Bromination of Anisoles Using N-Bromophthalimide: A Synthetic and Kinetic Approach

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ABSTRACT: N-Bromophthalimide (NBP)-triggered bromination of aromatic compounds has been studied in the presence of aqueous acetic acid. Reaction Kinetics indicated first order in [NBP] and zero order in [Anisole]. The reactions afforded very good yields of corresponding bromo derivatives under kinetic conditions. The mechanism of the reaction is explained through the formation of acetyl hypobromite due to the interaction of NBP and acetic acid, which in turn reacts with anisole to afford a bromo derivative of anisole. © 2015 Wiley Periodicals, Inc. Int J Chem Kinet 48: 98–105, 2015

INTRODUCTION

Bromination of aromatic compounds is an industrially important and fundamental chemical transformation in synthetic organic chemistry. Bromoaromatic compounds are used as precursors for the synthesis of a wide number of organometallic compounds, agrochemicals, and pharmaceuticals, and some of the aromatic bromides are known to exhibit significant antibacterial properties [1–5]. Several insecticides, herbicides, pesticides, and medicinally and pharmaceutically active molecules carry bromo functionality [6]. Molecular bromine is generally used in nuclear bromination, which generates toxic and corrosive HBr as a side product. Unused (excess) molecular bromine and the liberated HBr cause hazardous and harmful environment when sent to the drain [7–9]. However, the need for bromo aromatic compounds has led the chemists to develop alternative environmentally safe and ecofriendly bromination protocols [10]. Nath and Chaudhry reported ecofriendly and environmentally benign protocol for bromination of aromatic compounds, using KBr/H_2O_2 in the presence of boric acid as a recyclable catalyst [11]. Potassium bromide in the presence of poly(4-vinylpyridine)-supported bromate in nonaqueous solution is used as a mild reagent for efficient bromination of aromatic compounds [12]. Monobromination of electron-rich aromatic compounds at room temperature has been achieved using $CuBr_2$ [13,14]. Regioselective bromination of aromatic compounds has been found using KBr in the presence of benzyltriphenylphosphonium peroxodisulfate in acetonitrile medium under reflux condition [15]. Oxybromination of activated aromatics has been afforded using shape selective zeolite such as HZSM-5, CrZSM-5(30) [16] as a catalyst, H_2O_2 as an oxidant, and KBr as a bromine source in AcOH

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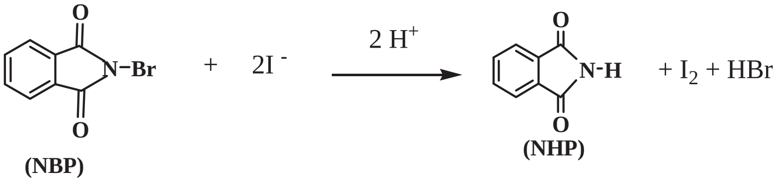
medium. In recent past, the Vilsmeier–Haack reagent [17] has been reported for efficient bromination of aromatic compounds using KBr under a conventional and solvent-free mortar–pestle condition from our laboratories. Even though few protocols have also been developed for bromination of aromatic compounds using *N*-bromosuccinimide (NBS) [18–23], such studies are not found using *N*-bromophthalimide (NBP) as a brominating agent. In this part of the work, we would like to present certain synthetic and kinetic aspects of bromination of anisoles using NBP. Nevertheless, we have recently reported kinetics of oxidation of few organic compounds [24].

EXPERIMENTAL

The reagents employed in this study were (Merck, India) and NBP (Sigma Aldrich, India). All the chemicals used were of analytical grade. Acetic acid was refluxed with chromic oxide and acetic anhydride for 6 h and then fractionally distilled according to literature procedures [25]. All aqueous solutions were prepared in doubly distilled water. Freshly prepared NBP solution was used throughout the experiment. Stock solution of NBP was prepared by dissolving a requisite amount of NBP in acetic acid. The NBP content estimated iodometrically using standard solution of sodium thiosulfate ($Na_2S_2O_3$) and 1% solution of freshly prepared starch as an indicator. The concentration of NBP was calculated using the following stoichiometric equation:



$$I_2 + 2\,Na_2S_2O_3 \rightarrow 2\,NaI + Na_2S_4O_6$$

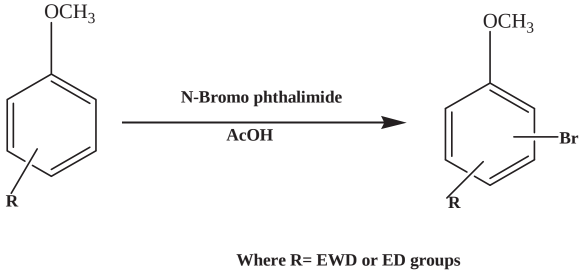
General Procedure for Conventional Synthesis of Bromo Aromatic Compounds Using NBP

