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Oxyhalogen-Sulfur Chemistry: Kinetics and Mechanism of Oxidation of N-acetylthiourea by Aqueous Bromate and Acidified Bromate

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ABSTRACT

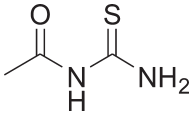
The oxidation of N-acetylthiourea (ACTU) by acidic bromate has been studied by observing formation of bromine in excess bromate conditions. The reaction displays an induction period before formation of bromine. The stoichiometry of the reaction was determined to be 4:3: $4BrO_3^- + 3(CH_3CO)NH(NH_2)C{=}S + 3H_2O \rightarrow 4Br^- + 3(CH_3CO)NH(NH_2)C{=}O + 3SO_4^{2-} + 6H^+$ (A) with a complete desulfurization of ACTU to its urea analogue. In excess bromate conditions the stoichiometry was 8:5: $8BrO_3^- + 5(CH_3CO)NH(NH_2)C{=}S + H_2O \rightarrow 4Br_2 + 5(CH_3CO)NH(NH_2)C{=}O + 5SO_4^{2-} + 2H^+$ (B). Bromine is derived from an extraneous reaction in which bromide from stoichiometry (A) reacts with excess acidic bromate. The oxidation of ACTU by aqueous bromine gave stoichiometry (C): $4Br_2(aq) + (CH_3CO)NH(NH_2)C{=}S + 5H_2O \rightarrow 8Br^- + (CH_3CO)NH(NH_2)C{=}O + SO_4^{2-} + 10H^+$. Reaction (C) is much faster than reactions (A) and (B), with a lower limit bimolecular rate constant of 2.1×10^5 M^{-1} s^{-1} such that appearance of bromine signals complete consumption of ACTU. We were unable to trap any intermediate sulfur oxo-acids of ACTU on its oxidation pathway to N-acetylurea. As opposed to other substituted thioureas, none of its intermediates were stable enough to be isolated and detected.

KEYWORDS

Kinetics, mechanisms, oxyhalogen chemistry, s-oxygenation, bioactivation.

1. Introduction

The chemistry of thiourea and its derivatives has received considerable attention because of its important applications in synthesis of biologically-active compounds. They form the backbone in structures of these drugs and the biological activities of most of the thiourea-derived drugs depend on the existence of the thiourea moiety.[1] Thiourea and its derivatives are thus a vast group of very active biological molecules.[2–8] Major pathway to their bioactivation is oxidative and specifically *via* S-oxygenation in which there is a successive addition of oxygen to the sulfur center until oxidative saturation is attained at sulfate.[9–11] Small molecule thioureas are oxygenated predominantly by catalysis from the flavin-containing monooxygenases[12,13] to form reactive sulfenic acids that reversibly react with glutathione[14–19] to drive oxidative stress through a redox cycle. The higher molecular weight versions tend to be metabolized by the CYP450 system of enzymes.[20–22] There is a new thrust in medicinal chemistry that involves substituted thioureas as therapeutic drugs for several diseases.[23] No other pharmacophore possesses such a wide range of biological activity. For example, comparatively, the 4-aminoquinoline pharmacophore has been exploited in a variety of ways to derive antimalarials[24–26], but it is exclusively for one disease and has not found significant use for any other disease. The ease of synthesis of substituted thioureas[27–33] means that there are now hundreds of these analogues available which have not yet been characterized.[7,34] Although effective, drugs containing the thiourea functional group have been found to exhibit some toxicity. Methimazole, for example, an antithyroid drug used in the treatment of hyperthyroidism and Graves Disease, has been associated with idiosyncratic toxicity, characterized by skin reactions, leucopenia, agranulocytosis, aplastic anemia, hepatitis and cholestasis.[35,36] The relationship between idiosyncratic adverse reactions and reactive metabolites is not well established. There is circumstantial evidence, however, that reactive metabolites are involved in the onset of idiosyncratic adverse reactions.[37,38] Sulfur atom has been thought to be the site of bioactivation of these organosulfur compounds resulting in conceivably toxic metabolites.[39] Biological oxidations of small molecules such as N-acetylthiourea, N-methylthiourea show that sulfur is a soft nucleophile, and is easily oxidized by oxidants such as iodine, HOBr and HOCl, which are found in the physiological environment albeit in low concentrations.[40] The difference in oxidative environment and oxidizing species has a large bearing on the intermediates and subsequent products. Although there are similarities in the oxidation patterns displayed by these small molecules, they is no generic pathway for their oxidation. Kinetics and mechanistic studies of N-acetyl thiourea (ACTU) with chlorite, showed complex behaviour[41] which is different from the behaviour displayed when unsubstituted thiourea is oxidized by chlorite in acidic medium.[42]



Structure of N-acetyl thiourea.

