Optimising Bromination of Phenols: Investigating the Role of pH and Oxidizer in Electrophilic Substitution Reaction

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Optimising Bromination of Phenols: Investigating the Role of pH and Oxidizer in Electrophilic Substitution Reaction

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Abstract

This study investigated the influence of pH and the choice of brominating agent (KBr-chKBrO3 vs NBS-KBr) on the kinetics of Phenol bromination for aromatic substitution by altering pH levels and assessing reaction rates using thin-layer chromatography (TLC). The results revealed that the optimal pH for bromination (pH 3-10) was found to be pH 3 for the KBr system (in acetic acid/water) and pH 4 for NBS. Optimal reactivity was observed in acidic media, specifically pH 3, for the NBS system, and in acetonitrile. The activation energy (E_a) for the bromination increased linearly with pH for both systems, indicating a higher energy barrier for the reaction under less acidic conditions. Detailed mechanisms were proposed, involving the generation of active electrophiles via pH-dependent equilibria, followed by rate-determining electrophilic attack on the Phenol ring.

Introduction

Electrophilic substitution reactions, such as the bromination of aromatic compounds, play a crucial role in various industries due to their significance as intermediates in cross-coupling chemical processes [1]. Brominated compounds are also vital in cross-coupling reactions involving C-C bonds such as Suzuki, Heck, Stille, and Sonogashira reactions [2]. These processes serve as a fundamental basis for understanding aromatic halogenation, and given their widespread application in numerous chemical reactions, optimizing mass production in terms of efficiency and product formation is essential [3].

Even though bromination is widely used in many chemical reactions, the literature on suitable and optimum conditions for bromination remains extremely scanty. The commonly employed technique involves the use of Phenol with bromine water, which acts as both the oxidizing agent and the source of bromide, functioning almost like a dual-purpose reagent [4]. One of the few methods mentioned in classic NCERT Class 12 chemistry literature is referred to as a 'specific high-yield' approach; however, beyond this, there is no widely accessible method for such reactions. Bromine water, a solution of elemental bromine (Br_2) in water, is a traditional reagent for bromination reactions. However, its use poses several challenges. Elemental bromine is highly reactive and toxic, which creates significant handling risks [5]. Additionally, the toxicity of bromine and bromine-containing products raises environmental and health concerns [6]. Considering these concerns, alternative reagents with lower toxicity, such as potassium bromate ($KBrO_3$) and potassium bromide (KBr), have been explored, with $KBrO_3$ serving as an oxidizer in the reaction [7]. Another alternative involves the use of N-bromosuccinimide (NBS), which offers a safer option than bromine water [8].

Despite the significance of these alternative bromination methods, there is a noticeable lack of research addressing their efficiency, selectivity, and optimization for various conditions. The existing literature mainly focuses on the quantitative bromination of Phenols [9] and regioselective bromination using NBS and $KBrO_3$ [2]. However, these studies primarily detail the products formed and the materials required rather than delving into the underlying reaction mechanisms or optimizing conditions. Consequently, a research gap exists regarding the bromination of Phenol via the Koppeschaar method, necessitating further experimental investigations [9].

Phenol is an activated compound with high resonance stability, making bromination of Phenols a complex process [10]. To address this challenge, this study investigated the influence of pH on Phenol activation for aromatic substitution by altering pH levels and assessing reaction rates using thin-layer chromatography (TLC). Additionally, the study examined whether the choice of oxidizers impacts bromination efficiency by conducting reactions using both NBS and $KBrO_3$ as oxidizers in conjunction with KBr. It has been well-established that the aromatic bromination of Phenols is favored in polar solvents such as dimethylformamide (DMF) and acetonitrile (CH_3CN) [11]. Thus, the study aimed to determine the optimal pH for bromination and assess how pH variations influence reaction rates while also evaluating the role of different oxidizers.

