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Research Paper

Mechanism of Oxidation of Methionine by Bromate based on Semi Empirical Method

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Abstract: *Oxidation of methionine is one of the degradation pathways of proteins. Bromate as a strong oxidizing agent can oxidize methionine to methionine sulphoxide. Computational chemistry was used to investigate the mechanism of oxidation of methionine by bromate at molecular level, using semi-empirical method at PM3 level. The mechanism involves seven consecutive steps. The heats of reaction of the computed proposed reaction mechanism are calculated to be -78.71kJ/mol,-3.5kJ/mol at 0^oC and 25^oC respectively. The stoichiometry of the reaction was found to be 2:1 bromate to methionine,and the rate limiting step involves the reaction between $HBrO_3$ and methionine, which leads to the formation of intermediates that react and disproportionate to give the products. The equilibrium and rate constants support the rate determining step.*

Keywords: Mechanism, methionine, semi-empirical, bromate oxidation.

Introduction

Bromate in the form of sodium, Calcium, and potassium salts are used as: flour or dough “improver” or maturing agent (Mack, 1998), an ingredient in neutralizer solutions in permanent wave hair careproducts (De Angelo et al; 1998). Potassium bromate is also used in certaintypes of beer and cheese making. Living things get exposed to bromate from water through ozonation disinfection of drinking water or treatment of water with concentrated hypochlorite (Haag and Holgne; 1983). Acute bromate intoxication in humans is caused by accidental or suicidal ingestion of products containing either 2% potassium bromate or 10% sodium bromate (Bathisa and Joan; 2001). Severe gastrointestinal irritation (vomiting, pain and diarrhea) and CNS (lethargy, hypotension, hypo toxicity and loss of reflexes) are the most common acute signs. Anaemia from intravascular hemolysis may

also occur. These effects are usually reversible. Later sequel (usually within several days) includes marked renal injury and hearing loss. Death from renal failure may ensue if medical intervention is not successful. On successful treatment renal function generally returns after 5-10 days Hearing loss is usually irreversible. Estimated doses in these cases ranged from about 20-1000mg BrO^{3-}/Kg. Several studies (Bathisa and Joan; 2001) describe the potential carcinogenic properties of bromate as multisite carcinogen, inducing mesothelioma, kidney tumors and thyroid tumors.

In vitro studies indicates that bromates interact with sulfuryldyl containing compounds e.g. Gluthathione methionine etc (Tanaka et al ; 1984) in some parts of the body. Methionine is one of the sulfurydyl containing amino acid. Natural proteins in the body as well as man-made proteins used for therapy consist of methionine as one of its backbone. Proteins can be degraded through chemical pathways under various stresses encountered.one of themajor chemical degradation pathways is methionine oxidation due to many possible reasons e.g. the presence of reactive oxygen species such as hydrogen peroxide hydroxyl radicals, superoxide radicals, bromate etc. oxidation of methionine residues changes the bioactivity and structure of protein (Brian et al ; 2005). Experimental studies on the mechanism of oxidation of methionine by several oxidizing agents e.g. iodate (Chikawa et al; 2009), bromated (Idris et al; 2010), chromium (VI) (Subbiah and Rajagopal; 2003), iron (III) (Vani et al; 2001) etc. have been carried out, but little studies on the computational simulation of the mechanism to explain the mechanism dependence on the reaction activation energy and PH. And most of the studies do not determine the thermodynamic parameters. The presence study proposed a mechanism for the oxidation ofmethionine by bromate using semi empirical model at the different basis set, to testthe potentiality of the method in the elucidation of the mechanism.

Computational Methods

Semi-empirical methods were used to compute the optimized structures, vibration frequencies, and thermodynamic properties of all species involved in the mechanism. Geometry optimization with full relaxation of all atoms was performed using PM3 basis set. SPARTAN 08, was used on COMPAQ-PC having AMD Athlon (tm)X2, Dual core QL-64 processor and 1.00 memory on window 7 for all the computation.