N-acetylthiourea and its derivatives serve as highly potent and isozyme selective activators for the recombinant form of human histone deacetylase-8 in the assay system containing fluor-de-lys

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as a fluorescent substrate.[43] This is an activity not manifested by the parent thiourea. We report, in this manuscript, on the oxidation mechanism of ACTU by acidic bromate and aqueous bromine. Its oxidation mechanism can be correlated with its physiological effect.

2. Experimental Procedures

2.1. Materials

The following reagent grade chemicals were used without further purification: sodium bromate, perchloric acid (70–72 %), sodium bromide, bromine, sodium perchlorate, soluble starch, sodium thiosulfate (Fisher), and ACTU (Sigma). Bromine solutions, being volatile, were kept capped and standardized spectrophotometrically before each set of experiments. Stock solutions of N acetyl thiourea were prepared just before use.

2.2. Methods

The rapid reactions of ACTU with bromine were followed on a Hi-Tech Scientific™ SF61-DX2 double-mixing stopped-flow spectrophotometer. These reactions were monitored by following formation of bromine at 390 nm ($\varepsilon = 142\ M^{-1}cm^{-1}$). ACTU has no absorbance in the visible region, while aqueous bromine has an isolated peak at 390 nm. Thus absorbance at this peak was used for analytical determination of aqueous bromine. Slower reactions involving N-acetylurea formation following oxidation of ACTU by acidified bromate were monitored on a conventional Perkin-Elmer Lambda 25 UV-Vis spectrophotometer. All kinetics experiments were performed at 25.0 ± 0.1 °C and at an ionic strength of 1 M ($NaClO_4$). All solutions were prepared using doubly-distilled deionized water from a Barnstead Sybron Corporation water purification unit capable of producing both distilled and deionized water (Nanopure). Mass spectra of product solutions were taken on a Thermo Scientific LTQ-Orbitrap XL Discovery mass spectrometer (San Jose, CA) equipped with an electrospray ionization source operated in the positive mode.

3. Results

3.1. Stoichiometry

The stoichiometry in excess acidic bromate was determined spectrophotometrically using the bromine absorbance at 390 nm. Figure 1 shows the combined spectra of ACTU, aqueous bromine and product solution at excess bromate conditions. ACTU has no absorbance in the visible region, and thus the aqueous bromine peak at 390 nm is isolated and can be used for analytical determination of bromine at the end of the reaction. This spectrophotometric method worked for a limited range of oxidant to reductant ratios; $R = [BrO_3^-]_0/[ACTU]_0$. At values of R greater than 1.6; the observed final absorbance of bromine saturated, and further increases in oxidant did not produce any changes in observed final bromine concentrations. In excess ACTU conditions, the stoichiometry was determined titrimetrically by utilizing excess oxidant and determining residual oxidizing power for a fixed amount of ACTU and varying acidic bromate.

Figure 2 shows the iodometric titration utilized for the determination of the stoichiometry of the reaction in excess reductant, though the determination was performed in excess oxidant. These titrimetric determinations were performed in triplicates. The titre varied linearly with increase in bromate concentrations. A plot of titre *vs* bromate concentrations for a fixed amount of $[ACTU]_0$ of 1.0 mM gave a straight line with an intercept of 1.33 mM (= 4/3). This intercept value represents the amount of bromate needed to just completely oxidize 1.0 mM with no excess bromate left to form bromine which will result in a titre against thiousulfate. The stoichiometry is thus solidly 4:3:

$$4BrO_3^- + 3(CH_3CO)N(NH_2)C{=}S + 3H_2O \rightarrow 4Br^- + 3(CH_3CO)N(NH_2)C{=}O + 3SO_4^{2-} + 6H^+ \quad \text{R1}$$

Spectrophotometric determination in excess bromate conditions gave a stoichiometry of 8:5:

$$8BrO_3^- + 5(CH_3CO)N(NH_2)C{=}S + H_2O \rightarrow 4Br_2 + 5(CH_3CO)N(NH_2)C{=}O + 5SO_4^{2-} + 2H^+ \quad \text{R2}$$

At high excess of bromate, amount of bromine formed was determined by initial concentrations of ACTU. This can be seen in Fig. 6 (*vide infra*).