The findings revealed that the KBr-$KBrO_3$ method exhibited the fastest reactivity at pH 3, with no observable reactivity at pH 10, even after overnight stirring. In contrast, the NBS-KBr method showed the highest reactivity at pH 4 and no reactivity at pH 10 after 13 hours of mixing under an inert atmosphere. The solvents used in these specific reactions were glacial acetic acid and CH_3CN, respectively. The reaction time for the KBr-$KBrO_3$ method was recorded at 48 minutes (at optimal pH), whereas the NBS-KBr reaction required 1 hour and 23 minutes (at optimal pH), as determined through titration and TLC. These results demonstrate that both pH and the choice of oxidizer play a crucial role in governing the reaction kinetics and overall efficiency of bromination [11].

Methodology

Scheme 1: KBr-$KBrO_3$ System

This section outlines the methodology employed to determine the rate of reaction at various pH levels using the KBr-$KBrO_3$ system, including the reagents, equipment, and reaction procedure. The reagents utilized were HCl, NaOH, Phenol, KBr, $KBrO_3$, glacial acetic acid, and distilled water. Eight 100 ml flasks were labeled with pH values 3, 4, 5, 6, 7, 8, 9, and 10. For acidic/neutral conditions (pH 3-7): Approximately 1 g of Phenol was weighed and added to a 100 ml flask, followed by the addition of 40 ml of glacial acetic acid as the solvent. Then, 15 ml of a 0.1 N KBr-$KBrO_3$ solution was added. KBr and $KBrO_3$ were used in a 5:1 molar ratio (as required by stoichiometry, see Eq. **??**), prepared according to standard methods (e.g., Koppeschaar method [9]). The solution was stirred briefly (approx. 200 rpm). Subsequently, 0.1 N HCl (prepared by diluting 8.177 ml of 37.5% HCl to 1000 ml) was added dropwise to adjust the pH to 3, 4, 5, and 6. For pH 7, water was used to dilute the acetic acid slightly if needed, or the initial mixture was close enough. For basic conditions (pH 8-10): Water was used as the solvent instead of glacial acetic acid. Approximately 1 g of Phenol was dissolved in 40 ml of water, followed by 15 ml of the 0.1 N KBr-$KBrO_3$ solution. Then, 0.1 N NaOH was added dropwise to adjust the pH to 8, 9, and 10. After pH adjustment, each reaction mixture was stirred continuously at 250 rpm.

Scheme 2: NBS-KBr System

In Scheme 2, the NBS-KBr reaction was conducted. The reagents employed were CH_3CN, HCl, NaOH, NBS, KBr, Phenol, and distilled water. NBS served as the brominating agent source, potentially facilitated by KBr [12] Eight 100ml flasks were labeled 3, 4, 5, 6, 7, 8, 9, and 10. First, approximately 1 g of Phenol was weighed and added to each flask, followed by 50 ml of CH_3CN as the solvent. Next, approximately 1.8 g of NBS was added directly to the solution and stirred briefly (approx. 200 rpm). Subsequently, approximately 3.164 g of KBr was added to each flask. For Flasks 3, 4, 5, and 6 (acidic/neutral), 0.1 N HCl (prepared as above) was added dropwise to achieve the target pH. For Flask 7 (neutral), minimal or no acid/base was typically needed. For Flasks 8, 9, and 10 (basic), 0.1 N NaOH was added dropwise to attain the required pH. The reactions were carried out under an inert atmosphere (e.g., Nitrogen or Argon) and stirred continuously at 250 rpm.

Note that all reactions for both schemes were run simultaneously at a controlled temperature, initially at 27°C (300 K or 303 K - be precise). The entire experiment set was then repeated at a higher temperature, 40°C (313 K) or similar (e.g., 315 K / 319 K used in later calculations - ensure consistency), to determine the temperature dependence of the rate constant and calculate activation energy. Reaction progress was monitored over time using TLC and potentially titration (e.g., quenching aliquots and titrating remaining Phenol or bromine).

