ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
http://www.e-journals.net
2011, **8(1)**, 1-8

Mechanism of Oxidation of (*p*-Substituted Phenylthio)acetic Acids with *N*-Bromophthalimide

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Received 25 May 2010; Accepted 31 July 2010

Abstract: The kinetics of oxidation of (phenylthio)acetic acid (PTAA) by *N*-Bromophthalimide (NBP) in acetonitrile-water solvent mixture at 298 K in the presence of perchloric acid has been followed potentiometrically. The reaction is first-order each in NBP and PTAA and inverse fractional-order in H^+. Also, it has been found that the reaction rate is not affected by changes in ionic strength of the reaction medium or by the addition of chemicals such as phthalimide, acrylonitrile and potassium bromide. However, an increase in the water content of the solvent mixture causes an increase in the rate of reaction. These observations have been well analyzed in favour of a S_N2-type mechanism, involving NBP itself as the reactive species. Effect of substituents on the reaction rate has been analysed by employing various (*p*-sustituted phenylthio)acetic acids. The electron-releasing substituent in the phenyl ring of PTAA accelerates the reaction rate while the electron-withdrawing substituent retards the rate. The excellently linear Hammett plot yields a large negative ρ value, supporting the involvement a bromosulphonium ion intermediate in the rate-determining step.

Keywords: Potentiometry, *N*-Bromophthalimide, (Phenylthio)acetic acid, Oxidation, Bromosulphonium ion.

Introduction

The application of *N*-halo compounds in the field of organic synthesis is very wide, such as oxidation reactions, deprotection and protection of different functional groups, halogenation of saturated and unsaturated compounds, acylation of alcohols, phenols, amines or thiols, epoxidation of alkenes, aziridination and finding more and more applications[1,2]. The diverse nature of the chemistry of these compounds is due to their ability to act as sources of halonium cations, hypohalite species and nitrogen anions, which act both as bases and nucleophiles[3]. A review of literature shows that *N*-halo compounds such as *N*-halosuccinimides[4-7], *N*-halosulphonamides[8-11] (chloramine-T, bromamine-T, chloramine-B, bromamine-B, *etc.*), *N*-haloamides[12-14] (*N*-haloacetamides, *N*-bromobenzamide, *N*-chloronicotinamide, *etc.*), *N*-halosaccharins[15-17] and *N*-bromophthalimide[18,19] are commonly used for the oxidation of various organic compounds such as alcohols, aldehydes, amino acids, keto acids, sulphides, *etc*. However, no detailed kinetic study of oxidation of (phenylthio)acetic acid with *N*-bromophthalimide has so far been attempted. Herein we report the results obtained from a detailed kinetic study on the oxidation of several (*p*-substituted phenylthio)acetic acids (p-$XC_6H_4SCH_2COOH$; X = OCH_3, CH_3, H, F, Cl or NO_2) with NBP.

Experimental

The (phenylthio)acetic acids were prepared by known methods[20] and were purified by repeated recrystallisations from aqueous ethanol. Doubly distilled water was used throughout the experiment, the second distillation being from permanganate. AR grade *N*-bromophthalimide (Aldrich), perchloric acid (E.Merck) and GR grade sodium perchlorate were used as received. Acetonitrile was purified[21] by refluxing with P_2O_5.

Kinetic measurements

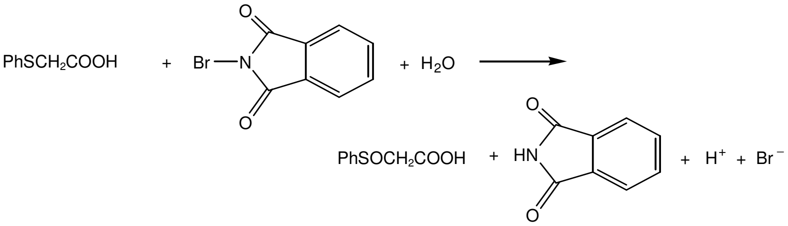
The kinetic runs were carried out in 80% acetonitrile - 20% water (v/v) solvent mixture in acid medium, the acid strength being maintained by the addition of $HClO_4$ and the ionic strength by $NaClO_4$. The kinetics were followed potentiometrically in a manner as described earlier[22]. The emf of the cell was measured periodically using an Equip-Tronics potentiometer while the reaction mixture was magnetically stirred continuously. The temperature of the reaction mixture was maintained at the desired value to an accuracy of ± 0.1 °C by circulating thermostated water in the reaction vessel. The pseudo first-order rate constants (k_{obs}) were calculated from the slopes of $\ln(E_t - E_\infty)$ *versus* time plots ($r > 0.990$) and the results were reproducible to an accuracy of ± 5%. The second-order rate constants (k_2) were obtained as k_{obs}/[PTAA].

