

Carbon-Centered Radicals

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6.1 General Remarks

The carbon-centered radicals that one deals with in the free-radical chemistry of DNA are not simple alkyl radicals but carry substituents that determine the reactivity of the radical. The property of a radical (e.g., its redox property) may change considerably when a substituent is protonated or deprotonated. For this reason, the pK_a values of radicals are discussed first. Besides redox-reactions, H-transfer reactions play an important role. In the free-radical chemistry of DNA, such H-transfer processes can even cause two opposite effects: repair by an external H-donor such as a thiol and damage amplification by intramolecular H-transfer. Addition of carbon-centered radicals to C=C double bonds is a well-established process and technically widely exploited (cf. radical-induced polymerization), but it will be shown that an addition to C=N double bonds occurs as well. This reaction is of quite some importance in purine free-radical chemistry. The reverse of the addition reaction is the homolytic β-fragmentation. When adequately substituted, carbon-centered radicals also undergo heterolytic β-fragmentation, and in DNA such a reaction leads to strand breakage and a short-lived radical cation. The strong oxidative power of the radical cation can amplify the damage by oxidizing a neighboring G. Details of the DNA-related free-radical chemistry are discussed in Chapter 12, but the fundamental aspects are discussed here. Most carbon-centered radicals react with O₂ at close to diffusion-controlled rate forming peroxy radicals. Thus, in a natural environment the slower ones of those free-radical reactions that are discussed in the present chapter will be interfered with by O₂, and peroxy radicals will be formed. The chemistry of peroxy radicals is discussed in Chapter 8. There is now a wealth of rate constants of the reactions of carbon-centered radicals available (for a compilation see Asmus and Bonifacic 1984; Beckwith et al. 1984; for the chemistry undergone by radical ions see, e.g. Schmittel and Ghorai 2001).

6.2 pK_a Values of Radicals

Most of the pK_a values of free radicals have been determined by pulse radiolysis, and it is therefore useful to recall, how fast pK equilibria become established. In general, the reaction of H⁺ with an acid anion is practically diffusion-controlled [reaction (2); *k* ranging between 5 × 10⁹ dm³ mol⁻¹ s⁻¹ and 5 × 10¹⁰ dm³ mol⁻¹ s⁻¹ (Eigen et al. 1964; Perrin et al. 1981)]. The same holds for the deprotonation of an acid by OH⁻ [reaction (3)]. The rates of reaction (4) can be calculated from the pK_a value taking into account that K_w = [H⁺] × [OH⁻] = 10⁻¹⁴ mol² dm⁻⁶.





Thus, the pK_a values of an acid is only determined by its rate of dissociation [reaction (1)]. Hence, in a homologous series, electron-withdrawing substituents reduce the pK_a value by rendering the environment of the acidic function more positive and thereby accelerating the rate of dissociation of the (positively charged) proton. In contrast, an electron-donating substituent increases the pK_a value.

The time required to reach equilibrium very much depends on the pK_a value of the acid. An acid with a pK_a value of 4, for example, deprotonates with a rate of $\sim 10^6 \text{ s}^{-1}$. Thus, the equilibrium is established within a few microseconds. On the other hand, an acid with a pK_a value of 7 dissociates with a rate of ca. 10^3 s^{-1} , and the equilibrium becomes established only on the millisecond time range. In a pulse radiolytic experiment, a large part of the radicals will thus have disappeared in bimolecular termination reactions, before an equilibrium is reached. Buffers speed-up the protonation/deprotonation reactions, and their addition can overcome this problem. Yet, they deprotonate acids and protonate their corresponding anions typically two to three orders of magnitude more slowly than OH^- and H^+ (for a DNA-related example, see Chap. 10.4; for potential artifacts in the determination of pK_a values using too low buffer concentrations, see, e.g., von Sonntag et al. 2002).

Rapid protonation is not restricted to carboxylate ions, but is generally valid for other heteroatom atoms such as oxygen, nitrogen and sulfur in alcohols, amines and thiols. Also in these reactions, no rehybridization and skeletal rearrangements reduces the rate below diffusion-controlled. On the other hand, such factors play a major role when carbanions are protonated, and the rate of their protonation is generally considerably slower. The same factors reduce the rate of deprotonation of acidic C–H groups. For example, the pK_a value of barbituric acid is 4.0. In this acid, the keto/enol equilibrium (5) is largely on the side of the keto form which dissociates with a rate of only $6.9 \times 10^3 \text{ s}^{-1}$ despite its low pK_a value (Eigen et al. 1965; Koffer 1975; Schuchmann and von Sonntag 1982).

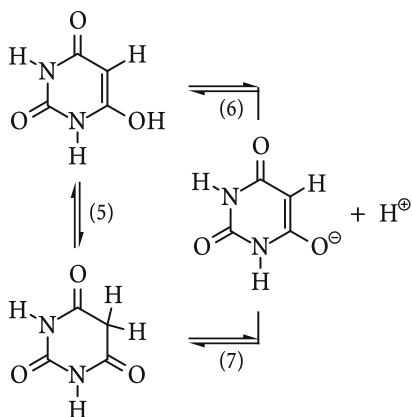


Table 6.1. pK_a values of some radicals in comparison with those of their parent compounds, wherefrom these radicals may be formed by H-abstraction. For comparison, the pK_a values of some radicals are also given which can only produced by electron addition and subsequent protonation (indicated with an asterisk)

