S∴N and S∴O Three-electron-bonded Radicals and Radical Cations in Aqueous Solutions

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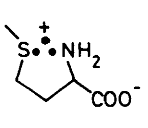
Intramolecularly formed S∴N three-electron-bonded radical cations have been identified as transient intermediates in the ˙OH radical-induced oxidation of 3-(methylthio)propylamine, methionine, and methionine ethyl ester. A similarly bonded radical is also indicated in the reduction of dehydromethionine by hydrated electrons. Intramolecular S∴O-bonded intermediates are suggested to be formed in the ˙OH-induced oxidation of 4-(methylthio)butyric acid and *S*-methylcysteine. All these three-electron-bonded species exhibit optical absorptions with maxima in the 380—400 nm range. The observable S∴O-bonded transient from *S*-methylcysteine is presumed to be protonated at oxygen. Favourable steric structures, particularly five-membered rings, significantly increase the probability of formation and the overall stability of a particular three-electron bond. Under comparable conditions, *i.e.* structure, substituents, consecutive chemistry, *etc.*, the S∴O bond appears to be considerably weaker than corresponding S∴N and S∴S bonds.

It is now well established that one-electron oxidized sulphur atoms in organic sulphides generally show a high tendency to be stabilized in S∴S or S∴X bonds by co-ordination with a second sulphur or heteroatom.[1–21] These three-electron bonds result from interaction of the unpaired *p*-electron in $(R{-}\underset{\cdot}{S}\dot{R})^+$ with a free *p*-electron pair of the second S or X, and consist of two bonding σ-electrons and one antibonding σ* electron. Their stability depends markedly on the electron-donating or -withdrawing properties of the substituents at S and X, and also on the geometry of the system which affects the extent of orbital interaction necessary for the three-electron-bond formation.[5,6,20] Numerous $(R_2S{\therefore}SR_2)^+$ radical cations[1–12,20,21] and some neutral $R_2S{\therefore}SR$ radicals [14–16] have been identified experimentally and described in the literature. Some S∴X-bonded species, charged and neutral, with X = halogen, and N and O have also been observed although not necessarily assigned to this electronic structure.[3,17–19,22] One important reason for the relatively limited number of these species seems to be that increasing differences between the electronegativity of S and X generally lower the stability of the three-electron bond. This conclusion is derived from experimental data on $R_2S{\therefore}$Hal (Hal = Cl, Br, or I) radicals[18] as well as from theoretical calculations on S∴S and various X∴Y systems (X, Y = S, Cl, P *etc.*)[23]

The relative stability of S∴N and S∴O bonds with respect to each other and to S∴S bonds has been of particular concern in the oxidation mechanism of sulphur compounds containing functional groups with nitrogen and oxygen. Controversial assignments on intermediates have been reported, for example, in the oxidation of the sulphur-containing amino acid methionine.[9,24,25] The particular question in this case has been whether the ˙OH radical-induced decarboxylation proceeds *via* an intermediate intramolecular S∴N- or S∴O-bonded species (I) or (II).

In this paper we present further examples for both S∴N- and S∴O-bonded species and will discuss the general stability question in the light of these results. The experimental method applied has been pulse radiolysis which very conveniently allows direct and time-resolved optical measurements of short lived species. Optical absorptions have been found to be a characteristic feature for the three-electron-bonded species and result from a (in first approximation) $\sigma \longrightarrow \sigma^*$ transition.[6] Within each series of similarly structured S∴S or S∴X species these absorptions provide also a sensitive measure for the stability of three-electron bonds.[20]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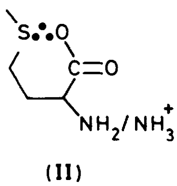

(II)

Experimental

The experiments were carried out with aqueous solutions of the various solutes. The solutes were used as received and of the highest commercially available purity. Dehydromethionine was synthesized as described in the literature.[26] The water was Millipore-filtered and deionized. The solutions were deoxygenated by bubbling with N_2O or N_2 for *ca.* 1 h dm^{-3}. Volatile solutes, *i.e.* generally liquid solutes, were added through a septum after this procedure. If added in higher quantities (> 1% v/v) they were deoxygenated separately.

Irradiation of an aqueous solution leads to the formation of ˙OH radicals, hydrated electrons, e_{aq}^-, and hydrogen atoms, H˙, as reactive primary species. The yield of the former two is *ca.* 3×10^{-7} moles per J absorbed energy (or $G = 3$ species per 100 eV) whereas hydrogen atoms are formed at a comparatively lower yield of *ca.* 0.6×10^{-7} mole H˙ per J. The function of N_2O in the solution is to convert hydrated electrons into ˙OH radicals *via* $N_2O + e_{aq}^- \longrightarrow N_2 + OH^- + {}^{\cdot}OH$. As a result *ca.* 90% of the radiation chemically produced primary reactive species are oxidizing ˙OH radicals.

The irradiation energy was introduced into the solutions by applying short pulses of high-energy electrons from either a 1.5 or a 3.8 MeV Van de Graaff accelerator; typical pulse widths were 1 μs and 50 ns for these two machines, respectively. Typical doses were in the order of 3—10 J kg^{-1} (3—10 Gy or 300—1 000 rad) yielding an ˙OH radical concentration of *ca.* (2—6) × 10^{-6} mol dm^{-3} generated per pulse in N_2O-bubbled solutions. In N_2-saturated solutions ˙OH and e_{aq}^- are formed with half these concentrations each.

