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# Oxidation Processes of *N*,*S*-Diacetyl-L-cysteine Ethyl Ester: Influence of S-Acetylation

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The mechanism of the •OH-induced oxidation of *N*,*S*-diacetyl-L-cysteine ethyl ester (SNACET) was investigated in aqueous solutions using pulse radiolysis and steady-state $\gamma$-radiolysis combined with chromatographic and ESR techniques. The reaction of hydroxyl radicals with SNACET at slightly acidic to neutral pH results in the degradation into acetaldehyde. The underlying mechanism involves a very fast fragmentation of an initially formed hydroxysulfuranyl radical ($k_{\mathrm{fragm}} \geq 7.9 \times 10^7$ s$^{-1}$) into acyl radicals ($H_3C{-}CO\bullet$) and the respective sulfenic acid (RSOH). Subsequently, these intermediates react via a hydrogen abstraction reaction that yields acetaldehyde and the respective sulfinyl radical (RSO•). In contrast, in very acidic solutions (pH $<$ 2), the •OH-induced oxidation results in the formation of the monomeric sulfur radical cation (SNACET$>$S$\bullet^+$) which absorbs at $\lambda_{\mathrm{max}} = 420$ nm. This intermediate is formed with the absolute bimolecular rate constant $k = 3.9 \times 10^9$ M$^{-1}$ s$^{-1}$. It decays in a SNACET concentration independent process ($k_{\mathrm{d}} = 2.5 \times 10^5$ s$^{-1}$) and in a SNACET concentration dependent process ($k_{\mathrm{S-S}} = 2.2 \times 10^7$ M$^{-1}$ s$^{-1}$). The first process involves mainly fragmentation of the carbon−sulfur bond and yields acetylthiyl radical ($CH_2{=}C(OH){-}S\bullet$). The latter intermediate was identified via its reaction with oxygen as the thiylperoxyl radical (RSOO•), characterized by a transient absorption band with $\lambda_{\mathrm{max}} = 540$ nm. The second process represents the association of the monomeric sulfur radical cation (SNACET$>$S$\bullet^+$) with a second nonoxidized SNACET molecule to form intermolecularly three-electron-bonded $(>S\therefore S<)^+$ dimeric radical cation. The low rate constant ($k_{\mathrm{S-S}}$) is in line with the high stability of the monomeric sulfur radical cation (SNACET$>$S$\bullet^+$) because of spin delocalization in the carbonyl group. The monomeric radical cation (SNACET$>$S$\bullet^+$) is alternatively produced in slightly acidic solutions using the sulfate radical anion, $SO_4^{\bullet-}$, as an one-electron oxidant. This paper provides further evidence that the nature of the neighboring group affects the ultimate course of the sulfide oxidation.

## Introduction

A large research effort has been undertaken to characterize reactive intermediates, which are involved in the oxidation of organic sulfides and their corresponding reaction mechanism.[1−3] Hydroxyl radicals, owing to their electrophilic character, are well-known to initiate oxidation of sulfides, $R_2S$, by addition to the free electron pair at sulfur (reaction 1).

$$R_2S + \bullet OH \rightarrow R_2S\bullet{-}OH \tag{1}$$

The resulting hydroxysulfuranyl radical ($R_2S\bullet{-}OH$) has been experimentally identified,[4−7] and several routes for its decomposition have been established.[5,6,8−12] The $R_2S\bullet{-}OH$ radicals derived from simple aliphatic sulfides generally have rather short lifetimes, slightly less than 1 $\mu$s. Depending on the sulfide concentration and pH, hydroxysulfuranyl radicals can yield dimeric sulfur−sulfur (S∴S) three-electron-bonded radical cations (reaction 2),[7,13,14] monomeric sulfur radical cations via spontaneous and/or proton-catalyzed dissociation (reaction 3), carbon-centered (α-alkylthio)alkyl radicals (reaction 4), or dimeric sulfur−sulfur (S∴S) three-electron-bonded radical cations by reaction with a second sulfide molecule (reaction 5).

$$R_2S\bullet{-}OH + R_2S \rightarrow (R_2S\therefore SR_2)^+ + OH^- \tag{2}$$

$$R_2S\bullet{-}OH + H^+ \rightarrow R_2S\bullet^+ + H_2O \tag{3}$$

$$R_2S\bullet^+ \rightarrow -C\bullet H{-}S{-}R + H^+ \tag{4}$$

$$R_2S\bullet^+ + R_2S \rightleftarrows (R_2S\therefore SR_2)^+ \tag{5}$$

The participation of neighboring groups has been identified as a crucial mechanistic detail.[15] Recently, detailed studies were concerned with the hydroxysulfuranyl radical stability, particularly, if the substituent R contained some functional groups. For example, the formation of relatively stable hydroxysulfuranyl radicals of 2-(methylthio)acetic acid methyl ester and 3-(methylthio)acetaldehyde dimethyl acetal has been reported,[4] which decompose ca. 20-fold and 6-fold slower, respectively, than the corresponding hydroxysulfuranyl radical from dimethyl sulfide[6] due to the intramolecular hydrogen bonding of the H atom of the $\sigma\sigma^*$-bonded •OH to an oxygen atom of a carbonyl or methoxy group.[4] In contrast, hydroxysulfuranyl radicals are significantly less stable for the corresponding 2-(methylthio)-acetic acid and 2,2′-thiodiethanoic acid, where intramolecular protons catalyze sulfur radical cation formation followed by their decarboxylation.[5] Other examples of neighboring groups af-

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fecting the stability of hydroxysulfuranyl radicals occur in (carboxyalkyl)thiopropionic acid derivatives, where intramolecular sulfur−carboxylate oxygen (S−O) bonded radicals are formed,[9] and in 2-(methylthio)ethanol and 2,2′-dihydroxydiethyl sulfide, where a rapid intramolecular hydrogen transfer from the adjacent hydroxyl groups leads to (alkylthio)ethoxy radicals.[6]

The present paper investigates the radical-induced oxidation mechanism of *N*,*S*-diacetyl-L-cysteine ethyl ester (SNACET) and focuses particularly on the effect of the electron-withdrawing functional group (acetyl group, $CH_3C(=O)$) on the stability of the hydroxysulfuranyl radical and the sulfur radical cationic intermediates. In the case of the latter species the stability of the monomeric sulfur radical cation ($R_2S^{\bullet+}$) should be relatively high because of spin delocalization onto the carbonyl group. On the other hand, electron induction into the $2\sigma/1\sigma^*$ three-electron bond exerted by the adjacent electron-withdrawing acetyl group should strengthen the $S\therefore S$ bond and cause a blue shift in the optical absorption. This paper provides further evidence that the nature of the neighboring group affects the ultimate course of the sulfide oxidation. The fate of the reactive species formed by an initial attack at a sulfur atom is of interest in following the course of the reaction mechanism since SNACET has been used as a protective agent against UV radiation.[16]

## Experimental Section

**Materials.** All the chemical compounds used for the experiments were of the purest commercially available grade and were used as received. *N*,*S*-diacetyl-L-cysteine ethyl ester (SNACET) was a gift from the Pasteur Institut, Paris.

**Solutions.** All solutions were made up freshly in Millipore water and their respective pH values were adjusted through addition of NaOH or $HClO_4$. They were subsequently purged for at least 30 min per 500 mL sample with the desired gas, Ar, $N_2$, or $N_2O$ before irradiation.