Product analysis

In a typical experiment, the reaction mixture containing 50 fold excess of PTAA over NBP was kept overnight under stirring. The solvent was removed by distillation. The residue was then extracted with ether. The extract was dried over anhydrous sodium sulphate and the solvent evaporated. The residue was subjected to TLC analysis on a silica gel plate developed in a solvent system of *n*-butanol-acetic acid-water (40-10-50%, upper layer was used). The residue gave two spots, which were made visible by exposure to iodine; one corresponding to (phenylthio)acetic acid (R_f = 0.84) and the other to phenylsulphinylacetic acid (R_f = 0.45). Further, the IR spectra of the residue showed an intense absorption band at 1050 cm^{-1} characteristic of SO stretching frequency. The formation of corresponding phenylsulphinylacetic acid as the product was also confirmed with other (*p*-substituted phenylthio)acetic acids also.

Stoichiometry

In a typical experiment, a reaction mixture containing 10 times excess of NBP over PTAA was prepared and allowed to react overnight. Then the unreacted NBP was estimated, which established a 1:1 stoichiometry between NBP and PTAA, as represented in the Scheme 1.



Scheme 1

Results and Discussion

The kinetics of oxidation of PTAA by NBP was carried out potentiometrically in 80:20 (v/v) acetonitrile-water mixture at 298 K in the presence of perchloric acid at constant ionic strength under pseudo-first-order conditions ([PTAA] >> [NBP]). The ionic strength of the medium was maintained by the addition of $NaClO_4$. The pseudo-first-order rate constants, k_{obs} and the second-order rate constants, k_2 at different initial concentrations of NBP, PTAA and H^+ are presented in Table 1. At constant initial concentration of PTAA, k_{obs} values remain almost constant upon varying the initial concentration of NBP; this coupled with the observation of linear $\ln(E_t - E_\infty)$ *versus* time plots ensures that the order of the reaction in NBP is one. Also, the rate data in Table 1 point out that k_{obs} value increases linearly in a first-order fashion with increase in the initial concentration of PTAA. Similar trend is observed in the k_{obs} and k_2 values for the oxidation of other (*p*-substituted phenylthio)acetic acids. The constancy of k_2 at varying initial concentrations of PTAA (Table 1) and the excellent linearity of the plot of log k_{obs} *versus* log [PTAA] with unit slope (slope = 1.02 ± 0.04, r = 0.997) indicate that the reaction follows first-order kinetics with respect to [PTAA].

Table 1. Pseudo-first-order and second-order rate constants for the oxidation of PTAA by NBP in aqueous acetonitrile at 298 K[a,b]

10^3[PTAA]$_o$, M	10^4[NBP]$_o$, M	$10^4[H^+]_o$, M	$10^4 k_{\mathrm{obs}}$[c], s^{-1}	$10^2 k_2$[d], $M^{-1}s^{-1}$
1.0	1.0	1.4	4.19 ± 0.29	41.8 ± 2.9
2.0	1.0	1.4	8.48 ± 0.68	42.3 ± 3.5
4.0	1.0	1.4	20.0 ± 1.2	42.5 ± 3.0
7.0	1.0	1.4	29.9 ± 2.4	42.7 ± 3.4
10.0	1.0	1.4	43.3 ± 3.9	43.3 ± 3.9
2.0	0.4	1.4	8.08 ± 0.74	40.6 ± 3.8
2.0	0.7	1.4	8.24 ± 0.66	41.0 ± 3.3
2.0	1.3	1.4	8.32 ± 0.70	41.8 ± 3.5
2.0	1.6	1.4	8.48 ± 0.79	42.3 ± 4.0
2.0	1.0	0.2	15.8 ± 1.4	79.0 ± 7.0
2.0	1.0	0.6	13.4 ± 0.8	67.0 ± 4.0
2.0	1.0	1.0	10.8 ± 1.0	54.0 ± 5.0
2.0	1.0	2.0	6.62 ± 0.58	33.1 ± 2.9