The formation of transient species was directly observed by

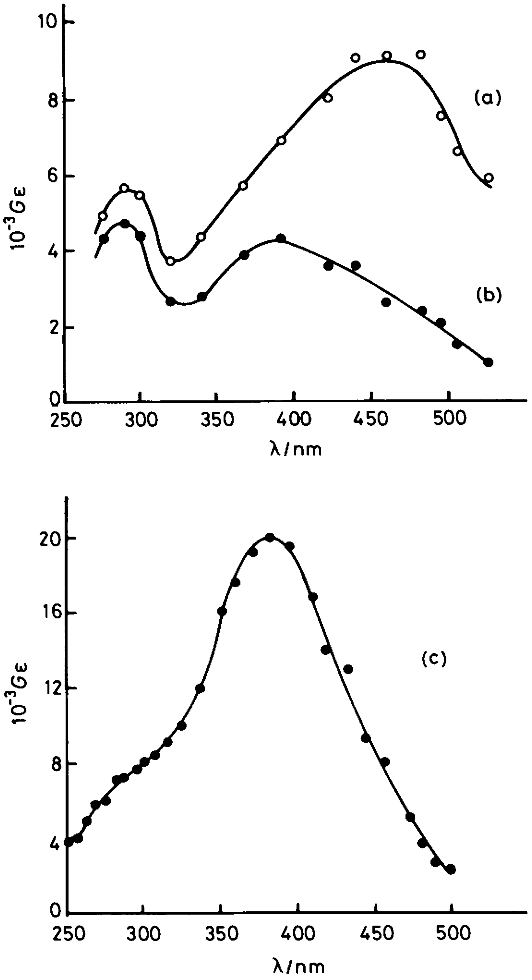


Figure 1. Absorption spectrum recorded in pulse-irradiated, N_2O-saturated, pH 1.5 solutions of 10^{-3} mol dm^{-3} 3-(methylthio)propylamine at (a) 10 μs after the pulse, and (b) 110 μs after the pulse. (c) Absorption spectrum recorded 5 μs after the pulse in the same solution at pH 3.2

recording the optical density of the pulsed solution as a function of time. Details and principles of the pulse radiolysis technique and the evaluation of data have already been reported.[27]

All experiments were carried out at room temperature.

Results and Discussion

3-(Methylthio)propylamine (*3-MTPA*).—The reaction of $^{\bullet}OH$ radicals with $CH_3SCH_2CH_2CH_2NH_2/NH_3^+$ (3-MTPA) has been investigated in pulse-irradiated N_2O-saturated aqueous solutions containing 10^{-3} mol dm^{-3} 3-MTPA. At this solute concentration the initial step in the $^{\bullet}OH$ + 3-MTPA reaction is completed already during the generally applied 1—2 μs pulse. Depending on pH-different transient optical absorption spectra were observed. In very acid solutions, *e.g.* at pH 1.5 (adjusted by $HClO_4$)-spectrum (a) in Figure 1 has been recorded a few μs after the pulse. It is seen to exhibit an intensive broad band in the visible with $\lambda_{max.}$ 465 nm and a smaller band in the u.v. with $\lambda_{max.}$ 290 nm. The 465 nm peak shows all characteristics which are typical for the well established $(R_2S\therefore SR_2)^+$-type radical cation.[2,6] The latter are known to exist in the general equilibrium (1). Accordingly yield and stability of the three-electron-bonded radical cation increase with increasing 3-MTPA concentration.

$$R_2S^{+\bullet} + R_2S \rightleftharpoons (R_2S\therefore SR_2)^+ \quad (1)$$

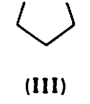
The 290 nm band is attributed to the $R_2S(-H)^{\bullet}$-type α-thio radicals $\dot{C}HSCH_2$ ∿ and $CH_3S\dot{C}H$ ∿ also by analogy with many such species observable in the oxidation of aliphatic sulphides.[2,9,28] These species result from $H^{\bullet}$ atom abstraction by $^{\bullet}OH$ and $H^{\bullet}$, and deprotonation of the molecular sulphur-centred radical cation $R_2S^{+\bullet}$

The spectrum which remains at 110 μs after the pulse is shown in curve (b) of Figure 1. It can be seen that the 290 nm band suffers only a *ca.* 20% decrease during this time period, *i.e.* the $R_2S(-H)^{\bullet}$-type radicals are rather long lived. The 465 nm band, on the other hand, has practically disappeared, *i.e.* the $(R_2S\therefore SR_2)^+$ radical cation is a much shorter lived species (the first half-life is 46 μs at the applied dose of *ca.* 4.5 Gy). Particularly interesting is the shift of $\lambda_{max.}$ from 465 to 385 nm as this band decays. It would thus appear (and will be supported by the experimental findings described below) that the visible absorption band is not only composed of the $(R_2S\therefore SR_2)^+$ absorption but also includes a contribution of a species which absorbs with $\lambda_{max.}$ 385 nm. It is therefore not feasible to compare the $\lambda_{max.}$ 465 nm observable immediately after the pulse directly with the numerically identical $\lambda_{max.}$ of the all-methylated $(Me_2S\therefore SMe_2)^+$ radical cation.[20] The real $\lambda_{max.}$ of the $(R_2S\therefore SR_2)^+$ of 3-MTPA possibly lies at slightly longer wavelengths.