**Pulse Radiolysis.** Pulse radiolysis experiments were performed with 5−17 ns pulses of 6 MeV electrons from the Lodz Technical University ELU-6 linear accelerator.[17] Absorbed doses were on the order of 8−15 Gy (1 Gy = 1 J/kg). Signal averaging methods were used. A description of the pulse radiolysis setup and data collection has been reported elsewhere.[17,18] The $N_2O$-saturated $10^{-2}$ M solutions of potassium thiocyanate were used as the dosimeter, taking a radiation chemical yield of 6.13 and a molar extinction coefficient of 7580 $M^{-1}\,cm^{-1}$ at 472 nm.[19] All experiments were carried out with continuously flowing solutions.

**Electron Spin Resonance.** Electron spin resonance (ESR) experiments were performed using a Bruker-ESP300 spectrometer operating in the X-band (9.5 GHz) equipped with a cryostat and a variable temperature unit over the temperature range of 77−293 K. The samples of polycrystalline SNACET were irradiated in spectrosil tubes (immersed in liquid nitrogen) with doses of about 5 kGy from a $^{60}Co$ $\gamma$-source (Issledovatel, USSR) at the Institute of Nuclear Chemistry and Technology (Warsaw). The measurements were performed either in a vacuum or in the presence of oxygen. The $\gamma$-irradiation and ESR methodology used to generate and study radical transients has been described in detail in earlier work.[20] The ESR spectra were analyzed by computer simulations using the Bruker software, Symphony.

**Analysis of Stable Products.** Identification of carbon monoxide (CO) was performed by the carbon monoxide/hemoglobin complexometry experiments[21] to detect the eventual formation of CO in irradiated solutions. Ferrous hemoglobin (64.5 kDa) reacts stoichiometrically with CO to form the carbon monoxide derivative which exhibits a very sharp Soret band at $\lambda = 419$ nm with an extinction coefficient $\epsilon_{419} = 1.91 \times 10^4$ $M^{-1}\,cm^{-1}$. The lowest detection level is typically 1 $\mu$M. $\gamma$-Irradiations were performed with an IBL 637 irradiator composed of a $^{137}Cs$ source (222 TBq, Institut Curie, Paris) using a dose rate of 9.8 Gy $min^{-1}$. UV−vis absorption spectra were recorded using a Beckman DU 70 spectrophotometer.

Acetaldehyde was analyzed based on the derivatization technique with PFBOA [*O*-(2,3,4,5,6-pentafluorobenzylo)hydroxyloamine] and extraction in the LLE system (liquid−liquid extraction) with hexane. The products of this reaction are oximes, characterized by very high volatility. Therefore, they can be analyzed by means of the GC technique with the ECD detector. An aliquot of an irradiated solution was acidified to pH 2, and derivatized by the addition of the PFBOA by heating the sample at 45 °C for 2 h. Subsequently the reaction mixture was cooled to room temperature and was extracted with hexane.

## Results

**Radiolysis of Water.** Pulse irradiation of water leads to the formation of the primary radical species shown in reaction 6.[22] In $N_2O$-saturated solutions ($[N_2O]_{sat} \approx 2 \times 10^{-2}$ M),[23] the hydrated electrons, $e_{aq}^-$, are converted into $^\bullet OH$ radicals according to eq 7 ($k_7 = 9.1 \times 10^9\ M^{-1}\,s^{-1}$).[23] Reaction 7 nearly doubles the amount of $^\bullet OH$ radicals available for reactions with substrates.

$$H_2O \rightarrow {}^\bullet OH,\ e_{aq}^-,\ {}^\bullet H \tag{6}$$

$$e_{aq}^- + N_2O \rightarrow {}^\bullet OH + OH^- + N_2 \tag{7}$$

At pH < 4 the diffusion-controlled reaction of $e_{aq}^-$ with protons becomes important $k = 2.0 \times 10^{10}\ M^{-1}\,s^{-1}$),[24] resulting in a pH-dependent lowered yield of $^\bullet OH$ radicals and a correspondingly increased yield of $^\bullet H$ atoms. Some of the experiments were carried out in very acidic solutions (pH 1), where most of hydrated electrons are converted into H atoms. Under these conditions the yield of $^\bullet H$ atoms is comparable to the yield of $^\bullet OH$ radicals. To check the contribution of the reaction between $^\bullet H$ atoms and SNACET, the solution was acidified to pH 1, and 0.5 M 2-methyl-2-propanol (*tert*-butyl alcohol, *t*-BuOH) was added to the solution in order to scavenge the $^\bullet OH$ radicals ($k = 6.8 \times 10^8\ M^{-1}\,s^{-1}$).[24] No transient absorption spectra were observed over the wavelength range investigated (250−700 nm), indicating that contribution of any products formed in the reaction of H atoms with SNACET to the absorption spectra recorded in $N_2O$-saturated solutions at pH 1 is negligible.

**Mechanistic Studies with the Hydroxyl Radical.** The reaction of $^\bullet OH$ radicals with SNACET was investigated in $N_2O$-saturated solutions over the concentration range of $2 \times 10^{-4}$−$5 \times 10^{-2}$ M and pH range of 1−6.

*Influence of pH.* Depending on the pH, pulse irradiation leads to different transient optical spectra. Figure 1A displays the transient optical spectra recorded after irradiation of $N_2O$-saturated aqueous solutions at pH 1 and 6, containing $10^{-3}$ M SNACET. An intense absorption band was observed 5.3 $\mu$s after the pulse, with $\lambda_{max} = 420$ nm and a small absorption band peaking at $\lambda_{max} = 280$ nm at pH 1 (Figure 1A, curve a). On the other hand, the transient optical spectrum recorded 0.8 $\mu$s after the pulse, at pH 6, was characterized by a strong absorption band with $\lambda_{max} = 280$ nm and an additional weak shoulder in the wavelength region between 330 and 380 nm (Figure 1A, curve b). This shoulder is better developed at longer time scale, i.e., 66 $\mu$s after the pulse (Figure 1A, curve c). A distinct absorption band with $\lambda_{max} = 280$ nm indicates the presence of α-(alkylthio)alkyl radicals which can be formed either via direct

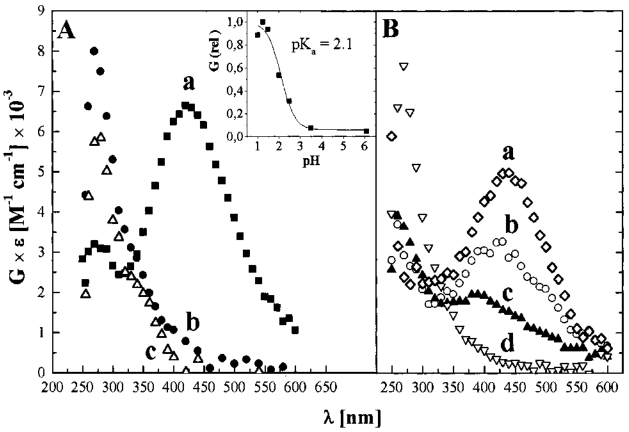
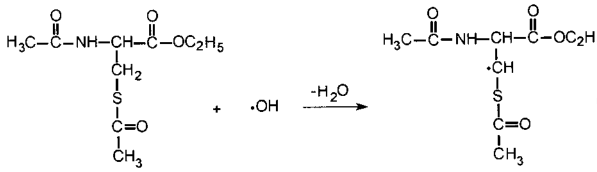