[a] *As determined by a potentiometric technique following the disappearance of NBP; the error quoted in k values is the 95% confidence limit of 'Student t test'*[23] *.* [b] *General conditions: [I] = 0.501 M; Solvent = 80:20 (v/v) acetonitrile-water.* [c] *Estimated from pseudo-first-order plots over 60% reaction.* [d] *Individual* k_2 *values estimated as* $k_{obs}/[PTAA]_o$

Also, the plot of $1/k_{\mathrm{obs}}$ *versus* 1/[PTAA] is linear passing through origin (Figure 1), thus excluding a Michaelis-Menten type of mechanism.

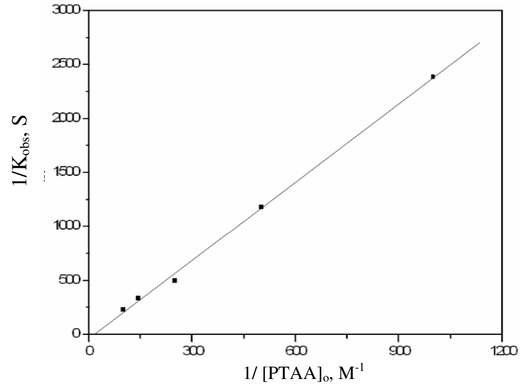


Figure 1. Double reciprocal plot for the oxidation of PTAA with NBP

The k_{obs} values measured at different initial concentrations of H^+ for the oxidation of PTAA (Table 1) reveal that the reaction rate decreases slightly with increase in the concentration of H^+. The plot of k_2 *versus* $[H^+]$ is linear (r = 0.989) with a negative slope (Figure 2), establishing the inhibitory role of H^+. The result obtained in the present study can be rationalized if NBP itself is considered to be the oxidizing species. A similar conclusion has been arrived at in the oxidation of alkyl phenyl and diphenyl sulphides with NCS[24].

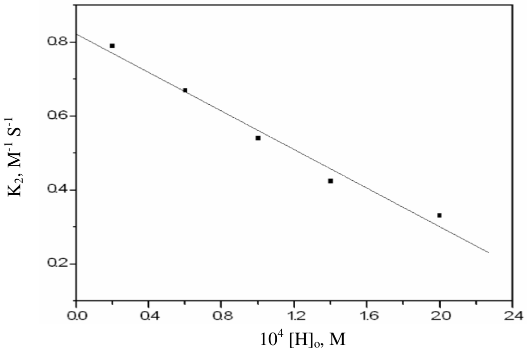


Figure 2. Effect of $[H^+]$ in the oxidation of PTAA with NBP

The rate of the reaction is not significantly affected by the change in the ionic strength of the medium (Table 2) brought about by the addition of sodium perchlorate, pointing out the participation of a neutral species as a reactant in the rate-determining step. The addition of saccharin has no effect on the rate of oxidation (Table 2), suggesting that the step in which saccharin is formed as one of the products is not reversible.

Table 2. Influence of ionic strength and phthalimide on reaction rate for the oxidation of PTAA with NBP at 298 K[a]

[I], M	$10^4 k_{obs}$, s^{-1}	10^4[phthalimide], M	$10^4 k_{obs}$, s^{-1}
0.216	6.86 ± 0.61	0	8.48 ± 0.68
0.359	7.46 ± 0.70	1.0	8.24 ± 0.77
0.501	8.48 ± 0.68	3.0	8.40 ± 0.74
0.609	9.20 ± 0.82		

[a]*General conditions: [NBP] = 0.0001 M; [PTAA] = 0.002 M; $[H^+]$ = 0.00014 M; [I] = 0.501 M unless otherwise stated; Solvent = 80:20 (v/v) acetonitrile-water*

The involvement of free-radical intermediates during the reaction can be excluded as the rate constant is not affected by the addition of acrylonitrile (Table 3). The added KBr has no effect on the rate of oxidation (Table 3), establishing that the course of the oxidation does not involve Br^+ ion or Br_2 as active species. An increase in the water content of acetonitrile-water solvent system causes an increase in the rate of oxidation (Table 3). A plot of log k_{obs} *versus* 1/ε is linear (Figure 3; r = 0.996) with a negative slope indicating that the transition state is more polarized than the two reactants together in the initial state.