Pulse irradiation of the same solution but at pH 3.2 (or anywhere between pH 3 and 9) leads to the transient spectrum (c) in Figure 1 which has been recorded 5 μs after the pulse, *i.e.* at about the same time as spectrum (a) from the pH 1.5 solution. It shows a strong band with a pronounced maximum at 385 nm and a shoulder at the low wavelength side. The latter is attributed again to the $R_2S(-H)^{\bullet}$ radicals. The $(R_2S\therefore SR_2)^+$ absorption which would be expected in the visible is not present any longer.

The 385 nm band decays exponentially with $\tau_{\frac{1}{2}}$ *ca.* 600 μs up to pH *ca.* 8.5, *i.e.* it is even longer lived than the $(R_2S\therefore SR_2)^+$ band [see Figure 1(b)]. At higher pH the decay becomes however increasingly faster which is indicative of a reaction of this transient with OH^- ions. Most important, the position of $\lambda_{max.}$ does not change with time, and furthermore the decay rate and yield do not depend on the solute concentration.

All these results clearly suggest the existence of a new transient species the formation of which seems to be complementary to that of $(R_2S\therefore SR_2)^+$ and appears to be related to the presence of the amino group in the molecule. Considering shape and broadness of the 385 nm absorption band which is typical for three-electron-bonded radicals, and considering also the general possibility of an oxidized sulphur atom to be stabilized by a *p*-electron pair from any heteroatom, we assign structure (III) to this new species. This radical cation is



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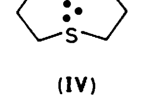


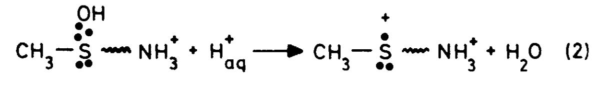
(IV)

characterized by a 2σ–1σ* three-electron bond and is assumed to be formed in an intramolecular process. Its particular stability arises from the sterically most favourable five-membered ring configuration which provides optimum orbital interaction between nitrogen and sulphur.

The optical absorption at 385 nm in spectrum (c) amounts to $G\varepsilon = 2.0 \times 10^4$ mol^{-1} dm^3 cm^{-1}. Assuming the yield of (III) to be equal to the yield of the primary >S∴OH adduct and the latter to amount to 80% of the total available ˙OH radicals as for methionine,[9] G(III) *ca.* 4.5 can be estimated. From this the extinction coefficient would be calculated to be ε *ca.* 4 500 mol^{-1} dm^3 cm^{-1}, which compares well with ε 5 000—7 000 mol^{-1} dm^3 cm^{-1} for most of the $(R_2S∴SR_2)^+$ radical cations and $R_2S∴X$ radicals (X = halide).[2,5,18]

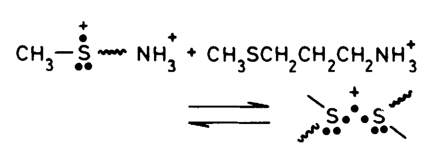
It is interesting to note that the only other relatively stable S∴N-bonded radical cation described so far with respect to its absorption spectrum, namely (**IV**) from the oxidation of 5-methyl-1-thia-5-azacyclo-octane, also involves five-membered ring structures.[13,29] In a recent study an absorption spectrum with $\lambda_{max.}$ 500 nm has been attributed to species (**IV**).[29]

The underlying mechanism of the ˙OH-induced oxidation of 3-MTPA is based on an addition of the electrophilic ˙OH to the sulphur atom as initial step. In analogy to a mechanism outlined recently on the oxidation of 2-(ethylthio)ethanol[30] the consecutive steps would then depend on pH. In very acid solutions any such ˙OH adduct in its reaction (2) with external



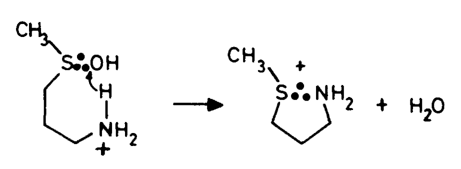
$$CH_3-\overset{OH}{\underset{\bullet\bullet}{\overset{\bullet\bullet}{S}}}\sim NH_3^+ + H_{aq}^+ \longrightarrow CH_3-\underset{\bullet\bullet}{\overset{+}{\dot{S}}}\sim NH_3^+ + H_2O \quad (2)$$

protons yields a doubly positively charged radical cation. Owing to these charges at both sulphur and nitrogen, and to the lack of a free electron pair at nitrogen this species is not expected to stabilize in an intramolecular process with S∴N bond formation. As more favourable we suggest the intermolecular equilibration (3) with a second unattacked



(3)

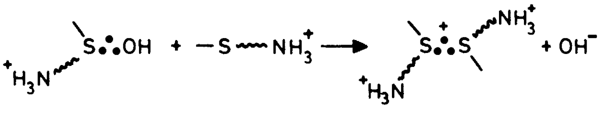
molecule and formation of an S∴S-bonded radical cation. With increasing pH an intramolecular process takes over in which the protons necessary for the elimination of the hydroxy group at sulphur are provided by the protonated amino group. Simultaneously this mechanism leaves a free electron pair for the establishment of an S∴N three-electron bond. The mechanism formally involves a seven-membered transition state but is particularly assisted by the sterically most favourable five-membered ring configuration of the resulting radical cation (**III**).