Result and Discussion

Effect of pH on Rate Constants

Halogenation of Phenols can often be described by second-order kinetics, where the rate depends on the concentrations of both Phenol and the active brominating species

$$-d[\text{C6H5OH}]/dt = k_{obs}[\text{C6H5OH}][\text{Brominating Agent}]$$

Where k_{obs} is the observed rate constant under specific conditions (like constant pH), [Phenol] is the concentration of Phenol, and [Brominating Agent] represents the concentration of the effective brominating species (which might be complex and pH-dependent). [5]

Using the integrated forms of rate laws or initial rate methods based on experimental data (concentration vs. time derived from TLC/titration), we determined the observed rate constants (k) at various pH levels. The bromination of Phenol exhibited a strong pH dependence for both systems studied, with rate constants (k) decreasing significantly as pH increased from 3 to 10. This trend was consistent for both KBr-KBrO$_3$ and NBS-KBr systems, although the magnitudes of the rate constants differed. Over this pH range (3 to 10), the observed rate constant decreased substantially, highlighting the profound impact of pH on the reaction kinetics [12].

The highest k values were observed at acidic pH: pH 3 for KBr-KBrO$_3$ (k = 37.03 x 10^{-4} M^{-1} s^{-1}) and pH 3 for NBS-KBr (k = 721.5 x 10^{-4} M^{-1} s^{-1}) under the specific solvent and temperature conditions used. This suggests that the protonation state of either the Phenol (less likely activation) or, more probably, the brominating intermediates plays a crucial role. While phenoxide ion (favored at high pH) is highly activated, the generation or potency of the electrophilic bromine species appears to be strongly favored by acidic conditions [5]. The experimental data demonstrated a clear relationship where the rate constant decreased as pH increased, which could be modeled empirically using an exponential decay function:

$$k = a \cdot e^{-b \cdot \text{pH}}$$

Where 'a' and 'b' are empirical constants fitted to the data. For KBr-KBrO$_3$, the fit yielded $a \approx 0.0133$ and $b \approx 0.427$, while for NBS-KBr, $a \approx 0.2639$ and $b \approx 0.406$ (based on the plots provided). The negative exponent confirms the decrease in rate constant with increasing pH.

The reaction rates were determined by monitoring the disappearance of Phenol over time using thin-layer chromatography (TLC) and observing any accompanying color change (e.g., disappearance of Br$_2$ color if applicable) [5]. Phenol spots on TLC plates were visualized (e.g., UV light or staining reagent), and their intensity compared to standards or used to mark reaction completion. Quantitative data might have been obtained by quenching reaction aliquots at different times and using titration (e.g., iodometric titration for excess bromine or direct titration of Phenol). A calibration curve relating spot size/intensity or titre volume to Phenol concentration would allow calculation of rate constants [5].