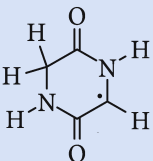
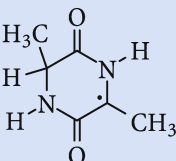
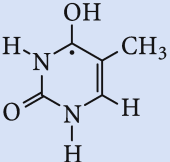
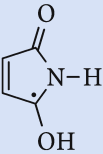
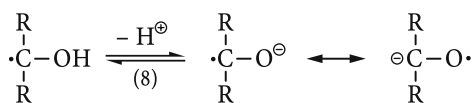
Radical	pK _a	Parent compound	ΔpK _a	Reference
•CH ₂ OH	10.71 10.7	MeOH	-4.38	Laroff and Fessenden (1973) Asmus et al. (1966)
•CH(CH ₃)OH	11.51 11.6	EtOH	-4.42	Laroff and Fessenden (1973) Asmus et al. (1966)
•C(CH ₃) ₂ OH	12.03 12.2	2-PrOH	-5.07	Laroff and Fessenden (1973) Asmus et al. (1966)
•C(CF ₃) ₂ OH	1.70	Hexafluoro-2-PrOH	-8.1	Laroff and Fessenden (1973)
•CH(OH) ₂	9.5	Formaldehyde hydrate	-3.8	Stockhausen and Henglein (1971)
•CO ₂ H	2.3	Formic acid	-1.45	Flyunt et al. (2001)
•CH ₂ C(O)OH	4.8 4.2	Acetic acid	0 -0.6	Neta et al. (1969) Schuchmann et al. (1989)
•CH(NH ₃ ⁺)CONH ₂	4.3	Glycinamide	-3.6	Rao and Hayon (1975)
	9.8	Glycine anhydride	-12.2	Mieden and von Sonntag (1989) Muñoz et al. (2000)
	10.6	Alanine anhydride	-	Mieden and von Sonntag (1989)
•CH ₂ -CH=C(OR)OH	5.5	Acrylate*	-	Takács et al. (2000)
	6.9	Thy*	-	Hayon (1969)

Table 6.1. Continued

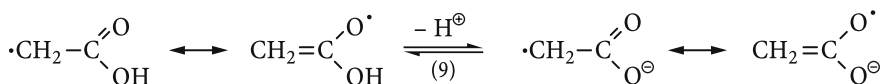
Radical	pK _a	Parent compound	ΔpK _a	Reference
	2.8	Maleimide*	–	Hayon and Simic (1972) von Sonntag et al. (2002)

This general phenomenon is also of some importance in the case of the protonation of radical anions which can protonate at a heteroatom or at carbon. Kinetically, protonation at the heteroatom is always faster even when protonation at carbon is thermodynamically favored. A case in point is the protonation of the Thy radical anion (Chap. 10.4).

α-Hydroxyalkyl radicals are less solvated than their parent alcohols due to a lower polarity of the C–O bond and lower H-bond acceptor ability of the oxygen atom (Block et al. 1999). They are considerably more acidic than their parent alcohols by four or more pK units (Table 6.1). The same effect is observed even more dramatically in the case of the cyclic dipeptides (Merenyi et al. 1986; Mieden and von Sonntag 1989). This increase in acidity is possibly largely due to an increase in mesomery such as shown in reaction (8), and captodative substituent effects (Viehe et al. 1985) seem to contribute further in the case of the peptide radicals.



Interestingly, the pK_a values of acetic acid and its corresponding radical are practically identical (Table 6.1; Neta et al. 1969; Schuchmann et al. 1989, see also Schuchmann et al. 2000). In this case, not only the anion, but also the acid experiences a gain in mesomery [reaction (9)].

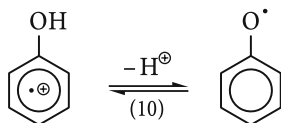


There is a continuing discussion as to the pK_a value of $\cdot\text{CO}_2\text{H}$ radical. In the literature, values are found ranging from –0.2 (Jeevarajan et al. 1990), 1.4 (Buxton and Sellers 1973), 2.3 (Flyunt et al. 2001) to 3.9 (Fojtik et al. 1970). Why the value

of 2.3 has been chosen here (Table 6.1), has been discussed in the given reference.

Methyl substitution increases the electron density at the neighboring carbon due to hyperconjugation effects and thus shifts the pK_a of the radical to higher values as it does with the parent compound (Table 6.1).

As expected, radical cations may have especially low pK_a values due to their positive charge. A good example is phenol ($pK_a = 10$) whose radical cation has a pK_a value of -2 (Dixon and Murphy 1976). Here, the difference with respect to its parent is as large as 12 pK units [equilibrium (10)].



Similar effects are observed with the nucleobase-derived radical cations (Chap. 10.2).

6.3 Oxidation of Carbon-Centered Radicals

Reduction potentials of radicals may be determined by pulse radiolysis (Chap. 13.3) or photomodulated voltammetry (Wayner and Houman 1998; for a compilation, see Steenken 1985; Wardman 1989).

Carbon-centered radicals which are substituted by electron-donating groups such as $-OR$ or $-NR_2$ are readily oxidized. A convenient one-electron oxidant is $Fe(CN)_6^{3-}$. For example, it oxidizes α -hydroxyalkyl or α -alkoxyalkyl radicals at practically diffusion-controlled rates ($k \approx 2 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$; Adams and Willson 1969). Substitution by electron-donating groups that are not capable of rapid deprotonation, such as $-OCH_3$, stabilizes the resulting carbocation. They then can have a considerable lifetime in water (Steenken et al. 1986b) while the lifetime of the parent, $C_2H_4^{\bullet+}$, is only ~ 100 fs (Mohr et al. 2000).

In the case of α -hydroxyalkyl radicals, the corresponding carbonyl compounds are formed in full yields. In contrast, the oxidation of α -alkoxyalkyl radicals by $Fe(CN)_6^{3-}$ may not always be a straightforward outer-sphere ET reaction (Janik et al. 2000a,b). Details are as yet not fully understood.

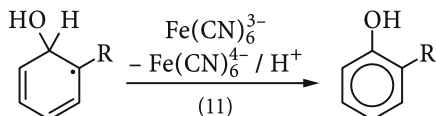
In studies on the $\bullet OH$ -induced aromatic hydroxylation, the oxidation of hydroxycyclohexadienyl radicals by $Fe(CN)_6^{3-}$ has often been used for the determination of the yield of a given precursor radical (Volkert et al. 1967; Volkert and Schulte-Frohlinde 1968; Klein et al. 1975). Other oxidants such as Cu^{2+} , Ag^+ , Fe^{3+} or Cr^{3+} give lower yields, and complications are apparent, since, for example, the oxidation potential of Ag^+ (0.8 V) is higher than that of $Fe(CN)_6^{3-}$ (0.36 V; Bhatia and Schuler 1974). The substituent has a strong influence on the rate of oxidation (Table 6.2), and quantitative oxidation to the corresponding phenol [reaction (11)] is only observed with electron-donating substituents (Buxton et al. 1986). Even the terephthalate ion $\bullet OH$ -adduct requires the stronger oxidant