**Figure 1.** (A) Transient absorption spectra observed (a) 5.3 $\mu$s after pulse irradiation of $N_2O$-saturated aqueous solution at pH 1 containing $10^{-3}$ M SNACET; (b) 0.8 $\mu$s and (c) 66 $\mu$s after pulse irradiation of $N_2O$-saturated aqueous solution at pH 6 containing $10^{-3}$ M SNACET. Insert: Plot of the yield of the 420 nm species (normalized to the actual •OH radical concentration) as a function of pH. (B) Transient absorption spectra observed in Ar-saturated aqueous solution at pH 5.5 containing $10^{-3}$ M SNACET, $5 \times 10^{-3}$ M $S_2O_8^{2-}$, and 0.5 M *tert*-butyl alcohol (a) 60 ns, (b) 1.2 $\mu$s, (c) 2.3 $\mu$s, and (d) 15 $\mu$s after pulse irradiation.

hydrogen abstraction from the adjacent methylene group (reaction 8)


(8)

$$CH_3C(=O)NHCH(CH_2SC(=O)CH_3)C(=O)OC_2H_5 + {}^\bullet OH \xrightarrow{-H_2O} CH_3C(=O)NHCH({}^\bullet CHSC(=O)CH_3)C(=O)OC_2H_5 \quad (8)$$

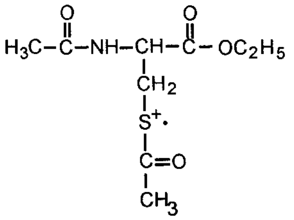
or via deprotonation of the monomeric sulfur radical cation (SNACET>S•$^+$) in the reaction analogous to reaction 4. An assignment of the weak shoulder between 330 and 380 nm will be discussed later (vide infra). To study the pH dependence of the formation of the 420 nm species, pulse radiolysis experiments were performed in $N_2O$-saturated aqueous solutions containing $10^{-3}$ M SNACET at different pH values over the range 1−6. The yield of the 420 nm species (normalized to the actual yield of •OH radical concentration) was found to decrease with increasing pH (Figure 1A, insert). The plot of the normalized $G \times \epsilon_{420}$ ($G_{rel}$) takes a sigmoidal shape down to about pH 3.4 with the inflection point observed at pH 2.1.

*Influence of the SNACET Concentration.* Since low pH and high concentrations of sulfides facilitate the formation of dimer radical cations through reaction of a monomeric sulfur radical cation (>S•$^+$) with a nonoxidized sulfide (reaction 5),[7,25] one might suspect that the 420 nm species is the dimeric radical cation $(S\therefore S)^+$ derived from SNACET. To determine whether such an assignment is correct, pulse radiolysis experiments were performed with various concentrations, $1 \times 10^{-3}$−$5 \times 10^{-2}$ M, of SNACET. Solutions of pH 1 were used to ensure a high concentration of protons to promote the elimination of water and the fast formation of monomeric sulfur radical cation (>S•$^+$) according to reaction 3.

It can be seen from Table 1 that the radiation chemical yields, expressed as $G \times \epsilon_{420}$, were found to increase with the concentration of SNACET. Based on the formula given by Schuler et al.[26] which relates the *G*-value of solute radicals generated by •OH radicals to the product of the rate constant for the reaction of •OH radicals with the solute and the solute concentration, one can calculate the *G*-value of •OH radicals available for reaction with SNACET. From these calculations it can be shown that the immediate oxidation product, (SNACET)>S•$^+$, can be increased by only ~15−20% with increasing SNACET concentration from $1 \times 10^{-3}$ to $5 \times 10^{-2}$ M. Since the radiation chemical yields of the 420 nm species ($G \times \epsilon_{420}$) are seen to increase in a similar way, this provides a preliminary rationale for the lack of an equilibrium between (SNACET)>S•$^+$ and (SNACET)$(S\therefore S)^+$. A detailed kinetic analysis of the decay of 420 nm band shows that its half-life does not increase with SNACET concentration as would be expected for (SNACET)$(S\therefore S)^+$. Moreover, it shows an opposite trend: shorter lifetimes for higher SNACET concentrations. Therefore, one can conclude that a primary intermediate whose absorption spectrum maximizes at 420 nm might be due to the monomeric sulfur radical cation, (SNACET)>S•$^+$,

**TABLE 1: Radiation Chemical Yields, Expressed as $G \times \epsilon_{420}$, as a Function of the Concentration of SNACET**

| concn (mM) | $G \times \epsilon_{420}$ ($M^{-1}$ $cm^{-1}$) |
|---|---|
| 1.0 | 8087 |
| 5.0 | 9132 |
| 10.0 | 9122 |
| 25.0 | 9951 |
| 50.0 | 9620 |



$$CH_3C(=O)NHCH(CH_2S^{+\bullet}C(=O)CH_3)C(=O)OC_2H_5$$

with only minor contribution, if any, of the dimeric form, (SNACET)$(S\therefore S)^+$.

At this point in the exposition, we are not able to assign definitively the 420 nm absorption band to the monomeric sulfur radical cation, (SNACET)>S•$^+$, since most alkyl monomeric radical cations ($R_2S^{\bullet +}$) exhibit an absorption band in the UV region around 300 nm.[3,27,28] However, we note that $\lambda_{max}$ of the absorption band formed at low SNACET concentration ($2 \times 10^{-4}$ M) is similar to $\lambda_{max}$ values observed for acetylthiyl radical having neighboring carbonyl group.[29] Since practically all alkylthiyl radicals usually display a weak absorption band in the UV with $\lambda_{max}$ around 330 nm with extinction coefficients typically less than 500 $M^{-1}$ $cm^{-1}$,[1] the red shift of the spectrum and the higher value of the extinction coefficient at the maximum of the absorption of the $CH_3C(=O)S^\bullet$ radical are attributed to the resonance stabilization of sulfur radical by the carbonyl group. Based on the analogy to previous assignments in thiol systems, the correlation between locations of $\lambda_{max}$ values of the absorption bands of sulfur-centered radicals containing neighboring carbonyl group adjacent to the sulfur functionality with those of sulfur-centered radicals containing only aliphatic groups strongly suggests that the 420 nm absorption band is due to the monomeric sulfur radical cation, (SNACET)>S•$^+$ (see Figure 1A, curve a).

Titration of the buildup rate of the 420 nm absorption versus the SNACET concentration at pH 1 provides a convenient method to determine the rate constant of •OH radicals with SNACET. From the slope of a linear fit of the observed rates ($k_{obs}$) vs [SNACET], the bimolecular rate constant $k_{420} = 3.9 \times 10^9$ $M^{-1}$ $s^{-1}$ was computed. Since the plot of $k_{obs}(420)$ vs [SNACET] does not show departure from the linearity and since the decay of the initially formed hydroxysulfuranyl radicals of SNACET is expected to be very fast at high proton concentra-

