

# Heteroatom-Centered Radicals

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## 7.1 General Remarks

With the nucleobases, radicals may be formed which carry the spin predominantly at a heteroatom, oxygen or nitrogen. In addition, the importance of glutathione and possibly also the surrounding proteins in modifying DNA free-radical damage in a cellular environment will at one stage involve heteroatom-centered radicals, that is, also at sulfur. In many aspects, heteroatom free-radical chemistry differs from that of carbon-centered radicals, although these radicals are often highly delocalized with a considerable spin density at carbon.

When the binding energy of a hydrogen to a heteroatom is weak, heteroatom-centered radicals are readily produced by H-abstraction or one-electron oxidation followed by  $H^+$  loss. Typical examples are phenols (e.g., vitamin E in non-aqueous media), tryptophan and related compounds and thiols. Deprotonation of radical cations is indeed often a source of heteroatom-centered radicals even if a deprotonation at carbon or  $OH^-$  addition upon reaction with water would be thermodynamically favored. The reason for this is the ready deprotonation at a heteroatom (Chap. 6.2).

Among the oxygen-centered radicals,  $\cdot OH$  and  $ROO\cdot$  play a major role, and their chemistries are discussed in Chapters 3 and 8, respectively. Here we deal with some other oxygen-centered species such as  $RO\cdot$  and phenoxy radicals. Oxy radicals are formed in the bimolecular decay of peroxy radicals (Chap. 8.8), thermal and photolytic decomposition of peroxides or their reductive cleavage (Chaps 2.4 and 3.3). Due to their short lifetime, which is discussed below in some detail, their DNA damaging property is only marginal (Chap. 2.4). The aromatic phenoxy radicals, on the other hand, are of little reactivity, but they seem to take part in DNA-protein cross-linking. They have also some oxidizing properties and may be taken as model systems for the guanine radical,  $G^*$ , whose chemistry is as yet not fully elucidated.

The chemistries of nitrogen-centered and sulfur-centered radicals have been reviewed in detail (Alfassi 1997, 1999), and here only some aspects can be discussed that seem pertinent to the formation, reactions and repair of DNA radicals.

A common feature of heteroatom-centered radicals is that they react reversibly, only slowly or not at all with  $O_2$  (Schuchmann and von Sonntag 1997), and this property is shared by the purine radicals  $G^*$  and  $A^*$  (Chap. 10.2).

## 7.2 Oxygen-Centered Radicals

The logarithm of the rate constants of H-abstraction by reactive oxygen species decreases with decreasing O–H bond dissociation energy from  $\cdot OH$  [ $BDE(HO-H) = 497 \text{ kJ mol}^{-1}$ ] >  $RO\cdot$  [ $BDE(RO-H) = 439 \text{ kJ mol}^{-1}$ ] >  $ROO\cdot$  [ $BDE(ROO-H) = 372 \text{ kJ mol}^{-1}$ ], and this sequence also includes the even less reactive metal-oxo complexes, e.g., permanganate (Mayer 1998).

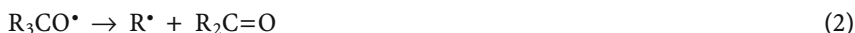
## 7.2.1

 $\beta$ -Fragmentation, 1,2-H-Shift and H-Abstraction Reactions

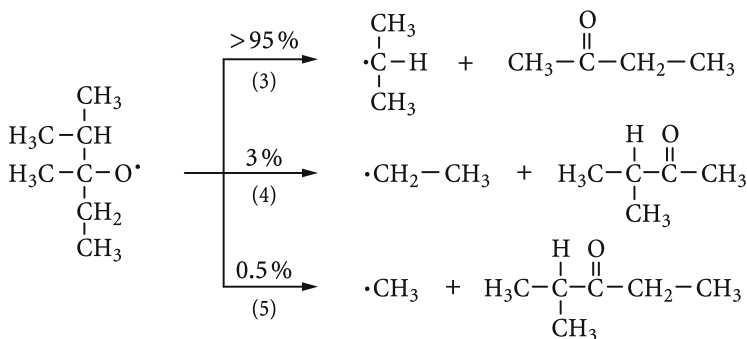
Many O-centered radicals undergo facile  $\beta$ -fragmentation. For example, acyloxy radicals which are intermediates in the electrolytic oxidation of acids (Kolbe electrolysis), rapidly decompose into alkyl radicals and  $\text{CO}_2$  [reaction (1)]. The rate of these reactions is in the order of  $10^9 \text{ s}^{-1}$  and increases with increasing branching of the alkyl substituent, i.e., decreasing C-CO<sub>2</sub>• bond energy (Table 7.1).



Similarly, the  $\beta$ -fragmentation of tertiary alkoxy radicals [reaction (2)] is a well-known process. Interestingly, this unimolecular decay is speeded up in a polar environment. For example, the decay of the *tert*-butoxy radical into acetone and a methyl radical proceeds in the gas phase at a rate of  $10^3 \text{ s}^{-1}$  (for kinetic details and quantum-mechanical calculations; see Fittschen et al. 2000), increases with increasing solvent polarity (Walling and Wagner 1964), and in water it is faster than  $10^6 \text{ s}^{-1}$  (Gilbert et al. 1981; Table 7.2).



When different substituents can be cleaved by  $\beta$ -scission the larger substituent leaves preferentially [Rüchardt 1987; cf. reactions (3)-(5)].



