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# Inverse Phase-Transfer Catalysis by Cyclodextrins. Palladium-Catalyzed Reduction of Bromoanisoles with Sodium Formate

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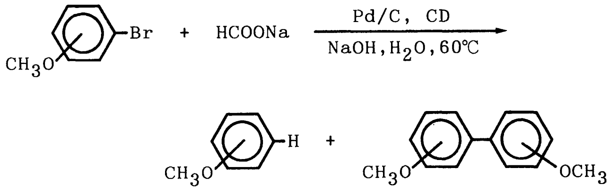
Bromoanisoles have been reduced to hydrocarbons with sodium formate in high yields under mild conditions using palladium on charcoal and cyclodextrins as catalysts. In aqueous phase-organic phase reactions employing a solid-phase catalyst (Pd/C), cyclodextrins function as inverse phase-transfer catalysts which transfer the substrate into the aqueous phase.

Phase-transfer catalysts, such as quaternary ammonium salts and crown ethers, facilitate reactions between two immiscible reactants through the transport of a water-soluble reactant into an organic phase; these have been extensively studied. However, there have only been a few reports concerning the utilization of the carrier agents capable of transporting hydrophobic organic molecules into an aqueous phase.[1—5] For example, the use of cyclodextrins (CDs) as inverse phase-transfer catalysts has been limited to the nucleophilic displacement of 1-bromoalkane,[1] oxidation of olefins to ketones,[2] epoxidation of alkenes with iodosylbenzene,[3] and isomerization of 4-allylanisole[4] in aqueous–organic two-phase systems.

We have therefore examined the effects of CDs on the reduction of aryl bromides with sodium formate using palladium on charcoal, which is a heterogeneous hydrogenation catalyst, in order to find wide applications of inverse phase-transfer catalysis by CDs to organic synthesis.



## Results and Discussion

Results concerning the reduction of bromoanisoles under various conditions are summarized in Table 1. The addition of $\beta$-CD to these three-phase reactions considerably accelerates the rate of the reaction (Entries 1—5). It is clear that the CD's capability of including a variety of lipophilic guests in the cavity takes part in the catalysis, since no acceleration effect is observed when methyl $\alpha$-D-glucopyranoside is added to

Table 1. Palladium-Catalyzed Reduction of Bromoanisoles with Sodium Formate[a]

| Entry | Anisole | Cyclodextrin | NaOH | Conversion | Yields of products[b,c]/% | |
|---|---|---|---|---|---|---|
| | | mmol | mmol | % | Anisole | Dimethoxybiphenyl[d] |
| 1 | 4-Br | $\beta$ 1.0 | 90 | 72 | 51 (71) | 21 (29) |
| 2 | 4-Br | $\beta$ 3.0 | 90 | 94 | 66 (70) | 28 (30) |
| 3 | 4-Br | $\beta$ 6.0 | 90 | 96 | 68 (71) | 28 (29) |
| 4 | 4-Br | G[e] 21.0 | 90 | 23 | 13 (57) | 10 (43) |
| 5 | 4-Br | None | 90 | 22 | 13 (59) | 9 (41) |
| 6 | 4-Br | $\beta$ 3.0 | 60 | 60 | 42 (70) | 18 (30) |
| 7 | 4-Br | None | 60 | 22 | 15 (68) | 7 (32) |
| 8 | 4-Br | $\beta$ 3.0 | 30 | 31 | 23 (74) | 8 (26) |
| 9 | 4-Br | None | 30 | 33 | 27 (82) | 6 (18) |
| 10 | 4-Br | $\alpha$ 3.0 | 90 | 77 | 47 (61) | 30 (39) |
| 11 | 4-Br | $\gamma$ 3.0 | 90 | 44 | 33 (75) | 11 (25) |
| 12 | 3-Br | $\alpha$ 3.0 | 90 | 71 | 40 (56) | 31 (44) |
| 13 | 3-Br | $\beta$ 3.0 | 90 | 92 | 55 (60) | 37 (40) |
| 14 | 3-Br | $\gamma$ 3.0 | 90 | 45 | 28 (62) | 17 (38) |
| 15 | 3-Br | None | 90 | 40 | 20 (50) | 20 (50) |
| 16 | 2-Br | $\alpha$ 3.0 | 90 | 41 | 35 (85) | 6 (15) |
| 17 | 2-Br | $\beta$ 3.0 | 90 | 43 | 36 (84) | 7 (16) |
| 18 | 2-Br | $\gamma$ 3.0 | 90 | 40 | 31 (78) | 9 (22) |
| 19 | 2-Br | None | 90 | 12 | 10 (83) | 2 (17) |

a) Conditions; bromoanisole 30 mmol, HCOONa 60 mmol, 5% Pd/C 0.2 mmol, water 20 ml, temp 60 °C, time 4 h. b) Based on used substrate. c) Relative yields of anisole and dimethoxybiphenyl were in parentheses. d) Entries 1—11: 4,4′-dimethoxybiphenyl, mp 174.9—176.0 °C (lit,[9] 176.5—177.0 °C). Entries 12—15: 3,3′-dimethoxybiphenyl, mp 33.7—33.9 °C (lit,[10] 34—35 °C: instable modification). Entries 16—19: 2,2′-dimethoxybiphenyl, mp 154.8—155.5 °C (lit,[11] 156—156.5 °C). e) Methyl $\alpha$-D-glucopyranoside.

the reaction mixture.