98% of the sulfur in ACTU was gravimetrically analyzed as sulfate. One important reaction in the reaction mixture is the direct oxidation of ACTU by aqueous bromine. The stoichiometry was determined titrimetrically, as shown in Fig. 2b, by titrating bromine in aqueous iodine enhanced by soluble starch. The stoichiometry was determined to be 4:1:

$$4Br_2(aq) + (CH_3CO)N(NH_2)C{=}S + 5H_2O \rightarrow 8Br^- + (CH_3CO)N(NH_2)C{=}O + SO_4^{2-} + 10H^+ \quad \text{R3}$$

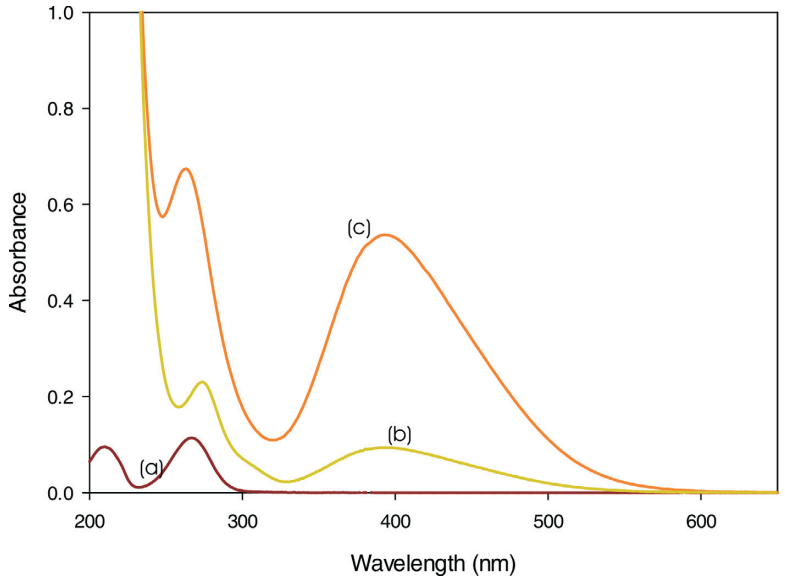

Figure 1 UV spectra of (a): [ACTU] = 0.00001 M, (b): $[Br_2]$ = 0.004 M, (c): [ACTU] = 0.001 M, $[H^+]$ = 0.2 M, and $[BrO_3^-]$ = 0.005 M.