Table 6.2. Rate constants of the oxidation of hydroxycyclohexadienyl radicals by IrCl_6^{2-} and $\text{Fe}(\text{CN})_6^{3-}$ (unit: $10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$)

Substrate	IrCl_6^{2-}	$\text{Fe}(\text{CN})_6^{3-}$	Reference
Anisol	3.1	2.3	Buxton et al. (1986)
Acetylaniline		1.5	Buxton et al. (1986)
Toluene	3.0	0.16/0.019 ^a	Buxton et al. (1986)
Benzene	3.1	0.015	Buxton et al. (1986)
Benzene- <i>d</i> ₆		0.012	Buxton et al. (1986)
Fluorobenzene	2.4	0.01	Buxton et al. (1986)
Chlorobenzene	1.6	0.0055	Buxton et al. (1986)
Benzonitrile	0.45	<0.0002	Buxton et al. (1986)
Terephthalate	0.077		Fang et al. (1996)

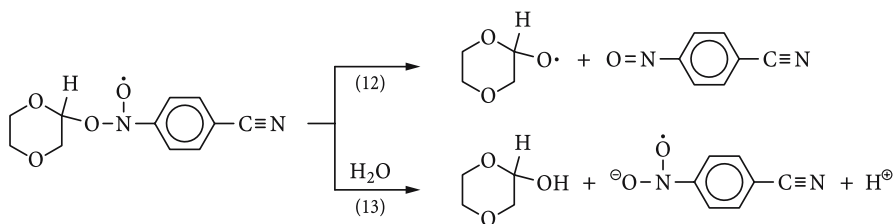
^aRates of oxidation of two different isomers

IrCl_6^{2-} for complete (i.e., sufficiently rapid with respect to the bimolecular decay of the radicals) oxidation (Fang et al. 1996).



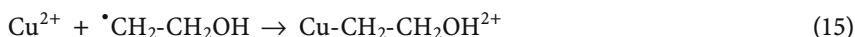
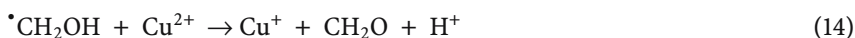
In these oxidation processes, often the kinetically favored rather than the thermodynamically favored product is formed. A case in point is the oxidation of pyrimidine-6-yl radicals by $\text{Fe}(\text{CN})_6^{3-}$ to an isopyrimidine which is only a short-lived intermediate that results in the formation of the pyrimidine and its hydrate (Chap. 10.3).

In pulse radiolysis experiments, TNM is often preferred as an oxidant over $\text{Fe}(\text{CN})_6^{3-}$ because the strongly absorbing nitroform anion is formed which can be used to determine the yield of reducing radicals (Chap. 10.3). TNM is only capable of oxidizing strongly reducing radicals, but with less reducing radicals an adduct may be formed which usually absorbs at shorter wavelengths and has a lower absorption coefficient (Schuchmann et al. 1995). In fact, the formation of adducts is common in the oxidation of radicals by nitro compounds. These adducts may decompose into two directions [e.g., reactions (12) and (13)] (Nese et al. 1995).

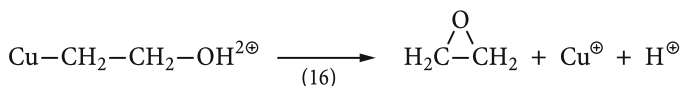


In rare cases, the one-electron oxidized products are also readily oxidized, and the three-electron oxidized product is observed. A case in point is the oxidation of the 4-chlorobenzyl radicals by $\text{Fe}(\text{CN})_6^{3-}$ to the corresponding benzaldehyde. The 4-chlorobenzylalcohol is not the intermediate that is further oxidized by $\text{Fe}(\text{CN})_6^{3-}$, and thus the mechanism of the formation of 4-chlorobenzaldehyde is rather complex (Merga et al. 1996). Since $\text{Fe}(\text{CN})_6^{3-}$ is commonly used as a simple and effective oxidant also in DNA free-radical chemistry, such potential complexities have to be kept in mind.

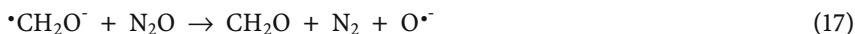
Although α -hydroxyalkyl radicals such as the hydroxymethyl radical are oxidized without an adduct being noticed [reaction (14); $k = 1.6 \times 10^8 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$], such a complex becomes apparent in the case of β -hydroxyalkyl radicals [reactions (15) and (16); $k_{15} = 3 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$; $k_{16} = 330 \text{ s}^{-1}$; Freiberg and Meyerstein 1980], whereby the epoxide is formed (Söylemez and von Sonntag 1980).



Although α -hydroxyalkyl radicals are good reducing agents their reduction po-



tential is often not sufficiently low to undergo electron transfer reactions. However, they might do so, when they are deprotonated. A case in point is the reaction of the hydroxymethyl radical with nitrous oxide [reaction (17)] (Wang et al. 1996; for other reducing radicals that undergo chain reactions with nitrous oxide, see Sherman 1967a-c; Al-Sheikhly et al. 1985).



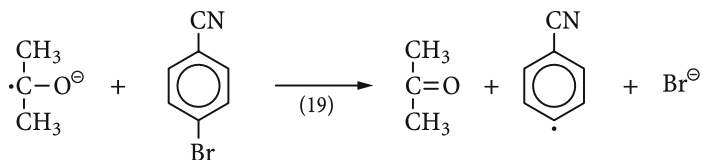
The reduction of disulfides is also only given by the hydroxymethyl radical anion [reaction (18)] while the hydroxymethyl radical itself is practically unreactive (Akhlq et al. 1989).



The 2-hydroxy-2-propyl radical anion is a stronger reductant than the hydroxymethyl radical anion. Thus, a number of reactions are readily given by the for-

mer, while the latter remains unreactive. For example, only 2-hydroxy-2-propyl radical anion transfers electron to 4-bromobenzonitrile thereby inducing an efficient chain reaction. The ET reaction (19) is so fast that it is not the rate-limiting step in this chain reaction (Fang et al. 1997).