(4)

(III)

The formation of S∴S- or S∴N-bonded radical cations depends therefore primarily on the competition between reactions (2) and (4) the rates of which appear to be equal at pH *ca.* 2, *i.e.* at $[H_{aq}^+]$ *ca.* 10^{-2} mol dm^{-3}. Assuming $k_2 \geq 10^{10}$ mol^{-1} dm^3 s^{-1} for the external protonation [equation (2)] this would mean a rate constant of $k_4 = k_2\,[H_{aq}^+] \geq 10^8$ s^{-1} for the intramolecular process (4). This high rate constant also explains why direct reaction (5) of the primary >S∴OH adduct with an unattacked sulphide to form the S∴S bonded radical cation cannot compete with reaction (4) at the experimentally achievable 3-MTPA concentrations. Also, protonation (6) of the S∴N-bonded radical cation which would



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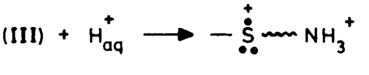
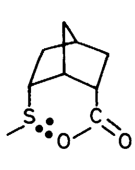


$$(III) + H_{aq}^+ \longrightarrow -\underset{\bullet\bullet}{\overset{+}{\dot{S}}}\sim NH_3^+ \quad (6)$$

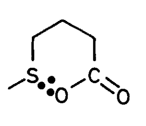
immediately result in stabilization of the S∴S-bonded radical cation *via* reaction (3) does not appear to take place during the lifetime of (**III**). This seems very reasonable, however, not only because of the positive charge of both (**III**) and H_{aq}^+ but also in view of the considerable S∴N bond energy which has to be overcome. By comparison with corresponding S∴S-bonded species the latter is estimated to be *ca.* 100 kJ mol^{-1}, probably even more.[23,31]

2-(*Ethylthio*)*ethylamine* (2-*ETEA*).—In order to check the steric argument with respect to the stability of species (**III**) oxidation of 2-(ethylthio)ethylamine (2-ETEA), $CH_3CH_2SCH_2CH_2NH_2/NH_3^+$, has also been investigated. In this case any intramolecular S∴N formation would require a sterically much less favourable four-membered ring configuration. If formed at all, it should exhibit a much shorter lifetime and a red-shifted $\lambda_{max.}$ compared with (**III**) by analogy with the corresponding S∴S-bonded radical cations.[5,6,20] Pulse radiolysis of an N_2O-saturated solution of 10^{-3} mol dm^{-3} 2-ETEA did not yield any evidence for an S∴N-bonded species from 2-ETEA. At pH $\gtrsim 1$ the only transient absorption observable from the ˙OH + 2-ETEA reaction showed a maximum at 275 nm. As in the case of other sulphides this is attributed to the $R_2S(-H)^\bullet$-type radicals $CH_3CHSCH_2CH_2NH_2/NH_3^+$ and $CH_3CH_2SCHCH_2NH_2/NH_3^+$. Only in very acid solutions containing $\gtrsim 10^{-1}$ mol dm^{-3} $HClO_4$ does a strong transient absorption band, with $\lambda_{max.}$ 490 nm, appear. By analogy with ˙OH-induced oxidation of 3-MTPA, and similar findings with 2-(ethylthio)ethanol and methionine, and based on the general oxidative mechanism discussed in a later section this is attributed to the $(R_2S∴SR_2)^+$-type radical cation of 2-ETEA. It is noted that $\lambda_{max.}$ of the latter is close to that of the all-ethylated $(Et_2S∴SEt_2)^+$.[20]

4-(*Methylthio*)*butyric Acid* (4-*MTBA*).—The results presented so far have clearly demonstrated that sulphur–nitrogen interaction including formation of an S∴N three-electron bond is possible under suitable steric conditions. This does, at this stage, however not yet prove that sulphur–nitrogen interaction must also occur in the oxidation of the amino acid methionine, *i.e.* that transient (I) would be favoured over (II) (see Introduction). Sulphur–oxygen interaction may equally be envisaged in oxidized molecules which contain suitable oxygen functions. Most recently we reported the formation of the radical (V) in the oxidation of 6-*endo*-(methylthio)bicyclo-



(V)



(VI)

[2.2.1]heptane-2-*endo*-carboxylic acid.[32] It exhibits an optical absorption with $\lambda_{max.}$ 385 nm over the entire accessible pH 3—10 range and a half-life of, for example, *ca.* 70 μs at pH 9.0. This means that this S∴O three-electron-bonded radical (V) [which would resemble species (II)] shows almost identical properties as the radical cation (**III**) [which resembles species

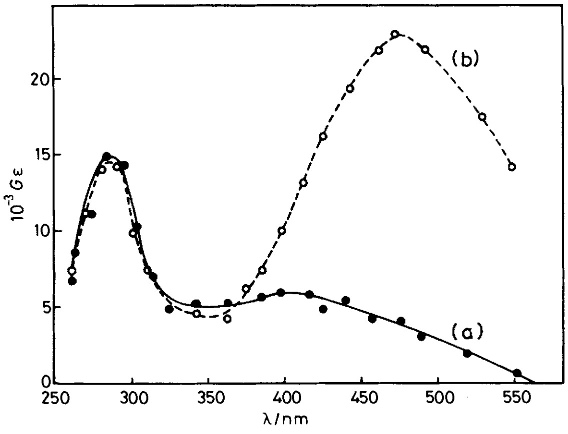


Figure 2. Absorption spectrum recorded immediately after the *ca.* 2 μs pulse in pulse-irradiated, N_2O-saturated, pH 4.1 solutions of *ca.* 10^{-3} mol dm^{-3} (○) and *ca.* 10^{-3} mol dm^{-4} (●) 4-(methylthio)butyric acid

(I)]. A particularly stabilizing factor in the norbornane derivative is however its rigidity. In order to decide between (I) and (II) as an intermediate in the oxidation of methionine the stability of species (III) should be compared with radical (VI) rather than with (V). We therefore now investigated the ˙OH radical-induced oxidation of 4-(methylthio)butyric acid (4-MTBA).