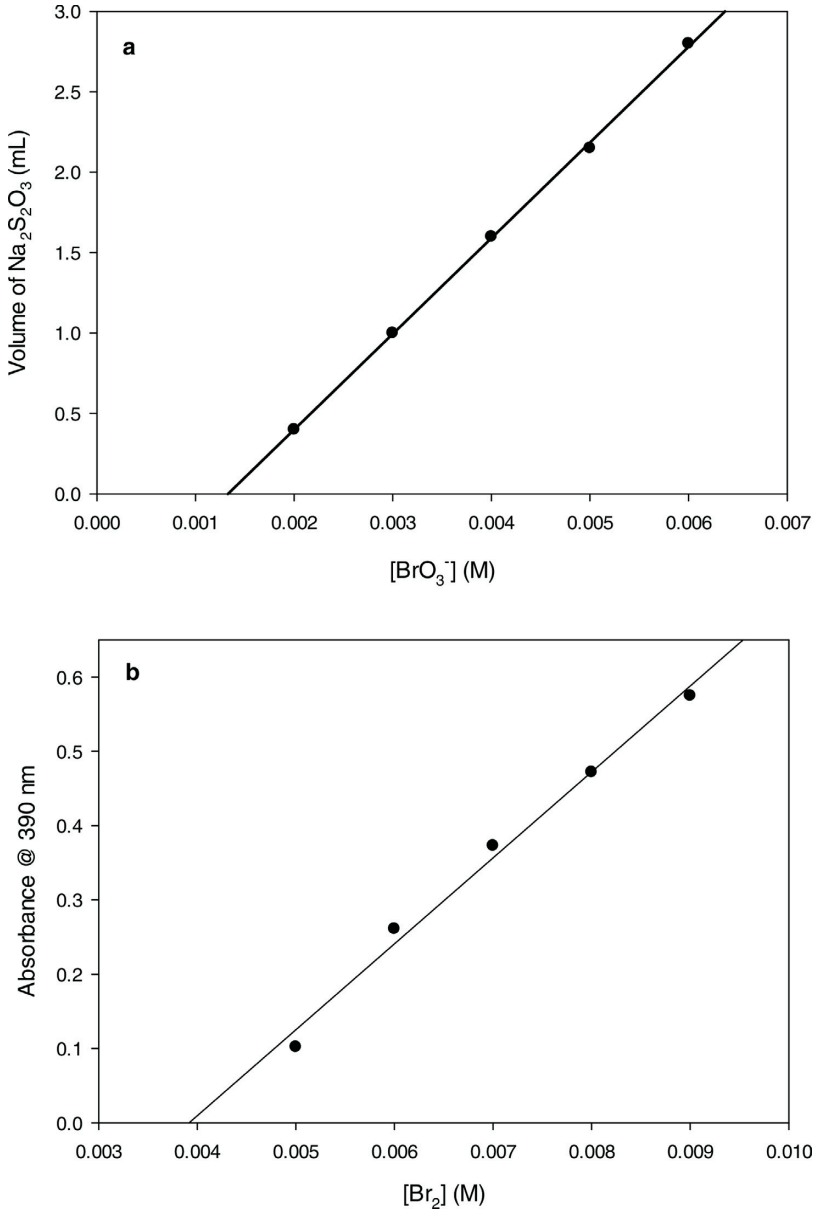

Figure 2 (**a**) Iodometric titration to determine stoichiometry of ACTU and BrO_3^- reaction R1. Fixed: [ACTU] = 0.001 M, $[H^+]$ = 0.4 M, and varied $[BrO_3^-]$ from 0.002 M to 0.006 M. X-axis intercept = 0.001327. The ratio is 4:3. (**b**) Spectrophotometric determination of stoichiometry in the ACTU vs bromine reaction. Fixed: [ACTU] = 0.001 M, and varied $[Br_2]$ from 0.005 M to 0.009 M, X-axis intercept = 0.0039 M. The ratio is 1:4.

3.2. Kinetics

In excess acidic bromate, the reaction showed a monotonic increase in absorbance of aqueous bromine after a short induction period. No other active absorbance peaks were observed (see Fig. 3).

No bromine formation was observed when oxidant to reductant ratio was less than 1.33, i.e. stoichiometry R1. This indicates that reaction of bromine and ACTU is so rapid that these two cannot coexist on the time scale of reaction R1.

All kinetics traces shown in Figures 4 to 7 were obtained in triplicates. The reaction is strongly catalyzed by acid (see Fig. 4). Acid, however, is not a reactant in the reaction under study, but it decreases the quiescent period before commencement of bromine formation and also rapidly increases the rate of formation bromine after the induction period. Generally, there was an inverse square dependence of the induction period with acid over a limited range of acid concentrations. This effect tailed off and became an inverse first-order dependence at high acid concentrations. The formation of bromine, however, was strongly second order in acid. The reaction was run in highly excess acid conditions such that it could be assumed that acid concentrations remained invariant over the lifetime of the reaction; i.e. essentially buffered. None of the other reagents' concentrations, $[BrO_3^-]_t$, $[ACTU]_t$ could be determined at the onset of formation of bromine such that no relevant kinetics constants could be evaluated for the rate of formation of bromine. Acid did not alter final amount of bromine obtained based on stoichiometry R2, but accelerated the rate of attainment of the final bromine concentrations.

Figure 5 shows the effect of bromate concentrations on the reaction. In this case, induction period has an inverse dependence on initial bromate concentrations and a linear dependence on rate of formation of bromine after the induction period. For all the scans in Fig. 5 the oxidant reductant ratios were greater than 1.6. The different bromate concentrations, provided that the oxidant to reductant ratios were greater than 1.6, did not alter the final amount of bromine formed. Figure 6 shows the effect of ACTU concentrations at constant acid and bromate concentra-

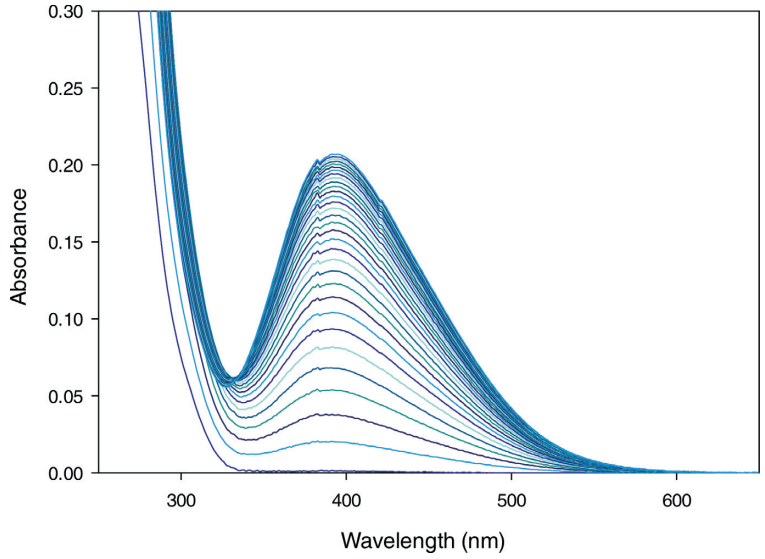

Figure 3 Multiple scan of ACTU in acidified bromate, each scan acquired after 30 s. [ACTU] = 0.001 M, $[H^+]$ = 0.1 M and $[BrO_3^-]$ = 0.1 M.