Typically, the reactivity of the halogen substituent follows the sequence $I > Br > Cl$ (Lemmes and von Sonntag 1982), and three-electron-bonded adducts to

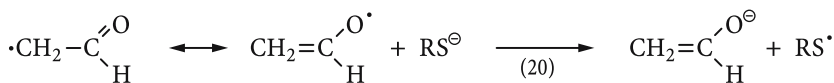


the halogen are potential intermediates (for similar intermediates see Chaps 5.2 and 7.4). This type of reaction is also given by 5IUra and 5BrUra (Chap. 10.7).

6.4 Reduction of Carbon-Centered Radicals by Electron Transfer

In the reduction of radicals by ET, simple carbanions are practically never formed, and one-electron reduction of a carbon-centered radicals is only effective if the electron can be accommodated by the substituent, e.g., a carbonyl group [reaction (24), whereby upon electron transfer the enolate is formed (Akhlaq et al. 1987)]. Thus, in their reduction reactions these radicals react like heteroatom-centered radicals despite the fact that major spin density is at carbon.

The mesomeric forms of the pyrimidine C(6)-adduct radicals may be written with the free spin at a heteroatom and hence have as oxidizing properties.



Their yields have been determined with the help of a strong reductant, TMPD (Chap. 10.3). Other convenient probes for monitoring oxidizing radicals are, for example, ABTS and ascorbate (Wolfenden and Willson 1982; Bahnemann et al. 1983).

Radical cations are especially strong oxidants, since they are highly electron deficient. They are intermediates in $\cdot\text{OH}$ -induced DNA strand breakage and are capable of oxidizing a neighboring G (Chaps 12.4 and 12.9).

Table 6.3. Compilation of some R-H BDEs (unit: kJ mol⁻¹)

R-H bond	BDE/kJ mol ⁻¹	Reference
C-H (aromatic)	465	Berkowitz et al. (1994)
C-H (vinylic)	465	Berkowitz et al. (1994)
C-H (primary)	423	Berkowitz et al. (1994)
C-H (primary in MeOH)	402	Berkowitz et al. (1994)
C-H (secondary)	412	Berkowitz et al. (1994)
C-H (secondary in EtOH)	396	Reid et al. (2003)
C-H (tertiary)	403	Berkowitz et al. (1994)
C-H (tertiary in 2-PrOH)	393	Reid et al. (2003)
C-H (allylic)	367	Berkowitz et al. (1994)
C-H (benzylic)	367	Berkowitz et al. (1994)
C-H (pentadienylic)	343	Schöneich et al. (1990)
C-H (in peptides)	330-370	Reid et al. (2003)
O-H (alcoholic)	436	Berkowitz et al. (1994)
O-H (water)	499	Berkowitz et al. (1994)
O-H (phenolic)	360	Parsons (2000)
O-H (hydroperoxidic)	366	Golden et al. (1990)
S-H (thiolic)	366	Armstrong (1999)
S-H (thiophenolic)	330	Armstrong (1999)

6.5 H-Transfer Reactions

The C-H bond dissociation energies (BDEs) decrease in the sequence vinylic \approx phenylic > primary > secondary > tertiary > allylic > pentadienylic \approx benzylic considerably (Table 6.3).

R-H BDEs energies are certainly one parameter that has to be taken into account when discussing H-transfer reactions, yet many other aspects have to be considered to account for the kinetics of such a reaction (for the calculation of activation energies in H-abstraction reactions, see Zavitsas and Chatgialloglu 1995).

Table 6.4. Compilation of the H-abstraction rate constants (unit: $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$) of some radicals from alcohols in aqueous solution at room temperature

Radical	Substrate	Rate constant	Reference
Uracil-5-yl	2-PrOH	4.1×10^7	Mertens and von Sonntag (1994)
Phenyl	2-PrOH	1.2×10^7	Mertens and von Sonntag (1994)
Vinyl	2-PrOH	2×10^5	Mertens and von Sonntag (1994)
Trichlorovinyl	<i>t</i> BuOH	1.6×10^5	Mertens and von Sonntag (1994)
	MeOH	6.3×10^6	Mertens and von Sonntag (1994)
	EtOH	2.4×10^7	Mertens and von Sonntag (1994)
	2-PrOH	4.1×10^7	Mertens and von Sonntag (1994)
Methyl	MeOH	220	Thomas (1967)
	EtOH	590	Thomas (1967)
	2-PrOH	3400	Thomas (1967)
2-Hydroxypropyl	2-PrOH	430	Burchill and Wollner (1972)
2-Hydroxy-2-methylpropyl	2-PrOH	~700	Schuchmann H-P and von Sonntag (1988)

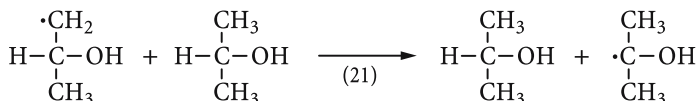
For inactivation of reactive free radicals by thiols and the repair of DNA radicals (Chaps 11.2 and 12.10), it is of relevance that the RS-H bond is especially weak and renders thiols good H-donors. Although phenols and hydroperoxides have also low O-H BDEs, they are rather poor H-donors in water. For example, the rate of H-abstraction of $\cdot\text{CH}_3$ from H_2O_2 is 1000-fold lower in water than in the gas phase (Ulanski et al. 1999; see also below). H-abstraction from O-H is strongly influenced by the solvent (Das et al. 1981), and the variation of the rate constant of H-abstraction from phenols and *tert*-butylhydroperoxide by the cumyloxy radical with the solvent was interpreted in terms of hydrogen-bonding between solvent and phenol, i.e., the stronger the hydrogen bonding the lower the rate constant (Avila et al. 1995; for kinetic solvent effects in H-abstraction reactions see also Valgimigli et al. 1995; Banks et al. 1996; Snelgrove et al. 2001).

It is important to note that the rate of reaction of alkyl radicals with thiols does not simply correlate with the exothermicity of the reaction, i.e., with the BDE of the C-H bond to be formed. For example, the tertiary 2-hydroxypropyl radical reacts more readily with thiols than the primary hydroxymethyl radical, and this reacts even faster than the methyl radical (Table 6.4). The reason for this surprising behavior has been discussed in terms of the charge and

spin polarization in the transition state, as determined by AIM analysis and in terms of orbital interaction theory (Reid et al. 2002).

