $ArCH_3$) | [B] |
| (7b) | $CD_3OD$ | 7.35 (1 H, br s, H2), 6.90 (1 H, br d, *J* 8.0, H4), 7.15 (1 H, t, *J* 8.0, H5), 7.30 (1 H, br d, *J* 8.0, H6) | [B] |
| (9a) | $CD_3OD$ | 7.35 (1 H, d, *J* 8.5, H5), 6.83 (1 H, d, *J* 3.0, H2), 6.63 (1 H, dd, *J* 8.5 and 3.0, H6), 3.74 (3 H, s, $OCH_3$), 2.32 (3 H, s, $ArCH_3$) | [24] |
| (9b) | $CD_3OD$ | 7.47 (1 H, d, *J* 2.5, H2), 7.41 (1 H, d, *J* 8.5, H5), 7.28 (1 H, dd, *J* 8.5 and 2.5, H6) | [25] |
| (11a) | $CD_3OD$ | 7.49 (1 H, d, *J* 9.0, H5), 6.80 (1 H, d, *J* 9.0, H6) | [B] |
| (11b) | $CD_3OD$ | 7.53 (1 H, d, *J* 8.5, H5) | [26] |
| (13a) | $CD_3OD$ | 7.60 (1 H, s, H6), 6.69 (1 H, s, H3) | [B] |
| (13b) | $CD_3OD$ | 7.60 (1 H, br s, H6), 7.76 (1 H, s, H3) | [26] |
| (14a) | $CD_3OD$ | 7.79 (1 H, s, H5) | [B] |
| (14b) | $CD_3OD$ | 7.87 (1 H, s, H5) | [26] |
| (X) | $CD_3OD$ | 7.12 (1 H, ddq, *J* 8.5, 3.0 and 0.5), 7.68 (1 H, d, *J* 8.5) | — |

[A] Discrete signals were not observed for all resonances; those which could not be unambiguously assigned are not shown.
[B] Spectrum of an authentic sample.




**Scheme 1.**

In the reactions of anisole (3a) and acetanilide (3b), both α- and β-cyclodextrin change the ratios of formation of the monobrominated products (4a), (4b), (5a), and (5b) in favour of the *para*-substituted isomers (5a) and (5b) (Table 1, entries 1–6). The effect is greatest with α-cyclodextrin. It is thus apparent that the cyclodextrins limit *ortho* bromination of the substrates (3a) and (3b), presumably through the formation of inclusion complexes which restrict access of the brominating agent, in a manner that is directly analogous to the effect of cyclodextrins on chlorination reported previously.[9–12] In the case of anisole (3a), the cyclodextrins also limit the extent of formation of the dibromide (6a), and again it is α-cyclodextrin that has the greatest effect. It seems likely that this is mainly due to the cyclodextrins retarding further bromination of the monobromide (5a) by blocking the 2-position. The net result of these effects is an increase in the yields of the monobromides (5a) and (5b), from 73 to 94, and 55 to 98%, respectively, and a substantial decrease in the quantity of the corresponding by-products, from 27 to 6, and 45 to 2%. The cyclodextrins do not alter the regioselectivity of bromination of phenyl acetate (3c), although β-cyclodextrin decreases the extent of reaction (Table 1, entries 7–9). In the reactions of the methylanisole (7a) and methylacetanilide (7b), the cyclodextrins increase the yields of the monobromides (9a) and (9b), probably by limiting the subsequent reactions of (9a) and (9b) to give the dibromides (11a), (11b), (13a), and (13b) and tribromides (14a) and (14b), as well as by decreasing the extent of reaction by way of the monobromides (8a), (8b), (10a), (10b), (12a), and (12b), to give (11a), (11b), (13a), (13b), (14a), and (14b). Again the effect of the cyclodextrins is to prevent bromination adjacent to the methoxy and acetamido groups, in a similar manner to that seen with anisole (3a) and acetanilide (3b), but in the methylated systems β-cyclodextrin has the greatest effect. When 1.1 mol equiv. of the brominating agent was used with β-cyclodextrin, the yields of the monobromides (9a) and (9b) increased from 37 to 86, and 39 to 72%, respectively, and there was a substantial decrease in




