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ORIGINAL PAPER

# Selectivity enhancement of aromatic halogenation reactions at the micellar interface: effect of highly ionic media

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**Abstract** Halogenation (iodination and bromination) of various aromatic compounds has been studied in micellar media in order to observe the effect on regioselectivity and conversion of the reaction. The addition of surfactant causes a change in the chemical shifts of the aromatic proton resonance of phenol which proves the orientation of the aromatic compound on the micellar surface. However, increase in ionic strength of the reaction media affects the selectivity of reaction by disturbing this spatial orientation of the aromatic compound in the micelle. Selectivity towards particular isomers is dependent on the concentration of the surfactant. In bromination of chlorobenzene (deactivated aromatic compound) enhancement in selectivity and conversion towards the *para* isomer has been observed.

**Keywords** Micelles · Aromatic halogenation · Electrophilic substitution

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## Introduction

Micelles are self-assembled nanostructures of amphiphilic monomers forming a hydrophilic outer shell area and a hydrophobic core. The use of micelles as reaction media is widespread and has been investigated in detail for different reactions in aqueous and organic media [1]. Most aromatic compounds have a very low solubility in water and the presence of water adversely affects the product yield; hence organic solvents (nonpolar media) are often used for aromatic substitution reactions [2]. The cost-effective and eco-friendly use of micellar aggregates as microreactors enhances the scope of organic reactions. The interface of micellar aggregates is located between the outer hydrophilic bulk and the inner organic (hydrophobic) core. This anisotropic area is known as the palisade layer. It provides a useful reaction site to enhance the conversion and selectivity of various reactions [3]. As part of our ongoing research into selectivity improvement in organic synthesis [4–12], we have already described improvement in the regioselectivity of chlorination of phenol and *o*-chlorophenol in the presence of micelles [4]. We now present a study of selectivity enhancement in aromatic halogenation reactions.

Halogenated aromatic compounds are of great use in pharmaceuticals [13]. In the literature various methods have been reported to improve the regioselectivity in the iodination and bromination of activated aromatic compounds and these include employing specific techniques [14, 15], catalysts [16–18], and reagents [19–25]. However, most of these methods have some limitations such as the use of strong and/or specialized halogenating agents, toxic and expensive reagents, low yields, and long reaction times. The pioneering kinetic studies were done on chlorination and bromination reactions [26, 27].

Synthetic methods involving a source of positive iodine as the reactive species [28–30] seem to be the most convenient method for the direct halogenation of aromatics. However, the use of iodine for the synthesis of this important class of compounds is not extensively applied because of the weaker electrophilic nature of iodine than chlorine and bromine. These limitations in generating haloaromatics and their important applications in various fields have increased research interest in finding methodologies of aromatic halogenation that are suitable in later stages of total synthesis and with substrates containing complex functionalities. Selectivity improvement towards a particular product in total synthesis of bioactive compounds is the key factor to affect the overall yield and consequently implementation of such a process in industry. Halogenation reactions in micellar or aqueous systems proved to be very useful [31–36].

In that regard, we intend to present our study of the halogenation of aromatic compounds in micellar media. The objective of the present work is to study the effect of micellar media on the regioselectivity of iodination and bromination and to observe the effect of halogenating reagents on the orientation of an aromatic compound in a micelle with the help of proton NMR spectroscopy. The use of micellar interface as reaction site is well known; however, mechanistic studies of this micellar catalyst system for particular reactions are limited. Although fluorination, chlorination, bromination, and iodination are all halogenation reactions, the different properties (e.g., size, charge, electrophilicity, etc.) of the attacking species in the corresponding reactions mean that the selectivity and conversion vary for each reaction. Hence, the complete study for each halogenation reaction in micellar media for various aromatic compounds (activated as well as deactivated) will serve as an important contribution to the study of electrophilic substitution reaction pathways. Each halogenation reaction produces different products depending on the polarity of substrates used, reactivity of attacking species, and ionic environment in which this micellar interface acts as reaction site.

## Results and discussion

In chlorination of phenol using hydrogen peroxide and hydrochloric acid it was observed that the nature of the substituent on the aromatic ring affects the balance of hydrophobicity of the molecule [4]. The solute molecule exists in a preferred average orientation in the domain of the surfactant micelle. Substituted aromatic compounds show orientation in micelles depending on the polarity of the substituent group, and due to this spatial orientation, increases in the conversion and the selectivity towards a particular product were observed [4].