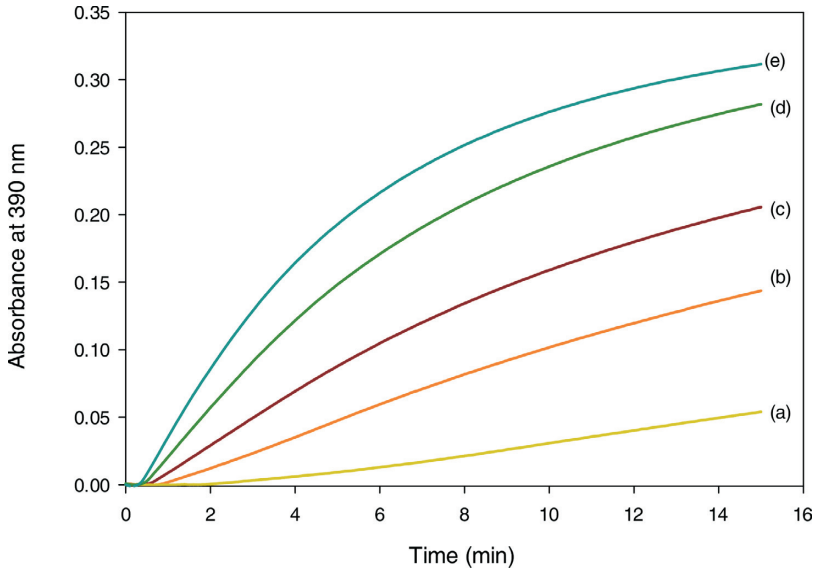

Figure 4 Effect of acid variation on the reaction between BrO_3^- and ACTU. Fixed: [ACTU] = 0.003 M, $[BrO_3^-]$ = 0.006 M, and varied $[H^+]$= (a) 0.1 M, (b) 0.15 M, (c) 0.2 M, (d) 0.25 M and (e) 0.3 M. $I_{NaClO-4}$ = 1 M.

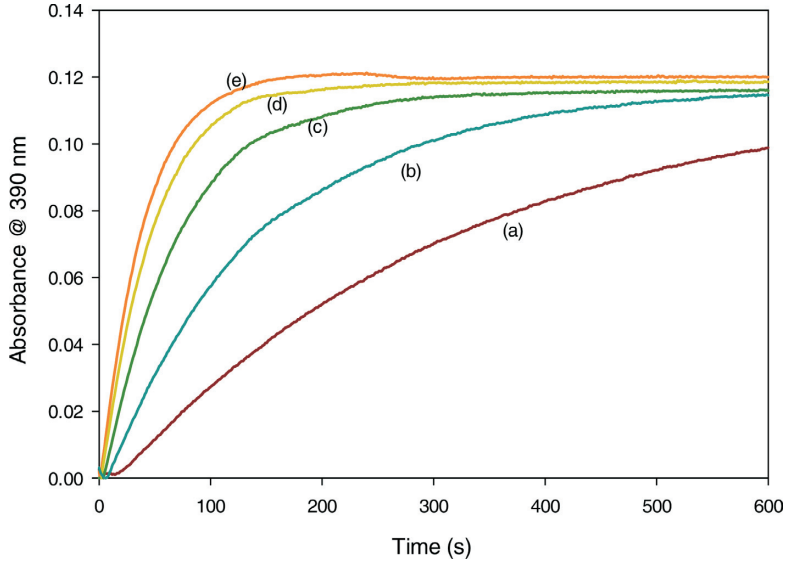

Figure 5 Effect of BrO_3^- variation on the reaction. Fixed: [ACTU] = 0.001 M, $[H^+]$ = 0.1 M and varied $[BrO_3^-]$ = (a) 0.0025 M, (b) 0.05 M, (c) 0.1 M, (d) 0.15 M and (e) 0.2 M. $I_{NaClO-4}$ = 1.0 M

tions. All these experiments were performed at oxidant to reductant ratios greater than 1.6 (reaction R2) and thus the amount of final bromine formed is determined by $[ACTU]_0$. Final bromine concentrations were $0.80[ACTU]_0$ according to reaction R2 stoichiometry. At these conditions of high ratios, the induction period was invariant with rate of formation of bromine obeying a first order dependence on $[ACTU]_0$. No ACTU is available at the commencement of bromine formation (Reaction R3 is fast), and so formation of bromine is dependent on reactive species derived from the oxidation of ACTU.