**Scheme 2.**

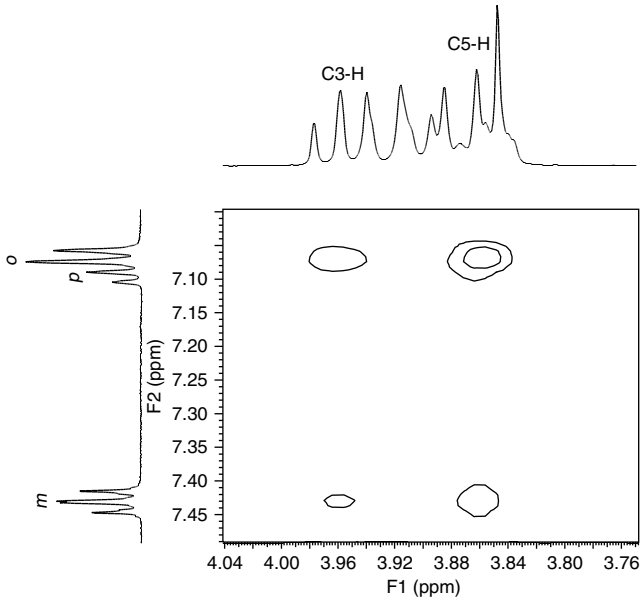



**Fig. 1.** A portion of the ROESY spectrum (500 MHz) recorded for a solution of anisole (3a) (10 mM) and α-cyclodextrin (10 mM) in $D_2O$, showing interactions between resonances of the cyclodextrin (*x* axis) and those of the anisole (3a) (*y* axis).

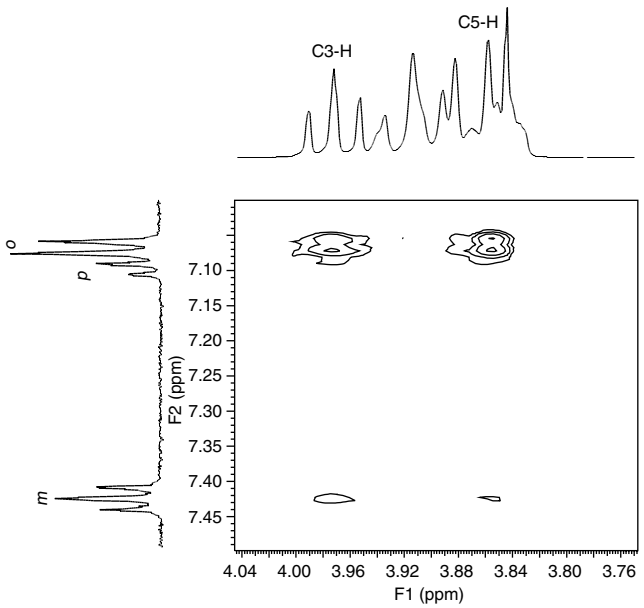



**Fig. 2.** A portion of the ROESY spectrum (500 MHz) recorded for a solution of anisole (3a) (2 mM) and β-cyclodextrin (2 mM) in $D_2O$, showing interactions between resonances of the cyclodextrin (*x* axis) and those of the anisole (3a) (*y* axis).

the quantity of the corresponding by-products, from 63 to 14, and 61 to 28%.

It is not obvious why α-cyclodextrin has the greatest effect on the bromination of anisole (3a) and acetanilide (3b), yet the reactions of the methylated substrates (7a) and (7b) are most affected by β-cyclodextrin. The outcomes will depend on the extent of inclusion of the reagent, pyridinium dichlorobromate, as well as the substrates (3a), (3b), (7a), and (7b), and the relative reactivity of the free and included species. The systems are further complicated by possible complexation of the primary products such as the monobromides (8a), (8b), (9a), (9b), (10a), and (10b), affecting their subsequent reactions. Nevertheless, it seems likely that a major contributing factor to the regiocontrol provided by the cyclodextrins derives from complexation of the substrates (3a), (3b), (7a), and (7b) in such a way as to restrict access of the reagent adjacent to the methoxy and acetamido substituents. Such shielding is reflected in rotating-frame Overhauser enhancement spectroscopy (ROESY) spectra of mixtures of anisole (3a) and α- and β-cyclodextrin (Figs. 1 and 2, respectively), which both show nuclear Overhauser effects (NOEs) between the resonances of the *ortho* hydrogen atoms of the substrate (3a) and the cyclodextrin C3–H and C5–H resonances. ROESY spectra of mixtures of the other substrates (3b), (7a), and (7b) with cyclodextrins also show NOEs between the resonances of the substrate and cyclodextrin hydrogen atoms. These show that the substrates are included in the cyclodextrins in aqueous solution but further interpretation of the data is impractical in these cases due to overlapping substrate resonances and changes in the chemical shifts of the substrate resonances induced by the cyclodextrins.