When alkoxy radicals contain a hydrogen atom at the neighboring carbon, a rapid 1,2-H-shift ( $k \approx 10^6 \text{ s}^{-1}$  or even faster) occurs in aqueous solution [reaction (6); Berdnikov et al. 1972; Gilbert et al. 1976, 1977; Schuchmann and von Sonntag 1981] with a KIE  $\approx 50$  in the  $\text{CH}_3\text{CH}_2\text{O}^\bullet/\text{CD}_3\text{CD}_2\text{O}^\bullet$  system (Bonifacic et al. 2003).



This process must be water assisted (see also Elford and Roberts 1996), since this reaction requires a high activation energy in the gas phase (Batt et al. 1981;

**Table 7.1.** Rate of decay of some acyloxy radicals. (Hilborn and Pincock 1991)

Substituent	$k / 10^9 \text{ s}^{-1}$
CH <sub>3</sub>	<1.3
CH <sub>2</sub> CH <sub>3</sub>	2.0
(CH <sub>3</sub> ) <sub>2</sub> CH	6.5
(CH <sub>3</sub> ) <sub>3</sub> C	11

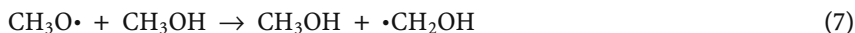
**Table 7.2.** Activation parameters and rate constants (at 295 K) of the  $\beta$ -scission of the *tert*-butoxy radical

Solvent	$\log(A/\text{s}^{-1})$	$E_a/\text{kJ mol}^{-1}$	$k/10^3 \text{ s}^{-1}$	Reference
Gas phase	14.04	62.5	1.63	Batt et al. (1998)
CCl <sub>4</sub>	13.4±0.5	53±4	10±2	Tsentlovich et al. (1998)
C <sub>6</sub> H <sub>6</sub>	13.4±0.6	52±4	14±3	Tsentlovich et al. (1998)
CH <sub>3</sub> CN	13.2±0.4	48±3	64±11	Tsentlovich et al. (1998)
(CH <sub>3</sub> ) <sub>2</sub> COH	12.4±0.6	40±5	190±40	Tsentlovich et al. (1998)
CH <sub>3</sub> CO <sub>2</sub> H	12.1±0.3	37±3	340±60	Tsentlovich et al. (1998)
H <sub>2</sub> O			1400±150	Erben-Russ et al. (1987)

Adams et al. 1982; Saebo et al. 1983; Sosa and Schlegel 1987). The resulting hydroxyalkyl radical is of lower energy, and this is the driving force of this reaction (for the opposite situation in sulfur free-radical chemistry see below). In secondary alkoxy radicals the 1,2-H-shift reaction may be even faster than the also very rapid  $\beta$ -fragmentation. For example, this ratio is near 3-4 in the case of CH<sub>3</sub>CH(O $\cdot$ )OCH<sub>2</sub>CH<sub>3</sub> while the corresponding oxyl radical derived from poly(ethylene glycol) only undergoes  $\beta$ -fragmentation (Schuchmann and von Sonntag 1982; cf. also Gröllmann and Schnabel 1980). In the poly(ethylene glycol) system,  $\beta$ -fragmentation is speeded up due to the formation a stabilized -OCH<sub>2</sub> $\cdot$  radical, while in the former case a less stabilized  $\cdot$ CH<sub>3</sub> radical has to be eliminated.

Similar to  $\cdot$ OH, alkoxy radicals are also good H-abstractors [e.g., reaction (7)], although they react with much lower rates (e.g.,  $k_7 = 2.6 \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; Ellison et al. 1972; the tertiary butoxy has a similar rate constant; Paul et

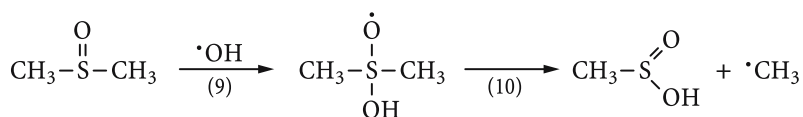
al. 1978; for kinetic isotope effects in H-abstraction reactions, see Tanko et al. 2001).



Alkoxy radicals are practically as readily reduced by  $\text{Fe}^{2+}$  as  $\cdot\text{OH}$  (e.g., reaction (8),  $k = 3 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; Mihaljevic et al. 1999). Due to the high rate of competing reactions (see above), such a reaction can only be observed at high  $\text{Fe}^{2+}$  concentrations.



Oxyl radicals are also formed upon the addition of  $\cdot\text{OH}$  to sulfoxides. Like other tertiary alkoxy radicals they undergo rapid fragmentation [reactions (9) and (10); Veltwisch et al. 1980].

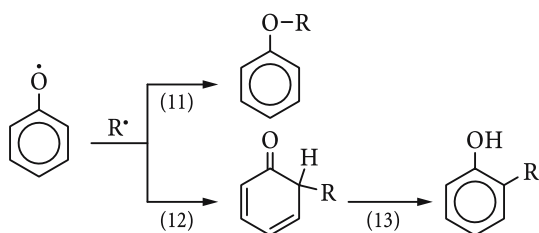


The tertiary butoxy radical reacts with sulfides by H-abstraction (Adams 1970) rather than by an oxidation of the sulfur as  $\cdot\text{OH}$  does (see below).