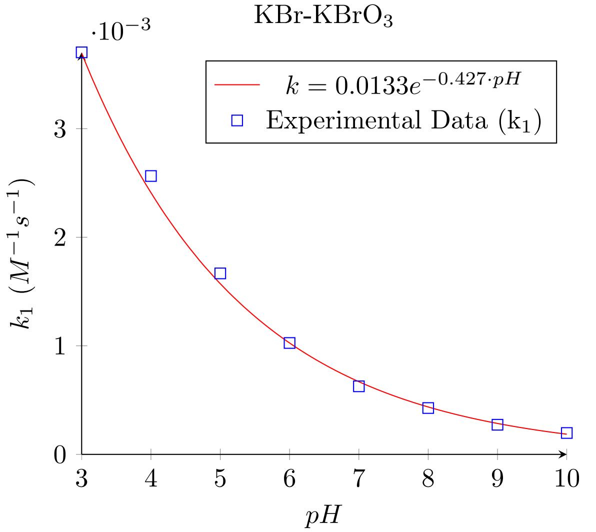

Figure 1: Rate Constant (k$_1$) vs pH for KBr-KBrO$_3$ at 27°C

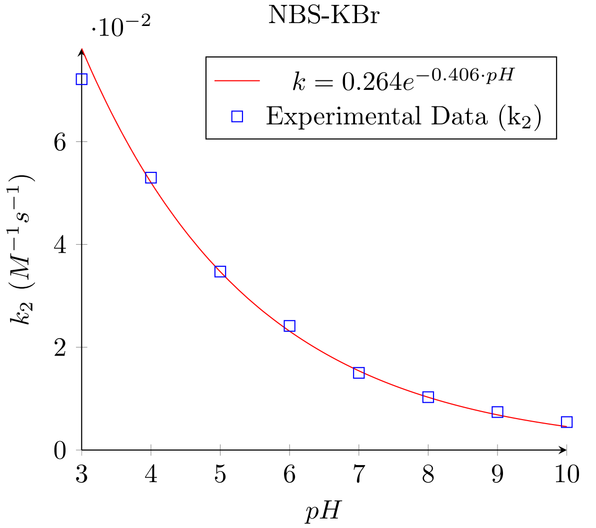

Figure 2: Rate Constant (k$_2$) vs pH for NBS-KBr at 27°C

Table 1: Values of observed rate constant (k) correspondence to pH for KBr-KBrO$_3$ (k$_1$) and NBS-KBr (k$_2$) systems at 27°C.

pH	**k$_1$** (10^{-4}) $(M^{-1}s^{-1})$	**k$_2$** (10^{-4}) $(M^{-1}s^{-1})$
3	37.03	721.5
4	25.64	529.9
5	16.67	347.2
6	10.26	241.5
7	6.27	150.15
8	4.27	102.9
9	2.73	73.9
10	1.97	54.4

Effect of Oxidizers on Reaction

A comparative analysis of the NBS-KBr and KBr-KBrO$_3$ systems reveals significant differences in reaction rates under the investigated conditions. Bromination is essential in synthesis [1], and finding efficient methods is key. Our results show that the NBS-KBr system (in CH$_3$CN) generally proceeds much faster than the KBr-KBrO$_3$ system (in glacial acetic acid/water) across the studied pH range (compare k$_1$ and k$_2$ in Table 1).

NBS acts as a source of electrophilic bromine, potentially involving intermediates like Br$^+$ or in-situ generated Br$_2$ when reacting with KBr [12]. The reaction mechanism likely involves electrophilic aromatic substitution (EAS), though radical pathways can occur under different conditions [8]. The use of polar aprotic solvents like acetonitrile (CH$_3$CN) can facilitate the reaction [1].

The KBr-KBrO$_3$ system generates Br$_2$ in situ via an acid-catalyzed redox reaction:

$$\mathrm{KBrO_3} + 5\,\mathrm{KBr} + 6\,\mathrm{H^+} \longrightarrow 3\,\mathrm{Br_2} + 6\,\mathrm{K^+} + 3\,\mathrm{H_2O} \tag{1}$$

This process inherently requires acidic conditions to proceed efficiently [13]. The generated Br$_2$ then acts as the electrophile in the EAS reaction with Phenol. The rate-limiting step could be either the generation of Br$_2$ (especially at higher pH) or the subsequent electrophilic attack. The use of glacial acetic acid/water mixtures affects polarity and potentially the speciation of bromine (Br$_2$, HOBr, etc.).

NBS-KBr is often effective for activated aromatics like Phenols and anilines [1, 8], sometimes offering good regioselectivity, especially towards monobromination under controlled conditions [12]. KBr-KBrO$_3$ can have a broader substrate scope, capable of brominating less activated systems, alkenes, etc., due to the direct generation of Br$_2$ [14]. However, control over polybromination can be challenging, especially with highly activated substrates like Phenol. Reaction conditions differ: NBS-KBr can work in various organic solvents, sometimes with acid catalysts [1, 8]. KBr-KBrO$_3$ necessitates acidic aqueous or mixed aqueous/organic media [13].

Our kinetic results (NBS-KBr being faster) suggest that under the chosen conditions, the generation or reactivity of the active brominating species from the NBS-KBr system in CH$_3$CN is more efficient than the Br$_2$ generation and subsequent reaction from KBr-KBrO$_3$ in acetic acid/water.