A centimolar (0.01 mol) organic substrate, 0.01 mol of NBP and about 0.002 mol $Hg(OAc)_2$ and solvent (AcOH) were taken in a previously cleaned round bottom flask and stirred for about 9–13 h at room temperature. After completion of the reaction, as confirmed by TLC, the reaction mixture was treated with $NaHCO_3$ solution, followed by the addition of ethyl acetate. The organic layer was separated, dried over Na_2SO_4, and evaporated under vacuum, purified with column chromatography to get a pure product (Table I).

Table I Bromination of Aromatic Compounds by NBP under Conventional Conditions

Entry	Substrate	Product	Yield (%)
1	Anisole	4-Bromoanisole	85
2	4-Chloroanisole	2-Bromo-4-chloro anisole	78
3	4-Nitroanisole	2-Bromo-4-nitro anisole	74
4	4-Methylanisole	2-Bromo-4-methyl anisole	79
5	4-Ethylanisole	2-Bromo-4-ethyl anisole	76
6	4-Methoxyanisole	2-Bromo-4-methoxy anisole	75
7	4-Bromoanisole	2,4-Dibromo anisole	71
8	4-Isopropyl anisole	2-Bromo-4-isopropyl anisole	73

Reaction time: Conventional 10–13 h.



Stoichiometry and Product Analysis

The stoichiometry of the reaction was determined by taking known excess of [NBP] over [anisole] in aqueous acetic acid media at desired temperature. The progress of the reaction was followed for several days to ensure the completion of the reaction. The unreacted [NBP] in aliquots was estimated every day till a constancy in the titer value is obtained. Final analysis indicated that the reactants ratio [NBP]: [anisole] was found to be 1:1. The products of the

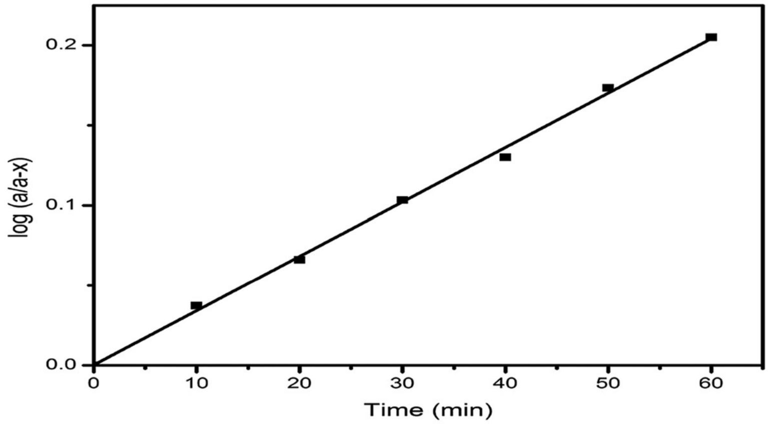


Figure 1 Order in [NBP] in the oxidation of anisole by NBP.

reactions were characterized by mass and H-NMR techniques and compared with literature reports. The NMR spectra were recorded on a Bruker Avance DEX 500 and 300 MHz instrument. The spectra were measured in $CDCl_3$ relative to TMS (0.00 ppm). As typical examples, data for **2-b**romo-4-methylanisole and 2-bromo-1-methoxy-4-nitrobenzene are given below.

2-Bromo-4-methylanisole : ‘H-NMR 6 2.27 (3H, s), 3.86 (3H, s), 6.79 (lH, d, $J = 8.2$ Hz), 7.06 (lH, dd, $J = 2.2$ and 8.2 Hz), 7.36 (lH, d, $J = 2.2$ Hz).

2-Bromo-1-methoxy-4-nitrobenzene **:** mp 108–110°C; 1H NMR ($CDCl_3$, 400 MHz) δ 8.75 (d, $J =$ 4 Hz, 1H), 8.45 (dd, $J_1 = 8$ Hz, $J_2 = 4$ Hz, 1H), 7.23 (d, $J = 8$ Hz, 1H), 4.10 (s, 3H).