### *Iodination and bromination of phenol*

In continuation of this approach for halogenation reactions in micellar media, iodination and bromination of phenol using potassium iodide/sodium bromide, sulfuric acid, and hydrogen peroxide was performed. However, to our surprise, in both cases enhancement in selectivity towards the *para*-halogenated product was observed. The conversion in the case of bromination was higher; however, enhancement in *para* selectivity was less as compared with the iodination (Table 1). The change in the selectivity of the reaction is clearly attributed to the effect of micelles on these halogenation reactions. In the case of chlorination of phenol using potassium chloride, sulfuric acid, and hydrogen peroxide a change in *ortho* selectivity was observed (Table 2). It was anticipated that the selectivity towards a particular product in halogenation reaction in micellar media depends on the nature of reagents used for halogenation.

### *Orientation of phenol in micelle*

To know the reason for this change in selectivity of halogenation with respect to the reagents used, solubilization studies of phenol in micelles were carried out using $^{1}$H NMR spectroscopy (Fig. 1). To study the effect of various ionic species on the orientation of phenol, a similar ionic atmosphere was maintained with the same ionic strength of solution as the initial ionic strength of halogenation reactions.

Table 3 shows the change in the chemical shifts of the aromatic proton resonance of phenol due to the addition of sodium dodecyl sulfate (SDS). The aromatic proton resonance of the phenol molecule shifts to lower $\delta$ values in the presence of SDS. This shift is highest for H3–H5 and smallest for H2 and H6 protons (Table 3, entry 1). This indicates that the H3–H5 protons experience a more nonpolar environment in the presence of SDS micelles, whereas H2 and H6 protons have essentially the same polar environment in both the presence and absence of SDS micelles. This suggests that the *ortho*-substituted hydrogens of phenol are present in the bulk water. On the other hand, *meta*- and *para*-substituted hydrogens are present inside the micellar interface. Thus the phenol molecule is not fully inside the micelle, but adsorbed on the micellar surface. The increase in the ionic strength of media also failed to cause any shift in aromatic proton resonance of the phenol molecule (Table 3, entries 2 and 3). This may be because the complete phenol molecule is in contact with bulk water. This indicates the presence of ionic species disturbing the spatial orientation of phenol in micelles. Though the exact model for this loose assemblage of surfactant monomers in highly ionic media is not yet clear,

**Table 1** Halogenation of various substituted aromatics

| Substrate | SDS/mM | Conversion/%[a] (yield/%)[b] | | Selectivity/% | |
|---|---|---|---|---|---|
| | | Bromo | Iodo | Bromo | Iodo |
| Phenol | 0 | 26 (22) | 25 (22) | 4-Br (66), 2-Br (34) | 4-I (70), 2-I (30) |
| | 20 | 39 (35) | 32 (30) | 4-Br (90), 2-Br (10) | 4-I (94), 2-I (6) |
| *m*-Cresol | 0 | 36 (34) | 35 (33) | 4-Br (72), 6-Br (28) | 4-I (75), 6-I (25) |
| | 20 | 42 (40) | 40 (37) | 4-Br (90), 6-Br (10) | 4-I (98), 6-I (2) |
| *o*-Cresol | 0 | 38 (35) | 38 (35) | 4-Br (71), 6-Br (29) | 4-I (85), 6-I (15) |
| | 20 | 41 (40) | 42 (39) | 4-Br (91), 6-Br (9) | 4-I (98), 6-I (2) |
| 3,5-Xylenol | 0 | 42 (40) | 40 (38) | 4-Br (62), 2-Br (38) | 4-I (60), 2-I (40) |
| | 20 | 48 (46) | 45 (43) | 4-Br (92), 2-Br (8) | 4-I (75), 2-I (25) |
| Acetanilide | 0 | 15 (12) | 15 (12) | Anilines (60), 4-Br (30), 2-Br (10) | Anilines (60), 4-I (30), 2-I (10) |
| | 20 | 28 (25) | 28 (25) | Anilines (70), 4-Br (25), 2-Br (5) | Anilines (70), 4-I (25), 2-I (5) |
| *o*-Cl-phenol | 0 | 22 (20) | 11 (10) | 4-Br (64), 6-Br (36) | 4-I (64), 6-I (36) |
| | 30 | 30 (28) | 16 (14) | 4-Br (77), 6-Br (23) | 4-I (81), 6-I (19) |
| Chlorobenzene | 0 | 3 (2) | 0 (−) | 4-Br (67), 2-Br (33) | – |
| | 30 | 6 (5) | 0 (−) | 4-Br (83), 2-Br (17) | – |
| Nitrobenzene | 0 | 0 (−) | 0 (−) | – | – |
| | 30 | 0 (−) | 0 (−) | – | – |