Effect of pH on Activation energy

Relationship between Activation Energy and pH

The activation energy (E_a) provides insight into the temperature sensitivity of the reaction rate and the energy barrier that must be overcome. We can relate E_a to pH by combining the empirical pH dependence of the rate constant with the Arrhenius equation. The empirical relationship observed is:

$$k = a \cdot e^{-b \cdot \mathrm{pH}} \tag{2}$$

The Arrhenius equation is:

$$k = A \cdot e^{-\frac{E_a}{RT}} \tag{3}$$

where A is the pre-exponential factor, R is the gas constant (8.314 J mol^{-1} K^{-1}), and T is the absolute temperature (in K). Equating the two expressions for k:

$$a \cdot e^{-b \cdot \mathrm{pH}} = A \cdot e^{-\frac{E_a}{RT}} \tag{4}$$

Taking the natural logarithm of both sides:

$$\ln(a) - b \cdot \mathrm{pH} = \ln(A) - \frac{E_a}{RT} \tag{5}$$

Rearranging for E_a:

$$\frac{E_a}{RT} = \ln(A) - \ln(a) + b \cdot \mathrm{pH} \tag{6}$$

$$E_a = RT \cdot [\ln(A) - \ln(a)] + (b \cdot RT) \cdot \mathrm{pH} \tag{7}$$

$$E_a = (bRT) \cdot \mathrm{pH} + RT \cdot \ln\left(\frac{A}{a}\right) \tag{8}$$

This equation shows a linear relationship between the activation energy E_a and pH, assuming A, a, and b are constant over the temperature range studied. The term $RT \cdot \ln(A/a)$ represents the activation energy extrapolated to pH = 0, and the slope of the E_a vs pH plot is bRT. Since b is positive in our empirical fit (k decreases with pH), the activation energy E_a is predicted to increase linearly with increasing pH.

E_a and A were determined by measuring the rate constants (k) at two different temperatures (T_1 and T_2) for each pH value and using the Arrhenius equation in its linear form: $\ln(k) = \ln(A) - \frac{E_a}{R}\left(\frac{1}{T}\right)$. Plotting $\ln(k)$ vs $1/T$ gives a slope of $-E_a/R$ and an intercept of $\ln(A)$. Alternatively, using data at only two temperatures: $E_a = \frac{R \cdot \ln(k_2/k_1)}{\frac{1}{T_1} - \frac{1}{T_2}}$ and $\ln(A) = \ln(k_1) + \frac{E_a}{RT_1}$.

Activation Energy (E_a) for the KBr-KBrO$_3$ System

For the KBr-KBrO$_3$ system, using the empirical fit parameters $a = 0.0133$, $b = 0.427$, and experimentally determined pre-exponential factors $A_1 \approx 6.84 \times 10^5$ s^{-1} at T$_1$ = 303 K and $A_2 \approx 7.10 \times 10^5$ s^{-1} at T$_2$ = 315 K (values derived from table data assuming they represent A), the calculated activation energies at different pH values are shown in Table 2.

Activation Energy (E_a) for the NBS-KBr System

Similarly, for the NBS-KBr system, with $a = 0.2639$, $b = 0.406$, and determined pre-exponential factors $A_1 \approx 1.81 \times 10^7$ s^{-1} at $T_1 = 300$ K and $A_2 \approx 4.94 \times 10^7$ s^{-1} at $T_2 = 319$ K, the calculated activation energies are presented in Table 3.

Table 2: Calculated Activation Energy (E_a) vs pH for KBr-$KBrO_3$ System.

pH	**E_a (J/mol) at 303 K**	**E_a (J/mol) at 315 K**
3	45387	50139
4	46459	51269
5	47532	52398
6	48605	53528
7	49677	54658
8	50750	55787
9	51823	56917
10	52896	58046

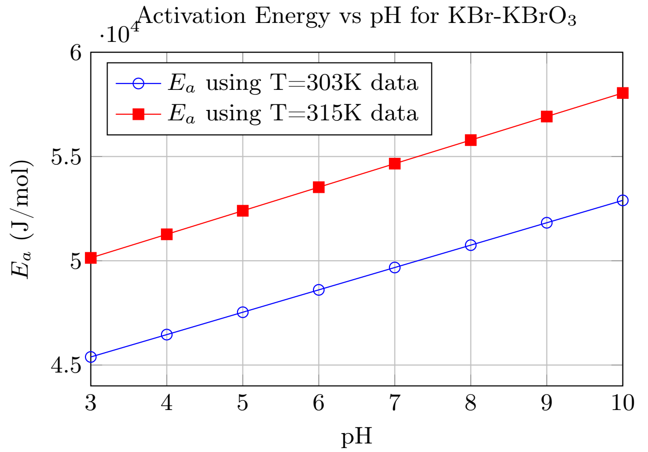

Figure 3: Calculated Activation Energy vs. pH for KBr-$KBrO_3$ System.

