

Kinetics & Mechanism of Oxidation of Methionine by Sodium N-Bromotoluenesulphonamide in Aqueous Solution

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Kinetics of oxidation of DL-methionine (Mt) in the presence of HClO_4 , HCl , H_2SO_4 and NaOH by bromamine-T (BAT) has been investigated at 45°C . Same rate law is obtained in all the acid media which depends on $[\text{BAT}]^1$, $[\text{H}^+]^2$ and $[\text{Mt}]_0^0$. Halide ions catalyse the reaction. In alkaline medium, the rate law shows first order dependence each on $[\text{BAT}]_0$ and $[\text{OH}^-]$ and is independent of $[\text{Mt}]_0$. Addition of the reaction product, *p*-toluenesulphonamide retards the reaction in the alkaline medium. Solvent isotope effect has been studied. Mechanisms proposed and the derived rate laws are in agreement with the observed results.

There are but a few reports¹⁻³ on the kinetics of oxidation of organic substrates by bromamine-T (*p*- $\text{CH}_3-\text{C}_6\text{H}_4\text{SO}_2\text{NBrNa} \cdot 3\text{H}_2\text{O}$ or BAT) in comparison to similar studies with CAT as the oxidant⁴.

Methionine (Mt) is an optically active essential amino acid. Except for the work of Gensch and Higuchi⁵ and Young and Hsieh⁶, so far no kinetic data are available on the oxidation of Mt. Recently, Os(VIII)-catalysed oxidation of D-proline and L(-)-methionine has been kinetically investigated by Upadhyay⁷, and kinetics of oxidation of DL-methionine by HOCl ⁸ and chloramine-T⁸ and chloramine-B⁹ have been reported from our laboratory.

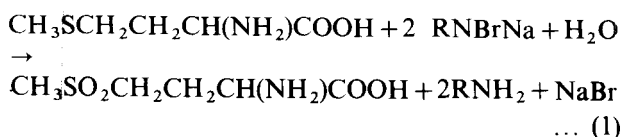
As a part of our studies on the mechanistic aspects of oxidation of substrates by aromatic bromamines, we have investigated the kinetics of oxidation of methionine by bromamine-T (BAT) in acid and alkaline media and report for the first time, the mechanism of BAT oxidation of a sulphur containing amino acid.

Materials and Methods

Preparation and characterisation of BAT have been described in earlier communications^{10b}. Aqueous solutions of methionine were employed. Experimental details have been described elsewhere¹⁰.

Stoichiometry

Mixtures containing varying ratios of BAT to amino acid in the presence of acid or alkali were equilibrated at 45°C for 24 hr. The unreacted BAT was determined by iodometric titration. The observed stoichiometry is represented by Eq. (1).



where $\text{R} = p\text{-CH}_3 - \text{C}_6\text{H}_4\text{SO}_2 -$.

p-Toluenesulphonamide and methionine sulphone among the reaction products were identified⁸ by paper chromatography.

Results

Acid medium

The kinetics of oxidation of Mt by BAT was studied in the presence of HClO_4 , HCl and H_2SO_4 . The results were found to be similar in these media and simultaneous catalysis by H^+ and Cl^- ions was observed with HCl . Hence results of investigations in the presence of HClO_4 alone are presented in this paper.

At constant $[\text{H}^+]$, with the substrate in stoichiometric excess, plots of $\log [\text{BAT}]$ versus time

Table 1—Effect of Varying Concentrations of Reactants on Rate of Oxidation of Methionine by BAT in Presence of HClO_4

$[\text{HClO}_4] = 0.07 \text{ mol dm}^{-3}$; $\mu = 0.5 \text{ mol dm}^{-3}$; temp. = 45°C

$10^3 [\text{BAT}]_0$ (mol dm^{-3})	$10^3 [\text{Mt}]_0$ (mol dm^{-3})	$10^4 k'$ (s^{-1})
4.0	10.0	4.83
5.0	10.0	4.90
6.0	10.0	4.51
7.0	10.0	4.52
8.0	10.0	4.59
9.0	10.0	5.11
7.0	5.0	4.80
7.0	8.0	4.67
7.0	15.0	4.34
7.0	20.0	4.00
7.0	30.0	3.62
7.0	40.0	3.20
7.0	50.0	3.00

are linear ($r > 0.9940$), indicating first order dependence of rate on [oxidant], (see Table 1). Values of k' are unaffected with increase in $[\text{Mt}]_0$, indicating a zero order dependence on $[\text{Mt}]$. A slight decrease in k' values at higher $[\text{Mt}]_0$ may be attributed to a dielectric effect (Table 1).