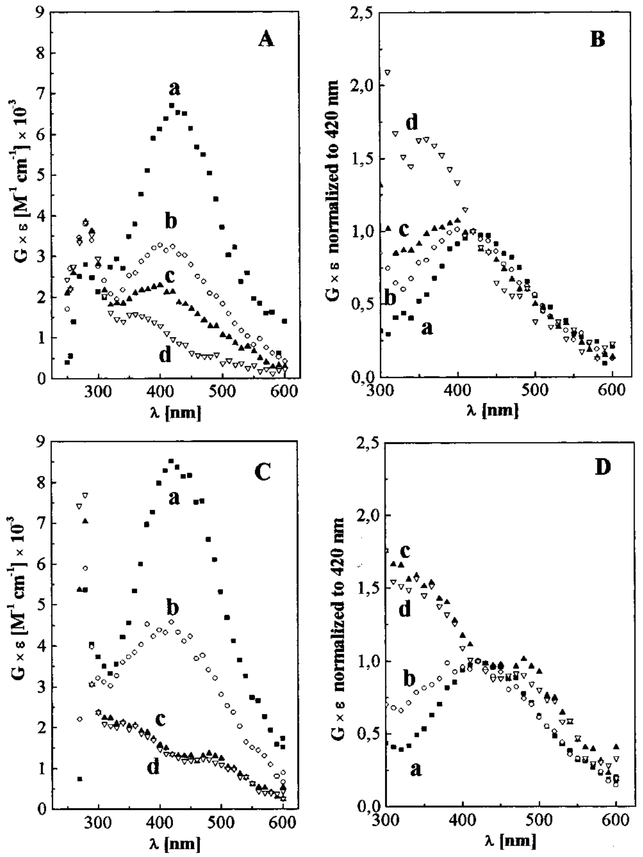


**Figure 2.** (A) Transient absorption spectra observed in $N_2O$-saturated aqueous solution at pH 1 containing $10^{-3}$ M SNACET (a) 680 ns, (b) 3.8 $\mu$s, (c) 5.8 $\mu$s, and (d) 10 $\mu$s after pulse irradiation. (B) Transient absorption spectra normalized to the 420 nm absorption observed in $N_2O$-saturated aqueous solution at pH 1 containing $10^{-3}$ M SNACET (a) 680 ns, (b) 3.8 $\mu$s, (c) 5.8 $\mu$s, and (d) 10 $\mu$s after pulse irradiation. (C) Transient absorption spectra observed in $N_2O$-saturated aqueous solution at pH 1 containing $5 \times 10^{-2}$ M SNACET (a) 85 ns, (b) 640 ns, (c) 5.8 $\mu$s, and (d) 10 $\mu$s after pulse irradiation. (D) Transient absorption spectra normalized to the 420 nm absorption observed in $N_2O$-saturated aqueous solution at pH 1 containing $5 \times 10^{-2}$ M SNACET (a) 680 ns, (b) 3.8 $\mu$s, (c) 5.8 $\mu$s, and (d) 10 $\mu$s after pulse irradiation.

tions (in the reaction analogous to reaction 3), the formation rate constant of the 420 nm intermediate ($k_{420}$) should correspond to the rate constant of •OH radicals reacting with SNACET. The $k_{420}$ value is smaller than the reported values of rate constants for dialkyl sulfides.[7] This clearly indicates that the presence of the electron-withdrawing group (acetyl) decreases the electron density at sulfur in SNACET and consequently decreases the rate constant with a strong electrophile such as the •OH radical.

It can be seen in Figure 2 that the transient spectra recorded at pH 1 for two extreme concentrations (1 and 50 mM) of SNACET change substantially with elapsing time. For all SNACET solutions over the concentration range of 1−50 mM, the spectra recorded in time windows after 420 nm traces reached their respective plateaus for each concentration of SNACET consisted of an intense band with $\lambda_{max} = 420$ nm (Figure 2A,C). There is also one weaker absorption band on the UV side with $\lambda_{max}$ in the neighborhood of 280−290 nm. The latter band became more pronounced in solution containing 1 mM SNACET 3.8 $\mu$s after the pulse (Figure 2A). At longer times (5.8 $\mu$s after the pulse), the intensity of that band remained constant. In addition, a broad spectrum with $\lambda_{max} \sim 380-390$ nm developed. It is noteworthy that at high SNACET concentration (50 mM) the spectrum recorded at a similar time (5.7 $\mu$s after the pulse) is even broader (Figure 2C) or at least has a greatly enhanced absorption at 350 nm compared to solution containing 1 mM SNACET. Moreover, at these delay times, a new feature becomes pronounced that was not observed in 1 mM SNACET, i.e., a weak shoulder around 470−500 nm.

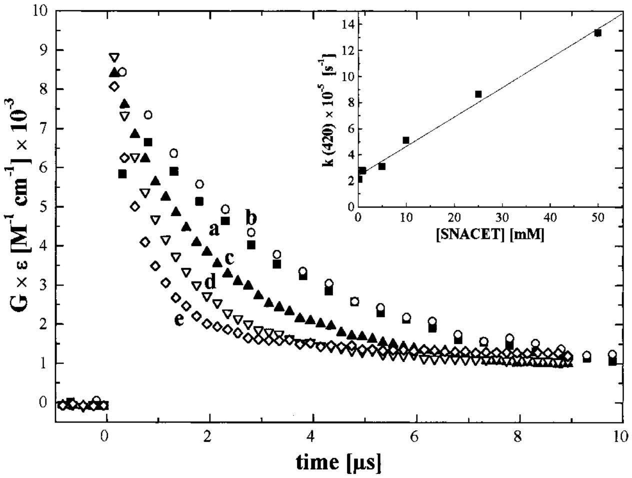


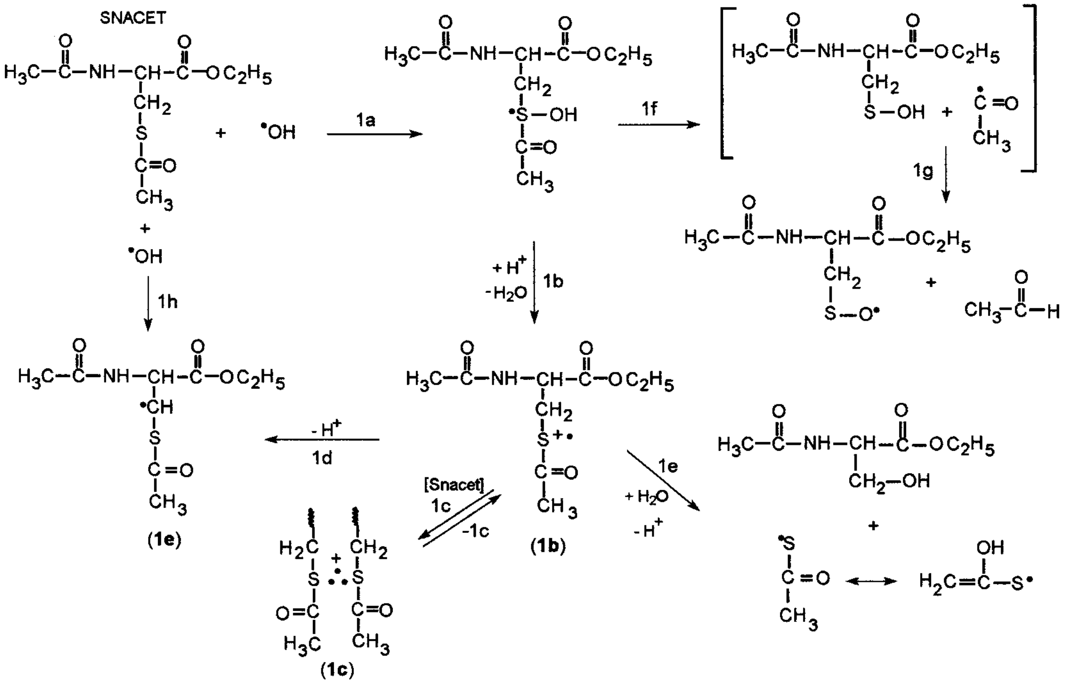
**Figure 3.** Kinetic traces for decay of the SNACET($>S^{\bullet+}$) absorbance observed at 420 nm after pulse irradiation of $N_2O$-saturated aqueous solutions at pH 1 containing different concentrations of SNACET: (a) $10^{-3}$ M, (b) $5.0 \times 10^{-3}$ M, (c) $10^{-2}$ M, (d) $2.5 \times 10^{-2}$ M, and (e) $5.0 \times 10^{-2}$ M. Insert: Plot of the observed first-order rate constants of the decay of SNACET($>S^{\bullet+}$) as a function of SNACET concentration.