In summary, both α- and β-cyclodextrin affect the regioselectivity of bromination of anisole (3a) and acetanilide

(3b), and the methylated analogues (7a) and (7b), to increase the yields of the corresponding bromides (4a), (4b), (9a), and (9b). A corollary of this is that the reactions are further improved by the substantial reduction in the yields of the by-products. Since the brominations occur readily in water at ambient temperature, and they require only stoichiometric quantities of reagents, the cyclodextrins make them very efficient chemical transformations.

## Experimental

*General*

$^1$H NMR spectra were recorded on either a Varian Inova 500 spectrometer or a Varian Gemini 300 spectrometer. Spectra were referenced against tetramethylsilane ($\delta$ 0.00 ppm) for $CDCl_3$ solutions, external 3-(trimethylsilyl)-3,3,2,2-tetradeuteropropionic acid sodium salt for $D_2O$ solutions, or residual protons for other deuterated solvents. ROESY spectra were recorded on a Varian Inova 500 spectrometer employing a mixing time of 250 ms. The sample tubes were sealed with RotoTite valves purchased from Wilmad Glass, and samples were repeatedly degassed by freeze–pump–thaw cycling before spectra were recorded. The samples contained either α-cyclodextrin (0.01 M) and anisole (3a) (0.01 M), or β-cyclodextrin (0.002 M) and anisole (3a) (0.002 M), in $D_2O$.

α-Cyclodextrin and β-cyclodextrin were generous gifts of Nihon Shokuhin Kako Co., Japan. They were recrystallized from water and dried under vacuum over $P_2O_5$ to constant weight before use. Water was purified with a MilliQ water system.

Anisole (3a), phenyl acetate (3c), 4-bromoanisole (5a), 4-bromoacetanilide (5b), 3-methylanisole (7a), and *m*-toluidine were purchased from Sigma–Aldrich. Acetanilide (3b) was bought from Ajax Chemicals and 2-bromoanisole (4a) was purchased from Fluka. Pyridinium dichlorobromate was prepared as described by Muathen.[18] Anisole (3a) was purified by distillation (bp 153–154°C) before use. 3-Methylacetanilide (7b) was prepared by acetylating *m*-toluidine.[27] Samples of 2,4-dibromo-3-methylanisole (11a), 2,4-dibromo-5-methylanisole (13a), and 2,4,6-tribromo-3-methylanisole (14a) were prepared by bromination of 3-methylanisole (7a) with bromine in acetic acid.[28]

*General Bromination Procedure*

The aromatic substrate (3a)–(3c), (7a), or (7b) (0.2 mmol) in methanol (1.5 mL) was added to water (100 mL) that contained either no cyclodextrin or α- or β-cyclodextrin (2.0 mmol), and the resulting mixture was stirred vigorously. Pyridinium dichlorobromate (0.22 mmol) was added and the total volume of the solution was made up to 150 mL with water. The resulting mixture was stirred at room temperature, for 1 h with (3a), (3b), (7a), and (7b), and for 16 h with (3c), and the reaction was then quenched through the addition of an excess of $NaHSO_3$. The solution was extracted with ether (2 × 80 mL), and the ether extracts were washed with water (100 mL), dried, and concentrated under reduced pressure. The residue was analyzed using $^1$H NMR spectroscopy. Spectra were recorded in either $CDCl_3$, $CD_3OD$, or [$D_6$]DMSO, depending on the solubility of the components. The ratios of the components present are shown in Table 1, as determined by integration of key resonances that are listed in Table 2.

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