Table 3: Calculated Activation Energy (E_a) vs pH for NBS-KBr System.

pH	**E_a (J/mol) at 300 K**	**E_a (J/mol) at 319 K**
3	47542	52029
4	48553	53113
5	49565	54197
6	50577	55281
7	51588	56365
8	52600	57448
9	53611	58532
10	54623	59616

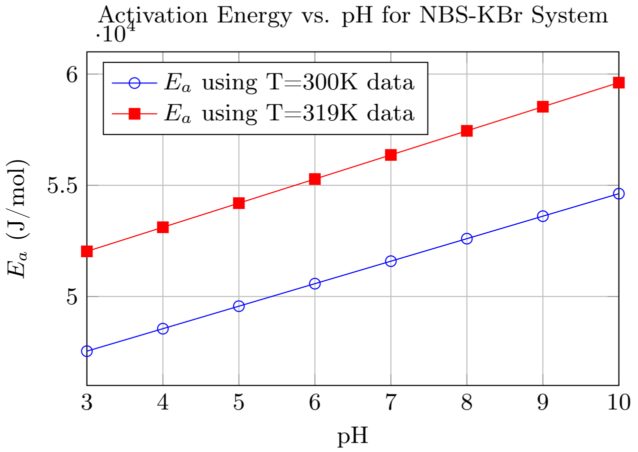

Figure 4: Calculated Activation Energy vs. pH for NBS-KBr System.

In both systems, the activation energy increases as the pH increases, consistent with the decreasing rate constants. This indicates that the reaction becomes more sensitive to temperature at higher pH values, but more importantly, the energy barrier for the rate-determining step increases significantly in less acidic conditions. This strongly supports the idea that protonation (likely of a bromine-containing intermediate) is crucial for facilitating the electrophilic attack.

Refined Mechanistic Discussion

Consideration of Kinetic Orders

The observed exponential dependence of the rate constant k on pH ($k = a \cdot e^{-b\cdot\mathrm{pH}}$) implies a complex relationship with the hydrogen ion concentration, $[H^+]$. Since pH $= -\log_{10}[H^+]$ or $[H^+] = 10^{-\mathrm{pH}}$, we can rewrite the empirical rate law: $k \propto e^{-b\cdot\mathrm{pH}} = (10^{\mathrm{pH}})^{-b\ln(e)/\ln(10)} = ([H^+]^{-1})^{-0.434b} = [H^+]^{0.434b}$. Using the fitted b values (approx 0.4), the rate constant k appears to be proportional to $[H^+]^{\approx 0.18}$.

This suggests an apparent fractional order dependence on $[H^+]$ for the overall reaction under these conditions.

$$\text{rate} \approx k''[\text{Phenol}][\text{Brominating Species}]_{total}[H^+]^{0.18} \tag{9}$$

Fractional kinetic orders often arise from multi-step mechanisms involving pre-equilibria or multiple competing pathways where the concentration of the key reactive intermediate is not linearly dependent on the concentration of a measured reactant like H^+.

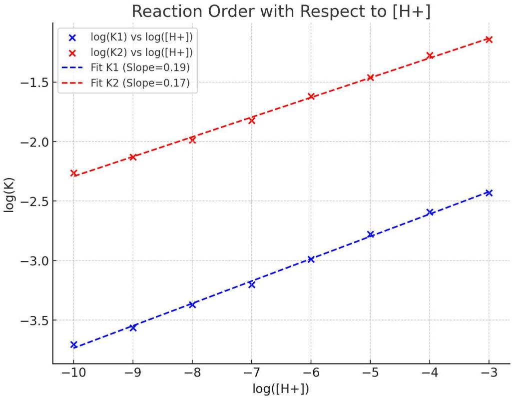

Figure 5: Log-log plot showing regression analysis of rate constant vs $[H^+]$ (Example, actual plot depends on data used for fitting 'b').