The transient absorption spectra recorded from N_2O-saturated, pH 4.1 solutions of 10^{-4} and 10^{-3} mol dm^{-3} 4-MTBA immediately after the 1—2 μs pulse are shown in curves (a) and (b) of Figure 2, respectively. Both spectra include a peak at *ca.* 280 nm attributable to $R_2S(-H)^{\cdot}$-type radicals $\dot{C}H_2SCH_2CH_2COO^-$ and $CH_3S\dot{C}HCH_2CH_2COO^-$ (or possibly the undissociated forms ∿∿COOH). The broad absorption band in the visible with ν_{max} 475 nm in the high-concentration spectrum (b) is attributed to the $(R_2S\therefore SR_2)^+$-type radical cation of 4-MTBA since it shows all characteristics for such species. At 10^{-3} mol dm^{-3}, for example, $G\varepsilon$ 2.2×10^4 mol^{-3} dm^3 cm^{-1} and $\tau_{\frac{1}{2}}$ 12 μs have been measured (pH 4.1).

A different spectrum is obtained at the low 4-MTBA concentration. The 475 nm band is now absent and instead a broad, rather flat, and not very characteristic absorption is to be seen at *ca.* 400 nm. It is rather short lived and decays exponentially with $\tau_{\frac{1}{2}}$ 3 μs (measured at 390 nm). Considering that this absorption is not found in the oxidation of corresponding sulphides without the carboxy group, and based of course on the finding with the norbane-derived radical (V), we assign the $S\therefore O$-bonded structure (VI) to this new species.

In view of the much lower stability of the $S\therefore O$ bond in (VI) as compared with the $S\therefore N$ bond in (III) it may be surprising that both species absorb with practically the same $\lambda_{max.}$. However, the position of the energy levels between which the optical transition occurs strongly depends on the overall electronic structure. This is particularly true for the lower, *i.e.* the σ, level which in fact includes a considerable contribution from non-bonding electrons.[31] Thus it is only meaningful to correlate $\lambda_{max.}$ with the stability of a three-electron bond within a series of species with the same heteroatom combination.

The formation of (VI) is based on the same principle as described for the corresponding amine (3-MTPA). At pH < p*K*(–COOH) intramolecular protonation of the primary $>S\therefore OH$ adduct by the carboxy proton and water elimination results in the $S\therefore O$-bonded radical. At higher pH where the carboxy group is ionized ring closure is achieved by replacement of OH^- from the sulphur function. For further mechanistic details we refer to the following paper.[33]

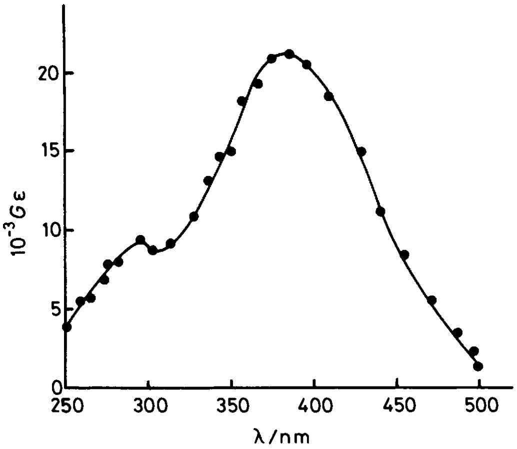
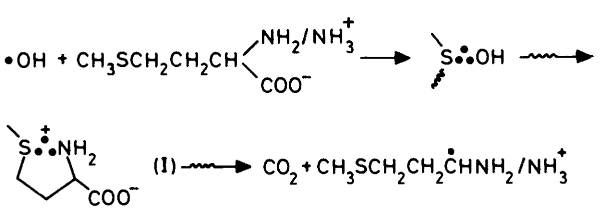


Figure 3. Absorption spectrum recorded *ca.* 50 μs after the *ca.* 2 μs pulse in a pulse-irradiated, N_2O-saturated, pH 3.2 solution of 10^{-3} mol dm^{-3} L-methionine ethyl ester

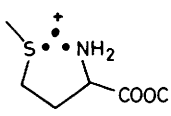
Methionine and Derivatives.—An important conclusion to be drawn from the experimental results so far is that for similarly structured species a possible $S\therefore O$ three-electron bond appears to be significantly weaker than a corresponding $S\therefore N$ bond. This of course seems reasonable in view of the respective differences in electronegativity of the heteroatoms involved in these bonds. The results would therefore strongly suggest that this thermodynamic argument also holds for the ˙OH radical-induced oxidation of methionine. Accordingly, the decarboxylation which occurs at pH $\gtrsim 3$ would indeed proceed *via* an $S\therefore N$-bonded intermediate [species (I)] as described by us before[9] rather than interaction of the oxidized sulphur function with the carboxylate as in species (II).[24,25] (The decarboxylation mechanism involves opening of the $S\therefore N$ bond to the N-centred radical cation, establishment of the mesomeric $^{\cdot +}H_2N\text{-}\overset{|}{\underset{|}{C}}\text{-}COO^- \leftrightarrow H_2N\text{-}\overset{|}{\underset{|}{C}}\text{-}CO_2^{\cdot}$ and CO_2 cleavage of the latter.[9]) The mechanism of the $S\therefore N$ bond formation from the initial ˙OH adduct ($>S\therefore OH$) incidentally should be the same as described for 3-MTPA.