Kinetic Method

The reaction mixture contained requisite amounts of thermally equilibrated NBP, anisole, and mercuric acetate solutions prepared in aqueous acetic acid. Kinetics of the bromination reactions were studied under pseudo–first-order conditions with [anisole] >>> [NBP] in a constant temperature bath at a desired temperature. The reaction was initiated by adding NBP as the last component to rest of the reactant solutions, viz. anisole, Hg(II) acetate, salt, etc. The progress of the reaction was followed by iodometric determination of the unreacted [NBP] in aliquots of the reaction mixture withdrawn into aqueous KI solutions at regular time intervals. The iodine liberated was titrated against the standard sodium thiosulfate solution using a starch indicator. Mercuric acetate was used in the reaction mixture as a bromide scavenger, which did not affect the rate of reaction to any significant extent, which was observed by earlier workers in NBS- and NBP-initiated reactions [26,27]. Under the conditions [anisole] >>> [NBP], the linear plot log ($a/(a - x)$) versus time, passing through the origin indicated the order in [NBP] to be unity (Fig. 1).

Variation of [anisole] over a wide concentration range under pseudoconditions did not alter the rate constant to any significant extent. This observation can be seen from the small magnitude of slope (<0. 2) presented in the logarithmic plot of rate constant (k') as a function of [anisole] (Fig. 2). This observation may suggest a “zero”-order kinetics (actual order $n = 0.11$) in [anisole].

According to the theory of absolute reaction rates (Eyring’s theory), the rate constant k and free energy of activation $\Delta G^{\#}$ correlated as

$$k = (RT/Nh)\exp(-\Delta G^{\#}/RT)$$

where R is the gas constant, h is the Plank’s constant, N is the Avogadro’s number, and T is the temperature in an absolute scale. The above equation is used to calculate the free energy of activation ($\Delta G^{\#}$) at various temperatures [28]. Accordingly, free energy of activation $\Delta G^{\#}$ has been calculated from the rearranged form of Eyring’s equation at different temperatures:

$$\Delta G^{\#} = RT\ \ln(RT/Nhk)$$

Free energy of activation ($\Delta G^{\#}$) values thus obtained were further used in the Gibbs–Helmholtz plot of ($\Delta G^{\#}$) versus T, using the following equation for the evaluation of enthalpy of activation ($\Delta H^{\#}$) and entropy of activation ($\Delta S^{\#}$), as shown in Table III.

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$$

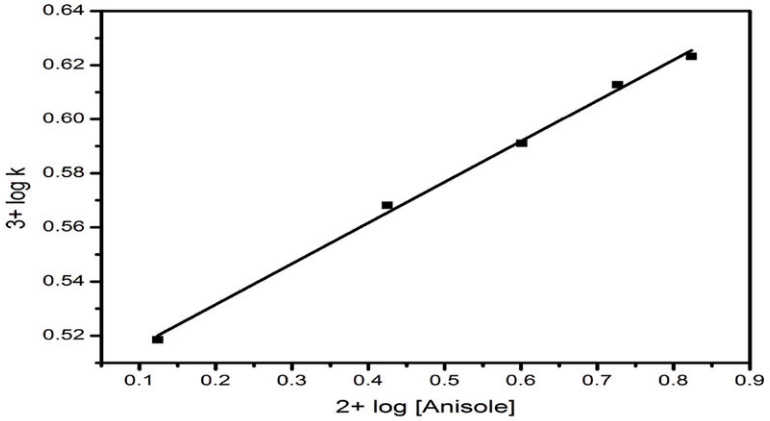


Figure 2 Effect of [anisole] on k' in the NBP–anisole reaction.

RESULTS AND DISCUSSION

NBP possesses a highly polar N–Br bond in the lines of other its structural analogue NBS. Therefore, NBP has also been reported as a good oxidizing and brominating agent by several earlier workers [24,26], and [27]. Because of large polarity of >N–Br bond NBP, like other similar *N*-halo imides such as NBS, may exist in various forms in acetic acid medium, i.e., free NBP, protonated NBP ($NBPH^+$), HOBr, $(H_2OBr)^+$, Br^+, and CH_3COOBr according to the following equilibria:

$$NBP + H_2O \rightleftharpoons HOBr + NHP \qquad (1)$$

$$NBP + H^+ \rightleftharpoons NHP + Br^+ \qquad (2)$$

$$NBP + H^+ \rightleftharpoons (NBHP)^+ \qquad (3)$$

$$HOBr + H^+ \rightleftharpoons (H_2OBr)^+ \qquad (4)$$

Reactive Species and Mechanism of Reaction

***First Approach (Case-1) Considering "Zero"-Order Kinetics in* [Anisole].** Effects of various additives such as [$HClO_4$] and [$NaClO_4$] may throw light on the influence of [Brønsted acid], ionic strength (μ), and dielectric constant (*D*) on the reaction rate are generally useful to analyze and ascertain the active species and thereby propose a plausible mechanism. A kinetic study in different compositions of binary solvent mixtures of acetic acid and water provided information of about the variation of dielectric constant (*D*) on the reaction rate.

Table II Effect of Variation of Different Additives on the Rate of NBP Bromination of Anisole

	Additive			
10^2 [NHP] (mol dm^{-3})	10^2 [$NaClO_4$] (mol dm^{-3})	HOAc% (v/v)	[$HClO_4$] (mol dm^{-3})	10^3 k'
0.6	–	50	–	2.8
1.3	–	50	–	2.7
2.0	–	50	–	2.8
2.6	–	50	–	2.9
3.3	–	50	–	3.1
–	0.6	50	–	2.9
–	1.3	50	–	2.7
–	2.0	50	–	2.8
–	2.6	50	–	2.6
–	3.3	50	–	2.5
–	–	54	–	2.9
–	–	40	–	3.2
–	–	27	–	3.4
–	–	14	–	3.5
–	–	7	–	3.9
–	–	50	0.005	2.8
–	–	50	0.020	2.9
–	–	50	0.026	3.0
–	–	50	0.033	3.1
–	–	50	0.330	3.0
–	–	50	1.50	3.1

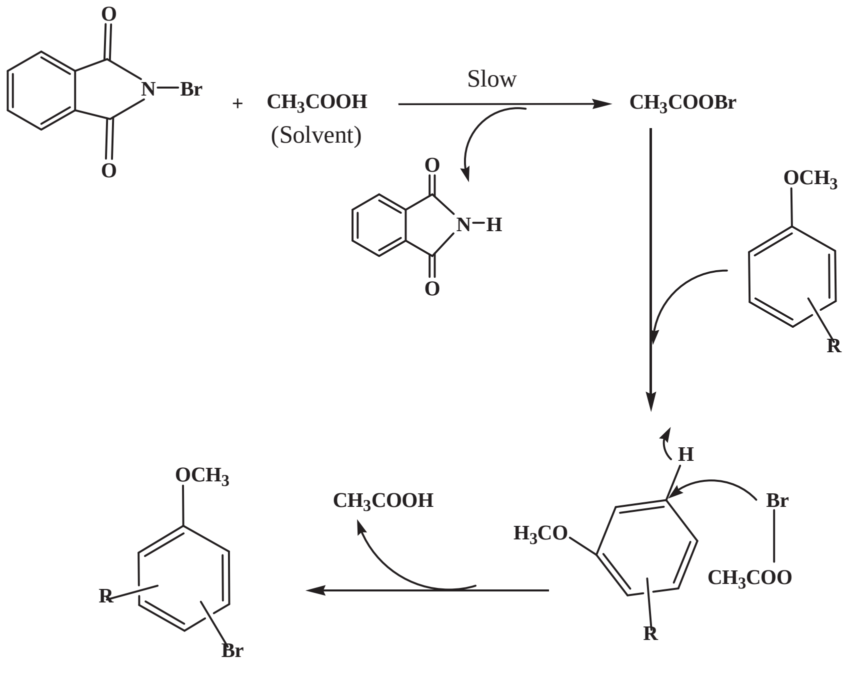
10^3[NBP] = 1.00 mol dm^{-3}; 10^2 [anisole] = 1.00 mol dm^{-3}; 10^3 [$Hg(OAc)_2$] = 2.00 mol dm^{-3}; temperature = 308 K.