The C-H BDE in peptides is even lower than that of the S-H BDE in thiols as a consequence of the exceptional stability of the radical products due to captodative stabilization (Viehe et al. 1985; Armstrong et al. 1996). Yet, the observed rate constants for the reaction of $\cdot\text{CH}_3$ and $\cdot\text{CH}_2\text{OH}$ with, e.g., alanine anhydride are markedly slower than with a thiol. This behavior has been discussed in terms of the charge and spin polarization in the transition state, as determined by AIM analysis, and in terms of orbital interaction theory (Reid et al. 2003). With respect to the 'repair' of DNA radicals by neighboring proteins, it follows that the reaction must be slow although thermodynamically favorable.

Although BDE is by far not the only factor that determines the kinetics of H-transfer reactions, within a given series of simple alkyl radical a correlation seems to hold (Table 6.4). In polymers, where the lifetime of the polymer-bound radicals may be long, radical transfer reactions by intramolecular H-abstraction (primary \rightarrow secondary \rightarrow tertiary) are common (Chap. 9.4). In general, whenever a system starts with a mixed radical system (e.g., in the reaction of $\cdot\text{OH}$ with 2-PrOH: 2-hydroxy-prop-2-yl and 2-hydroxypropyl) a steady-state is approached which is dominated by the lower-energy radical [here: 2-hydroxy-prop-2-yl, cf. reaction (21)]. This process is favored by low initiation rates and high substrate concentrations, and these two factors determine whether such an H-transfer manifests itself is also in the final products.



As far as DNA is concerned, the most weakly bound hydrogen is the allylic hydrogen of the methyl group in Thy. For dGuo, the sequence of the C-H BDE has been calculated as $\text{C}(1') < \text{C}(4') < \text{C}(3') < \text{C}(2') < \text{C}(5')$ (Table 6.5). In DNA, accessibility as determined by the given structure often overruns factors that are connected with the R-H BDE (Chap. 12.2).

In DNA, an H-transfer from the methyl group in Thy and from the sugar moiety to DNA radicals may occur. A well-documented radical that is capable of reacting with the sugar moiety is the uracil-5-yl radical formed upon photolysis and radiolysis of 5BrUra-containing DNA (Chaps 10.7 and 12.6). From Table 6.4, it is seen that this radical is indeed very reactive and thus this kind of H-abstraction is not unexpected. Steric conditions permitting, it will abstract any hydrogen from the sugar moiety. Less reactive radicals will undergo such a reaction not only more slowly but also much more selectively (note, for example, the high kinetic isotope effects of such reactions; $\cdot\text{CH}_3 + \text{CH}_3\text{OH}/\text{CD}_3\text{OH}$: $k_{\text{H}}/k_{\text{D}} = 8.2$ at 150 °C in the gas phase; Gray and Herod 1968). In DNA, an H-transfer from the sugar moiety to a base radical has never been proven with certainty, but in model systems such as poly(U) and poly(C) it is quite evident (Chap. 11.2). Here, H-transfer is believed to occur from $\text{C}(2')$, a position that in the *ribo*-polynucleotides is activated by the neighboring OH group. In DNA, the corresponding hydrogen is bound more strongly.

Table 6.5. Calculated bond dissociation energies (BDE) of the various C–H bonds in the sugar moiety of dGuo. (Steenken et al. 2001)

C–H bond	BDE/kJ mol ⁻¹
C(1')	367
C(2')	399
C(3')	385
C(4')	378
C(5')	386

It has been mentioned above that the weakest C-H bond in DNA is that of the methyl group in the Thy moiety. In Thd, this position is attacked, albeit slowly, even by peroxy radicals (Martini and Termini 1997), although they have only a low H-abstractive power (cf. the low BDE of ROO-H; Table 6.3). That this may also hold for DNA *in vivo* may be deduced from the observation that one of the corresponding oxidation products is excreted into the urine in rather large amounts (Chap. 12).

The (oxidizing) α -carboxyalkyl radicals do not react readily with thiols (Table 6.4). They are, however, rapidly reduced by thiolate ions [reaction (20)]. The reactions of thiols with DNA radicals play a very important role in the chemical repair of DNA radicals in cells (Chaps 12.10 and 12.11). The reversibility of the H-donation of thiols, that is, H-abstraction by thiyl radicals, is discussed in Chapter 7.4.

6.6 Conversion of Reducing Radicals into Oxidizing Ones (Umpolung)

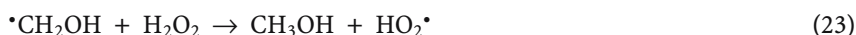
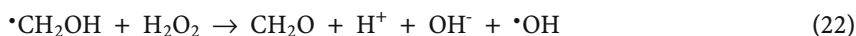
There are a number of reactions which change the redox property of the radical (Umpolung). A typical, DNA-relevant, case of Umpolung is the buffer-catalyzed conversion of the reducing Thy electron adduct protonated at oxygen into the oxidizing carbon-protonated tautomer (Chap. 10.3). Another example is the proton-catalyzed conversion of the (reducing) $\cdot\text{OH}$ -adduct at C(5) in pyrimidines to the oxidizing C(6) $\cdot\text{OH}$ -adducts (Chap. 10.3).

These reactions are real tautomerization reactions, but the quite common water elimination reactions can also completely change the redox property of a radical. A case in point is the radical derived from ethylene glycol which is a reducing α -hydroxyalkyl radical which is transformed by water elimination into the fonylmethyl radical (see below) whose oxidizing property has been discussed above [reaction (20)]. Similarly, the phenol $\cdot\text{OH}$ -adduct is a reason-

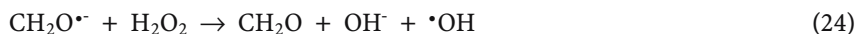
ably good reductant, while the phenoxy radical formed upon water elimination (Chap. 3.4) has oxidizing properties. Similar reactions play an important role in purine free-radical chemistry (Chap. 10.3).

6.7 Reactions with Hydrogen Peroxide

Hydrogen peroxide is rather unique in so far as it can act as an oxidant as well as an H-donor. This is exemplified its reaction with the hydroxymethyl radical. In this case, ET [reaction (22); $k = 6 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$] is faster than H-abstraction [reaction (32); $k = 2.75 \times 10^3 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (Ulanski and von Sonntag 1999)].