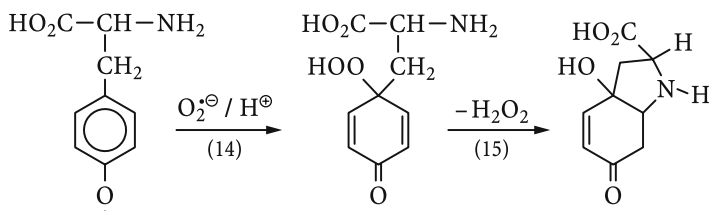
Because of the fast rates of [reactions (2) and (6)] in aqueous solutions, reactions of alkoxy radicals with DNA components can be neglected unless created within the DNA or in its very neighborhood (Chap. 2.4).

### 7.2.2 Phenoxy Radicals

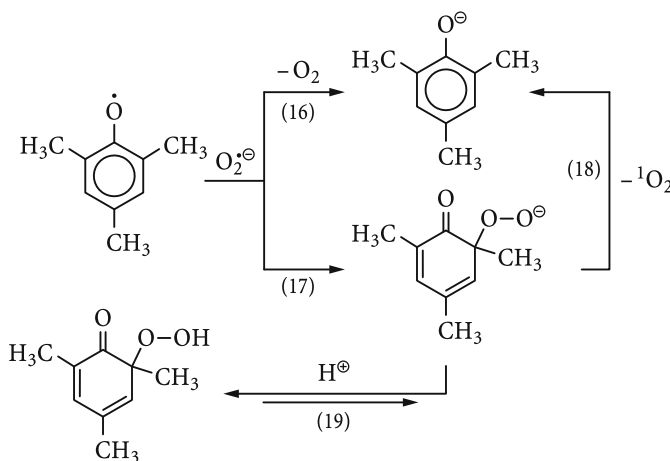
Phenoxy radicals have considerable spin density at the carbons in *ortho*- and *para*-position. Yet like  $\text{G}\cdot$ , they do not react with  $\text{O}_2$  (Jin et al. 1993), unless electron-donating groups provide a high enough electron density (Wang et al. 1994). In this case,  $\text{O}_2$  must bind at carbon because a reaction at oxygen would yield a very unstable trioxyl radical. In their cross-termination reactions, phenoxy radicals do not combine at oxygen yielding the corresponding peroxide (the reaction is endothermic, G. Merényi, pers. comm.). They react, however, at oxygen by forming C-O linkages [reaction (11); Benn et al. 1979; Ye and Schuler 1989, and DNA-protein cross-linking may indeed occur via such a reaction; Margolis et al. 1988; Dizdaroglu et al. 1989; Gajewski and Dizdaroglu 1990]. Upon addition at carbon in the *ortho* and *para* positions [e.g., reaction (12)], a cyclohexadienone is formed which rapidly reverts to the corresponding phenol [reaction (13); Bausch et al. 1976; Benn et al. 1979; for the rate constant see Capponi et al. 1986]. With the prototype, various dimers are formed (Ye and Schuler 1989). In the case of tyrosine-derived phenoxy radical, the major one is 2,2'-bityrosyl (Jin et al. 1993).



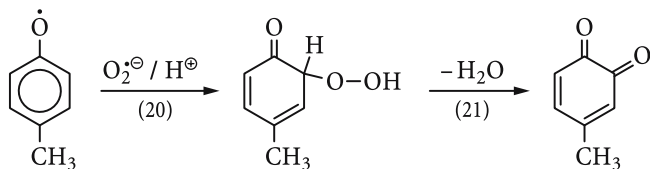
Phenoxyl radicals are oxidizing radicals (for a compilation of redox potentials see Wardman 1989). Thus, in their reactions with  $O_2^{\bullet -}$  ( $E^7 = -0.3$  V) there is ample driving force for a reduction by ET [cf. reaction (16)], and this has been thought for a long time to be the only (Hunter et al. 1989) or at least a major process, depending on the reduction potential of the (substituted) phenoxyl radical (Jonsson et al. 1993). Yet in the tyrosine system, despite of the high reduction potential of tyrosine phenoxyl radical ( $E^7 = 0.64$  V), the by far dominating process is addition, and the intermediate adduct is locked in by a Mannich reaction [reactions (14) and (15); Jin et al. 1993].



Reduction of a phenoxyl radical by  $O_2^{\bullet -}$  can nevertheless occur by an addition/elimination sequence as shown in reactions (17) and (18) (d'Alessandro et al. 2000). In the given case, the  $pK_a$  value of the hydroperoxide is 11.3 [equilibrium (19)], and  $O_2$  elimination occurs only from the anion [reaction (18);  $k = 1.3 \times 10^{-5} \text{ s}^{-1}$  at 23 °C,  $E_a = 105 \text{ kJ mol}^{-1}$ ].



In addition to the  $O_2$  elimination reaction (17) and the Mannich reaction (14), phenoxyl/ $O_2^{\bullet-}$  combination products can undergo a water elimination if the position where  $O_2^{\bullet-}$  has added to carries an H atom [e.g., reactions (20) and (21); d'Alessandro et al. 2000].



As mentioned above, these reactions are potentially of some heuristic importance also for DNA in so far as little is known about the fate of  $G^{\bullet}$  (notably its bimolecular decay; Chap 10.2). Both  $G^{\bullet}$  and phenoxyl radicals share quite some properties; they are aromatic with high spin density at oxygen, reasonably strong oxidants, do not react with  $O_2$  at an appreciable rate, but quite readily with  $O_2^{\bullet-}$ .