Rate data presented in Table II show that none of the above additives had any significant effect on the reaction rate. However, a marginal decrease in the rate due to an increase in the HOAc% (v/v) could be attributed

Table III Kinetic and Activation Parameters for the Bromination of Anisoles by NBP

Substrate	Temperature (K)	k (min)	$\Delta G^{\neq}$ (kJ/mol)	Gibbs-Helmholtz $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$ Equation with R^2	$\Delta H^{\neq}$ (kJ/mol)	$-\Delta S^{\neq}$ (J/K/mol)
Anisole	308	0.013	86.56	$y = 143.39x + 42475$, $R^2 = 0.9944$	42.47	143.39
	313	0.016	87.41			
	318	0.021	88.18			
	323	0.030	88.70			
	328	0.038	89.50			
p-Cl anisole	308	0.014	86.43	$y = 134.55x + 45106$, $R^2 = 0.9864$	45.10	134.55
	313	0.017	87.30			
	318	0.022	88.04			
	323	0.033	88.43			
	328	0.041	89.24			
p-NO_2 anisole	308	0.014	86.27	$y = 136.03x + 44373$, $R^2 = 0.9998$	44.37	136.03
	313	0.020	86.95			
	318	0.026	87.62			
	323	0.035	88.28			
	328	0.045	89.01			
p-CH_3 anisole	308	0.017	85.80	$y = 150.12x + 39679$, $R^2 = 0.9932$	39.67	150.12
	313	0.021	86.81			
	318	0.028	87.45			
	323	0.038	88.10			
	328	0.047	88.91			
p-C_2H_5 anisole	308	0.020	85.46	$y = 153.24x + 38259$, $R^2 = 0.9975$	38.25	153.24
	313	0.027	86.14			
	318	0.033	87.05			
	323	0.042	87.79			
	328	0.055	88.47			

10^3[NBP] = 1.00 mol dm^{-3}; 10^2 [anisole] = 1.00 mol dm^{-3}; AcOH = 50% (v/v); 10^3 [$Hg(OAc)_2$] = 2.00 mol dm^{-3}.



Where R= EWD or ED groups

Scheme 1 Mechanism of NBP-induced bromination.