The rate increases with increase in $[\text{HClO}_4]$. A plot of $\log k'$ versus $\log [\text{H}^+]$ is linear ($r = 0.9999$) with a slope of 2. Addition of Cl^- and Br^- ions increases the rate and log-log plots are linear ($r > 0.9921$) with slopes of 0.57 and 0.17 respectively.

Presence of ClO_4^- and SO_4^{2-} ions, addition of the reaction product, *p*-toluenesulphonamide ($\sim 0.007 \text{ mol dm}^{-3}$) or variation of ionic strength of the medium ($0.07\text{--}0.5 \text{ mol dm}^{-3}$) have no effect on the rate.

Addition of methanol (0–30%, v/v) increases the rate of reaction. A plot of $\log k'$ versus $1/D$, where D is the dielectric constant of medium is linear ($r = 0.9998$) with a positive slope.

Solvent isotope studies in D_2O medium show that, while $k'_{\text{H}_2\text{O}} = 4.52 \times 10^{-4} \text{ s}^{-1}$, $k'_{\text{D}_2\text{O}} = 8.60 \times 10^{-4} \text{ s}^{-1}$ giving $k'_{\text{D}_2\text{O}}/k'_{\text{H}_2\text{O}} = 1.90$. The reaction has been studied at different temperatures (308–323 K). From the linear plot of $\log k'$ versus $1/T$ ($r = 0.9980$), activation parameters have been computed and the values are as follows: $\log A = 10.7$; $\Delta H^\ddagger = 56.6 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -131.7 \text{ JK}^{-1} \text{ mol}^{-1}$; and $\Delta G^\ddagger = 98.2 \text{ kJ mol}^{-1}$.

Addition of reaction mixture to aqueous acrylamide solution does not initiate polymerization showing the absence of free radical species.

Alkaline medium

The reaction shows first order dependence on $[\text{BAT}]_0$ ($r > 0.9940$, Table 2) and the rate is not affected by an increase in $[\text{Mt}]_0$ (Table 2). Values of k' increase with increase in $[\text{OH}^-]$ and a plot of $\log k'$ versus $\log [\text{OH}^-]_R$, where $[\text{OH}^-]_R$ represents the reactive concentration of OH^- ion⁸ is linear with a slope of unity ($r = 0.9924$), confirming first order dependence on $[\text{OH}^-]$ (Table 3).

Addition of reaction product, *p*-toluenesulphonamide retards the rate (Table 3) indicating that the reaction product is involved in an equilibrium. A plot of $\log k'$ versus $\log [\text{RNH}_2]$ is linear ($r = 0.9876$) with a slope of -0.67 .

Addition of halide ions or variation of ionic strength has no effect on the rate. An increase in methanol content (0 to 30%, v/v) increases the rate of reaction. A plot of $\log k'$ against $1/D$ is linear ($r = 0.9901$) with a positive slope.

The solvent isotope effect, $k'_{\text{H}_2\text{O}}/k'_{\text{D}_2\text{O}}$ is found to be 1.15. Activation parameters in the temperature range 308–323 K are: $\log A = 10.2$; $\Delta H^\ddagger = 51.3 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -134.5 \text{ JK}^{-1} \text{ mol}^{-1}$; and $\Delta G^\ddagger = 93.7 \text{ kJ mol}^{-1}$.

Table 2—Effect of Varying Concentrations of BAT and Mt on Rate of Reaction in Alkaline Medium

$[\text{NaOH}]_R = 0.01 \text{ mol dm}^{-3}$; temp = 45°C ; $\mu = 0.5 \text{ mol dm}^{-3}$

$10^3 [\text{BAT}]_0$ (mol dm^{-3})	$10^3 \times [\text{Mt}]_0$ (mol dm^{-3})	$10^3 k'$ (s^{-1})
2.00	10.00	2.89
3.00	10.00	2.39
4.00	10.00	2.57
5.00	10.00	2.39
6.00	10.00	2.17
7.00	10.00	2.27
5.00	5.00	3.03
5.00	8.00	2.48
5.00	20.00	2.25
5.00	30.00	2.18
5.00	40.00	2.02

Table 3—Effect of Varying $[\text{OH}^-]_R$ and $[\text{RNH}_2]$ on Rate of Reaction

$[\text{BAT}] = 0.005 \text{ mol dm}^{-3}$; $[\text{Mt}]_0 = 0.01 \text{ mol dm}^{-3}$; temp = 45°C ; $\mu = 0.5 \text{ mol dm}^{-3}$

$10^3 [\text{OH}^-]_R$ (mol dm^{-3})	$10^4 k'$ (s^{-1})	$10^3 \times [\text{RNH}_2]^*$ (mol dm^{-3})	$10^4 k'$ (s^{-1})
2.0	3.55	1.0	20.00
5.0	8.54	1.5	16.60
6.0	10.56	2.0	14.40
8.0	16.71	3.0	11.70
10.0	23.90	4.0	8.50
12.0	26.40	5.0	6.94
		6.0	6.17

*At $[\text{NaOH}]_R = 0.01 \text{ mol dm}^{-3}$.