Proposed Mechanisms Accounting for pH Dependence

KBr-KBrO$_3$ System

The strong dependence on acidity points towards the importance of steps involving H^+.

Step 1: Generation of Bromine (Acid Catalyzed)

$$\mathrm{BrO_3^- + Br^- + H^+ \rightleftharpoons Br_2 + H_2O} \quad (K_1, \text{fast Equil.}) \tag{10}$$

This step clearly requires H^+ and its rate/Equil. position is highly pH-dependent. Lower pH favors Br$_2$ formation.

Step 2: Formation of Hypobromous Acid

$$\mathrm{Br_2 + H_2O \rightleftharpoons HOBr + H^+ + Br^-} \quad (K_2, \text{fast Equil.}) \tag{11}$$

HOBr itself can act as a brominating agent, but it's generally less reactive than Br$_2$ or protonated forms.

Step 3: Protonation of Hypobromous Acid (Potential Key Step)

$$\mathrm{HOBr + H^+ \rightleftharpoons H_2OBr^+} \quad (K_3, \text{fast Equil.}) \tag{12}$$

The protonated form, H$_2$OBr$^+$, is a much stronger electrophile than HOBr or potentially even Br$_2$. If this Equil. is important and not fully shifted to the right, the concentration of H$_2$OBr$^+$ would depend on both [HOBr] and $[H^+]$, potentially leading to complex dependencies if [HOBr] itself is linked to pH via K_1 and K_2.

Step 4: Electrophilic Attack (Rate-Determining Step) The attack on Phenol could involve Br$_2$ or H$_2$OBr$^+$. Given the strong pH effect persists even when Br$_2$ concentration might be substantial (low pH), attack by H$_2$OBr$^+$ seems plausible as the dominant pathway contributing to the pH dependence beyond just Br$_2$ generation.

$$\mathrm{C_6H_5OH + H_2OBr^+ \longrightarrow C_6H_5OH_2^+ + H_2O} \quad (k_{rds}, \text{slow}) \tag{13}$$

or

$$\mathrm{C_6H_5OH + Br_2 \longrightarrow C_6H_5OH_2^+ + Br^-} \quad (k'_{rds}, \text{slow}) \tag{14}$$

If multiple species (Br$_2$, HOBr, H$_2$OBr$^+$) contribute to bromination with different rate constants and their concentrations are pH-dependent through equilibria K_1, K_2, K_3, the overall observed rate constant k_{obs} would have a complex dependence on $[H^+]$, possibly resulting in the observed fractional order.

Step 5: Deprotonation

$$\mathrm{C_6H_5OH_2^+ + Base \longrightarrow C_6H_4BrOH + HB^+} \quad (\text{fast}) \tag{15}$$

Base can be water or other species present.

NBS-KBr System

NBS provides a source of electrophilic bromine, and KBr provides bromide ions.

Step 1: Possible generation of Br_2 or Br^+ NBS can react with Br^- (from KBr), potentially facilitated by acid (H^+), to generate species like Br_2 or a source of Br^+.

$$\mathrm{NBS} + \mathrm{Br}^-({}^+\mathrm{H}\equiv) \rightleftharpoons \mathrm{C_4H_4NO_2^-} + \mathrm{Br_2}({}^+\mathrm{H}\equiv) \quad \text{(Equil.)} \tag{16}$$

Or directly generating an electrophilic bromine species complexed with NBS or succinimide. The role of H+ here might be to protonate NBS or intermediates, enhancing reactivity.

Step 2: Electrophilic Attack (Rate-Determining Step) The attack on Phenol likely involves the electrophilic bromine species generated in Step 1 (e.g., Br_2 or a protonated/activated NBS-Br complex).

$$\mathrm{C_6H_5OH} + \mathrm{Br{+}source} \longrightarrow \mathrm{C_6H_5OH_2^+} \quad (k_{rds}, \text{slow}) \tag{17}$$

The observed pH dependence suggests that the formation or reactivity of the "Br+" source is enhanced by acidity, similar to the KBr-$KBrO_3$ system, potentially involving protonation steps.