Table 3. Influence of added acrylonitrile (AN), KBr and solvent composition on reaction rate for the oxidation of PTAA with NCSA at 298 K[a]

[AN], M	$10^4 k_{obs}$, s^{-1}	[KBr], M	$10^4 k_{obs}$,s^{-1}	% Water (v/v)[b]	$10^4 k_{obs}$, s^{-1}
0	8.48 ± 0.68	0	8.48 ± 0.68	20	8.48 ± 0.68
0.003	8.48 ± 0.80	0.001	8.44 ± 0.75	30	21.2 ± 1.6
0.006	8.56 ± 0.78	0.002	8.49 ± 0.78	40	44.5 ± 3.5
		0.004	8.53 ± 0.78	50	60.6 ± 5.6

[a]*General conditions: [NCSA] = 0.0001 M; [PTAA] = 0.002 M; [H^+] = 0.00014 M; [I] = 0.501 M; Solvent = 80:20 (v/v) acetonitrile-water unless otherwise stated;* [b]*Rest was acetonitrile*

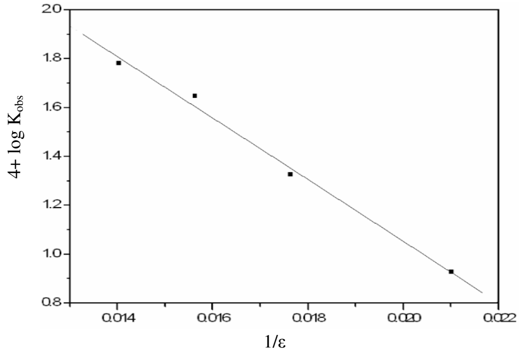


Figure 3. Plot of log k_{obs} *versus* 1/ε for the oxidation of PTAA with NBP

The effect of substituents at the 4-position of the phenyl ring of PTAA was also studied. The pseudo-first-order and second-order rate constants for the oxidation of these (*p*-substituted phenylthio)acetic acids with NBP at 298 K are collected Table 4. Electron-releasing substituents in the phenyl ring accelerate the rate, while electron-donating substituents produce the opposite effect. The log k_2 values show excellent correlation with σ_p values (Figure 4; slope = -3.22±0.05, r = 0.998). The negative value of ρ indicates an accumulation of positive charge at the reaction sulphur centre, while the magnitude of ρ value indicates the extent of charge development on the sulphur atom in the transition state of rate-determining step.

Table 4. Pseudo first-order and second-order rate constants for the oxidation of thioacids, $X\text{-}C_6H_5SCH_2COOH$ by NBP at 298 K[a]

X	$10^4 k_{obs}$, s^{-1}	$10^2 k_2$, M^{-1}s^{-1}
OMe	78.0 ± 6.9	390 ± 35
Me	33.9 ± 3.0	170 ± 15
H	8.48 ± 0.68	42.3 ± 3.5
F	5.65 ± 0.43	28.3 ± 2.2
Cl	1.73 ± 0.14	8.65 ± 0.70
NO_2	0.03 ± 0.00	0.15 ± 0.00

[b]*General conditions: [NBP]$_o$ = 0.0001 M; [Thioacid]$_o$ = 0.002 M; [H^+]$_o$ = 0.00014 M; Ionic strength = 0.501 M; Solvent = 80:20 (v/v) acetonitrile-water mixture*