(7)

In view of our present results and interpretations we have however to reassign the short-lived ($\tau_{\frac{1}{2}}$ 220 ns) transient absorption observable in the ˙OH-induced oxidation of methionine and exhibiting $\lambda_{max.}$ 400 nm to this $S\therefore N$-bonded radical cation (I). This absorption had previously been attributed to a dimer ˙OH adduct to methionine on the basis of mainly kinetic arguments,[9] which however could also be accommodated in the general mechanism outlined in the consecutive paper. One consequence of this reassignment is that the decarboxylation process can now be described kinetically exactly with *k* 3.2×10^6 s^{-1} from the first-order decay of (I).

If this concept is correct it should be possible to prolong the lifetime of the $S\therefore N$-bonded species not only by substitution of the carboxy group, *e.g.* by H as in (III), but also by esterification which would prevent fast decarboxylation. And indeed, pulse

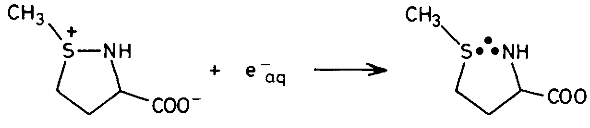


(VII)

radiolysis of N_2O-saturated solutions of methionine ethyl ester shows the formation of a long-lived transient absorption peaking at 385 nm. The spectrum shown in Figure 3 has been recorded from a 10^{-3} mol dm^{-3} solution at pH 3.2. It is attributed to the S∴N-bonded radical cation (VII). Other than (I) it decays almost exclusively by a second-order process with a first half-life of 1.1 ms at the applied dose of 4.5 Gy, and thus is even more stable than (III). As with the latter, species (VII) can also be observed in the pH 3—10 range with the lifetime becoming shorter however at high pH, presumably again due to OH^- reaction.

A relatively long-lived transient absorption with $\lambda_{max.}$ *ca.* 400 nm has also been observed in the ˙OH radical-induced oxidation of methionylglycine, $CH_3SCH_2CH_2CH(NH_3^+)CONHCH_2COO^-$, where the peptide linkage prevents the oxidized molecule from decarboxylation.[34] The primary ˙OH adduct at sulphur can however undergo ring closure as in reactions (4) or (7) or the process leading to species (VII) and we therefore suggest that the 400 nm absorption from methionyl glycine is also attributed to an S∴N bonded-radical cation.

All the results presented and discussed here strongly indicate that the oxidative mechanism leading to the decarboxylation of methionine proceeds *via* an interaction of the oxidized sulphur function with the nitrogen atom of the amino group rather than interaction with the carboxylate group. Further support for this conclusion may be derived from an experiment on the reduction of dehydromethionine by hydrated electrons. In this compound the S–N bond does already exist but can be weakened by accommodation of the incoming electron in the antibonding orbital of this bond. Reaction (8) does indeed lead to a short-lived ($\tau_{\frac{1}{2}}$ <0.5 μs) absorption with $\lambda_{max.}$ *ca.* 400 nm, *i.e.* to a species which resembles (I) except for the additional proton at nitrogen. Although reaction (8) is rapid with k_8 8.7 × 10^9 dm^3 mol^{-1} s^{-1} (measurable from the decay of the e_{aq}^- absorption) the yield of (VIII) measured in terms of G·ε amounts to only *ca.* 30% of G·ε for species (I) at pH 5. A quantitative understanding of these results should however not be attempted from these preliminary experiments.



(VIII) (8)

S-Methylcysteine (SMC).—The sulphur-containing amino acid *S*-methylcysteine, $CH_3SCH_2CH(NH_2)COOH$ (SMC), contains one methylene group less than methionine. It is also readily oxidized by ˙OH radicals but it is agreed for various reasons that the oxidation mechanism does not proceed *via* an interaction of the primarily oxidized sulphur with the amino group.[9,24] From the steric point of view, for example, the sulphur–nitrogen interaction would require a relatively unfavourable four-membered ring structure and any S∴N bond thus formed would therefore be considerably weaker than in a five-membered ring structure. In fact, with 2-(ethylthio)ethylamine such a four-membered S∴N ring structure is not stabilized at all as shown before. But even if a four-membered ring were formed it should exhibit a considerably red-shifted absorption as compared with the five-membered ring, *i.e.* show $\lambda_{max.} \gg$ 385—400 nm, as in principle has been demonstrated for analogous S∴S-bonded species.[5,6,20] It is therefore not unreasonable to assume, and in fact it has already been suggested by Davies *et al.* from their e.s.r. experiments,[24] that the oxidation process of *S*-methylcysteine proceeds *via* an intermediate of structure (IX). Sulphur–oxygen interaction may in this case well be favoured over sulphur–nitrogen interaction because of the five-membered ring structure which could be established in (IX). A corresponding transient absorption was however not detectable from the reaction of *S*-methylcysteine with ˙OH radicals at pH >3 on the experimentally observable time-scale. This would indicate that the decarboxylation process which has been suggested to be particularly facilitated by the α-positioned amino group[24] is very fast.