Figure 7 shows spectrophotometric traces of the direct Br_2 – ACTU reaction. They were all run in stoichiometric excess of bromine such that there is residual bromine at the end of the reaction. A plot of residual absorbance *vs* $[Br_2]_0$ gave an intercept value that corroborates stoichiometry R3 (plot not shown) This intercept value indicates the concentration of bromine needed to just completely oxidize the ACTU concentration utilized in all the series of experiments (0.90 mM). The reaction is nearly diffusion-controlled and is faster than the mixing time of our stopped-flow apparatus of 1 ms. The reaction is first order in both bromine and ACTU. Due to the imprecision in the kinetics measurements, we could only evaluate a lower-limit bimolecular rate constant of 2.1×10^5 M^{-1} s^{-1} (no error bars since this represents a lower limit value).

4. Mechanism

The reaction of the unsubstituted thiourea was studied by Simoyi *et al.*[44] in 1994. The remarkable difference is that reaction of ACTU is much faster. This would suggest that ACTU is unable to stabilize any intermediates on its oxidation pathway to product N-acetylurea. We ran different stoichiometric ratios of oxidant to reductant and obtained the ESI spectra of the final product in each case. In excess oxidant, the only peak obtained was for the product at m/z = 103.05. Figure 8 shows the ESI spectrum of a reaction solution in which the reductant, ACTU, is in stoichiometric excess. Any intermediates that can be stabilized should be detected in this environment. Only the unreacted substrate, at m/z = 119.03 and the product are observed. The expected peak for a possible sulfinic acid, m/z = 135.03 is not observed. Neither is a possible sulfonic acid at m/z = 151.03

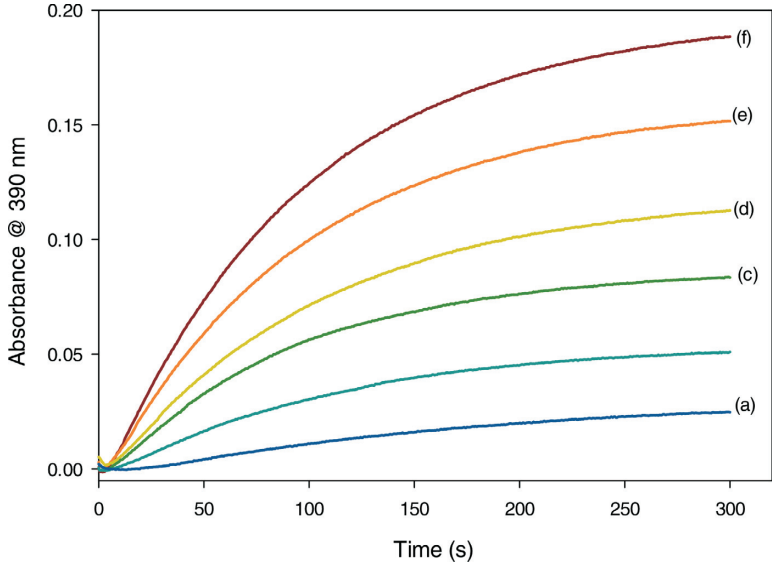

Figure 6 Fixed: $[H^+]_0$ = 0.1 M, $[BrO_3^-]_0$ = 0.05 M and varied $[ACTU]_0$ = (a) 0.00025 M, (b) 0.00050 M,(c) 0.00075 M,(d) 0.0010 M, (e) 0.0013 M and (f) 0.0015 M. $I_{NaClO-4}$ = 1.0 M.