The Published Mechanism

Idris et al, in their studies on the kinetics and mechanism of oxidation of methionine by bromate, proposed the following mechanism as shown in scheme 1:

Scheme 1

$$BrO_3^- + H^+ \rightleftharpoons H_2BrO_3^+ \quad \text{..... (1)}$$

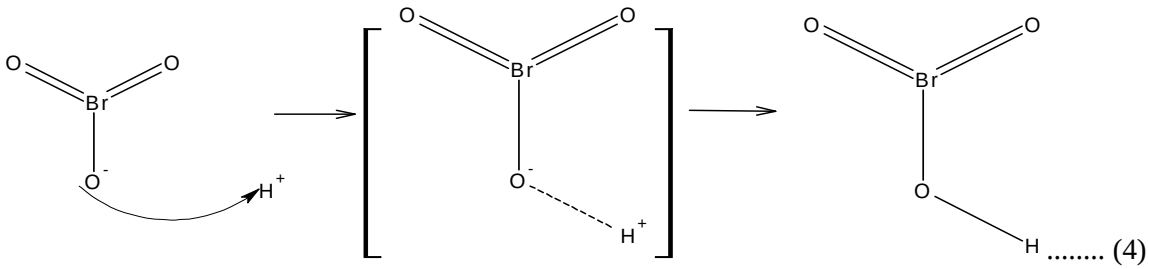
$$H_2BrO_3^+ + R^+SCH_3 \longrightarrow RSCH_3O + H_2BrO_2^+ \quad \text{..... (2)}$$

$$H_2BrO_2^+ + BrO_3^- \rightleftharpoons Br_2 + O_2 + H_2O \quad \text{..... (3)}$$

Proposed Mechanism of the Reaction

Step 1 of proposed mechanism: The proposed mechanism of the reaction computed was divided into steps as follows:

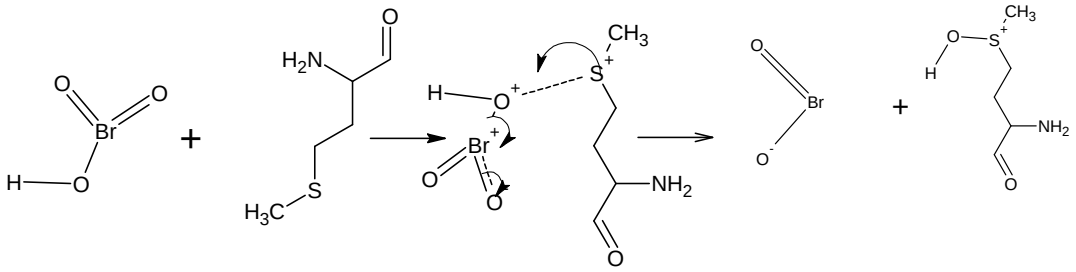
This involved protonation of the bromate ion i.e.



R1 TS1 P1 ..... (4)

This is more plausible than eqn(1) in scheme 1, which has ΔE= 950.14, as compared with eqn 4 in the proposed mechanism which has ΔE=211.1kJ/mol.

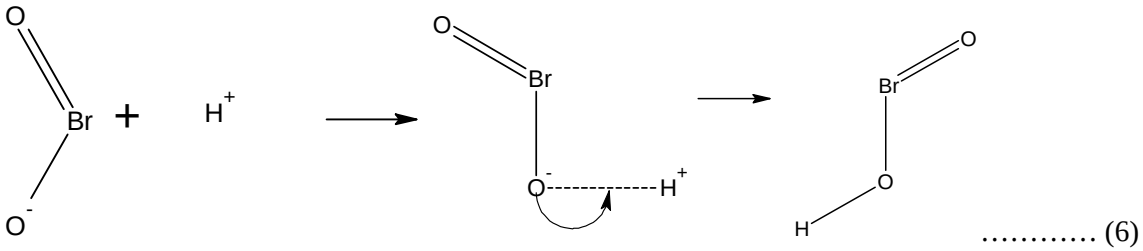
Step 2 of proposed mechanism: In this step HBrO3 react with the methionine to produce hydroxymethionine and bromite ion via a transition state TS2.



