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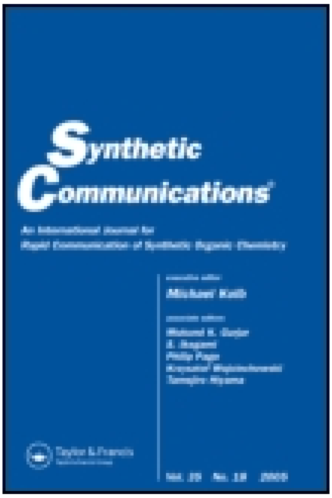

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Nuclear Versus Side-Chain Bromination of 4-Methoxy Toluene by an Electrochemical Method

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NUCLEAR VERSUS SIDE-CHAIN BROMINATION OF 4-METHOXY TOLUENE BY AN ELECTROCHEMICAL METHOD

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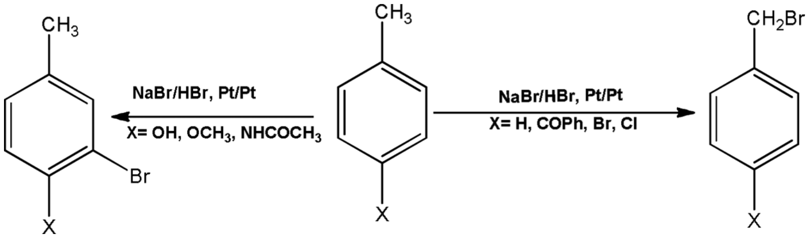
GRAPHICAL ABSTRACT



Abstract *The electrochemical bromination of 4-methoxy toluene by two-phase electrolysis yields 3-bromo 4-methoxy toluene at first, which subsequently undergoes side-chain bromination to give 3-bromo 4-methoxy benzyl bromide as a final product in 86% yield. The two-phase electrolysis consists of 25–50% NaBr as aqueous electrolyte and $CHCl_3$ containing aromatic compound as organic phase. The reaction temperature is maintained at 10–25 °C. The probable orientation of bromine atom in an alkyl aromatic compound (nuclear versus side chain) is explained from the experimental result.*

Keywords Aromatic compound; bromination; 3-bromo 4-methoxy benzyl bromide; electrochemical; organic phase; two-phase electrolysis

INTRODUCTION

Halogenated aromatic compounds have been used as intermediates for the synthesis of natural products and bioactive materials[1] and proved as important and useful reagents in organic syntheses by functionalization through carbon–carbon bond formation of diarenes and ethylenic condensations using transition metals.[2] In aromatic halogenations it is well known that bromine is more reactive than iodine and bromination gives more selective products than chlorination. When using elemental bromine it is difficult to control single bromination which depends

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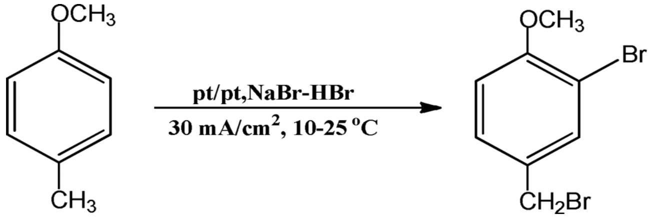


Scheme 1. Electrochemical bromination of 4-methoxy toluene.

on the reaction conditions,[3] especially for the electron-rich aromatic compounds. Thus there have been numerous reported bromination reagents such as NBS (*N*-bromosuccinimide),[4] HBr/TBHB (t-butylhydroperoxide),[5] quaternary ammonium tribromide,[6] PHP (pyridinium hydrobromide perbromide),[7] KBr/$NaBO_3$,[8] NaBr/$NaClO_2$/Mn$(acac)_3$/moist montmorillonite,[9] LiBr/CAN (ceric ammoniunm nitrate),[10] BuOBr/zeolite,[11] benzyltriphenyl phosphonium tribromide,[12] NaBr/dimethyl dioxirane,[13] and HBr/$NaBO_3$.[14] However, many of them suffer from regioselectivity of bromination of activated aromatic compounds, so the control over the degree of bromination and the regioselectivity is still needed.