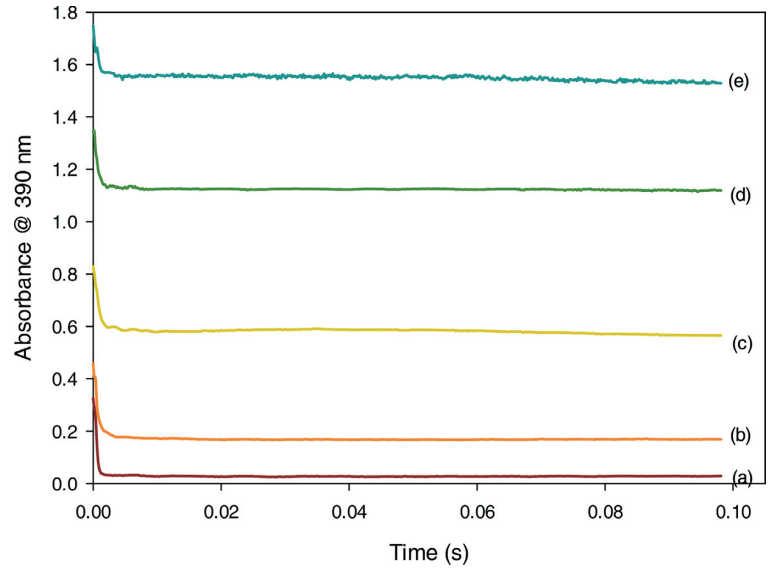

Figure 7 Effect of varying bromine during reaction with ACTU, in the presence of bromide ions . Fixed: [ACTU] = 0.0009 M, $[Br^-]$ = 1 M, and varied $[Br_2]$ = (a) 0.004 M, (b) 0.005 M, (c) 0.006 M, (d) 0.007 M, (e) 0.008 M.

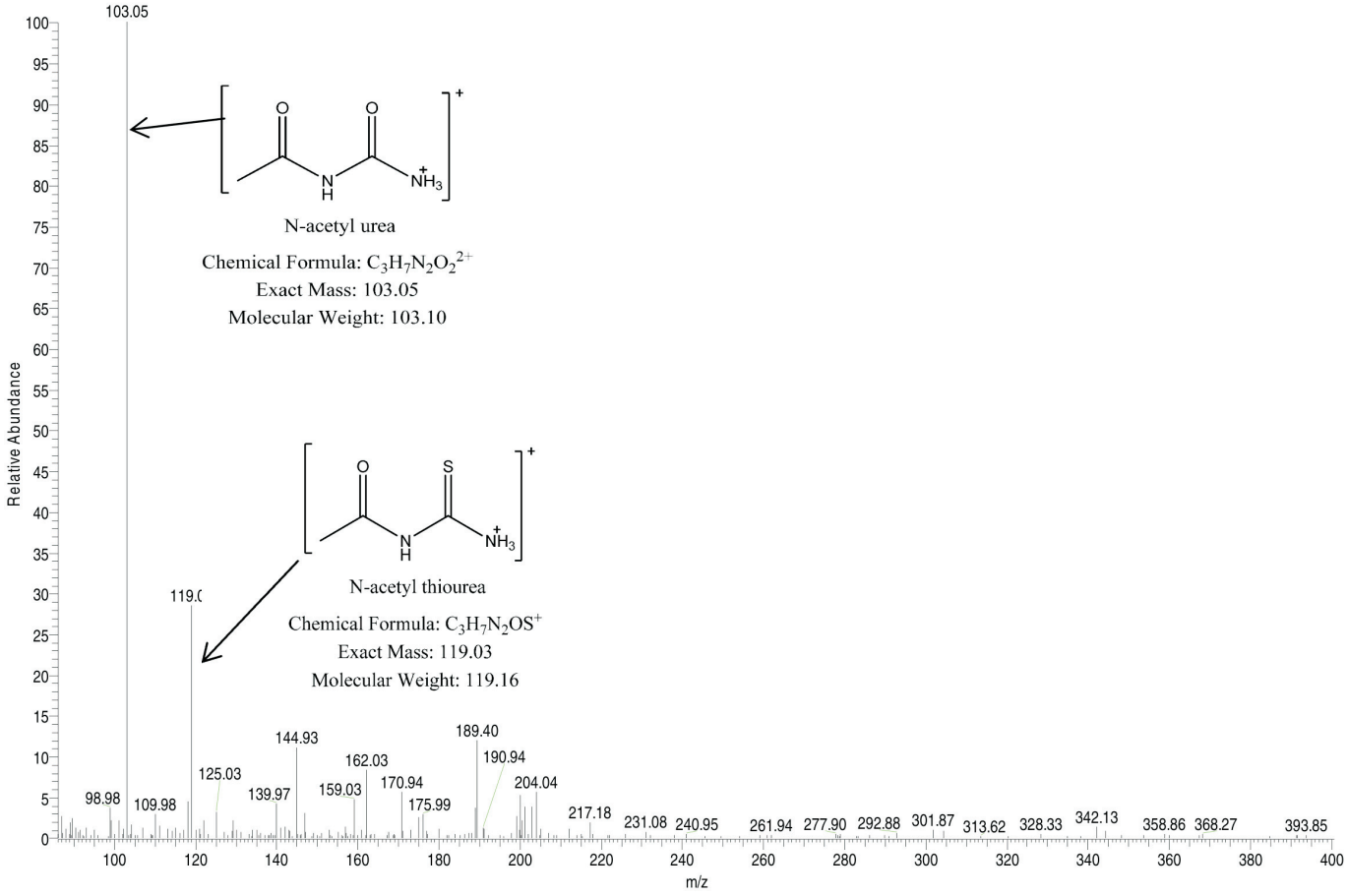

Figure 8 ESI spectrum of the product of oxidation of ACTU in stoichiometric excess of ACTU.