Since the changes of the absorption spectra with the elapsed time were very subtle, for the sake of better comparison, all spectra were normalized to the 420 nm absorption maximum (Figure 2B,D). In solutions containing 1 mM SNACET there is a buildup of the normalized absorption only in the range of wavelengths below 420 nm (Figure 2B); however, in solution containing 50 mM SNACET a buildup of the normalized absorption is seen in the range of wavelengths below 420 nm as well as above 470 nm (Figure 2D).

In principle, such behavior is indicative of the existence of at least two distinct species. The first species is characterized by an absorption spectrum with two maxima, one located in the region of $\lambda = 330-370$ nm and a second in the region of $\lambda = 470-500$ nm (Figure 2D, curves c and d). Since its formation is facilitated by the high concentration of SNACET, this suggests that the species responsible is the intermolecularly three-electron-bonded dimeric radical cation of SNACET. On the other hand, the second species is characterized by a broad absorption spectrum (Figure 2B, curve c) with the maximum located at $\lambda_{max} = 380-390$ nm, and its formation occurs at low concentrations of SNACET. This resembles the spectrum obtained upon •OH-induced oxidation of thiol acetic acid at pH 1 and thus can be assigned to the enolic form of the acetyl thiyl radical, $CH_2{=}C(OH)S^{\bullet}$ (vide infra).

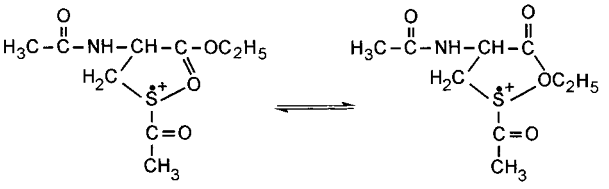
The plot of $k_{obs}$ determined from the decay of the 420 nm absorption band at various concentrations of SNACET gives a straight line (Figure 3, insert). The individual rate constant for the decay of (SNACET)$>S^{\bullet+}$ $k_5 = 2.2 \times 10^7$ $M^{-1}$ $s^{-1}$ (corresponding to reaction 1c in Scheme 1) was determined from the slope of a $k_{obs}$ vs [SNACET] plot. The value of $k_5$ is almost 2 orders of magnitude smaller than the reported values ($\sim 10^9$ $M^{-1}$ $s^{-1}$) found for similar reactions in other thioether systems.[30−32] Thus, this clearly indicates that the formation of SNACET($>S{\therefore}S<$)$^+$ is very inefficient over the concentration range studied from 0.2 mM up to 2 mM (taking into account the values of both $k_5$ and $k_{int}$).

**SCHEME 1**



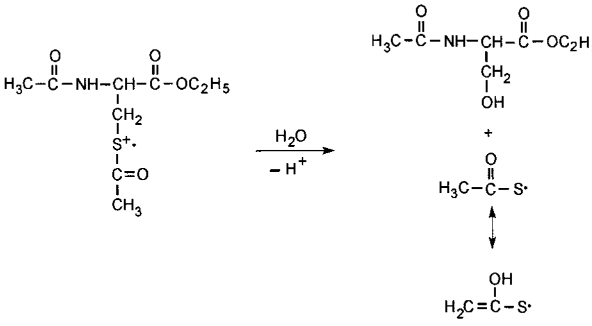
Extensive studies have shown that the stability constant for equilibria such as (5) is mainly controlled by the rate constant for the $S\therefore S$ bond dissociation which depends on the electron density release by the substituents that can stabilize the oxidized sulfur center, $S^{\bullet+}$ in an $S\therefore S$ bond.[33] Generally, the more electron donating the substituent, the weaker is the $S\therefore S$ bond.[34] Steric hindrance is an additional factor, which is assumed to exert an additional $S\therefore S$ bond weakening.[34] On the other hand, resonance stabilization is also postulated as a rationale for the relatively high stability of monomeric sulfur radical cations, $>S^{\bullet+}$. Among the aliphatic species the best evidence for a monomeric radical cation exists for $t\text{-}Bu_2S^{\bullet+}$, which derives its particular stability from internal resonance.[30] A similar rationale is also forwarded for the high stability of monomeric aromatic sulfide radical cations due to a spin delocalization on the aromatic ring.[35,36] The low $k_5$ value found for SNACET (determined as $k_{420}$, vide supra) follows the trend expected on the basis of the reduced propensity of the radical cation to form dimers because of the spin delocalization into carbonyl group. Preliminary quantum-mechanical calculations on a model compound containing a carbonyl group adjacent to the thioether group have confirmed spin delocalization on the carbonyl group.[37]

In principle, the monomeric sulfur radical cation derived from SNACET can undergo a rapid cyclization to the intramolecularly ($\bullet S{-}O$)-bonded species with a five-membered ring structure[6,9,11,38,39] involving the oxygen located in either the carbonyl group or the ethoxy group,

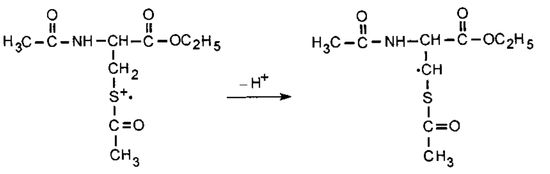


and thus the 420 nm absorption band can be alternatively assigned to that species as well. However, pulse radiolysis experiments on the model compound, *S*-ethyl thioacetate ($H_3C{-}C({=}O){-}S{-}CH_2{-}CH_3$), have shown the formation of a strong 420 nm absorption band in $N_2O$-saturated solutions at pH 1. This observation supports our earlier assignment of the 420 nm band to the monomeric sulfur radical cation and effectively eliminates the chance that 420 nm band is due to an intramolecularly $(\bullet S{-}O)^+$-bonded radical cation. Moreover, the resonance stabilization of the monomeric sulfur radical cation of SNACET ($(SNACET){>}S^{\bullet+}$) would reduce any efficient stabilization of the latter form as an intramolecularly $(\bullet S{-}O)^+$-bonded radical cation, as well.

The plot of a $k_{obs}$ vs [SNACET] (Figure 3, insert) exhibits an intercept ($k_{int} = 2.5 \times 10^5\ s^{-1}$) which can be associated with the first order decay component of the $(SNACET){>}S^{\bullet+}$. This first-order component could be rationalized as the fragmentation process of the $(SNACET){>}S^{\bullet+}$ via heterolytic C−S bond cleavage resulting in the formation of the enolic form of acetylthiyl radical, $CH_2{=}C(OH)S^{\bullet}$ (reaction 9) and the deprotonation process of $(SNACET){>}S^{\bullet+}$ leading to α-(alkylthio)alkyl radicals (reaction 10).