*SDS* sodium dodecyl sulfate

[a] Determined by gas chromatography

[b] Values in parentheses indicate isolated yields

**Table 2** Effect of reaction conditions on halogenation of phenol

| Entry | Conditions | Conversion[a]/% | Selectivity/% |
|---|---|---|---|
| 1[b] | HCl (5.15 M), $H_2O_2$ (1.99 M), 4 h | 35 | *Ortho* (30), *para* (70) |
| 2[b] | HCl (5.15 M), $H_2O_2$ (1.99 M), surfactant (0.5 mM), 4 h | 40 | *Ortho* (92), *para* (8) |
| 3 | KCl (2.5 M), $H_2O_2$ (2 M), $H_2SO_4$ (98%, 4.88 M), surfactant (20 mM), 4 h | 38 | *Ortho* (60), *para* (40) |
| 4 | KI (2.5 M), $H_2O_2$ (2 M), $H_2SO_4$ (98%, 4.88 M), surfactant (20 mM), 2 h | 32 | *Ortho* (94), *para* (6) |
| 5 | NaBr (2.5 M), $H_2O_2$ (2 M), $H_2SO_4$ (98%, 4.88 M), surfactant (20 mM), 2 h | 39 | *Ortho* (90), *para* (10) |

[a] Determined by gas chromatography

[b] Data from Ref. [4]

efforts are underway to elucidate it by using organic probe molecules in this system.

The enhancement in the selectivity towards *para*-halogenated phenol (in bromination and iodination) in micellar media indicates that the electrophilic attack must take place near the surface of the micelles, which is the perfect reaction site for a polar electrophile and comparatively nonpolar aromatic molecule.

*Effect of surfactant concentration*

Figure 2 explains the effect of surfactant concentration on the conversion towards *p*-bromophenol and *p*-iodophenol from phenol. Conversion was increased with increase in the surfactant concentration and attained a constant value beyond a certain surfactant concentration (25 mM SDS). The effect of two different types of surfactants, i.e., anionic (SDS and linear alkyl benzene sulfonate) and cationic (cetyltrimethylammonium bromide), on the halogenation of aromatic compounds was studied (Fig. 2a, b). Both types of surfactants, anionic and cationic, increased the conversion towards *para* halogenation and there was no noticeable difference observed for the conversion or yield of reaction product among the three surfactants. This indicates that the effect of hydrophobic and hydrophilic media is the influencing and crucial factor on halogenation reaction.

The sudden increase in the conversion at a particular concentration of surfactant (10–15 mM SDS for iodination) may be due to the effective micellar concentration