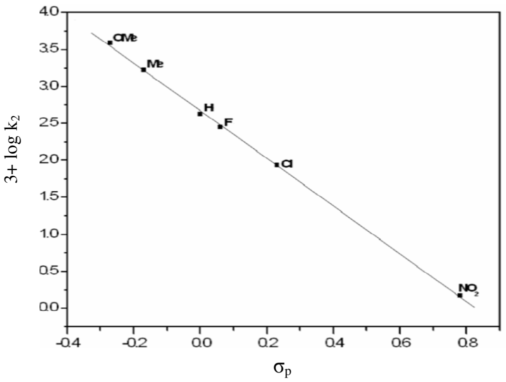
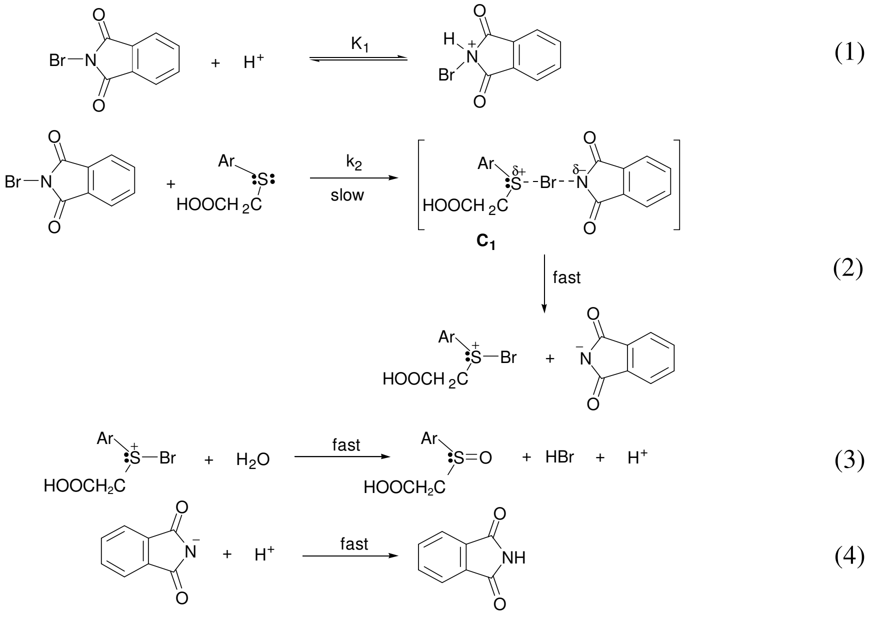


Figure 4. Hammett plot for the oxidation of (*p*-substituted phenylthio)acetic acids by NBP at 298 K

Mechanism

In earlier studies with N-halo compounds in aqueous acid medium, X^+, X_2, HOX, H_2O^+X and $>NXH^+$ are discussed[25] to be the probable reactive species. The observation that the reaction rate is not affected by added phthalimide excludes the possibility of HOBr or H_2O^+Br being the reactive species[26]. The reaction rate is independent of the added KBr concentration, which indicates that neither bromonium ion nor molecular bromine is involved in the rate-determining step of the reaction[27]. Also, the previous studies illustrate that a first-order dependence of rate of oxidation on $[H^+]$ is attributed to the involvement of H_2O^+X active species[26a], a zero-order dependence to the involvement of the HOX active species[28] and a fractional-order dependence to the involvement of the >NXH+ active species[24,29]. In the present investigation, therefore, the negative fractional-order dependence on $[H^+]$ establishes the involvement of NBP itself as reactive species. Based on these kinetic observations, the following mechanism (Scheme 2) has been proposed.



Scheme 2

The mechanism in Scheme 2 accounts for the decrease in rate of oxidation with increasing [H^+]. When the concentration of H^+ in the reaction solution is increased, more and more NBP becomes inactive in the form of $NBPH^+$ species (eq. 1), thereby causing a decrease in the rate of reaction. Similar conclusion has been arrived at in the studies of oxidation of acetophenone[30], aspirin[18] and α-hydroxy acids[31] by NBP, amino acids by NBS[32], secondary amines by CAT[32] and *L*-tyrosine by BAB[33], where the *N*-halo reagent itself has been proposed as reactive oxidizing species.

The rate law can be expressed as

$$\text{Rate} = k_2[\text{NBP}][\text{PTAA}] \tag{5}$$

The high ρ value (-3.22) obtained in the present study provides support for the chlorosulphonium ion intermediate, $(CH_2COOH)PhS^+Br$ in the reaction. This conclusion is further supported by the fact that the present ρ value is analogous to those reported for the oxidations of organic sulphides with NCS[24] (-3.33), NBA[34] (-2.37), NBB[13] (-3.18), CAT[35] (-4.25) and Br_2[36] (-3.2), where the intermediacy of such halosulphonium ions has been proposed.

Conclusion

The NBP oxidation of (*p*-substituted phenylthio)acetic acids follows a S_N2 type mechanism, in which NBP itself is the oxidizing species. The proposed mechanism has been well substantiated by substituent effect studies.

Acknowledgement

NMIA thanks UGC, Hyderabad for financial assistance in the form of Minor Research Project. The authors thank the College Management for providing the necessary facilities.

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