R2 TS2 P2

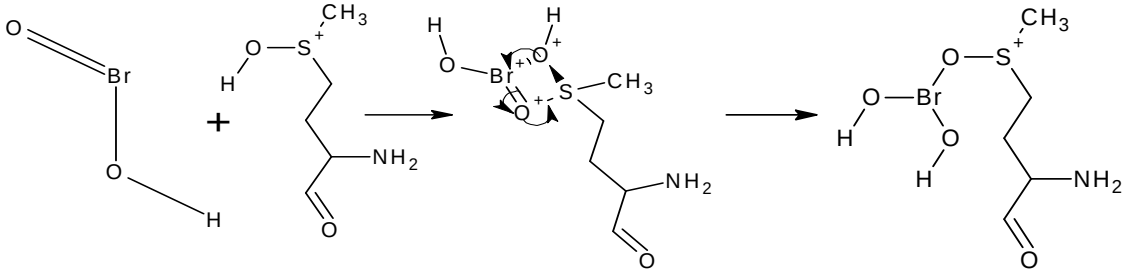
Step 2 of scheme 1 is similar to this step, but this is a reaction between neutral molecules which is more favorable than the reaction between molecular cations (electrophiles).

Step 3 of proposed mechanism: This step involves protonation of the bromite ion to $HBrO_2$.



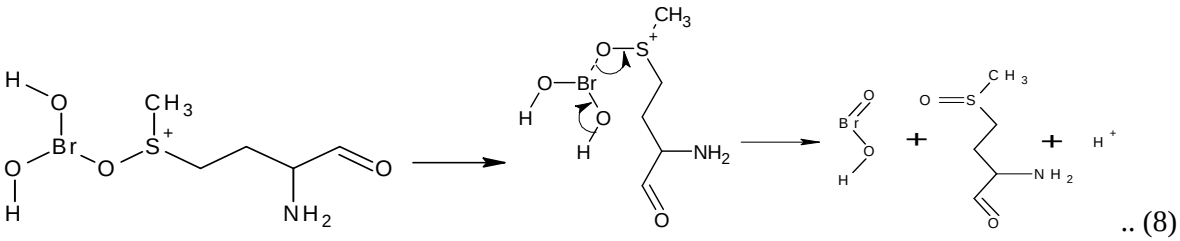
R3 TS3 P3 …… (6)

Step 4 of proposed mechanism: Reaction between $RSCH_3OH$ and $HBrO_2$ to give and intermediate $RCH_3S\text{-}O\text{-}H_2BrO_2$.



R4 TS4 P4…….. (7)

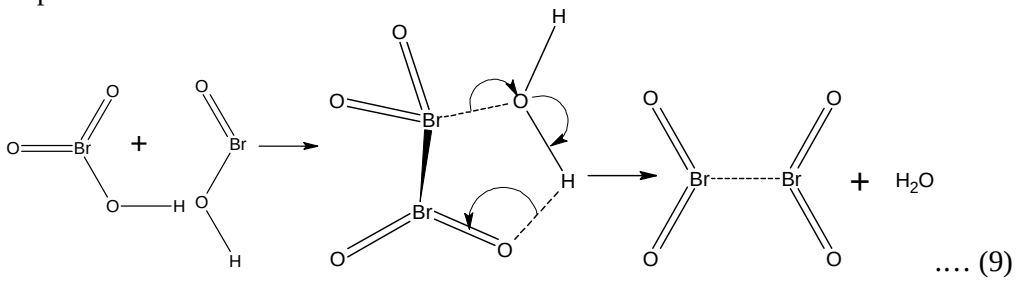
Step 5 of proposed mechanism: Decomposition of the intermediate, $RCH_3S\text{-}O\text{-}H_2BrO_2$(P4) to give methionine Sulphoxide and $HBrO_2$.



.. (8)

R5 TS5 P5

Step 6 of proposed mechanism: Reaction between $HBrO_3$ generatedin step 4 and $HBrO_2$ generated in step 8.