Many antioxidants quoted as potential protective agents against free-radical-induced DNA damage have more than one phenolic group. Their chemistry is, therefore, also of some interest in the present context. The semiquinone radicals, derived from hydroquinone by one-electron oxidation or from 1,4-benzoquinone by one-electron reduction, are in equilibrium with their parents (Roginsky et al. 1999), and these equilibria play a role in the autoxidation of hydroquinone (Eyer 1991; Roginsky and Barsukova 2000). Superoxide radicals are intermediates in these reactions.

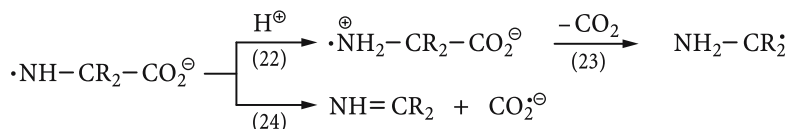
### 7.3 Nitrogen-Centered Radicals

In DNA free-radical chemistry, *N*-centered radicals are generated from some nucleobases upon one-electron oxidation (followed by  $H^+$  loss). They are also considered as important intermediates in the purine free-radical chemistry. It is, therefore, worthwhile to address very briefly some of the chemistry of *N*-centered radicals that were encountered in amines and amino acids.

The reaction of  $\bullet OH$  with trimethylamine in aqueous solution leads to the formation of the alkylaminium radical cation [ $CH_3N^{\bullet+}$ ], aminoalkyl radicals [ $(CH_3)_2NCH_2^{\bullet}$ ] and protonated aminoalkyl radicals [ $(CH_3)_2N(H^+)CH_2^{\bullet}$ ] which have markedly different properties (Das and von Sonntag 1986; for a theoretical study see Armstrong et al. 1992). The aminoalkyl radicals react rapidly with  $O_2$  thereby giving rise to  $O_2^{\bullet-}$  (Das et al. 1987).

Aminyl radicals formed in the reaction of  $\bullet OH$  with amino acids ( $\bullet NH-CR_2-CO_2^-$ ) are oxidizing radicals and readily react with phenols (Bonifacic et al. 2000a). In the presence of a proton donor, they are converted into the corresponding radical cation [reaction (22)] which immediately decarboxylates [reaction (23); see also Lü et al. (2001)]. It also may undergo  $\beta$ -fragmentation thereby forming  $CO_2^{\bullet-}$  [reaction (24); Bonifacic et al. 2000a; Hug et al. 2000a; Stefanic

et al. 2001; for further studies on the free-radical-induced decarboxylation of amino acids see Mönig et al. 1985].



The formation of the reducing aminoalkyl radical formed in reaction (23) that had escaped detection in the earlier studies (Neta and Fessenden 1971) has now also been confirmed by EPR (Hug et al. 2000b).

As purine free-radical chemistry is concerned, the 1,2-H-shift reaction (25) is of special interest.



The rate of such an (exothermic) reaction is not yet known. In the amino acids,  $\beta$ -fragmentation [reactions (22)–(24)] compete successfully (Bonifacic et al. 2000a; for DFT calculations see therein).

Tryptophan and its derivatives such as the *Hoechst* compounds (Adhikary et al. 2000) have reduction potentials below that of  $\text{G}^\bullet$  (tryptophan:  $E^7 = 1.0 \text{ V}$ ; Jovanovic and Simic 1985) and thus are capable of repairing some of the DNA damage (for a review on indol free-radical chemistry see Candeias 1998; for the thermochemistry of *N*-centered radicals see Armstrong 1998). In these reactions, radical cations and *N*-centered radicals are formed. Similar to phenoxyl radicals, these radical react with  $\text{O}_2^\bullet$  mainly by addition despite the large difference in the redox potential which would allow an ET as well (Fang et al. 1998).

## 7.4 Sulfur-Centered Radicals

The chemistry of *S*-centered radicals is so different from that of *C*-centered radicals and so surprisingly varied that it has found considerable attention (for reviews besides the one mentioned above see von Sonntag and Schuchmann 1980a,b; Anklam and Margaretha 1989; Asmus 1990a,b; Armstrong 1990; for the thermochemistry of sulfur radicals see Griller et al. 1990; Armstrong 1999; for their structures see Armstrong and Chipman 1999; for thiyl radicals in biology see Wardman 1999). In the present context of free-radical-induced DNA damage, there is a special interest, because thiols, notably glutathione which is present in cells at rather high concentrations, achieves a reduction of free-radical-induced DNA damage caused by ionizing radiation in cellular systems (Alper 1979; for more recent reviews, see Quintiliani 1983; von Sonntag and Schuchmann 1990; Wardman and von Sonntag 1995; see also Chap. 12.11).



**Table 7.3.** Rate constants (in units of  $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ ) of the reaction of some radicals with thiols

Radical	Thiol	pH	Rate constant	Reference
$\cdot\text{CH}_3$	Dithiothreitol	7	$7.4 \times 10^7$	Reid et al. (2002)
$\cdot\text{CH}_2\text{OH}$	2-Mercaptoethanol	10	$1.3 \times 10^8$	Karmann et al. (1969)
	Dithiothreitol	7	$6.8 \times 10^7$	Redpath (1973)
	Cysteamine	7.6	$4.7 \times 10^7$	Adams et al. (1968)
$\cdot\text{C}(\text{CH}_3)\text{HOH}$	2-Mercaptoethanol	10	$2.3 \times 10^8$	Karmann et al. (1969)
	Dithiothreitol	7	$9.6 \times 10^7$	
	Cysteamine	7.6	$1.4 \times 10^8$	Adams et al. (1968)
$\cdot\text{C}(\text{CH}_3)_2\text{OH}$	2-Mercaptoethanol	10	$5.1 \times 10^8$	Karmann et al. (1969)
	Dithiothreitol	7	$2.0 \times 10^8$	
$\cdot\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$	2-Mercaptoethanol	10	$8.2 \times 10^7$	Karmann et al. (1969)
	Dithiothreitol	7	$6.8 \times 10^7$	Redpath (1973)
	Cysteamine	7.6	$1.8 \times 10^7$	Adams et al. (1968)
$\cdot\text{CHRC}(\text{O})-$	Glutathione	8.4	Very slow	Tamba and Quintiliani (1984)
$\cdot\text{CH}_2\text{C}(\text{O})\text{H}$	Dithiothreitol	8.4	Very slow	Akhlaq et al. (1987b)
$\cdot\text{C}(\text{NH}_2)[\text{CH}_2\text{S}(\text{CH}_3)_2]\text{H}$	Lipoic acid	8.8	$(1-2) \times 10^9$	Hiller and Asmus (1983)