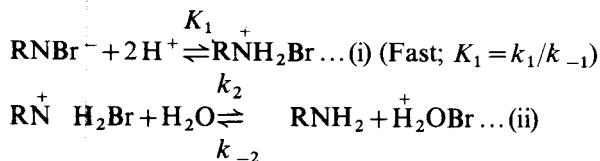
Absence of free radicals in the reaction mixture has been demonstrated by the acrylamide test.

Discussion

Mechanism in acid medium

In the case of bromamine-T reactive species are RNBr_2 , RNHBr , HOBr and Br_2 (in the presence of Br^- ion; see ref. 11). The probability of the dibromo compound as the reactive species is ruled out, since clean first order plots are obtained for the disappearance of $[\text{BAT}]$. Added *p*-toluenesulphonamide does not retard the reaction indicating that HOBr is not primarily involved in the rate-determining step. Formation of doubly protonated chloramine-T species, RNH_2Cl in acid solutions is reported by Narayanan and Rao¹² recently, with a value of 1.02×10^2 at 25°C for the second protonation constant. We believe that in the case of BAT also, protonated species RNH_2Br is involved. The rate dependence on $[\text{H}^+]^2$ and $[\text{BAT}]$ indicates a

protonation step involving the oxidant, since the rate is independent of $[Mt]_0$. Scheme 1 accounts for the observed kinetics.



(Forward reaction is rate-limiting step)



Scheme 1

Assuming steady state for $[\text{RNH}_2\text{Br}^+]$, rate law (2) can be derived:

$$-\frac{d[\text{BAT}]}{dt} = k[\text{BAT}][\text{H}^+]^2 \quad \dots(2)$$

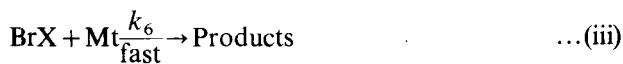
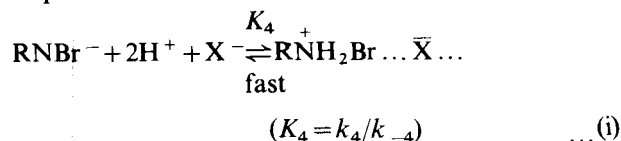
where,

$$k = \frac{k_1 k_2 [\text{H}_2\text{O}]}{k_{-1} + k_2 [\text{H}_2\text{O}]}$$

Scheme 1 is also able to explain the observed solvent isotope effect. It is seen that the protonation step (i) is followed by the rate-limiting hydrolysis (ii), where the normal kinetic isotopic effect, $k'_H/k'_D > 1$, while the solvent isotope effect k'_{H_2O}/k'_{D_2O} is predicted to be < 1 for pre-equilibrium proton transfer followed by the slow step. Thus the observed isotope effect is a composite of these two effects and has a reduced magnitude although D_3O^+ is ~ 3 times stronger¹³ than H_3O^+ .

With H_2OBr^+ as the reactive species, a reaction mechanism can be proposed in which the substrate is attacked at the nucleophilic sulphur site by the oxidant to form a sulphurane intermediate. The latter is attacked by the dipolar solvent. Elimination of H^+ and HBr results in the formation of methionine sulphoxide, which is oxidized by the second molecule of the oxidant.

Scheme 2 explains the results obtained in the presence of halide ion (X^-). The tight ion-pair¹⁴ formed in step (i) produces the interhalogen compound ClBr or Br_2 which would oxidize the substrate in a fast step:



Scheme 2

Scheme 2 leads to rate law (3),

$$\text{Rate} = \frac{k_5 K_4 [\text{BAT}][\text{H}^+]^2 [\text{X}^-]}{1 + K_4 [\text{H}^+]^2 [\text{X}^-]} \quad \dots(3)$$

which at constant $[\text{H}^+]$ reduces to

$$\text{Rate} = \frac{k_5 K_4 [\text{BAT}][\text{X}^-]}{1 + K_4 [\text{X}^-]} \quad \dots(4)$$