Step 3: Deprotonation

$$\mathrm{C_6H_5OH_2^+} + \mathrm{Base} \longrightarrow \mathrm{C_6H_4BrOH} + \mathrm{HB^+} \quad \text{(fast)} \tag{18}$$

The fractional order in $[H^+]$ in both systems likely arises from the interplay of multiple pH-dependent equilibria governing the concentration of the active electrophilic bromine species involved in the rate-determining attack on the Phenol ring.

Conclusion

This study systematically investigated the influence of pH and the choice of brominating system (KBr-$KBrO_3$ vs NBS-KBr) on the kinetics of Phenol bromination. Key findings demonstrate a strong dependence of the reaction rate on pH for both systems, with rates decreasing markedly as pH increases from acidic to basic conditions (pH 3-10). Optimal reactivity was observed in acidic media, specifically pH 3 for KBr-$KBrO_3$ (in acetic acid/water) and pH 4 for NBS-KBr (in acetonitrile).

Under the conditions tested, the NBS-KBr system exhibited significantly faster reaction rates compared to the KBr-$KBrO_3$ system across the pH range. The relationship between the observed rate constant (k) and pH was successfully modeled using an empirical exponential decay function ($k = a \cdot e^{-b \cdot \mathrm{pH}}$), which corresponds to an apparent fractional positive order dependence on $[H^+]$ concentration (≈ 0.18).

Furthermore, the activation energy (E_a) for the bromination was found to increase linearly with pH for both systems, indicating a higher energy barrier for the reaction under less acidic conditions. This reinforces the crucial role of proton concentration in facilitating the reaction, likely through the protonation of key bromine-containing intermediates (HOBr to H_2OBr^+ or activation of NBS-derived species).

Detailed mechanisms were proposed for both systems, involving the generation of active electrophiles (Br_2, H_2OBr^+, or NBS-derived "Br+") via pH-dependent equilibria, followed by rate-determining electrophilic attack on the Phenol ring. The observed fractional order kinetics are attributed to the complex interplay of these equilibria. These findings highlight the critical importance of pH control and careful selection of the brominating agent and solvent system for optimizing Phenol bromination processes.

Future Prospects

Based on the findings of this study and the existing literature, several avenues for future research emerge:

1. Detailed Mechanistic Elucidation: Employ advanced techniques like stopped-flow spectroscopy, in-situ NMR/IR monitoring, or computational modeling (DFT) to identify and characterize the proposed intermediates (H_2OBr^+, activated NBS species) and transition states. This could provide definitive evidence for the proposed mechanisms and clarify the origin of the fractional order kinetics.

2. Solvent System Optimization: Investigate the reaction kinetics and selectivity in a broader range of solvents, including greener alternatives like water (with appropriate phase transfer catalysts if needed), ionic liquids, or deep eutectic solvents, comparing their performance with conventional solvents like CH_3CN and acetic acid [14].

3. Substrate Scope Expansion: Extend the kinetic and mechanistic study to various substituted Phenols (electron-donating and withdrawing groups) and other activated aromatic/heteroaromatic substrates. This will assess the generality of the observed pH effects and probe how substrate electronics influence optimal conditions and reaction rates [1, 2].

4. Regioselectivity Studies: Systematically quantify the regioselectivity (ortho/para ratio) and the extent of mono- vs. poly-bromination as a function of pH, temperature, reaction time, and reagent stoichiometry for both KBr-$KBrO_3$ and NBS-KBr systems. Compare the selectivity profiles with other reported methods [2, 12].

5. Exploration of Alternative Reagents: Investigate other modern brominating agents, including different N-haloimides, enzymatic halogenases, or electrochemically generated bromine species, focusing on their efficiency, selectivity, safety, and environmental impact under optimized pH conditions [14].

6. Process Development and Scale-up: Based on the optimized conditions identified for rate and potentially selectivity, explore strategies for scaling up the reaction, considering factors such as mixing efficiency, heat transfer, continuous flow processing, and downstream purification for industrial relevance.

Addressing these points will contribute to a more comprehensive understanding of Phenol bromination and aid in the development of more efficient, selective, and sustainable synthetic methodologies.

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Consent to Participate declaration: not applicable.

Consent to Publish declaration: not applicable.

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Supplementary Files

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