(9)



(10)

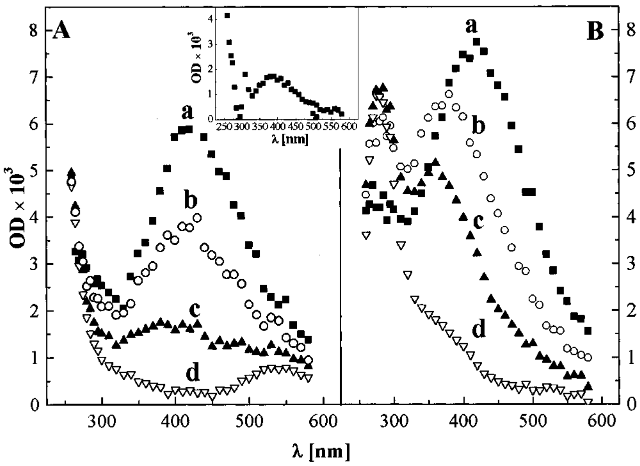


**Figure 4.** Transient absorption spectra observed in (A) $O_2$-saturated and (B) $N_2O$-saturated aqueous solution at pH 1 containing $10^{-3}$ M SNACET (a) 700 ns, (b) 3.5 $\mu$s, (c) 9 $\mu$s, and (d) 35 $\mu$s after pulse irradiation with dose ≈ 2 Gy. Insert: Transient absorption spectra observed 3.5 $\mu$s after pulse irradiation (dose ≈ 2 Gy) in $N_2O$-saturated aqueous solution at pH 1 containing $10^{-3}$ M thiol acetic acid.

*Influence of Oxygen.* Upon pulse radiolysis of oxygenated aqueous solutions, pH 1, containing 1 mM SNACET, the transient absorption spectrum observed 700 ns after the pulse is characterized by a strong absorption maximum at $\lambda_{max} = 420$ nm (Figure 4A, curve a). The intensity of the 420 nm absorption band is not much affected by the presence of oxygen, suggesting a contribution mainly of the cationic radical species to the 420 nm absorption band. By analogy to similar findings in $N_2O$-saturated solutions (Figure 4B, curve a), this observation confirms our earlier assignment of the 420 nm absorption band to the sulfur monomeric radical cation, SNACET($>S^{\bullet+}$), which at 700 ns after the pulse has not yet converted into other transients. The transient absorption spectra recorded at times greater than 9 $\mu$s exhibited a very broad absorption band with $\lambda_{max} = 380$ nm (Figure 4A, curve c). This absorption band can be assigned to the combined absorption bands of monomeric sulfur radical cations, SNACET($>S\bullet^+$), and acetylthiyl radicals in the tautomeric form $\mathrm{CH_2{=}C(OH)S\bullet}$ (vide infra). Figure 4A (curve d) shows that spectrum recorded 35 $\mu$s after the pulse is characterized by an absorption band with $\lambda_{max} = 540$ nm and a strong transient absorption band which steadily increases below 300 nm with $\lambda_{max} < 250$ nm whose characteristics appear to be compatible with an assignment to the thiylperoxyl radical RSOO• formed in the reversible process (reaction 11)[40-42]

$$\mathrm{CH_2{=}C(OH)S\bullet + O_2 \rightleftarrows CH_2{=}C(OH)SOO\bullet} \qquad (11)$$

Moreover, such a spectrum was not observed in $N_2O$-saturated solutions (Figure 4B, curve c). The observations reported above indicate that the decay of the monomeric sulfur radical cations, SNACET($>S\bullet^+$), has to occur by a cleavage of the C−S bond, which leads to the formation of the acetylthiyl radical.

Comparison of the absorption spectra obtained both in $O_2$- and $N_2O$-saturated solutions (Figure 4A,B, curves b and c) reveals another interesting feature that indicates the presence of an additional transient. The intensity of absorptions, observed in wavelength regions between 260−290 nm and 320−380 nm appears much higher for the $N_2O$-saturated solution, suggesting that there might be a contribution from C-centered radicals. In the presence of oxygen these radicals convert into their respective peroxyl radicals. It may be assumed that the first radical is the α-(alkylthio)alkyl radical (supporting our earlier assignment, vide supra) and the second one is the C-centered radical resulting from the H-abstraction from the α-carbon. Based on recent ab initio calculations,[43-45] one can expect a low $^{\alpha}$C−H bond dissociation energy and therefore the α-carbon center in SNACET might be also a potential major point of direct attack by •OH radicals.

**•OH-Induced Oxidation of Thiol Acetic Acid in Acid Solutions.** To gain insight into the absorption spectrum of acetylthiyl radical under experimental conditions similar to those where the decay of the monomeric sulfur radical cations, SNACET($>S\bullet^+$) were observed, the reaction of •OH radicals with thiol acetic acid was studied in $N_2O$-saturated solutions at pH 1. In this case acetylthiyl radicals are produced by hydrogen abstraction according to reactions 12 and 13:

$$\mathrm{\bullet OH + CH_3{-}C({=}O){-}SH \rightarrow CH_3{-}C({=}O){-}S\bullet + H_2O} \qquad (12)$$

$$\mathrm{\bullet H + CH_3{-}C({=}O){-}SH \rightarrow CH_3{-}C({=}O){-}S\bullet + H_2} \qquad (13)$$

The studies of Zhao et al.[29] provided information on the absorption spectrum in neutral solutions of the acetylthiyl radical that exhibits a broad absorption band with a maximum located at $\lambda_{max} = 420$ nm and with an extinction coefficient of $\epsilon_{420} = 3900\ \mathrm{M^{-1}\ cm^{-1}}$. It appears very surprising that the transient absorption spectrum recorded by us at 3.5 $\mu$s after the pulse, i.e., after the completion of reaction 12 and 13, does not resemble at all the spectrum of acetylthiyl radical $\mathrm{CH_3{-}C({=}O){-}S\bullet}$ obtained by Zhao et al. The spectrum exhibited a very broad absorption band in the region from 320 to 550 nm, with a maximum located at $\lambda_{max} = 380$ nm (Figure 4, insert). The extinction coefficient at the maximum was measured to be 430 $\mathrm{M^{-1}\ cm^{-1}}$ when the dithiocyanate radical anion $(SCN)_2\bullet^-$ was used as reference. Accordingly, we interpreted the blue shift from the spectrum of Zhao et al. and our lower extinction coefficient in acid solutions to a conversion of the keto form of acetylthiyl radical $\mathrm{CH_3{-}C({=}O){-}S\bullet}$ into the tautomeric enolic form $\mathrm{CH_2{=}C(OH){-}S\bullet}$.[46] Two important conclusions can be drawn from these observations. First, this means that the absorption band with a maximum located at $\lambda_{max} = 420$ nm observed in aqueous solutions containing SNACET at pH 1 can be definitely assigned to the monomeric sulfur radical cation, SNACET($>S\bullet^+$). Second, formation of the broad absorption band with $\lambda_{max} = 380$ nm, which occurs concomitantly with the decrease of the 420 nm absorption band, clearly shows that the decay of SNACET($>S\bullet^+$) involves fragmentation into the acetylthiyl radical.