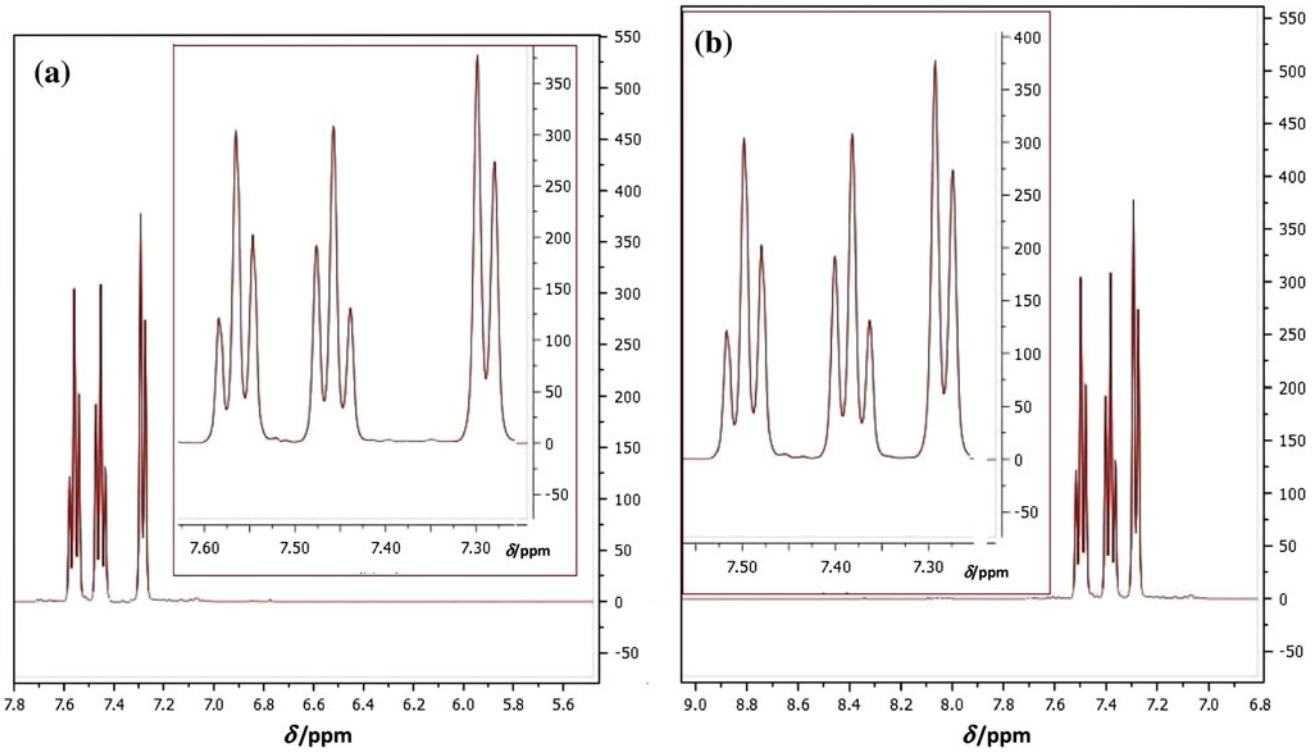


**Fig. 1** $^{1}$H NMR spectra of phenol in different media: **a** phenol + $D_2O$, **b** phenol + SDS (30 mM) + $D_2O$

**Table 3** Shift in the $\delta$ values of aromatic proton resonance of phenol due to the different media

| Entry | Conditions[a] | Ionic strength/mol $dm^{-3}$ | Chemical shift[b] |
|---|---|---|---|
| 1 | SDS (60 mM), $D_2O$ | 5 | H2 (0.010), H3 (0.050), H4 (0.055), H5 (0.050), H6 (0.010) |
| 2 | SDS (60 mM), $D_2O$, KI (2.5 M), $K_2SO_4$ (4.88 M) | 22 | H2 (0.010), H3 (0.013), H4 (0.014), H5 (0.013), H6 (0.010) |
| 3 | SDS (60 mM), $D_2O$, NaBr (2.5 M), $K_2SO_4$ (4.88 M) | 22 | H2 (0.010), H3 (0.012), H4 (0.013), H5 (0.012), H6 (0.010) |

[a] Values in parentheses indicate concentrations

[b] Values in parentheses indicate shifts

(EMC). Sufficient numbers of micelles formed at that concentration enhance the conversion of the reaction. At high concentration of surfactant (25 mM and above), conversion remained almost constant. This limit is reached when the number of micelles rises above that of substrate molecules. Acidic pH of reaction media lowers the critical micellar concentration (CMC) of the surfactant. The presence of strong electrolytes decreases the CMC of dissolved surfactant by screening the charges of ionic surfactants.

*Scope of the halogenation reaction in micellar media*

The applicability of this halogenation reaction for various aromatic compounds is shown in Table 1. Aromatic compounds with electron-donating functionalities were converted to their corresponding halogenated derivatives in excellent yield. The conversion and selectivity towards 4-bromochlorobenzene (containing the electronegative chlorine substituent) were increased in the bromination reaction of chlorobenzene in micellar media (Table 1).

In the case of methyl-substituted phenols, the order of *para* selectivity enhancement and conversion of iodination were observed to increase from phenol to *o*-cresol and *m*-cresol, probably because the solubility of methyl-substituted phenols in the micelle increases from phenol to 3,5-xylenol. However, this increasing order of *para* selectivity enhancement does not seem to continue for iodination of 3,5-xylenol. This may be because the polar and bulky iodine electrophile experienced a barrier and steric hindrance from two methyl groups when it attacks