### 7.4.1

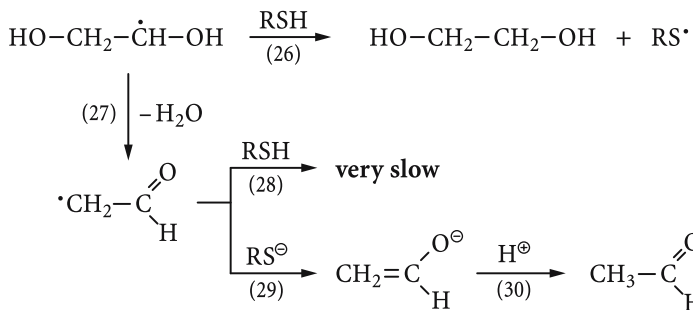
#### Hydrogen and Electron-Transfer Reactions by Thiols/Thiolate Ions

The S-H bond is weak (alkylmercaptans:  $\text{BDE} \approx 366 \text{ kJ mol}^{-1}$ , thiophenol:  $\text{BDE} \approx 330 \text{ kJ mol}^{-1}$ ; Armstrong 1999), and for this reason thiols can serve as H-donors [reaction (26)]. Thus thiols can play an important role in the repair of free-radical-induced damage (for some early studies see Adams et al. 1967, 1968, 1969). Some rate constants are compiled in Table 7.3. Compared to aqueous solutions, the rate of H-transfer by thiols is slower in organic solvents (Tronche et al. 1996).

It is seen from this table that the rate of reaction increases  $\cdot\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH} < \cdot\text{CH}_2\text{OH} < \cdot\text{C}(\text{CH}_3)\text{HOH} < \cdot\text{C}(\text{CH}_3)_2\text{OH}$  despite the fact that the exothermicity of the reaction *decreases* in the same direction. This unexpected behavior has been discussed in terms of the charge and spin polarization in the transition state, as determined by the AIM analysis, and in terms of orbital interaction theory (Reid et al. 2002). Rate constants, calculated by transition state theory, were in good agreement with the experimental data.

Even in neutral solution, a small, but sometimes noticeable, fraction is present as thiolate ion ( $pK_a(\text{thiophenol}) = 6.6$ ; Armstrong et al. 1996;  $pK_a(\text{alkylmercaptans}) \approx 9.5$ ;  $pK_a(\text{GSH}) = 9.2$ ). The thiolates are reasonably good reducing agents and can act as electron donors.

It is seen from Table 7.3 that some 'oxidizing radicals' such as the formylmethyl radical are not reduced effectively by thiols. They are, however, readily reduced by thiolate ions. A good example for the different reactivities of thiols/thiolate ions toward reducing and oxidizing radicals is the ethylene glycol system (Akhlag et al. 1987b). The radical derived by H-abstraction is a 'reducing'  $\alpha$ -hydroxyalkyl radical and hence rapidly reduced by a thiol. This radical can eliminate spontaneously and acid/base-catalyzed water yielding the 'oxidizing' formylmethyl radical [reaction (27); Chap. 6.9]. The latter no longer reacts with the thiol at an appreciable rate [reaction (28);  $k \ll 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ] but rapidly with the thiolate ion [reaction (29);  $k = 3.5 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; with DTT at pH 11.1], possibly by ET. Although acetaldehyde is the final product [overall reaction (30)], its enol will be an intermediate for kinetic reasons (faster protonation at oxygen than at carbon; see Chap. 6.2).



The repair of the  $\bullet\text{OH}$ -induced radicals derived from carbohydrates is rarely 100% on the pulse radiolysis time scale (Held et al. 1985). This is in agreement with the above. It is especially low for ribose-5-phosphate (60%), where the very rapid phosphate elimination increases the yield of 'oxidizing' radicals.

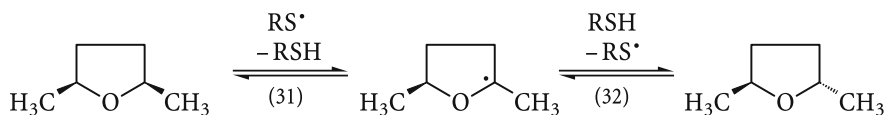
The (oxidizing) peroxy radicals behave in a similar fashion. They do not react readily with thiols, not even with thiophenols whose H atoms are very weakly bound, but they are readily reduced by the corresponding thiolate ion in contrast to alkyl radicals which are poor electron acceptors and hence do not react with thiolate ions (Simic and Hunter 1986).