It is noteworthy that the conversion of bromoanisole increases linearly with increasing amounts of sodium hydroxide in the reduction with β-CD (Entries 2, 6, and 8), whereas it decreases to some extent in reduction without β-CD (Entries 5, 7, and 9). When an inclusion compound of β-CD with 4-bromoanisole was prepared, and then used for the reduction with sodium formate using palladium on charcoal in aqueous alkaline solution, the yields of anisole and 4,4′-dimethoxybiphenyl were 76 and 24%, respectively. These yields were substantially identical to the relative ones for Entries 1—3, 6, and 8. From this and the above-mentioned fact that conversion in a reaction with CD is directly proportional to the concentration of sodium hydroxide in the aqueous phase, it is considered that the reaction occurs predominantly in the aqueous phase; therefore, CD transports the substrate molecules into the aqueous phase via host–guest complexation.

The reaction is dependent on the nature of the CD, the relative catalytic activities being $\beta(2.1)>\alpha(1.8)>\gamma(1.0)$ in the reaction of 4-bromoanisole (Entries 2, 10, and 11). This pattern may be a reflection of the magnitude of the cavity diameters in different CDs, since the preferable structure of the inclusion complexes is sufficiently loose to allow a substrate molecule to emerge from the torus of the CD and to interact with the surface of the palladium catalyst, which is also applicable to the case for replacing a product molecule included in the cavity of CD with a new substrate molecule. The same pattern was observed for those activities in the case of substrate 3-bromoanisole (Entries 12—14); regarding the reaction of 2-bromoanisole (Entries 16—18), no difference in those activities was detected.

As can be seen from a comparison of the conversion data listed in Table 1, the substrate-selectivities by the CDs in this reaction system are generally low. This is reminiscent of the presumption of Fornasier et al.[6] that the interactions between the CD–acylpyridine inclusion complexes and the palladium catalyst are almost negligible in the hydrogenation and, hence, most of the reaction is probably carried out by uncomplexed species.

When, by reference to an example of method for the dehalogenation of aromatic compounds which was described by Bamfield and Quan,[7] hexadecyltrimethylammonium bromide was used in place of CD, without changing other reaction conditions, 4-bromoanisole was only slightly converted into anisole and/or 4,4′-dimethoxybiphenyl. The result shows that, under the reaction conditions used, the CDs are much more effective than hexadecyltrimethylammonium bromide, which is well-known as a normal phase-transfer catalyst.

It is concluded that the CDs, particularly β-CD, function effectively as inverse phase-transfer catalysts for the reduction of aryl bromides with sodium formate using palladium on charcoal as a heterogeneous hydrogenation catalyst. Because of rate acceleration, the use of sodium formate (which is a very attractive hydrogen donor), and ease of isolation of products, these new reaction conditions are useful for synthetic organic reactions, e.g., reductions of aryl halides with sodium deuterioformate to deuterio derivatives.[8]

## Experimental

**General.** All substrates and catalysts were commercial materials and used without further purification.

Gas-chromatographic (GC) analyses were performed on a Shimadzu GC-12A instrument equipped with a flame ionization (FI) detector using a glass column (OV-17 3%, 1 m×3 mm i.d.). A relative response factor method was employed for the quantitative determination of both reactants and products.

Melting points were determined with a Mettler FP 5/52 melting-point apparatus and uncorrected. IR spectra were recorded on a JASCO A-3 spectrometer. EI mass spectra were measured on a JEOL JMS-AX500 mass spectrometer at 70 eV. $^1$H NMR spectra were recorded on a JEOL JNM-EX90 spectrometer using chloroform-*d* as a solvent.

**Typical Procedure for Reduction of Bromoanisoles with CD.** Bromoanisole (30 mmol) was added to a mixture of CD (3.0 mmol), sodium formate (60 mmol), sodium hydroxide (90 mmol), 5% palladium (0.2 mmol) on charcoal, and water (20 ml). After the reaction mixture was stirred magnetically at 60 °C for 4 h, the palladium catalyst was filtered off and washed with successive, chloroform (50 ml), water (20 ml), and chloroform (30 ml). The aqueous layer of filtrates was extracted with chloroform (50 ml). The combined organic layer was dried over anhydrous sodium sulfate and subjected to a GC analysis. In all cases, the detected products were only anisole and dimethoxybiphenyl.

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