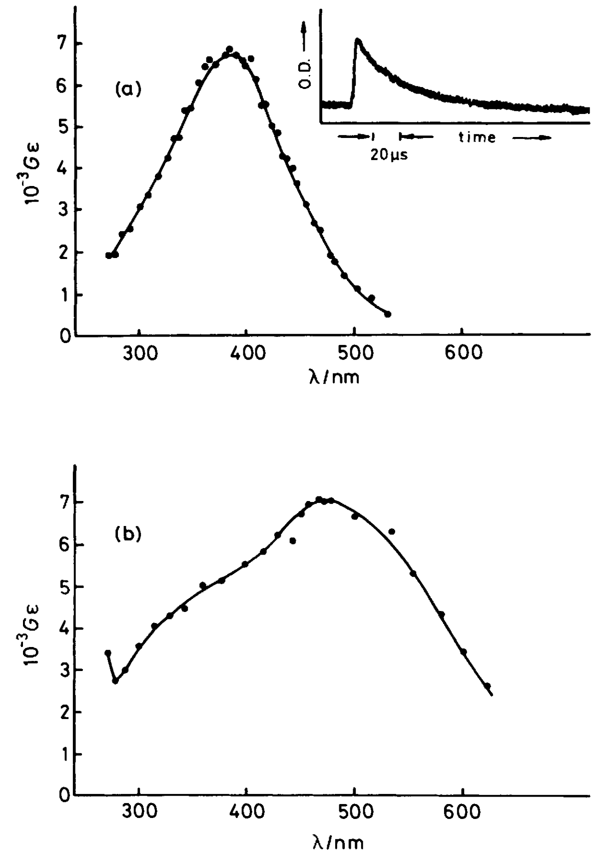
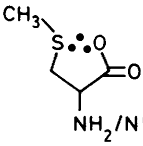
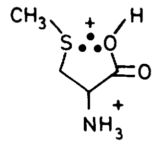


Figure 4. Absorption spectrum recorded immediately after the *ca.* 1—2 μs pulse in pulse-irradiated pH 0 solutions of (a) 2 × 10^{-4} mol dm^{-3}, and (b) 2 × 10^{-2} mol dm^{-3} *S*-methylcysteine. Insert, absorption–time curve in solution (a) at 380 nm



(IX)

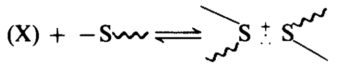


(X)

A transient absorption spectrum could however be observed in pulse-irradiated solutions of 2 × 10^{-4} mol dm^{-3} *S*-methylcysteine at pH 0, *i.e.* at very high proton concentrations. This is shown in Figure 4(a) and exhibits $\lambda_{max.}$ 385 nm with G·ε 7 000 mol^{-1} dm^3 cm^{-1}. As shown in the insert the species decays exponentially with a half-life of 27 μs. Since this absorption appears only under very acid conditions we assign this 385 nm absorption to the protonated form of (IX), *i.e.* (X) existing in the equilibrium (9). Such a species is possible since the oxygen atom is able to provide a free *p*-electron pair even if the carboxy group is protonated. The enhanced stability of (X) compared with (IX) can be associated with a change in chemical properties. Thus species (X) does not undergo decarboxylation while at higher pH CO_2 elimination readily occurs from the unprotonated S∴O bonded intermediate (IX)* as well as from the S∴N-bonded methionine intermediate (I).[9]

$$\textbf{(IX)} + H^+ \rightleftharpoons \textbf{(X)} \qquad (9)$$

Upon increase of the *S*-methylcysteine concentration in the pH 0 solutions the 385 nm absorption of (X) is gradually replaced by a visible band. At 2×10^{-2} mol dm^{-3} the latter exhibits $\lambda_{max.}$ 475 nm with $G \cdot \varepsilon$ 7 000 mol^{-1} dm^3 cm^{-1} as shown in Figure 4(b). It is attributed to the $(R_2S∴SR_2)^+$-type radical cation which at the higher solute concentrations results from an intermolecular process and, owing to the relative weakness of the S∴O bond, also from equilibration (10). Any intermolecular S∴O bond formation is not expected to compete with this S∴S stabilization since it does not receive steric assistance anymore. Intermolecular S∴N formation, finally, is of course also excluded since the amino group is fully protonated in the acid solutions.



(10)

Conclusions.—From the present results on the oxidation of organic sulphides carrying various functional groups and by comparison with previous data on simple sulphides it can be concluded that an S∴O three-electron bond is considerably weaker than corresponding S∴N and S∴S bonds. This is expected from the differences in electronegativity, and in energy levels of the interacting heteroatoms resulting therefrom. Such a conclusion implies however that the three-electron-bonded systems are of comparable structure. Formation of five- or six-membered rings, particularly if supported by an overall molecular rigidity, is particularly advantageous for the thermodynamic stabilization of such three-electron bonds. On the basis of these considerations and the experimental results we are therefore convinced that the ˙OH radical-induced oxidation of methionine proceeds *via* an intermediate S∴N-bonded radical cation. In case of *S*-methylcysteine, on the other hand, sulphur–oxygen interaction is favoured over sulphur–nitrogen interaction but solely on steric grounds.

Our stability conclusions are also reflected in the lifetimes of the three-electron-bonded species. For comparison, the half-lives of five-membered ring systems, namely the S∴S-bonded radical cation from oxidation of 2,6-dithiaheptane,[5] the S∴N-bonded species (III) and (VII), and the S∴O-bonded species (X) are 750, 600, 1 100, and 27 μs, respectively (at a dose of *ca.* 4.5 Gy). The overall lifetime is of course determined not only by the thermodynamic stability of the three-electron bond itself but also by the associated chemical reactions these species undergo.