observed. Another substituted thiourea, tertamethylthiourea, has shown all possible oxo-acid intermediates before formation of product tetramethylurea.[45]

Thus the mechanism involves simply the expected oxybromine kinetics.[46] Rate-determining step is the initial oxidation of ACTU; subsequent oxidations of the intermediates to N-acetylurea are facile. The rate of the overall reaction conforms to the rate law:

$$\text{Rate} = k_0[BrO_3^-][H^+]^2[\text{Red}] \quad (1)$$

In Equation (1), Red can be any 2-electron reductant. Involvement of acid is through protonation of bromate to bromic acid; followed by the acidification of bromic acid to produce the active oxidizing species:

$$H^+ + BrO_3^- \rightleftharpoons HBrO_3 \quad \text{R4}$$

$$HBrO_3 + H^+ \rightleftharpoons H_2BrO_3^+ \quad \text{R5}$$

$$H_2BrO_3^+ + 2e^- \rightarrow HBrO_2 + OH^- \quad \text{R6}$$

With reaction R6 as the rate-determining step, then overall rate law Equation (1) can be justified. Standard oxybromine kinetics involve Br^- as the 2-electron reductant which is oxidized to HOBr:

$$H_2BrO_3^+ + Br^- \rightleftharpoons HBrO_2 + HOBr \quad \text{R7}$$

Composite reaction R7 is written as:

$$BrO_3^- + 2H^+ + Br^- \rightleftharpoons HBrO_2 + HOBr \quad \text{R8}$$

If sequence R4 to R8 is correct, according to the standard oxybromine kinetics, then oxidation of the sulfur center should proceed through 2-electron oxidations *via* sulfenic (S(I)), sulfinic (S(II)) and sulfonic (S(IV)) acids. This is a sequence that has been suggested in several oxidations of thiols and thiocarbamides.[47]

Thus the initial oxidation of ACTU would be by the generated reactive species HOBr:

$$HOBr + (CH_3CO)NH(NH_2)C{=}S \rightarrow ((CH_3CO)NH)(NH_2)C\text{-}SOH + H^+ + Br^- \quad \text{R9}$$

$((CH_3CO)NH)(NH_2)C$-SOH is the expected unstable sulfenic acid which should subsequently be rapidly oxidized further to the sulfinic acid and sulfonic acids:

$$HOBr + ((CH_3CO)NH)(NH_2)C\text{-}SOH \rightarrow ((CH_3CO)NH)(NH_2)C\text{-}SO_2H + H^+ + Br^- \quad \text{R10}$$

$$HOBr + ((CH_3CO)NH)(NH_2)C\text{-}SO_2H \rightarrow ((CH_3CO)NH)(NH_2)C\text{-}SO_3H + H^+ + Br^- \quad \text{R11}$$

Cleavage of the C-S bond should occur on oxidation of the sulfonic acid:

$$HOBr + ((CH_3CO)NH)(NH_2)C\text{-}SO_3H + H_2O \rightarrow ((CH_3CO)NH)(NH_2)C{=}O + SO_4^{2-} + 3H^+ + Br^- \quad \text{R12}$$

With HOBr as the major oxidizing species, then observed rate law (1) will hold in the form of (2) through reaction R8:

$$\text{Rate} = k_0[BrO_3^-][H^+]^2[Br^-] \quad (2)$$

Initial bromide concentrations to initiate reaction R8 are derived from a direct reaction of bromic acid with ACTU:

$$HBrO_3 + (CH_3CO)NH(NH_2)C{=}S \rightarrow ((CH_3CO)NH)(NH_2)C\text{-}SOH + HBrO_2 \quad \text{R13}$$

$$HBrO_2 + (CH_3CO)NH(NH_2)C{=}S \rightarrow ((CH_3CO)NH)(NH_2)C\text{-}SOH + HOBr \quad \text{R14}$$

Followed by reaction R10. The trace amounts of bromide formed in R10 are amplified through reaction R8.

5. Conclusion

This short mechanistic study has shown that despite similarities in thioureas, their oxidations can differ wildly. ACTU is unable to generate stable sulfur oxo-acids on the pathway towards formation of product N-acetylurea. Thus it is much more easily oxidized that the parent thiourea and other substituted thioureas such as trimethyl- and tetramethylthiourea.

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