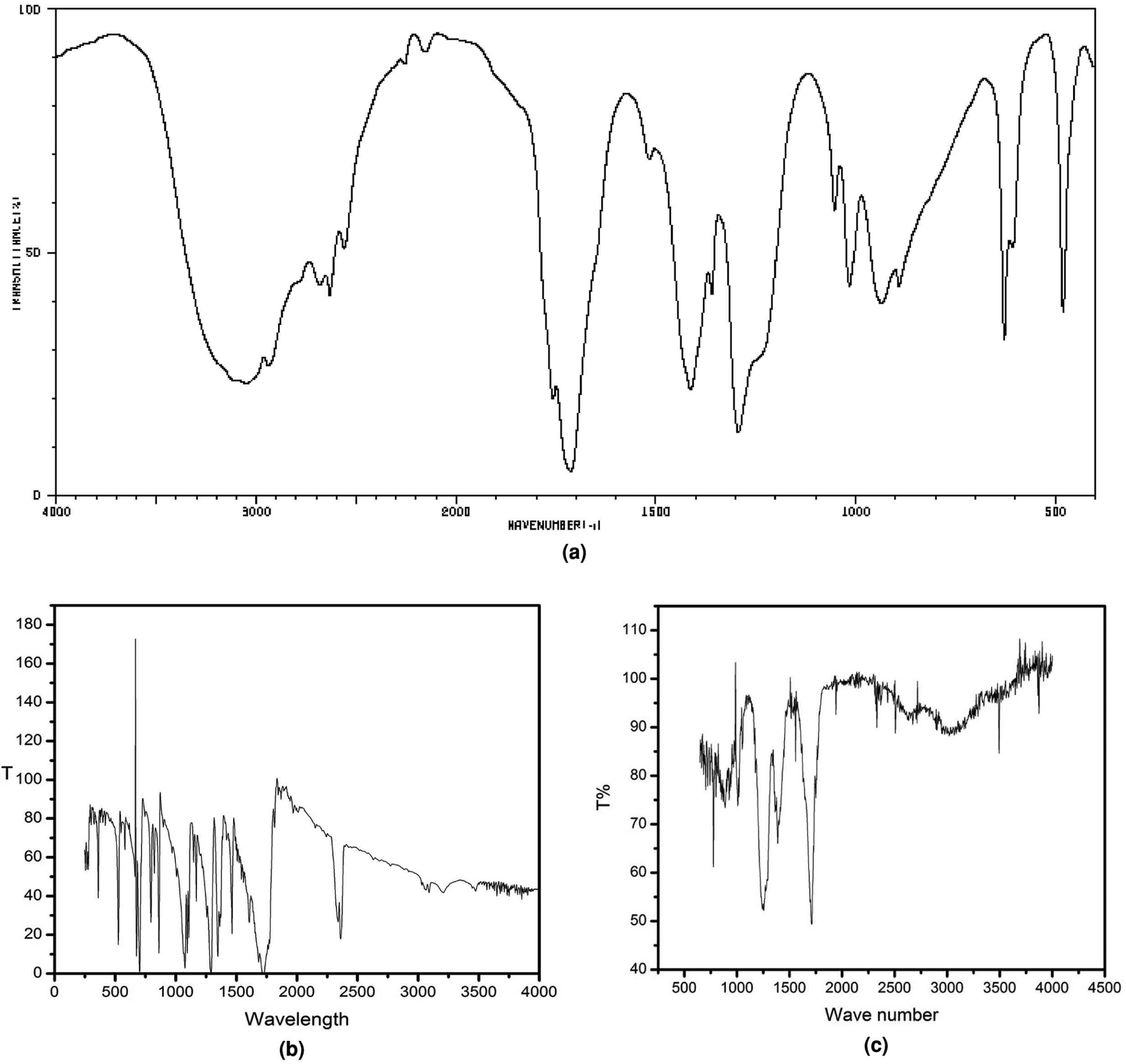
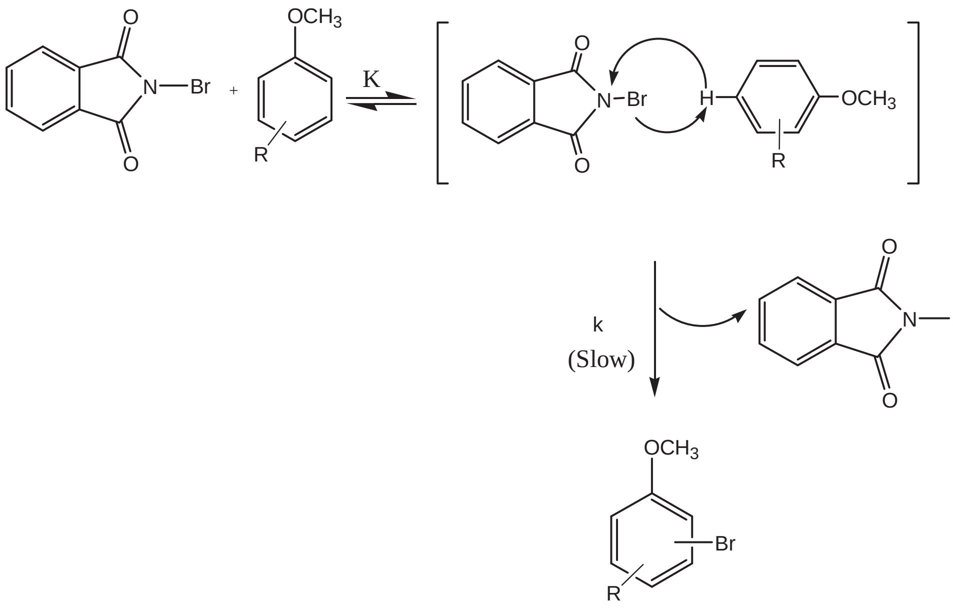


Figure 3 (A) IR spectrum of acetic acid(AcOH); (B) IR spectrum of NBP; (C) IR spectrum of (NBP+AcOH).

to the dimerization of acetic acid due to solvent–solvent interactions. If HOBr is assumed as the reactive species, the derived rate law should explain the negative effect of [phthalimide] according to equilibrium (i). But in the present study, the rate did not change with addition of phthalimide to the reaction mixture over a wide concentration range. Accordingly, participation of HOBr could be ruled out in the rate-limiting step. If protonated NBP $(NBPH)^+$ or $(H_2OBr)^+$ is taken as reactive species, the rate law should depict first-order kinetics with respect to $[H^+]$. Contrary to this aspect, our observation indicated that an increase in $[H^+]$ did not alter the rate to any significant extent, ruling out protonated NBP $(NBPH)^+$ or $(H_2OBr)^+$ is taken as a reactive species. On the other hand, observed negligible rate effects with the variation ionic strength, [NHP] and dielectric constant (Table II) may at best suggest the participation of NBP molecular species in the slow step. Since the order with respect to [anisole] is “zero,” NBP might generate acetyl hypobromite (CH_3COOBr) due to solvent (CH_3COOH)–solute (NBP) interactions as shown in Eq. (5).

$$CH_3COOH + NBP \rightarrow CH_3COOBr + NHP \quad (5)$$

Acetyl hypobromite may further react with an aromatic compound through the in situ generated bromonium ion (Br^+) to afford a corresponding bromo derivative followed by the regeneration acetic acid as shown in Scheme 1. For the above mechanism, given in



Scheme 2 NBP-induced bromination of anisoles.