…. (9)

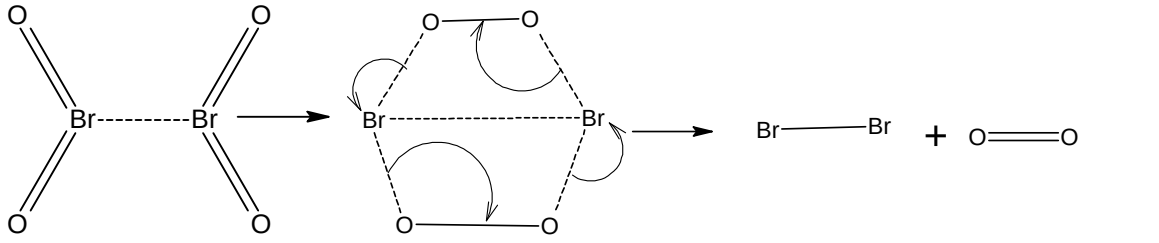
R6 TS6 P6

This equation is similar to the equation 10:

$HBrO2 + 2H^+ + 2BrO_3^- \leftrightarrow 3BrO_2^* + H2O$ …… (10)

Reported by (Nasiruddin et al; 2009), in their studies on bromate oxidation of neutral red, the bromite radical will easily dimerise to form Br_2O_4.

Step 7 of proposed mechanism: Formation of the dimer, Br_2O_4, which disproportionate to give the final products, Br_2 and O_2



R7 TS7 P7… (11)

The overall chemical equation for the reaction is therefore as given in equation 12,

$2BrO_3^- + 2H^+ + RSCH_3 \longrightarrow RCH_3SO + Br_2 + 2O_2 + H_2O$…….... (12)

Thermodynamic Properties and Rate Constants

The thermodynamic parameters of all the species appearing in the overall equation are given in table 1. This was used to calculate the heat of reaction, enthalpy, entropy, free energy changes, equilibrium and rate constants.

The equilibrium constants were calculated using equation 13:

$$LogK = \frac{\Delta G^o}{-2.303RT} \qquad \text{…….. (13)}$$

Where K= equilibrium constant; ΔG^O=Gibbs free energy change; R= ideal gas constant (8.31441J/mol.K); T= temperature (298.15K).

While the rate constants were computed using the relationship

$$\boldsymbol{k(298.15K) = \frac{k_B T}{hC^o} e^{-\Delta \neq G^o/RT}} \qquad \text{…….. (14)}$$

Where: k=rate constant, K_B = Boltzman constant (1.380662x10^{-23} J/K), T =Temperature 298.15Kh = Plank's constant (6.626176 x 10^{-34} JS), C^O = concentration (taken to be 1), $\Delta G^{\neq}$= free energy of activation in kJ/mol, R = ideal gas constant (8.31441J/mol.K).

The heat of reaction was calculated to be -78.71kJ/mol,-3.5kJ/mol at 0^{o}C and 25^{o}C respectively.
The ΔG, rate constant and equilibrium constant K is presented in table 2for the various steps.

Table1: Showing the heat of formation and the thermodynamic parameters of the species based on PM3 level of computation

SPECIES	ENERGY (kJ/mol)	H^o (kJ/mol)	S^o (J/mol K)	G^o (kJ/mol)
BrO_3-	-165.67	-127.81	296.57	-216.23
TS1	540.94	608.42	297.19	519.82
$HBrO_3$	45.47	111.45	296.69	22.99
RSCH3	-413.89	46.78	448.16	-86.84
TS2	1481.13	2004.7	567.96	1835.37
RCH_3S^+-OH	117.93	618.65	480.92	475.27
BrO_2^-	-49.89	-26.21	273.17	-107.65
TS3	134.77	183.77	276.24	101.41
$HBrO_2$	-2.54	54.84	282.37	-29.35
TS4	1047.34	1606.47	575.86	1434.77
RCH_3S-O-H_2BrO_2	-134.08	433.56	607.74	252.37
RCH_3SO	-532.26	-60.85	462.92	-198.87
TS5	1063.44	1631.24	562.62	1463.5
TS6	131.3	247.6	400.16	128.29
H_2O	-223.54	-156.22	188.24	-212.34
BrO_2..BrO_2	254.33	310.65	366.14	201.48
TS7	282.35	335.37	315.24	241.39
Br_2	20.61	33.52	245.88	-39.79
O_2	76.92	99.37	195.27	41.15
R1	-165.67	-127.81	296.57	-216.23
P1	45.47	111.45	296.69	22.99
R2	-368.42	158.23	744.85	-63.85
P2	68.04	592.44	754.09	367.62
R3	-49.89	-26.21	273.17	-107.65
P3	-2.54	54.84	282.37	-29.35
R4	115.39	673.49	763.29	445.92
P4	-134.08	433.56	607.74	252.37
R5	-134.08	433.56	607.74	252.37