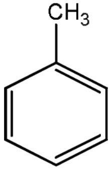
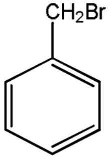
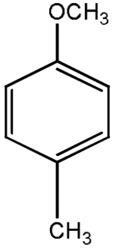
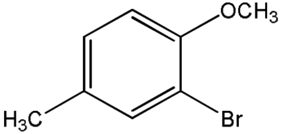
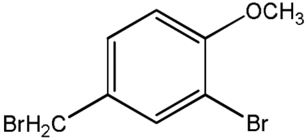
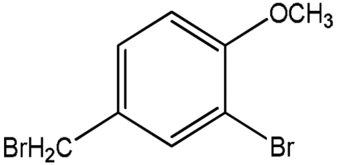
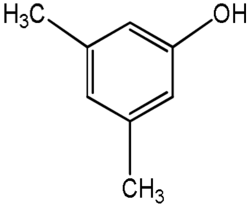
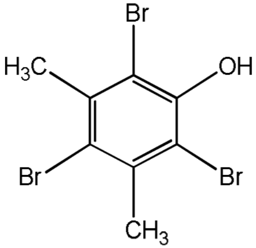
In our earlier publication we reported that two-phase electrolysis of aqueous NaBr yielded benzyl bromide (91% yield) form toluene and 4-bromoanisole (92% yield) from anisole.[15,16] Hence we studied the orientation of bromine in 4-metoxy toluene, which has both the methyl (prefers side-chain bromination) and methoxy (prefers nuclear bromination) groups. After passing a charge of 6 F/mol, 3-bromo-4-methoxy-benzyl bromide is obtained in 86% yield as shown in Scheme 1. The reaction was monitored through high-performance liquid chromatography (HPLC) to study the stepwise orientation of bromine. The experimental results of similar molecules are summarized in Table 1. The reaction was conducted galvanostatically at a current density of 30 mA/cm^2 at 10–25 °C using 50 ml of 25–50% NaBr solution containing 5 ml of 47% HBr. Platinum electrodes each of 10 cm^2 area were used as electrodes.

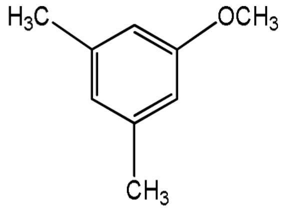
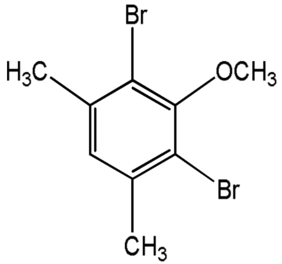
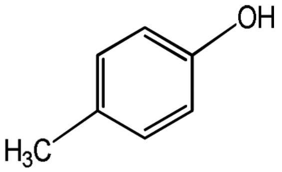
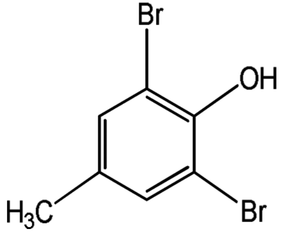
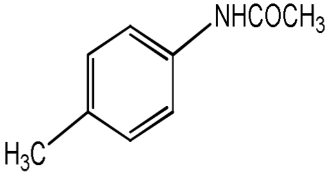
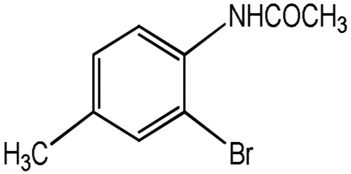
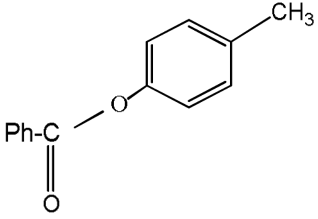
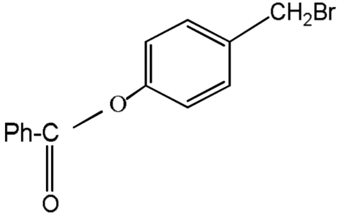
DISCUSSION

Generally a hydroxyl or methoxy group substituted benzene ring has greater reactivity in electrophilic substitution reactions than the unsubstituted one. In contrast a nitro group decreases the ring's reactivity. Thus the activation or deactivation of benzene ring toward electrophilic substitution may be correlated with the electron-donating or electron-withdrawing influence of the substituent by molecular dipole moments. The electron-donating substituents (blue dipoles) activate the benzene ring toward electrophilic attack, and electron-withdrawing substituents (red dipoles) deactivate the ring.