Scheme 1, the rate law comes out as

$$\text{Rate} = -\text{d[NBP]}/\text{d}t = k[\text{NBP}][\text{CH}_3\text{COOH}]$$

However, it is important to note that acetic acid is used as a solvent and its concentration is far greater than [NBP] and [anisole]. Therefore, the rate law simply comes out as

$$\text{Rate} = -\text{d[NBP]}/\text{d}t = k'[\text{NBP}]$$

The rate law is in consonance with the observed results such as first-order dependence on [NBP] and zero-order dependence on [anisole] (because, $n = 0.101$, very low $<< 1.0$). Formation of acetyl hyprobromite is supported by IR and UV spectroscopic studies. The characteristic IR peaks of the carboxylic –OH group observed as as a broad band a in the range of 3000–2500 cm^{-1}(shown in Fig. 3A) underwent a substantial decrease in the intensity in the presence of NBP (Fig. 3C). Similarly, a sharp peak observed in the range of 2300–2400 cm^{-1} corresponding to the C–N moiety of NBP spectrum (Fig. 3B) also underwent a remarkable decrease in the intensity. These observations further strengthen our contention for the in situ formation of acetyl hyprobromite. Formation of acetyl hypobromite and its properties were also explored by Reilley et al [29] and Hatanaka and co-workers [30].

***Alternative Mechanism (Case-2) Considering Complex (Fractional) Order in* [Anisole].** Alternatively, for a spur of moment if we have a closer look into the observed kinetic data, it depicts very small differences in the reaction rates of the structurally different anisoles and also with an increase in the concentration of anisole. The order in [anisole] obtained as a small fraction ($n = 0.101$, very low $<< 1.0$). By considering even this small fractional (complex) order in [anisole], the Michaelis–Menten type mechanism is proposed as shown in Scheme 2.

The rate law for the above mechanism can be written as

$$\text{Rate} = \frac{kK[\text{Anisole}][\text{NBP}]}{1 + K[\text{Anisole}]}$$

Reciprocal plots of ($1/k'$) versus 1/[anisole] afforded almost nearer decomposition constant (k) values (very small variations) in structurally different anisoles as substrates with the order of reactivity of anisoles was found to be in the following order: 4-ethylanisole > 4-methyl anisole > anisole > 4-chloroanisole > 4-nitroanisole. Hammett's plot of log k versus σ depicted very poor correlation ($R^2 = 0.69$) and small reaction constant ($\rho = -\ 0.182$). In view of these reasons, the "Michaelis–Menten-type mechanism discussed under Case-2" may not be more likely than the given in Scheme 1. Hence the authors feel that the reaction follows zero-order kinetics in [anisole] and follows Scheme 1 as the most plausible mechanism.

CONCLUSIONS

The NBP reaction with anisoles in aqueous acetic acid afforded very good yields of corresponding bromo derivatives in 10–13 h. The reaction followed first-order kinetics in [NBP] and zero order in [anisole], indicating the decomposition of NBP in the rate-limiting step to generate acetyl hypobromite, which in turn affords a bromo derivative of anisole. The bromination of anisoles is governed by the transfer of bromine (as Br(I)) to acetic acid.