P5	-534.8	-6.01	745.29	-228.22
R6	42.93	166.29	579.06	-6.36
P6	30.79	154.43	554.38	-10.86
R7	254.33	310.65	366.14	201.48
P7	97.53	132.89	441.15	80.94

The proposed mechanism can be summarized as follows:

$BrO_3^- + H^+ \longrightarrow H^+ \ldots BrO_3^- \longrightarrow HBrO_3$..... (15)
R1 TS1 P1

$HBrO_3 + RSCH_3 \longrightarrow BrO_2..HO..SRCH_3 \longrightarrow HOS^+RCH_3 + BrO_2^-$ … (16)
R2 TS2 P2

$BrO_2^- + H^+ \longrightarrow BrO_2^- \ldots H^+ \longrightarrow HBrO_2$ ……. (17)
R3 TS3 P3

$HOS^+RCH_3 + HBrO_2 \rightarrow RCH3S^+ \ldots OH \ldots HBrO_2 \rightarrow RCH_3S\text{-}O\text{-}H_2BrO_2$ … (18)
R4 TS4 P4

$RCH_3S\text{-}O\text{-}H_2BrO_2 \rightarrow RCH_3S\text{-}O..H..HBrO_2 \rightarrow HBrO_2 + RCH_3SO + H^+$ ……. (19)
R5 TS5 P5

$HBrO_3 + HBrO_2 \longrightarrow BrO_2..H\text{-}O..H..BrO_2 \longrightarrow Br_2O_4 + H_2O$
R6 TS6 P6 …… (20)

$Br_2O_4 \longrightarrow O\text{-}O..Br\text{-}Br \ldots O\text{-}O \longrightarrow Br_2 + 2O_2$ …… (21)
R7 TS7 P7

The overall chemical equation for the reaction is:

$2BrO_3^- + 2H^+ + RSCH_3 \longrightarrow RCH_3SO + Br_2 + 2O_2 + H_2O$ ……..... (22)

Where R stands for the reactant (s) TS transition state and P product (s). The figures indicate the step of the reaction. The structures of all these species are given in figure2 below:

The graph of heat of formation vs reaction progress is shown in the figure below:

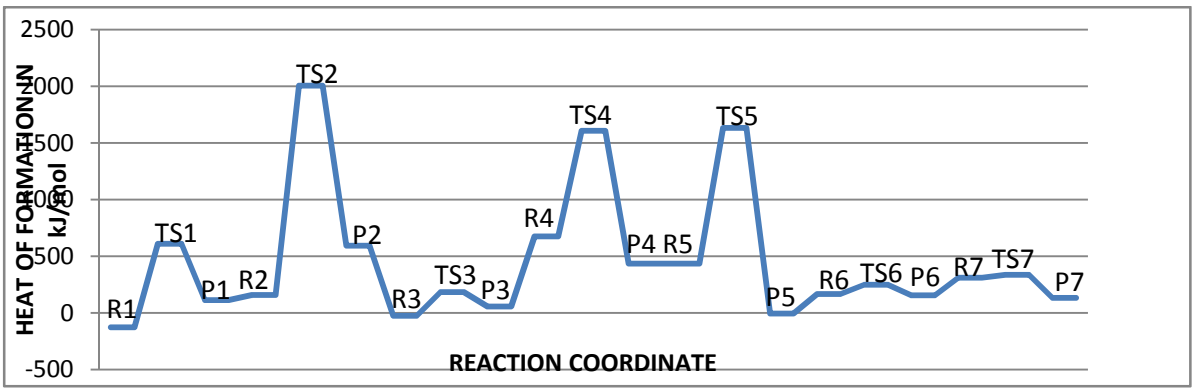


Fig 1: Showing a graph of heat of formation vs progress of reaction

According to this graph the rate determining steps is step2, which is in concordance with most of the experimental studies reportedwhere reaction between methionine and other generated species is the rate determining step.