The substituent can influence the reactivity of the benzene in two ways. The first one is the inductive effect of the substituent. The second effect exhibited is because of conjugation of a substituent function with the aromatic ring. This conjugative interaction facilitates electron pair donation or withdrawal to or from the benzene ring, in a manner different from the inductive effect.

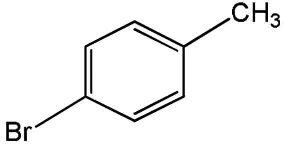
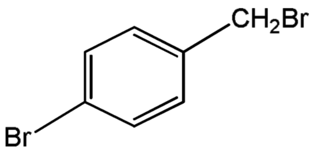
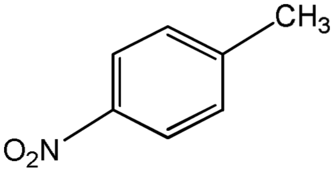
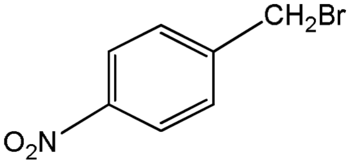
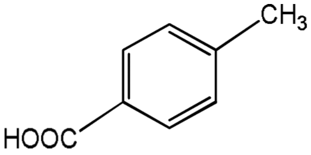
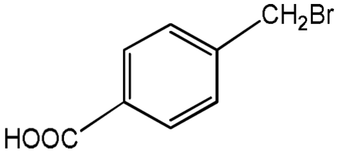
Table 1. Effect of substituent on the electrochemical bromination of aromatic compounds by two-phase electrolysis

No.	Substrate	Product	Charge passed (F)	Yield (%)	Current efficiency (%)
1			4.5	91	44
2			2	37	63
			4	56	64
			6	86	59
3			6	95	95

4			4	95	95
5			4	95	95
6			2	95	95
7			4	60	30

(*Continued*)

Table 1. Continued

No.	Substrate	Product	Charge passed (F)	Yield (%)	Current efficiency (%)
8			3	89	44
9			4	27	14
10			4	60	30

Under the reported electrochemical bromination conditions toluene (entry 1) gives benzyl bromide as a sole product in 91% yield. The reaction follows a free radical mechanism. When electron-donating groups such as -OH, –OMe (entries 3–6) are present at the benzene ring, the ring brominated products are formed after passing a charge of 2 F/mol. The reactive species involved in this reaction is bromonium ion, and the product formed is ring brominated compound due to electrophilic substitution. Two differently oriented bromine substituted compounds are obtained when the aromatic ring is substituted by either a mild activating group ($-CH_3$) or a strong activating group ($-OCH_3$, $-OH$).

In the case of 4-methoxy toluene (entry 2) on passing a charge of 2 F/mol a mixture of 3-bromo-4-methoxy toluene (37%) and 3-bromo-4-methoxy benzyl bromide (13%) is obtained along with starting material (50%). In this electrochemical reaction, the bromonium ion is formed first and attacks electron-rich benzene ring at the *ortho* position to the $-OCH_3$ group. Once the monobromination at the aromatic ring is over, subsequently the ring brominated compound undergoes side-chain bromination at the methyl group, even though some amount of starting material (4-methoxy toluene) is present as such. After passing a charge of 4 F/mol, 3-bromo-4-methoxy benzyl bromide is formed in 56% along with 34% 3-bromo-4-methoxy toluene. On further electrolysis 3-bromo-4-methoxy benzyl bromide is formed in 86% yield along with 14% 3-bromo-4-methoxy toluene after passing a charge of 6 F/mol. This is confirmed by NMR and HPLC analysis.

From these experimental results, it is observed that in the electrochemical bromination of 4-methoxy toluene, ring bromination is preferred over side-chain bromination at the initial stage and the final product 3-bromo-4-methoxy benzyl bromide is obtained after passing a total charge of 6 F/mol.