### 7.4.2

#### H-Abstraction by the Thiyl Radical

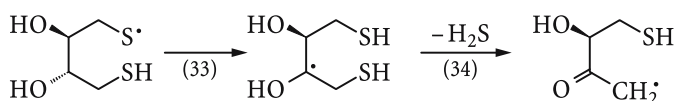
Reaction (26) is, in principle, reversible, and if the C-H BDE of the product RH is close to that of the S-H BDE of the thiol the reverse reaction becomes of importance. This has first been shown for 2,5-dimethyltetrahydrofuran, where thiyl radicals induce a *cis-trans* isomerization via a chain reaction [reactions

(31) and (32); Akhlaq et al. 1987a; for similar observations with tetrahydrofurfuryl acetate, see Cai and Roberts 1998].

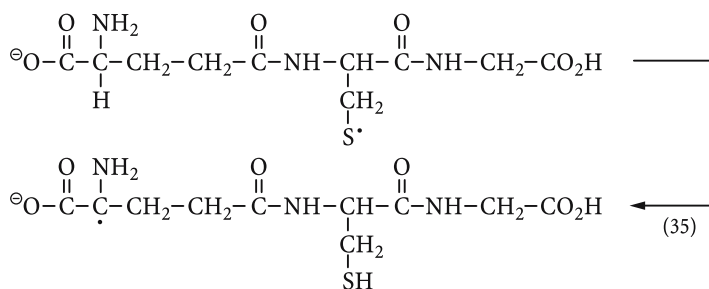


From pulse radiolysis experiments the rate of H-donation by the thiol has been determined at  $7 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ , while from the *cis-trans* isomerization data the rate of the H-abstraction by the thiyl radical has been calculated at ca.  $10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  (Akhlaq et al. 1987a). Similar data have been reported for the reaction of thiyl radicals with alcohols [ $k(\cdot\text{C}(\text{CH}_3)_2\text{OH} + \text{PenSH}) = 1.2 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}k$ ;  $(\text{PenS}^\bullet + 2\text{-PrOH}) = 1.4 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; Schöneich et al. 1989, 1990] and with carbohydrates (2-deoxyribose:  $2.7 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; Pogocki and Schöneich 2001). Thus, in these systems, the rate of H-donation by the thiol is four to five orders of magnitude faster than the rate of H-abstraction by the thiol, that is, these data are not in contradiction with the general conclusion that thiols do reduce C-centered free-radicals and that the reverse reaction is usually not observed. On the other hand, when the C-H BDE is lower such as in the case of the pentadienyl position in polyunsaturated fatty acids, the rate of H-abstraction by thiyl becomes very fast [ $k(\text{RS}^\bullet + \text{RH}) \approx 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; Schöneich and Asmus 1990; Schöneich et al. 1992], and it is not very likely that the reverse ('repair') reaction is of any importance here.

An H-transfer may also occur intramolecularly such as in DDT via a five-membered transition state [reaction (33); Akhlaq and von Sonntag 1986]. In the given case, an  $\text{H}_2\text{S}$  forming chain reaction is induced [cf. reaction (34) followed by the (slow) H-abstraction of the thus-formed radical from DTT] which comes to a halt when the thiyl radical is complexed as the disulfide radical anion at higher pH values [cf. reaction (40)].



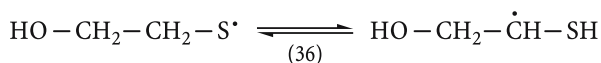
With GSH carbon-centered besides thiyl radical are formed upon  $\cdot\text{OH}$  attack, notably at  $\text{pH} > 7$  (Sjöberg et al. 1982; Eriksen and Fransson 1988). It has been shown subsequently that this is due to an intramolecular H-transfer [reaction (35); Grierson et al. 1992]. When the  $\alpha\text{-NH}_2$  group is no longer protonated as in neutral solution the C-H is only weakly bound and equilibrium (35) is shifted to the side of the C-centered radical.



When the amino group is fully deprotonated, the rate of the H-transfer is  $\sim 1.5 \times 10^5 \text{ s}^{-1}$ , but also around pH 7 the reaction is still fast, at the ms timescale (for a quantum mechanical study see Rauk et al. 2001). Upon the decay of the aminoalkyl radicals formed in reaction (35) ammonia is formed in a yield that points to disproportionation as the major process (Zhao et al. 1997). The fact that the aminoalkyl radical is the thermodynamically favored species does not mean that the repair of DNA radicals by GSH (Chap. 12.11) is not due to its action as a thiol. As with many other examples described in this book, the much faster kinetics that lead to a metastable intermediate (here: the formation of the thiyl radical) rather than the thermodynamics as determined by the most stable species (here: the aminoalkyl radical) determine the pathway of the reaction. In fact, the C-H BDE of the peptide linkage is lower than the S-H BDE and repair of DNA radicals by peptides, e.g., proteins would be thermodynamically favored over a repair by thiols but this reaction is retarded kinetically (Reid et al. 2003a,b).

Considering the ability of thiyl radicals to abstract  $\alpha$ -alkoxy-C-H, the question comes to mind, whether they might induce SSBs in DNA by abstracting the  $C(4')$ -H or induce  $\beta \rightarrow \alpha$ -anomerizations at  $C(1')$  after  $C(1')$ -H-abstraction. To our knowledge, this has never been shown, but conditions may be thought of, where this reaction can proceed in vitro. In vivo, GSH is the dominating thiol. Its thiyl radical has only a rather short intrinsic lifetime [reaction (35)], and this will strongly reduce the probability of attacking the sugar moiety. Moreover, GSH is negatively charged and so is  $\text{GS}^\bullet$ . This additionally reduces the rate of reaction notably within the minor groove with its high negative charge density.