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References

1 B. C. Gilbert, D. K. C. Hodgeman, and R. O. C. Norman, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1748.
2 M. Bonifačić, H. Möckel, D. Bahnemann, and K.-D. Asmus, *J. Chem. Soc., Perkin Trans. 2*, 1975, 675.
3 K.-D. Asmus, D. Bahnemann, M. Bonifačić, and H. A. Gillis, *Discuss. Faraday Soc.*, 1977, **63**, 1748.
4 R. L. Peterson, D. J. Nelson, and M. C. R. Symons, *J. Chem. Soc., Perkin Trans. 2*, 1978, 225.
5 K.-D. Asmus, D. Bahnemann, Ch.-H. Fischer, and D. Veltwisch, *J. Am. Chem. Soc.*, 1979, **101**, 5322.
6 K.-D. Asmus, *Acc. Chem. Res.*, 1979, **12**, 436.
7 W. B. Gara, J. R. M. Giles, and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1444.
8 S. A. Chaudhri and K.-D. Asmus, *Angew. Chem.*, 1981, **93**, 690; *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 672.
9 K.-O. Hiller, B. Masloch, M. Göbl, and K.-D. Asmus, *J. Am. Chem. Soc.*, 1981, **103**, 2734.
10 W. K. Musker and T. L. Wolford, *J. Am. Chem. Soc.*, 1976, **98**, 3055.
11 W. K. Musker, T. L. Wolford, and P. B. Roush, *J. Am. Chem. Soc.*, 1978, **100**, 6416.
12 W. K. Musker, B. V. Gorewit, P. B. Roush, and W. T. Wolford, *J. Org. Chem.*, 1978, **43**, 3235.
13 W. K. Musker, A. S. Hirschon, and J. T. Doi, *J. Am. Chem. Soc.*, 1978, **100**, 7754.
14 D. J. Nelson, R. L. Peterson, and M. C. R. Symons, *J. Chem. Soc., Perkin Trans. 2*, 1977, 2005.
15 B. C. Gilbert and P. R. Marriott, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1425.
16 J. R. M. Giles and B. P. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1497.
17 M. C. R. Symons and R. L. Petersen, *J. Chem. Soc., Perkin Trans. 2*, 1978, 210.
18 M. Bonifačić and K.-D. Asmus, *J. Chem. Soc., Perkin Trans. 2*, 1980, 758.
19 K.-O. Hiller and K.-D. Asmus, *Int. J. Radiat. Biol.*, 1981, **40**, 583.
20 M. Göbl, M. Bonifačić, and K.-D. Asmus, *J. Am. Chem. Soc.*, 1984, **106**, 5984.
21 S. A. Chaudhri, M. Göbl, T. Freyholdt, and K.-D. Asmus, *J. Am. Chem. Soc.*, 1984, **106**, 5988.
22 C. W. Perkins, J. C. Martin, A. J. Arduengo, W. Lau, A. Alegria, and J. K. Kochi, *J. Am. Chem. Soc.*, 1980, **102**, 7753.
23 T. Clark, *J. Comput. Chem.*, 1982, **3**, 112.
24 M. J. Davies, B. C. Gilbert, and R. O. C. Norman, *J. Chem. Soc., Perkin Trans. 2*, 1983, 731.
25 K.-O. Hiller, M. Göbl, B. Masloch, and K.-D. Asmus in 'Radiation Biology and Chemistry,' eds. H. E. Edwards, S. Navaratnam, B. J. Parsons, and G. O. Phillips, Elsevier, Amsterdam, 1979, p. 73.
26 R. S. Glass and J. R. Duchek, *J. Am. Chem. Soc.*, 1976, **98**, 965.
27 K.-D. Asmus, in 'Methods of Enzymology,' vol. 105, 'Oxygen Radicals in Biological Systems,' ed. L. Packer, Academic Press, New York, 1984, p. 167.
28 K.-O. Hiller and K.-D. Asmus, *Int. J. Radiat. Biol.*, 1981, **40**, 597.
29 W. K. Musker, P. S. Surdhar, R. Ahmad, and D. A. Armstrong, *Can. J. Chem.*, 1984, **62**, 1874.
30 M. Göbl and K.-D. Asmus, *J. Chem. Soc., Perkin Trans. 2*, 1984, 691.
31 T. Clark, *J. Comput. Chem.*, 1981, **2**, 261.
32 R. S. Glass, M. Hojjatie, G. S. Wilson, S. Mahling, M. Göbl, and K.-D. Asmus, *J. Am. Chem. Soc.*, 1984, **106**, 5382.
33 J. Mönig, M. Göbl, and K.-D. Asmus, following paper.
34 W. A. Prütz, F. Siebert, J. Butler, E. J. Land, A. Menez, and T. Montenay-Garestier, *Biochim. Biophys. Acta*, 1982, **705**, 139.
35 J. Mönig, D. Bahnemann, and K.-D. Asmus, *Chem.-Biol. Interact.*, 1983, **47**, 15; J. Mönig, R. Chapman, and K.-D. Asmus, *J. Phys. Chem.*, in the press.

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* The CO_2 measurements were done by means of gas chromatography (pH 0) and ion chromatography (pH > 3). Details on the analytical procedures are to be found in ref. 35.