BIBLIOGRAPHY

1. Normant, H. Adv Org Chem 1960, 2, 165.
2. Wakefield, B. J. The Chemistry of Organolithium Compounds; Pergamon Press: Oxford, UK, 1976.
3. Weast, R. C. CRC Handbook of Chemistry and Physics; CRC Press: Boca Raton, FL, 1977.
4. Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. N. J Org Chem 1995, 60, 5328–5331.
5. Matthew, L. M.; Yogesh, R. M.; Steven, M. Tetrahedron Lett 2005, 46, 4749–4751.
6. Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. Tetrahedron Lett 2003, 44, 4085–4088.
7. Chen, Q. H.; Wang, F. P. Chin Chem Lett 2001, 12, 421.
8. Bisaraya, S. C.; Rao, R. Synth Commun 1993, 23, 779.
9. Ghiaci, M.; Asghari, J. Bull Chem Soc Jpn 2001, 74, 1151.
10. Nivrutti, B. B.; Anil, S. G.; Radhika, D. W.; Ashutosh, V. B. Tetrahedran Lett 1998, 39, 6349–6350.
11. Natha, J.; Mihir, K. C. Green Chem Lett Rev 2008, V1(4), 223–230.
12. Tajik, H.; Shirini, F; Hassan-Zadeh, P.; Rashtabadi, H. R. Synth Commun 2005, 35, 1947–1952.
13. Suchitra, B.; Sandip, K. N. Synth Commun 2007, 37, 1381–1388.
14. Tajik, H.; Mohammadpoor-Baltork, I.; Albadi, J. Synth Commun 2007, 37, 323–328.
15. Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. Synth Commun 2000, 30 (20), 3669–3675.
16. Narender, N.; Krishna Mohan, K.V.V.; Vinod Reddy, R.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. J Mol Catal, A: Chem 2003, 192, 73–77.
17. Chakradhar, A.; Roopa, R.; Rajanna, K. C.; Saiprakash, P. K. Synth Commun 2009, 39, 1817–1824.
18. Ganguly, N. C.; Dutta, P. De. S. Synthesis 2005, 1103–1108.
19. Subramanya, R. K.; Pingali, A.; Monika Madhav, A.; Jursic, B. S. Tetrahedron Lett 2010, 51, 1383–1385.
20. Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. J Org Chem 2007, 72, 5867–5869.
21. Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. J Am Chem Soc 2004, 126, 15570–15776.
22. Heropoulos, G. A.; Cravotto, G.; Screttasa, C. G.; Steele, B. R. Tetrahedron Lett 2007, 48, 3247–3250.
23. Srinivasan, C.; Chellamani, A. React Kinet Catal Lett 1981, 18(1–2), 187–191
24. (a) Anjaiah, B.; Srinivas, P. J Appl Chem 2014, 3, 2123–2130; (b) Amena, A.; P. Srinivas,, Asian J Chem 2005, 17, 553–558.
25. Orton, K. J. P.; Bradfield, A. E. J Chem Soc 1927, 983–985
26. (a) Venkatasubramanian, N.; Thiagarajan, V. Can J Chem 1969, 47, 694; (b) Krishnakumar, V.; Balachandran, V.; Chithambarathanu, T. Spectrochim Acta 2005, 62, 918; (c) Khazaei, A. A.; Manesh, A. J Braz Chem Soc 2005, 16, 874; (d) Kirsch, A.; Luning,. U. J Prakt Chem 1998, 340, 129; (e) Kirsch, A.; Luning, U.; Kruger, O. J Prakt Chem 1999, 341, 649; (f) Ramachandrappa, R.; Puttaswamy, G.; Gowda, N. M. M. Int J Chem Kinet 1998, 30, 407; (g) Day, J. C.; Govindaraj, N.; McBain, D. S.; Skell, P. S.; Tanko, J. M. J Org Chem 1986, 51, 4959; (h) Das, C. M.; Indrasenan, P. Ind J Chem A 1986, 25, 605; Ind J Chem Sect A: Inorg, Bio-inorg, Phys, Theor Anal Chem. 1987, 26, 717.
27. (a) Singh, A. K.; Jain, B.; Negi, R.; Katre, Y.; Singh, S. P.; Sharma, V. K. Transition Met Chem 2009, 34, 521; (b) Katre, Y.; Goyal, N.; Sharma, R.; Singh, A. K. J Chil Chem Soc 2013, 58, 1524; (c) Singh, A. K.; Jain, B.; Negi, R.; Katre, Y.; Singh, S. P.; Sharma, V. K. Synth React Inorg Met OrgNano-Met Chem 2010; 40(2):71–77.
28. (a) Laidler, K. J.; King, M. C. J Phys Chem 1983, 87, 2657–2664; (b) Laidler, K. J.; Meiser, J. H.; Sanctuary, B. C. Physical Chemistry, 4th ed.; Houghton Mifflin: Boston, MA,2002; p. 819; (c) Glasstone, S.; Laidler, K. J.; Eyring, H. Theory of Rate Processes; McGraw–Hill: New York; 1940. (d) Eyring, H. J Phys Chem 1935, 3, 107.
29. Reilly, J. J.; Duncan, D. J.; Wunz, T. P.; Patsiga, R. A. J Org Chem 39, 1974, 3291
30. Hatanaka, Y.; Keefer, R. M.; Andrews, L. J. J Am Chem Soc 87, 1965, 4280