**Oxidation by the $SO_4^{\bullet-}$ Radical.** Direct formation of the sulfide radical cation can be achieved employing a typical one-electron oxidant such as sulfate radical anion, $SO_4^{\bullet-}$.[47] The reaction of the $SO_4^{\bullet-}$ radical with SNACET was investigated in Ar-saturated aqueous solution, pH 5.5, containing $10^{-3}$ M SNACET, $5 \times 10^{-3}$ M $S_2O_8^{2-}$, and 0.5 M *tert*-butyl alcohol. Under these conditions, the $SO_4^{\bullet-}$ radical anions are formed according to reaction 14 ($k_{14} = 1.2 \times 10^{10}\ \mathrm{M^{-1}\ s^{-1}}$).[24]

$$e_{aq}^{-} + S_2O_8^{2-} \rightarrow SO_4^{\bullet-} + SO_4^{2-} \qquad (14)$$

•OH radicals do not interfere with the measurement because of reaction 15.

$$\mathrm{\bullet OH + CH_3C(CH_3)_2OH \rightarrow H_2O + \bullet CH_2C(CH_3)_2OH} \qquad (15)$$

The formation of sulfide radical cations derived from SNACET can occur through the following reaction:

$$\mathrm{SO_4^{\bullet-} + SNACET \rightarrow SO_4^{2-} + (SNACET){>}S\bullet^+} \qquad (16)$$

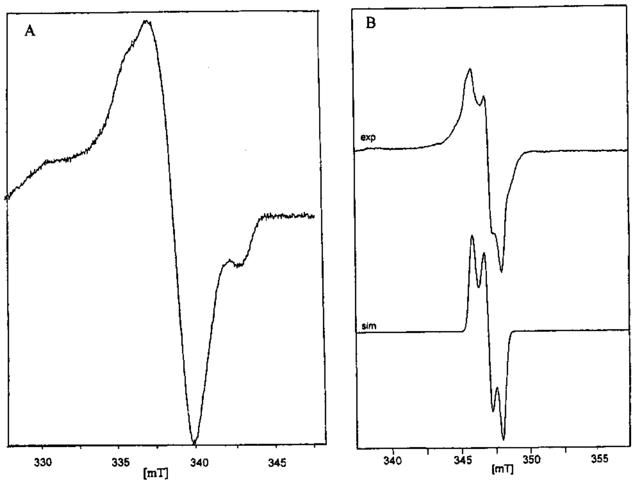


**Figure 5.** ESR spectra recorded in $\gamma$-irradiated polycrystalline SNACET samples: (A) experimental spectrum of the RS•-type radical detected at 273 K in evacuated samples; (B) experimental and simulated spectra of the RSO• radical detected at room temperature in the presence of oxygen.

The absorption band located at ∼450 nm observed 60 ns after the pulse irradiation was attributed to the $SO_{4}{}^{\bullet -}$ radical anion (Figure 1B, curve a).[48] The 450 nm band subsequently converts into a spectrum which exhibits 1.2 $\mu$s after the pulse an absorption band with $\lambda_{max} = 420$ nm (Figure 1B, curve b)). Considering that an analogous absorption band was observed during oxidation of SNACET by •OH radicals at pH 1 (vide supra), it can thus be concluded that the monomeric sulfur radical cation, (SNACET)>$S^{\bullet +}$, is produced as well by one-electron oxidation of SNACET by the $SO_4{}^{\bullet -}$ radical anion in slightly acidic solutions. The transient absorption spectrum, at times greater than 2 $\mu$s, exhibited a broad absorption spectrum with $\lambda_{max} = 380$ nm (Figure 1B, curve c). For chemical reasons it was anticipated that this absorption band can represent the combined absorption bands of the acetylthiyl radicals ($CH_3$–C(=O)–S•) originating from the fragmentation of any initially formed sulfur monomeric radical cations and the C-centered radicals resulting from the H-abstraction from the α-carbon (vide supra). This band decays within 15 $\mu$s after the pulse, leaving a transient absorption spectrum with a strong UV band having $\lambda_{max} = 280$ nm (Figure 1B, curve d). The 280 nm absorption spectrum represents the combined absorption of at least two separate species, one of them being α-(alkylthio)alkyl radical.

**ESR.** The main component of the ESR signal recorded in a $\gamma$-irradiated degassed polycrystalline sample of SNACET studied over the temperature range of 77–95 K was an anisotropic singlet with $g$-values $g_1 = 2.023$, $g_2 = 2.011$, and $g_3 = 2.002$. This spectrum was attributed to the monomeric sulfur radical cation (SNACET)>$S^{\bullet +}$ formed by direct ionization of a thioether sulfur. This observation is not surprising considering that this function exhibits the lowest ionization energy in comparison with other functions present in SNACET. Warming the samples of SNACET to 110–150 K resulted in the appearance of a new anisotropic singlet characterized by principal $g$-values $g_1 = 2.058$, $g_2 = 2.023$, and $g_3 = 1.999$. Similar spectra were observed in various thiols in the solid phase and were assigned either to the thiyl radicals (RS•) or to the perthiyl radicals (RSS•).[49] Since formation of RSS• radicals in SNACET is not possible, the spectrum observed in the polycrystalline SNACET up to 273 K (Figure 5A) could be assigned to the thiyl-type radicals (RS•). Additional evidence for the existence of RS• radicals in $\gamma$-irradiated SNACET was obtained in the presence of oxygen. The general picture observed up to 150 K was similar to that observed in the degassed sample of SNACET. However, as the temperature was further increased, a very characteristic anisotropic singlet ($g_{\parallel} = 2.035$ and $g_{\perp} = 2.0025$) of sulfur peroxyl radicals (RSOO•) appeared.[50] Annealing to 293 K resulted in its conversion to a new anisotropic singlet (Figure 5B) which can be simulated using $g$-tensor principal values $g_1 = 2.018$, $g_2 = 2.0094$, and $g_3 = 2.0035$ and a hyperfine splitting ($\Delta H = 0.43$ mT). These results indicate the conversion of sulfur peroxyl radicals (RSOO•) to SNACET-derived sulfinyl radicals (RSO•), which is in accord with earlier observations in glutathione, cysteine, and penicillamine.[51] Formation of RSO• radicals in the polycrystalline SNACET can be rationalized either by recombination of sulfur peroxyl radicals (RSOO•)[51] or by dissociation of the O–O bond in RSOO• radicals caused by visible irradiation.[52] The occurrence of the first process seems quite plausible in polycrystalline SNACET samples due to the long life of RSOO• radicals that were observable up to 270 K.

**Stable Products.** *CO Analysis.* The $\gamma$-irradiated (with a dose of 98 Gy) $N_2O$-saturated aqueous solutions containing SNACET at 1 mM concentration were purged by $N_2$ in order to release all dissolved gases and subsequently to insert them into hemoglobin solution at 3 $\mu$M concentration. The experiments were performed over the range of pH 2.4–7.8. Carbon monoxide was not detected in either case.

*Acetaldehyde Yields.* The $\gamma$-radiolysis of $N_2O$-saturated aqueous solutions at pH 1.0 and pH 6.0 containing SNACET at 1 mM concentration leads to the formation of relatively low concentration of acetaldehyde.

## Discussion

There are several significant features that are important to consider for a discussion of the mechanism of the •OH-induced oxidation of SNACET. (i) The oxidation leads at neutral pH exclusively to the 280 nm intermediate. However, the monomeric sulfur radical cation was not observed, and neither was the three-electron-bonded $(>S \therefore S<)^+$ radical cation, even at high solute concentrations ($5 \times 10^{-3}$ M). (ii) At high proton concentration (0.1 M), the oxidation leads to the 420 nm intermediate (assigned to the monomeric sulfur radical cation, SNACET>$S^{\bullet +}$) over a broad SNACET concentration range ($2 \times 10^{-4}$–$5 \times 10^{-2}$ M). (iii) During the decay of the monomeric sulfur radical cation (SNACET>$S^{\bullet +}$), the formation of two intermediates is observed: the enolic form of the acetylthiyl radical and the intermolecularly three-electron-bonded dimeric radical cation, SNACET$(>S \therefore S<)^+$, at very high concentration of SNACET (>10 mM).