While the former induces a chain reaction, the latter terminates the chain. The basic form of the hydroxymethyl radical, $\text{CH}_2\text{O}^{\bullet-}$ [$\text{p}K_{\text{a}}(\bullet\text{CH}_2\text{OH}) = 10.8$], is a stronger reducing agent [reaction (24); $k = 4 \times 10^5 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$], and the chain length increases with increasing pH.



At very high pH, H_2O_2 also dissociates [$\text{p}K_{\text{a}}(\text{H}_2\text{O}_2) = 11.6$]. Although the hydroxymethyl radical anion undergoes the H-abstraction even faster [reaction (25), $k = 2.9 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$] the chain length comes to a halt, because the anion of H_2O_2 is no longer a good electron acceptor.

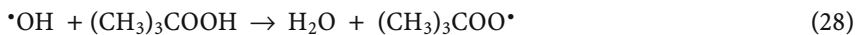


The methyl radicals can only undergo the H-abstraction reaction, and since the C-H BDE is higher by ca. 38 kJ mol^{-1} in methane than in MeOH (McMillen and Golden 1982; Golden et al. 1990; Berkowitz et al. 1994), the rate of reaction (26) is higher ($k = 2.7 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$; Ulanski et al. 1999) than that of reaction (23).



However, compared to the gas phase ($k_{26} = 3.3 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$; Tsang and Hampson 1986), the reaction is three orders of magnitude slower. A similar situation is found for $\bullet\text{OH}$ [reaction (27); $k(\text{in water}) = 2.7 \times 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (Buxton et al. 1988); $k(\text{gas phase}) = 1 \times 10^9 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (Baulch et al. 1984)]. In water, a low rate constant has also been found for the reaction of $\bullet\text{OH}$ with tertiary butylhydroperoxide [reaction (28); $k = 10^7 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$; (Phulkar et al. 1990)].





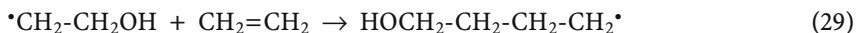
The reasons for this dramatic drop in the rate of reaction on going from the gas phase to aqueous solution have been discussed above. It may be recalled that the difference in the exothermicity of reactions (23) and (26) is as much as 38 kJ mol^{-1} . The relatively small effect of the thermochemistry on the rate can be rationalized by invoking the polar effect in the transition state (Russell 1973; Pross et al. 1991; Roberts 1996). Quantum mechanical studies on the solvent effect on the rate of the $\cdot\text{CH}_3$ plus H_2O_2 system can reproduce the dramatic drop upon going from the gas phase to aqueous solutions and indicate that the major reason is the difference between the solvation energies of H_2O_2 and $\text{HO}_2\cdot$ in water (Delabie et al. 2000).

The rate constants that we are concerned with here are quite moderate for free-radical reactions. Although *in vivo* H_2O_2 is always present at a low steady-state concentration, its reaction with DNA radicals will be negligible as compared to a reaction with O_2 . However, such reactions may no longer be negligible in model studies using Fenton systems (Theruvathu et al. 2001) or in the deactivation of micro-organisms by H_2O_2 (Chap. 12.7).

6.8 Addition to C–C and C–N Double Bonds

6.8.1 Addition to C–C Double Bonds

The addition of carbon-centered radicals to C–C double bonds (for a review see Giese 1983) is the key reaction in the free-radical-induced polymerization. In general, the rate constants of these reactions are only moderately high, but this process becomes fast and efficient, because in technical applications the polymerizing olefin is usually present at high concentrations. In aqueous solutions, the rate constant of the addition of the hydroxyethyl radical to ethene [reaction (29)], a non-activated C–C double bond, has been determined at $\sim 3 \times 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (Söylemez and von Sonntag 1980).



Alkyl radicals are nucleophilic radicals (cf. Walbiner et al. 1995; Wu and Fischer 1995; Wu et al. 1995; Heberger and Lopata 1998), and the preferred position of addition at a polarized C–C double bond is reversed compared to that of the electrophilic $\cdot\text{OH}$. Thus, in the case of Ura, the hydroxymethyl radical adds preferentially to the C(6)-position [$k \approx 10^4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (Schuchmann et al. 1986; Chap. 10.5)].

6.8.2 Addition to C–N Double Bonds

Technically, the addition of carbon-centered radicals to C–N double bonds is as yet of little if any importance. In the free-radical chemistry of DNA it plays, however, a considerable role in the formation of the C(5′)-C(8) linkage between the sugar moiety and the purines (Chap. 10.5). Because of its importance, even an immune assay has been developed for the sensitive detection of this kind of damage in DNA (Chap. 13.2). The addition of the C(5′) radical to the C(8) position of a purine is obviously facilitated for steric reasons (formation of a six-membered ring), but the same kind of reaction also occurs as an intermolecular reaction. Since alkyl radicals are nucleophilic, the rate of this reaction is noticeably increased upon protonation of the purine (Aravindakumar et al. 1994; for rate constants see Chap. 10.5).

This addition reaction is not restricted to α -hydroxyalkyl radicals, although this type of radical has been most widely investigated. Thus, allylic radical derived from 5MeCyt (Zhang and Wang 2003) and radicals derived from amino acids (Elad and Rosenthal 1969) are also reported to undergo this reaction. In DNA, they play a role in the formation of tandem lesions (Chap. 12.5), and it is likely that this kind of reaction contributes to free-radical-induced DNA/DNA and DNA/protein cross-linking.

6.9 β -Fragmentation Reactions

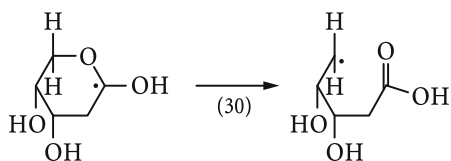
6.9.1 Homolytic Fragmentation

Carbon-centered radicals may undergo homolytic β -fragmentation reactions, whereby an olefin and a new radical is formed. This reaction is, in fact, the reverse of the polymerization reaction. With neighboring C–C bonds, these β -fragmentation reactions are usually slow, and only observable, at least on the pulse radiolysis time-scale with negatively-charged polymeric radicals whose lifetime is prolonged by electrostatic repulsion. Then, even the situation of equilibrium polymerization may be approached (Ulanski et al. 2000; Chap. 9.4).