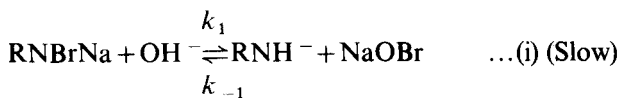
Equation (3) can be transformed into Eq. (5) for a double reciprocal plot of k' versus $[\text{Cl}^-]$ which is linear ($r = 0.9907$).

$$\frac{1}{k'} = \frac{1}{k_5 K_4 [\text{H}^+]^2 [\text{Cl}^-]} + \frac{1}{k_5} \quad \dots(5)$$

From the slope and intercept, values of k_5 and K_4 are found to be $2.17 \times 10^{-3} \text{ s}^{-1}$ and $2675.0 \text{ dm}^3 \text{ mol}^{-3}$ at $[\text{H}^+] = 0.07 \text{ mol dm}^{-3}$. When the solvent composition is varied, plot of $\log k'$ versus $1/D$ is linear with positive slope. This clearly suggests an ion-dipole reaction and supports Scheme 1.

Mechanism in alkaline medium

Oxidation of Mt by BAT in alkaline medium shows first order dependence each on the [oxidant] and $[\text{OH}^-]$ and a fractional order retardation with respect to the product of oxidation, *p*-toluenesulphonamide (RNH_2). Further, the rate is independent of [substrate]. Scheme 3 explains the observed results.



(Forward reaction is rate-determining step)



Scheme 3

There is ample evidence to indicate participation of hypobromous acid in reactions involving alkaline BAB solutions¹⁵. From Scheme 3, assuming steady state conditions for $[\text{NaOBr}]$ and with the approximation $[\text{RNH}^-] \approx [\text{RNH}_2]$, rate law (6) can be derived, in agreement with experimental results:

$$-\frac{d[\text{BAT}]}{dt} = \frac{k_1 k_2 [\text{BAT}][\text{OH}^-]}{k_{-1} [\text{RNH}_2] + k_2} \quad \dots(6)$$

It is interesting to note that contrary to expectations, the rate of reaction does not increase in D₂O medium though OD⁻ is a stronger base than OH⁻. The near equivalence of rates in H₂O and D₂O indicates that any increase in reaction rate is offset by the rate-limiting hydrolysis, where $k'_H/k'_D > 1$ is expected. Mechanism of oxidation of Mt by BAT in alkaline medium is similar to that in acid medium, except that the active species involved is HOBr instead of H₂OBr.

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References

- 1 Ruff F & Kucsman A, *J chem Soc, Perkin II* (1982) 1075.
- 2 Singh R N & Om Prakash, *Indian J Chem*, 21A (1982) 616.
- 3 Gunasekaran S & Venkatasubramanian N, *J chem Soc Perkin II*, (1983) 949; *Indian J Chem*, 22A (1983) 774.
- 4 Campbell M M & Johnson G, *Chem Rev*, 78 (1978) 65.
- 5 Gensch K H & Higuchi T, *J Pharm Sci*, 56 (1967) 177.
- 6 Young P R & Hsieh H, *J Am chem Soc*, 100 (1978) 7121.
- 7 Upadhyay S K, *Inter J chem Kinet*, 15 (1983) 669.
- 8 Mahadevappa D S, Ananda S, Gowda N M M & Rangappa K S, *J chem Soc, Perkin II* (1985) 39.
- 9 Mahadevappa D S, Gowda M B M & Rangappa K S, *Oxidation Comm*, 7 (1984) 167.
- 10 (a) Mahadevappa D S, Ananda S, Murthy A S A & Rangappa K S, *Tetrahedron*, 40 (1984) 1673; *Indian J Chem*, 23A (1984) 17.
(b) Mahadevappa D S, Ananda S, Made Gowda M B & Rangappa K S, *J Indian chem Soc*, 61 (1984) 323; *Indian J Chem*, 23A (1984) 325.
- 11 Bishop E & Jennings V J, *Talanta*, 1 (1958) 197.
- 12 Narayanan S S & Rao V R S, *Radiochem radioanal lett*, 49 (1981) 193.
- 13 (a) Collins C J & Bowman N S, *Isotope effect in chemical reactions* (Van Nostrand Reinhold. New York) 1970, 267.
(b) Wiberg K B, *Chem Rev*, 55 (1955) 713.
- 14 Gilliom R D, *Introduction to physical organic chemistry*, (Addison-Wesley, London) 1970, 168.
- 15 Hardy F F & Johnston J P, *J chem Soc Perkin II* (1973) 742.