**Mechanism.** The first step in the reaction of hydroxyl radicals with SNACET is an addition to the sulfur atom leading to the formation of hydroxysulfuranyl-type radicals (Scheme 1, reaction 1a). The subsequent reaction of this species depends on pH, solute concentration, and the presence of additional functionalities.

*Low pH Region.* At high proton concentrations, the initially formed hydroxysulfuranyl radicals undergo a very fast proton-catalyzed elimination of hydroxide ions (Scheme 1, reaction 1b). This reaction channel provides the basis for the observation of the monomeric sulfur radical cations (SNACET>$S^{\bullet +}$) characterized by an optical absorption band with $\lambda_{max} = 420$ nm. In principle, SNACET>$S^{\bullet +}$ radical cations are expected to be in equilibrium with the intermolecularly three-electron-bonded $(>S \therefore S<)^+$ dimeric radical cations (Scheme 1, reaction 1c/–1c). Formation of such species, however, is limited to very high concentration of SNACET because of the low equilibrium constant ($K = k_{1c}/k_{-1c}$), which, in turn, is a consequence of the spin delocalization into the carbonyl group of the acetyl group.

It is also noteworthy that the presence of the strong electron-withdrawing acetyl group adjacent to the sulfur function exerts a significant influence on the decay of the monomeric radical cation, SNACET>S•$^+$. Along with the anticipated deprotonation reaction of SNACET>S•$^+$ at the carbon in the α-position to the sulfur yielding α-(alkylthio)alkyl radicals (Scheme 1, reaction 1d) that occurs with the rate constant in the range of $10^4$−$10^5$ s$^{-1}$,[14,53] the fragmentation reaction of the SNACET>S•$^+$ (Scheme 1, reaction 1e) takes place as well. The observation of the acetylthiyl radical ($CH_2$=C(OH)−S•), and its peroxyl derivative (RSOO•), is thus in support of the fragmentation reaction involving C−S bond cleavage. This conclusion is fully supported by the ESR experiments in $\gamma$-irradiated polycrystalline SNACET samples where the radiation-induced processes start with ionization of a thioether function which leads directly to the formation of SNACET>S•$^+$. The existence of thiyl-type radicals, and sulfur peroxyl radicals (RSOO•) in the presence of oxygen, can be rationalized only in terms of the fragmentation mechanism.

*High pH Region.* At very low proton concentrations, in principle, hydroxysulfuranyl radical should be stable enough to permit observation of them on the submicrosecond time scale.[5,7] However, at neutral pH, no characteristic absorption band with $\lambda_{max} = 340$ nm, which could be assigned to such species, was observed. A very fast unimolecular concentration-independent dissociation of SNACET(>•S−OH) into SNACET>S•$^+$ and hydroxide ion (OH$^-$) can be ruled out since no absorption band with $\lambda_{max} = 420$ nm due to SNACET>S•$^+$ was detected. Moreover, the lack of the 420 nm absorption band cannot be rationalized in terms of the lower stability of the SNACET>S•$^+$ at higher pH because the 420 nm absorption band was observed under similar pH conditions during the $SO_4$•$^-$-induced oxidation of SNACET. Therefore, there must be another reaction pathway which can drastically shorten the lifetime of SNACET(>•S−OH) and thus prevents its observation. A mechanistically attractive and reasonable rationale for the short-lived SNACET(>•S−OH) is a fragmentation process (Scheme 1, reaction 1f) of the sulfur−carbon bond leading to the formation of acyl radicals and sulfenic acid. A similar fragmentation process was found to operate during photolysis of methyl-(*L*)-cobaloxime as a methyl radical source, in the presence of *S*-(4-chlorophenyl) thioacetate.[54] The reaction proceeds through the sulfuranyl-type radical, as “an intermediate or transition state” yielding acyl radicals and 4-chlorophenyl methyl sulfide. Such a mechanism of fragmentation of the hydroxysulfuranyl-type radicals has gained support through recent preliminary theoretical calculations.[37]

We are now left with the question whether the fragmentation reaction (reaction 1f in Scheme 1) can be experimentally verified. In general, acyl radicals should undergo an efficient fragmentation that leads to methyl radicals and CO.[55] This is, however, in contrast to the lack of CO in $\gamma$-irradiated SNACET samples (see the section Analysis of Stable Products), and thus it might indicate another reaction pathway for the acyl radicals. It should be pointed out that acetaldehyde was produced instead (see the section Analysis of Stable Products). Since sulfenic acids (RSOH) undergo readily hydrogen atom abstraction to fairly stable sulfinyl radicals (RSO•),[56] such abstraction reaction by acyl radicals to yield acetaldehyde is thermodynamically possible (Scheme 1, reaction 1g). Theoretical calculations at the PM3 level predict a 74 kcal mol$^{-1}$ value for the RSO−H bond dissociation energy (BDE).[57] On the other hand, the bond dissociation energy (BDE) for the reaction $H_3C-C(=O)-H \rightarrow H_3C-C(=O)^\bullet + H\bullet$ was given as 89.3 kcal mol$^{-1}$.[55] Moreover, the occurrence of the reaction 1g (Scheme 1) would be enhanced by the spatial closeness of the reactants in these circumstances.

Assuming that reactions 1b and 1f are the only two competitive processes for the decay of the SNACET>S•−OH, the inflection point at pH 2.1 obtained from the plot of the normalized $G \times \epsilon_{420}$ of (SNACET)>S•$^+$ (Figure 3, insert) allows one to calculate the rate of the fragmentation reaction (Scheme 1, reaction 1f). At pH 2.1, i.e., at [H$^+$] = ~$7.9 \times 10^{-3}$ M, the rates of the proton-catalyzed elimination of hydroxide ions (Scheme 1, reaction 1b) and of the fragmentation (Scheme 1, reaction 1f) appear to be equal: $k_{1f} = k_{1b}[H^+]$. Taking $k_{1b} \geq 10^{10}$ M$^{-1}$ s$^{-1}$ as typical for the external protonation reactions,[4,6] one can calculate the rate constant of fragmentation of (SNACET)>S•−OH, $k_{1f} \geq 7.9 \times 10^7$ s$^{-1}$. The high rate constant of reaction 1f might explain why a unimolecular concentration-independent dissociation of SNACET(>•S−OH) into SNACET>S•$^+$ and OH$^-$ cannot compete efficiently since generally the rate constants for such unimolecular spontaneous dissociation are in the range $10^4$−$10^6$ s$^{-1}$.[4−6]

## Conclusions

This paper provides experimental evidence that the nature of the neighboring group affects the ultimate course of the sulfide oxidation. The results from this study show that the adjacent electron-withdrawing acetyl group destabilizes hydroxysulfuranyl radicals because of a very fast fragmentation into acyl radicals and the respective sulfenic acid. The efficacy of that process depends on the extent to which hydroxysulfuranyl radicals undergo hydroxide ion elimination by the external proton catalysis, leading to the formation of monomeric sulfur radical cations. The latter species, in contrast, is stabilized by the adjacent acetyl group because of spin delocalization in the carbonyl group. The monomeric radical cation decays by two pathways: cleavage of the C−S bond producing acetyl thiyl radical, and deprotonation producing a carbon-centered (α-alkylthioalkyl type) radical.

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