In the nucleobases, this type of reaction is not possible due to the lack of adequate structural elements.

There is a wealth of information available on the free-radical reactions of carbohydrates in aqueous solution and in the solid state (for reviews see von Sonntag 1980; von Sonntag and Schuchmann 2001). According to this, there is no indication that β -fragmentation involving C–C double bond formation is a major process in such systems. However, β -fragmentation forming a C–O double bond is quite common, e.g., in disaccharides, where such a process can lead to the scission of the glycosidic linkage. It is also observed in monosaccharides, notably in 2-deoxyribose in the crystalline state (Hüttermann and Müller 1969a,b; von Sonntag et al. 1974; Schuchmann et al. 1981), where it is present as the β -py-

ranose form. Reaction (30) is one step in an interesting and very efficient chain reaction which is governed by the crystal structure (Schuchmann et al. 1981).

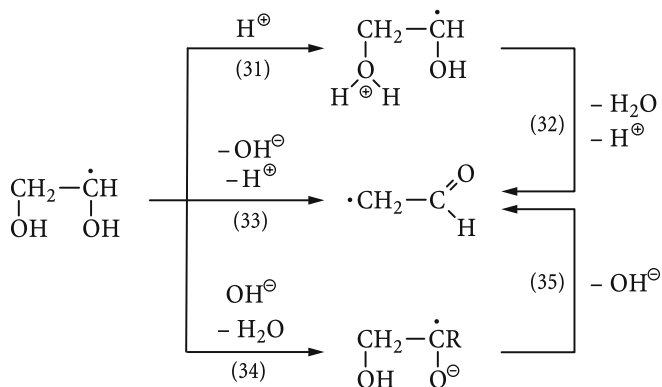


When the binding energy of the bond to be broken is considerably lower than that of a C-C single bond such as a C-SR bond, the rate of β -fragmentation can go up dramatically. This is the reason why the addition of thiyl radicals to the double bonds of the nucleobases is so strongly reversible (Chaps 7.4 and 10.5).

6.9.2

Water Elimination, Heterolytic β -Fragmentation and Formation of Radical Cations

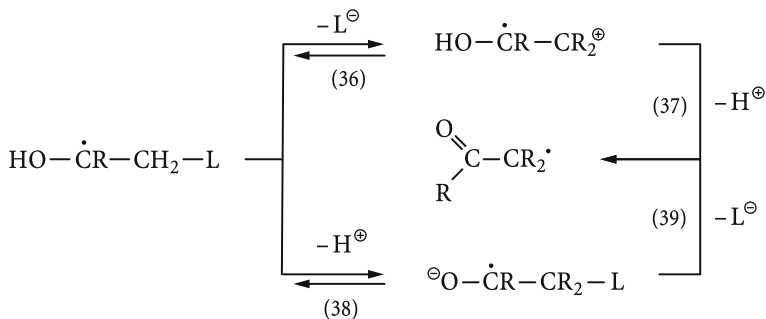
In DNA, the carbohydrate part has no free OH groups. Yet, salient aspects have been obtained by studying the free-radical chemistry of carbohydrates (von Sonntag 1984). A general feature in carbohydrate free-radical chemistry is the water elimination of 1,2-dihydroxyalkyl radicals [reactions (31)-(35)].



This reaction has been first observed by EPR (Buley et al. 1966) and subsequently established by product studies on ethylene glycol (Seidler and von Sonntag 1969; von Sonntag and Thoms 1970; Burchill and Perron 1971), meso-erythritol (Dizdaroglu et al. 1972) and 2-deoxy-D-ribose (Hartmann et al. 1970; Herak and Behrens 1986), D-ribose (von Sonntag and Dizdaroglu 1977; Herak and Behrens 1986) and D-glucose (Dizdaroglu et al. 1975b); for reviews on carbohydrate free-radical chemistry see von Sonntag (1980); Ershov (1998); von Sonntag and Schuchmann (2001); for a review on the photochemistry of carbohydrates see Binkley (1981). The formylmethyl radical that is formed by water elimination from ethylene glycol [reactions (31)-(35)] is capable of abstracting a hydrogen

from the substrate (von Sonntag and Thoms 1970). Possibly, this type of radical has to be made responsible for the formation of DNA SSBs induced by glycerol-derived radicals at high scavenger concentrations (Chap. 12.1).

The mechanism of this water elimination and related reactions, where the OH group in β -position is replaced by another leaving group (L), has been studied in some detail (Samuni and Neta 1973; Steenken et al. 1974; Behrens and Schulte-Frohlinde 1976; Behrens and Koltzenburg 1985; Schuchmann et al. 1995; Müller et al. 1997; Bales et al. 2001). Two processes which compete with one another have been recognized: heterolytic cleavage of the C-L bond which results in the formation of a radical cation followed by proton loss [reactions (36) and (37)] and the dissociation of the hydroxyl group followed by the loss of the leaving group [reactions (38) and (39)].



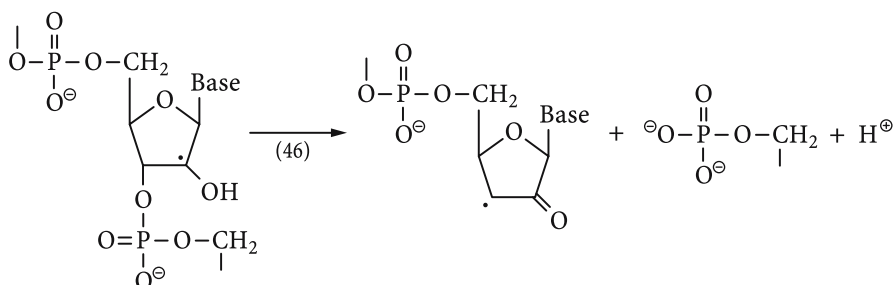
The rate of the elimination of the ligand [reactions (36) and (37)] is determined by the electrophilicity of the frame and the nucleofugacity of the ligand (Behrens and Koltzenburg 1985). Deprotonation of the frame [reaction (38)] strongly reduces its electrophilicity, and thus the radical anion may eliminate quite well also ligands which have an intrinsic poor nucleofugacity such as OH [see below; cf. reaction (39)]. The rate of reaction (38) is determined by the pK_a value of the α -hydroxyalkyl radical and is thus strongly influenced by the substituents R and L. As a measure of the nucleofugacity the pK_a value of the conjugate acid of the leaving group may be taken: HCl (negative pK_a), $\text{CH}_3\text{CO}_2\text{H}$ (4.7), NH_4^+ (9.3), i.e. a high pK_a corresponds to a low nucleofugacity. Thus, the OH group ($pK_a(\text{H}_2\text{O}) = 14$) is also a poor leaving group. However, upon protonation it becomes a very good leaving group ($pK_a(\text{H}_3\text{O}^+)$ is negative), and this is the reason why the water elimination is also acid catalyzed [cf. reaction (31); Steenken 1979; Steenken et al. 1986a].