The enthalpy change, entropy change, and free energy change have been calculated for each step from the difference between product and reactant as follows:

$\Delta H = H_P - H_R$ …….. (23)

$\Delta S = S_P - S_R$ …….. (24)

$\Delta G = G_P - G_R$ ..…… (25)

Where H_P is sum of the enthalpy of the product, and H_R sum of the enthalpy of the reactant. And other parameters are calculated in the same way. The result is shown in the table below:

Table 2: Showing the thermodynamic parameters for the various step at 298.5K

Reaction step	ΔE	ΔH^o	ΔS^o	ΔG^o
R1→P1	211.14	239.26	0.12	239.2
R2→P2	436.46	434.21	9.24	431.5
R3→P3	47.35	81.05	9.2	78.3
R4→P4	-249.5	-239.93	-156	-194
R5→P5	-400.7	-439.57	137.6	-481
R6→P6	-12.14	-11.86	-24.7	-4.5
R7→P7	-156.8	-177.76	75.01	-200

According to (Anthony and Bell, 2007) the rate limiting step is the one that has the highest ΔE and ΔG^o, therefore step 2 which involves reaction between HBrO3 and methionine is the rate limiting step.

The activation parameters were also calculated by the difference between the energy of the transition state and the reactant as follows:

$\Delta^{\#}H = H_{TS} - H_R$ …….. (26)

$\Delta^{\#}S = S_{TS} - S_R$ ..……. (27)

$\Delta^{\#}G = G_{TS} - G_R$ ……..…… (28)

Where H_{TS} is the energy of the transition state and H_R sum of the enthalpy of the reactant. And other parameters are calculated in the same way. The result is shown in the table below:

Table 3: Showing activation parameters equilibrium and rate constant for various steps

Reaction steps	$\Delta^{\#}E$ kJ/mol	$\Delta^{\#}H$ kJ/mol	$\Delta^{\#}S$ J/mol	$\Delta^{\#}G$ kJ/mol	Equilibrium constants	Rate constants S^{-1}
R1→P1	706.6	736.2	0.62	736.05	0.908	6.95×10^{-117}
R2→P2	1850	1846	-177	1899.22	0.84	1.16×10^{-320}
R3→P3	184.7	210	3.07	209.06	0.969	1.47×10^{-24}
R4→P4	932	933	-187	988.85	1.081	3.57×10^{-161}
R5→P5	1198	1198	-45.1	1211.13	1.214	4.08×10^{-200}
R6→P6	88.37	81.31	-178.9	134.65	1.002	1.59×10^{-11}

R7→P7	28.02	24.72	-50.9	39.91	1.084	$6.33x10^5$

The 3D geometries of all the optimized structures including the transition states are shown in the figure below:

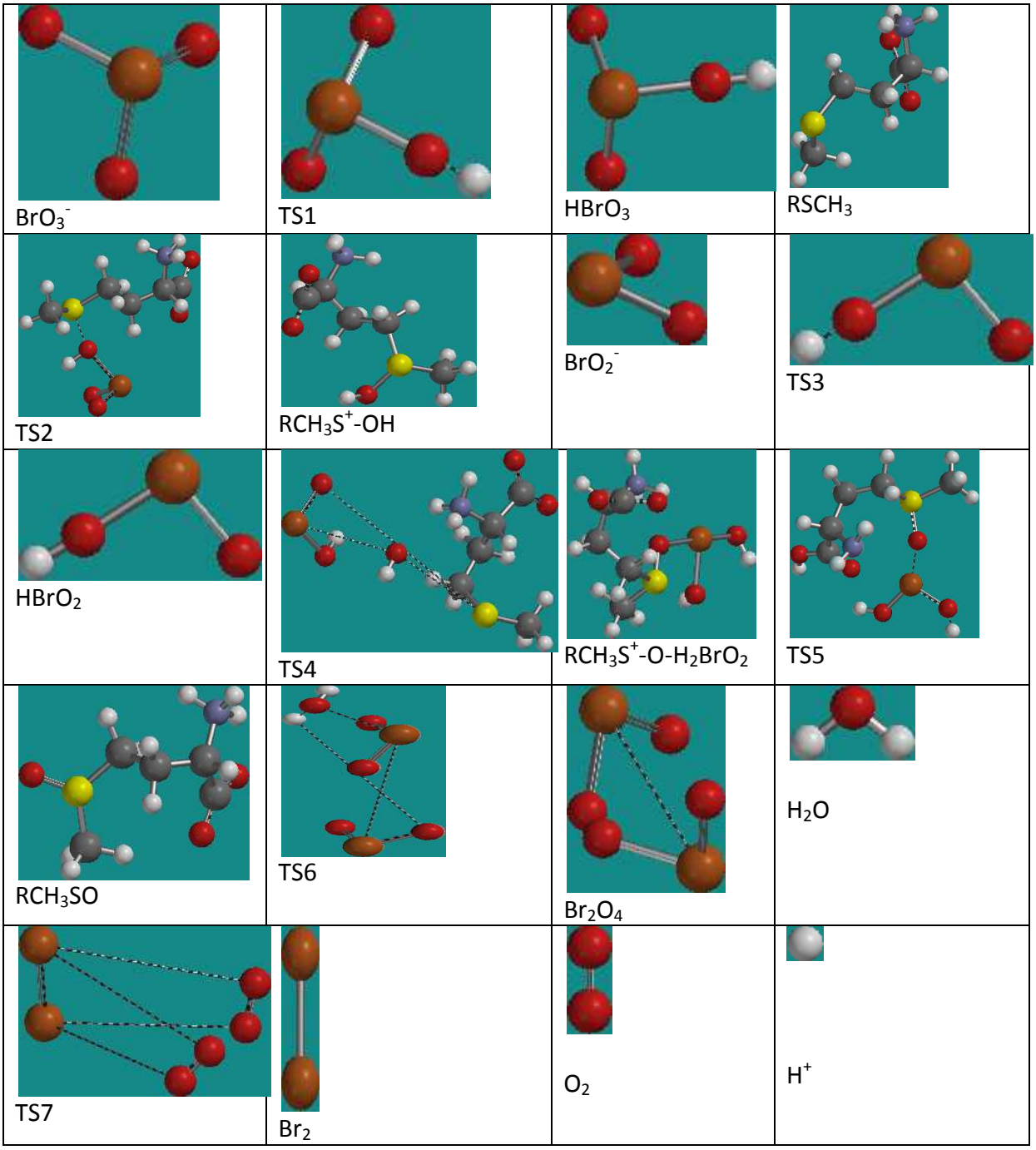


Figure 2: Showing the 3D structures of the reactants transition states and the products

Discussion

The heat of reactionof the overal reaction obtained using PM3is -78.71kJ/mol and,-3.5kJ/mol at 0^oC and 25^oC respectively. In the beginning of the reaction the bromate anion became uniprotonated and the energies associated with this step are ΔE = 211.1kJ/mol and ΔG^o = 239.2 kJ/mol at 298.15K. Step 2 involves the reaction between the HBrO3 and methionine which result in the formation of

intermediates RCH3S-OH and BrO2-. The Gibbs free energy change and energy change for this reaction are 431.5 and 436.5 kJ/mol respectively. This equation has the highest ΔE and ΔG^o therefore is the rate limiting step (Anthony and Bell,2007) as shown in table 3.Bromous acid is formed in step3 from the reaction of bromite with hydrogen ion. The ΔE and ΔG^o are 47.35 and 78.3kJ/mol respectively. Thus the first three steps are endothermic while the last four steps are exothermic Table 2.Step 5 being highly exothermic. Kinetically, step2 equation (5) has the lowest rate constant, therefore in close agreement with the rate determining step calculated thermodynamically. The step also has the lowest equilibrium constant of 0.84. This conforms to most of the experimentally determined rate determining steps, where reaction of methionine with other species used to be the slowest step.

Conclusion

The study proposed a more detailed mechanism of oxidation of methionine by bromate. The mechanism involve seven consecutive steps which shows how molecules interact with each other at molecular level.The reaction proceeds via initial uniprotonation of the bromate ion, and terminate at the reaction between $HBrO_3$ and $HBrO_2$ to give bromine and oxygen.The rate limiting step is a reaction between neutral molecules as against cationic molecules reported by Idris et al, and the energy of the first step of the proposed mechanism is lower than that reported in the published mechanism. Therefore the proposed mechanism is more plausible than the published one.

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