In the case of 3,5-dimethyl phenol (entry 3) the highly activating substituent ($-OH$) predominates in directing the orientation of bromine atom even though there are two mild activating $-CH_3$ groups present in the molecule. Consequently 2,4,6-tribromo-3,5-dimethyl phenol was obtained as a single product, after passing a charge of 6 F/mol (theoretical current required for three bromine substitution) and the molecule is confirmed by the absence of aromatic proton signal in ^1H NMR spectra.

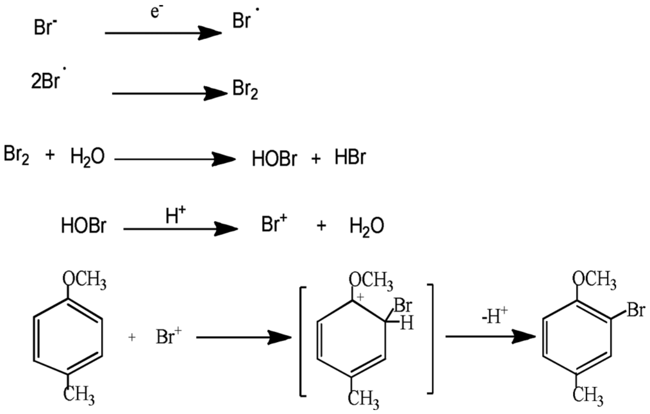
The bromination of 3,5-dimethyl phenol after protecting its phenolic group [to its methyl ether (entry 4)] afforded 2,6-dibromo-3,5-dimethyl anisole as product after passing a charge of 4 F/mol. In this case the bromination took place in a controlled manner; that is, only the *ortho*-position to the methoxy group is substituted even though the *para*-position is vacant. The reason may be that the presence of two methyl groups in the phenyl ring makes the molecule more electron rich.

2,6-Dibromo-4-methyl phenol is formed as a product in 95% yield when *p*-cresol (entry 5) is brominated. 4-Methyl acetanilide (entry 6) gives regioselective ring brominated products; that is, bromine is substituted at the *ortho*-position to the acetamide group. Side-chain bromination is preferred when the benzene ring is substituted with a nonactivating [–H, (entry 1)] or mild deactivating group ($-OCOPh$, $-COOH$, and $-Br$, entries 7–9) with an average yield of 60–89%. When a strong deactivating group $-NO_2$ is substituted (entry 10), side-chain brominated product is formed in lower yields (27%) with less current efficiency.

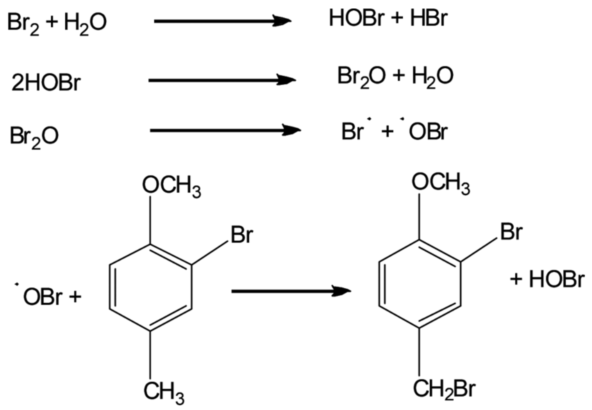
Mechanism

The electrochemically generated bromine molecule combines with water and gives one molecule of hypobromous acid and one molecule of HBr. As the hypobromous acid is unstable because of its high ionic nature and in the presence of hydrobromic acid, one molecule of water is removed from the hypobromous acid giving Br^+, which attacks the electron-rich aromatic ring (Scheme 2). The product obtained under these conditions is exclusively ring brominated (*ortho* to the $-OCH_3$ group). Subsequently on passing a further 2 F of charge benzylic bromination takes place by free radical mechanism (Scheme 3).

In conclusion when there are strong electron-denoting groups present at the aromatic ring, bromination occurs selectively on the aromatic ring with good yield. When slightly electron-donating, electron-neutral, or electron-withdrawing groups are attached, bromination occurs selectively on the benzylic position with lower yield.



Scheme 2. Mechanism for electrophilic substitution reaction.