In contrast to their oxygen- and nitrogen-centered analogs [reactions (6) and (25)], 1,2-H-shift reactions of thiyl radicals are not only slow but the equilibrium lies practically fully on the side of the thiyl radical [reaction (36); Zhang et al. 1994; Naumov and von Sonntag 2005].

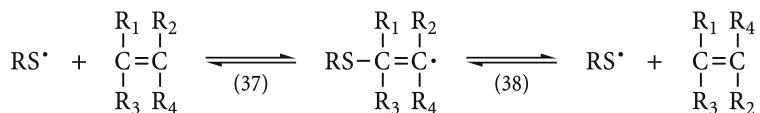


This equilibrium is only of any consequence when one of these two radicals does not react (or reacts reversibly) with a given substrate, while the other does ( $\text{O}_2$  is an example; Chap. 8.2).

## 7.4.3

## Addition of Thiyl Radicals to C-C Double Bonds

Thiyl radicals add to C-C double bonds, but this reaction is strongly reversible (Ito and Matsuda 1979, 1981, 1982; Ito 1992, 1995). As a consequence, *cis-trans* isomerization may occur [reactions (37) and (38)].

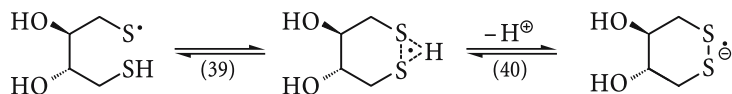


Typical examples are unsaturated fatty acids (Ferreri et al. 1999; Sprinz et al. 2000, 2001; Adhikari et al. 2001). The equilibrium constants for the oleic and linoleic systems are in the order of  $10 \text{ dm}^3 \text{ mol}^{-1}$  and the reverse reaction in the order of  $10^6 \text{ s}^{-1}$  (Sprinz et al. 2000 and Sprinz, pers. comm.). In polyunsaturated fatty acids, such isomerizations could, in principle, also occur by an H-abstraction/H-donation mechanism as discussed above. However, the rate of H-donation of RSH to the pentadienyl radicals must be very low (see above), and isomerization has been considered to occur only by the addition/elimination pathway (Sprinz et al. 2000). With the nucleobases, any thiyl addition can only be detected when the short-lived adduct is trapped by a fast reaction (Chap. 10.10).

## 7.4.4

## Three-Electron-Bonded Intermediates in Sulfur Radical Reactions

Sulfur free-radical chemistry is largely governed by the ability of sulfur to form three-electron bonded intermediates. A case in point is the complexation of a thiyl radical with a thiolate ion (for an analogy with the halide and other pseudo-halide systems, see Chap. 5.2). These disulfide radical anions are characterized by strong absorptions in the UV-Vis (Adams et al. 1967). Complexation can occur both intermolecularly as well as intramolecularly. For GSH, for example, the stability constant of the disulfide radical anion is  $2900 \text{ dm}^3 \text{ mol}^{-1}$  (Mezyk 1996a). The protonated disulfide radical anion is not stable, but such intermediates are known in the cases of the intramolecular complexes [reactions (39) and (40); Akhlaq and von Sonntag 1987].



The protonated intramolecular complexes absorb at slightly shorter wavelengths, while the thiyl radicals do not absorb in the wavelength region of interest. The five-membered complex is the most stable one (von Sonntag 1990), and its stability decreases both to smaller and larger ring sizes (Table 7.4). It can be seen from this table that in the case of the 4-membered ring system the absorption maximum is shifted significantly to longer wavelength than in the other

**Table 7.4.** Absorption maxima and molar absorption coefficients of cyclic disulfide radical anions and their protonated forms. According to von Sonntag (1990). The lipoic acid value has been taken from Hoffman and Hayon (1972). Note that the equilibria (cf. apparent  $pK_a$  values) include the ring-open forms which are not detectable

$\overline{\text{X-S-S}}$	$\overline{\text{X-S-S}}^{\bullet\ominus}$		$\overline{\text{X-S-SH}}^{\bullet}$		$pK_a$
	$\lambda_{\text{max}}$	$\epsilon$	$\lambda_{\text{max}}$	$\epsilon$	
$\overline{\text{CH}_2\text{-CH}_2\text{-S-S}}$	500	2900	460	240	6.7
$\overline{\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-S-S}}$	400	6800	380	4910	6.6
$\overline{\text{CH}_2\text{-CH}_2\text{-S-S-CH(CH}_2)_4\text{CO}_2\text{H}}$	410	9200	385	6900	5.85
$\overline{\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-S-S}}$	400	4540	380	290	7.0
$\overline{\text{CH}_2\text{-CH(OH)-CH(OH)-CH}_2\text{-S-S}}$	390	6600	380	450	5.2
$\overline{\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-S-S}}$	425	3830	370	155	9.4

systems. This is in keeping with a weaker three-electron bond due to ring strain (Asmus 1979).

The equilibria of a series of sulfhydryl groups containing amino acids have been investigated (Mezyk 1995, 1996a,b), and details governing these equilibria are now reasonably well understood (Mezyk and Armstrong 1999).