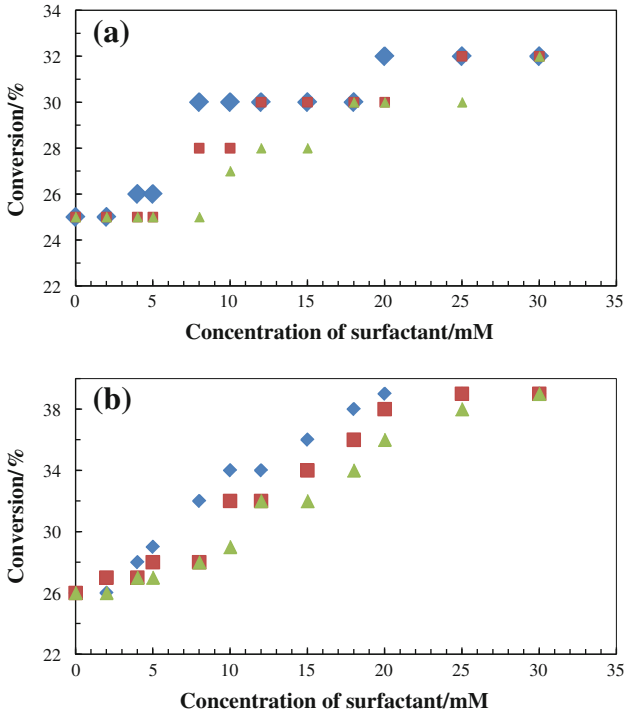


**Fig. 2** Effect of surfactant concentration (*filled diamond* SDS, *filled rectangle* LABS, *filled triangle* CTAB) on **a** iodination of phenol (1 M) in the presence of 40 $cm^3$ aqueous phase containing surfactant, sulfuric acid (98%, 4.88 M), potassium iodide (2.5 M), and hydrogen peroxide (50%, 2 M) at 35 °C for 2 h; **b** bromination of phenol (1 M) in the presence of 40 $cm^3$ aqueous phase containing surfactant, sulfuric acid (98%, 4.88 M), sodium bromide (2.5 M), and hydrogen peroxide (50%, 2 M) at 35 °C for 2 h

the *para* position of 3,5-xylenol. In the bromination and iodination of acetanilide in the presence of surfactant (Table 1), hydrolysis reaction predominates over halogenation reaction. Hence, the conversion into anilines was higher as compared with halogenated products of acetanilide.

In conclusion, the solubility study of phenol in different ionic media proves the effect of ionic strength on the orientation of phenol in micelles. Spatial orientation of phenol in micelles seems distorted as ionic strength increases from 5 to 22 mol $dm^{-3}$ and the enhanced formation of the *para*-halogenated product in these reaction systems was due to the surface adsorption phenomenon.

In the halogenation of methyl-substituted phenols, the order of *para* selectivity enhancement and conversion was observed to increase from phenol to *o*-cresol and *m*-cresol. Bromination in micellar media gave a twofold increase in conversion towards the *para*-brominated product for deactivated aromatic compounds like chlorobenzene. The effect of hydrophobic and hydrophilic media is the dominant influencing factor on the halogenation reaction. The overall scope of these halogenation reactions in micellar media was widened for various aromatic compounds.

## Materials and methods

All substrates were purchased from Aldrich Co. SDS, linear alkyl benzene sulfonate (LABS), and cetyltrimethylammonium bromide (CTAB) all in electrophoretic grade were obtained from Sigma-Aldrich Co. The purity of these surfactants was ascertained tensiometrically. All other reagents from commercial sources were used as received. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh ASTM).

For iodination of phenol, the reaction mixture was agitated for 2 h in a 250-$cm^3$ baffled glass reactor equipped with a six-bladed turbine agitator and 0.6-m internal diameter. The speed of agitation was maintained at 1.67 Hz. The aqueous phase (40 $cm^3$) contained surfactant (SDS), sulfuric acid (98%, 4.88 M), potassium iodide (2.5 M), and hydrogen peroxide (50%, 2 M), whereas the organic phase was pure substrate (1 M). Isothermal conditions were maintained at 303 ± 0.5 K. CTAB (30 mM) and 5 $cm^3$ water were added to the reaction mixture and agitated for a further 10 min. The mixture was filtered through a plug of Celite. The filtrate was extracted with diethyl ether (3 × 15 $cm^3$). The collected organic phase was concentrated under reduced pressure and purified by flash chromatography on silica gel using hexane to give the halogenated products. Conversion of the reaction was analyzed using a gas chromatograph (Chemito 8610) with a flame ionization detector. A stainless steel column (4 m × 0.37 cm) packed with 10% SE-30 on chromosorb WHP was employed for the analysis. Nitrogen at a flow rate of $0.5 \times 10^{-7}$ $m^3$ $s^{-1}$ was used as the carrier gas. All experiments were performed thrice. The variation in the results from the reported average values was within ±0.75%.

Phenol was solubilized in various solutions such as $D_2O$; SDS (30 mM) + $D_2O$; SDS (30 mM) + $D_2O$ + KI (2.5 M) + $K_2SO_4$ (4.88 M); SDS (30 mM) + $D_2O$ + NaBr (2.5 M) + $K_2SO_4$ (4.88 M) at room temperature and stirred for a sufficient length of time. $^1$H NMR spectra were obtained at ambient temperature in $D_2O$ on a Bruker spectrometer operating at 400 MHz. The $D_2O$ used was of 99.8% isotopic purity. Ionic strength for all solutions was determined by using an ELIT ion analyzer.

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