Scheme 3. Side-chain bromination of 3-bromo 4-methoxy toluene by free radical mechanism.

EXPERIMENTAL

General Procedure for Electrochemical Bromination

A solution of 4-methoxy toluene (0.625 g, 5 mmol) in 25 ml chloroform was taken in a beaker-type undivided cell. A 25% aqueous sodium bromide solution (50 ml) containing 5 ml of 47% HBr was added to it. Platinum electrodes (each of 10 cm^2 area) were placed in the upper layer of the aqueous phase. The organic phase alone was stirred with a magnetic stirrer at a rate of 40 rpm in such a way that the organic layer did not touch the electrodes. The electrolysis was conducted galvanostatically at a current density of 30 mA/cm^2 until the quantity of charge indicated in Table 1 was passed at 15 °C.

After completion of electrolysis, the lower organic phase was separated, washed with 10% sodium thiosulfate solution followed by water (2 × 25 ml), and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford 1.46 g (86% yield) of 3-bromo 4-methoxy benzylbromide as product.

The electrolysis was monitored by high-performance liquid chromatography (Shimadzu) using a Shimpack ODS column (120 × 4.5 mm) as the stationary phase. The eluent consisted of methanol–water (70:30) at a flow rate of 1 ml/min. Samples were analyzed using an ultraviolet (UV) detector at a wavelength of 254 nm. The proton NMR spectra were recorded with a Bruker NMR spectrometer (400 MHz).

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944; (b) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575–590; (c) Nicolau, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377–1385.
2. (a) Diederich, F.; Stang, P. J. *Metal-Catalysed Cross-coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998 (b) Merkushev, E. B. *Synthesis* **1988**, 923–937; (c) Heck, R. F. *Org. React.* **1982**, *27*, 345; (d) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (e) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419–422.
3. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 4th ed.; John Wiley and Sons: New York, 1992; p. 531.
4. (a) Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *Synlett* **1997**, *62*, 1241–1242; (b) Bloomer, J. L.; Zhengd, W. *Synth. Commun.* **1998**, *28*, 2087–2095; (c) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504–4506; (d) Cammidge, A. N.; Crepy, K. V.; Fugier, M. *Synth. Commun.* **1997**, *27*, 4159–4162; (e) Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328–5331.
5. (a) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127–11142; (b) Bharte, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 6349–6350; (c) Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 4085–4088.
6. (a) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247–249; (b) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.

Tetrahedron Lett. **1998**, *39*, 8163–8166; (c) Kajigaeshi, S.; Moriwaki, M.; Tanaka, T.; Fujisaki, S.; Kakinami, T.; Okamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 897–899.

7. Reeves, W. P.; Lu, C. V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. *Synth. Commun.* **1998**, *28*, 499–505.
8. (a) Bandgar, B. P.; Nigal, N. J. *Synth. Commun.* **1998**, *28*, 3225–3229; (b) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083–2085.
9. Hirano, M.; Yakabe, S.; Monobe, H.; Morimoto, T. *Synth. Commun.* **1998**, *28*, 669–676.
10. Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 6941–6942.
11. Smith, K.; El-Hiti, G. A.; Hammond, M. E. W.; Bahzad, D.; Li, Z.; Siquet, C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2745–2752.
12. Hajipour, A. R.; Mallakpour, S. E.; Imanieh, H.; Pourmousavi, S. A. *J. Chem. Res., Synth.* **2002**, 272–273.
13. Bovicelli, P.; Mincione, E.; Antonioletti, R.; Bernini, R.; Colombari, M. *Synth. Commun.* **2001**, *31*, 2955–2963.
14. Deshmukh, A. P.; Padiya, K. J.; Jadhav, V. K.; Salunkhe, M. M. *J. Chem. Res., Synth.* **1998**, 828–829.
15. Raju, T.; Kulangiappar, K.; Anbu Kulandainathan, M.; Muthukumaran, A. *Tetrahedron Lett.* **2005**, *46*, 7047–7050.
16. Raju, T.; Kulangiappar, K.; Anbu Kulandainathan, M.; Uma, U.; Malini, A.; Muthukumaran, A. *Tetrahedron Lett.* **2006**, *47*, 4581–4584.