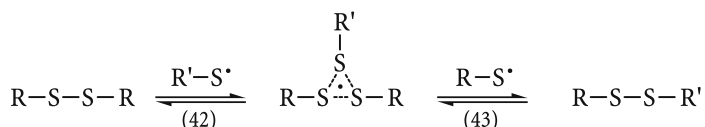
Metallothioneins are small ubiquitous oligopeptides containing a high proportion of cysteine residues but no disulfide bonds (Tsunoo et al. 1978; Suzuki and Maitani 1983). Mammalian metallothionins are made up of 61 amino acids, 20 of which are cysteine (Hamer 1986; for their protective effects see Chap. 12.10). Despite this, disulfide radical anion formation is mostly bimolecular (Fang et al. 1995).

The disulfide radical anions are also formed upon the reduction of the disulfide by  $\text{CO}_2^{\bullet-}$  [reaction (41)] and the thymine radical anion (Willson 1970; Elliot et al. 1984). For example, the reducing hydroxymethyl radical can reduce the disulfide (Anderson et al. 1986), but the rate is only fast when the hydroxymethyl radical is deprotonated (Akhlq et al. 1989) and thus its redox potential decreased.



Disulfide radical anions are rather strong reductants ( $E = -1.7$  V; Wardman 1989), and it has hence been proposed that in cellular systems these intermediates may contribute to the repair of DNA radicals (Prütz 1989).

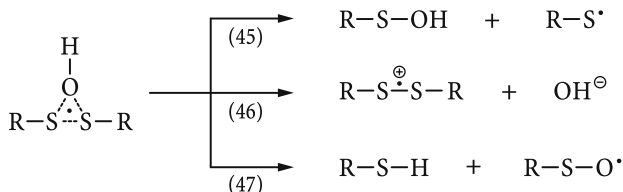
Similar three-electron-bonded intermediates must also be formed in the well-known thiyl radical-induced scrambling of disulfides (Owen and Ellis 1973). Mechanistic details have been studied using the pulse radiolysis technique which allowed the identification the three-bonded intermediate and the determination of some equilibrium constants, but also gave evidence that this system may be more complex than described by reactions (42) and (43) (Bonifacic and Asmus 1984).



The rate constant of the similar reaction (44) varies strongly with the substituent R and decreases in the case of  $\text{R}' = \text{phenyl}$  by two orders of magnitude on going from  $\text{R} = \text{methyl}$  to  $\text{R} = \textit{tert}$ -butyl,  $\text{R} = 2$ -propyl lying in between (Pryor and Smith 1970).

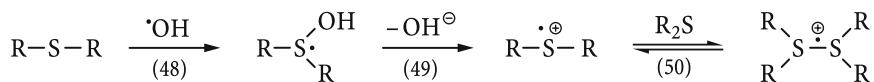


Addition to the disulfide function is also observed with  $\cdot\text{OH}$  (Bonifacic et al. 1975b). But here, in addition to the substitution reaction (45), generation of a disulfide radical cation and a hydroxide ion is also observed [reaction (46)]. The high solvation energy of the latter certainly provides additional driving force. There is EPR evidence that  $\text{RSO}^{\cdot}$  is also formed [reaction (47); Gilbert et al. 1975]. In dithiodipropionic acid and in cystine, the thiol is indeed a major product (30-40%; Elliot et al. 1981).



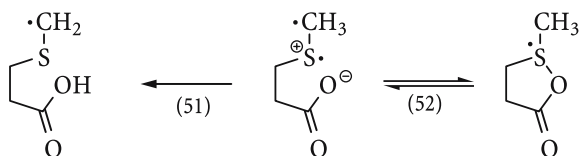
Cationic species are also formed when sulfides (Meissner et al. 1967; Adams 1970; Bonifacic et al. 1975a; Janata et al. 1980; Hiller et al. 1981; Davies et al. 1984; Ramakrishna Rao et al. 1984) or thioureas (Wang et al. 1999; Schuchmann et al. 2000) react with  $\cdot\text{OH}$ . Especially stable are the dimeric radical cations [reactions (48)–(50)]. In the case of thiourea, the high stability of the dimeric radical cation may contribute to the driving force which leads, in acid solution, to its forma-

tion even by reducing radicals such as the H atom and  $\alpha$ -hydroxyalkyl radicals (Schuchmann et al. 2000).



In addition to the complexation by the parent, the sulfide radical cation can undergo a deprotonation at a neighboring carbon [cf. reaction (51)]. Also, in the case of thiourea, deprotonation at nitrogen in basic solution competes with a complexation by the parent (Wang et al. 1999). This reaction is, of course, not given by its *N,N,N',N'*-tetramethyl derivative.

The sulfide radical cation can also complex with neighboring hydroxy, alkoxy and carboxylate groups (e.g., Glass et al. 1984; Asmus et al. 1985; Chatgialoglu et al. 1985; Mahling et al. 1987; Pogocki and Schöneich 2002). The reaction with the latter that gives rise to a sulfuranyl radical is shown in reaction (52).



All these radical cations are fairly strong oxidants. For example, the monomeric methionine radical cation is likely to propagate oxidative damage in peptides (Rauk et al. 2000). Yet in cellular systems, thiourea has radiation-protective properties (Bacq 1965). This may be accounted for considering that the oxidative power of its dimeric radical is not high enough to oxidize even G; it reacts only reasonably fast when G is deprotonated (Schuchmann et al. 2000), and this is a non-relevant situation in DNA.

Obviously, these sulfur-centered radical cations are good sinks for  $\text{O}_2^{\cdot-}$ , and, for example, disulfide radical cations give rise to sulfoxides in a very fast reaction [reaction (53),  $k = 1.6 \times 10^{10} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ ; Bonifacic et al. 2000b].



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