A much simpler situation is the anion loss from an α -alkoxyalkyl radical with a leaving group in the β -position, such as the phosphate release from the 2-phosphato-methoxyethyl radical (Behrens et al. 1978; for some further reactions of β -(phosphatoxy)alkyl radicals see Whitted et al. 1999; Crich et al. 2000). This reaction only proceeds by a heterolytic cleavage into a radical cation and a phosphate ion. The rate of this reaction strongly depends on the protonation state of the phosphate group [reactions (40)–(44)].

Table 6.6. Approximate rate constants of phosphate release from some α -methoxy- β -phosphatoalkyl radicals. (Behrens et al. 1978)

Radical	Rate constant/s ⁻¹
$\cdot\text{CH}(\text{OCH}_3)\text{CH}_2\text{OPO}_3\text{H}_2$	10^6
$\cdot\text{CH}(\text{OCH}_3)\text{CH}_2\text{OPO}_3\text{H}^-$	10^3
$\cdot\text{CH}(\text{OCH}_3)\text{CH}_2\text{OPO}_3^{2-}$	0.1 - 1
$\cdot\text{CH}(\text{OCH}_3)\text{CH}_2\text{OPO}_3(\text{CH}_2\text{CH}_2\text{OCH}_3)\text{H}$	10^7
$\cdot\text{CH}(\text{OCH}_3)\text{CH}_2\text{OPO}_3(\text{CH}_2\text{CH}_2\text{OCH}_3)^-$	$10^3 - 10^4$
$\cdot\text{CH}(\text{OCH}_3)\text{CH}_2\text{OPO}_3(\text{CH}_2\text{CH}_2\text{OCH}_3)_2$	4×10^7

sufficient to explain these differences in rate. It may hence be envisaged that a concerted proton loss speeds-up the phosphate release in the case of the α -hydroxy- β -phosphato radicals. In addition, intramolecular deprotonation by the phosphate group could further enhance the rate. In the free-radical chemistry of polyribonucleotides and RNA, this must have a bearing on the rate of strand breakage starting from the C(2') radical [reaction (46); Chap. 11.2].



The radical cations formed in all these reactions are not stable but react quite rapidly with water. This reaction is to a large extent kinetically controlled, and hence also radicals that are thermodynamically disfavored are formed as well. Table 6.7 shows a compilation of the ratios of radicals formed as studied by EPR spectroscopy.

Proton catalysis which regenerates the radical cation ultimately leads to the thermodynamically most stable radical. This can even proceed in two well-separated steps [reactions (47) and (48)]. Here, the second step is much slower and hence only observed at lower pH (Behrens et al. 1982).

Table 6.7. Hydrolysis of radicals with good leaving groups (L) in β -position to the radical center. (Behrens et al. 1982)


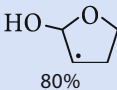



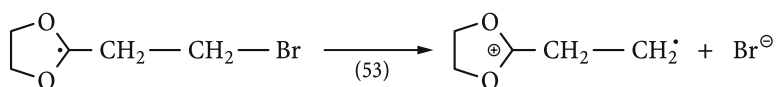
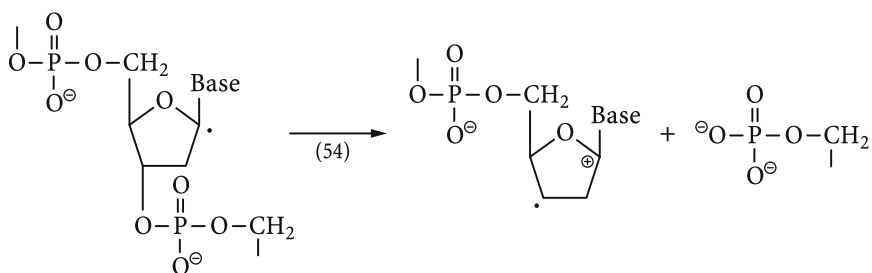
Radical	Product radicals	
$\text{CH}_3\text{O}-\dot{\text{C}}\text{H}-\text{CH}_2-\text{L}$	$\text{CH}_3\text{O}-\underset{\text{OH}}{\text{CH}}-\text{CH}_2\cdot$ 70%	$\text{CH}_3\text{O}-\dot{\text{C}}\text{H}-\text{CH}_2-\text{OH}$ 30%
$\text{CH}_3\text{O}-\underset{\text{CH}_3}{\dot{\text{C}}}-\text{CH}_2-\text{L}$	$\text{CH}_3\text{O}-\underset{\text{CH}_3}{\dot{\text{C}}}-\text{CH}_2-\text{OH}$ 100%	
$\text{CH}_3\text{O}-\underset{\text{CH}_3}{\dot{\text{C}}\text{H}}-\text{CH}-\text{L}$	$\text{CH}_3\text{O}-\underset{\text{OH}}{\text{CH}}-\underset{\text{CH}_3}{\dot{\text{C}}}$ 70%	$\text{CH}_3\text{O}-\underset{\text{CH}_3}{\dot{\text{C}}\text{H}}-\text{CH}-\text{OH}$ 30%
$\text{CH}_3\text{O}-\underset{\text{Cl}}{\dot{\text{C}}\text{H}}-\text{CH}-\text{L}(\text{Cl})$	$\text{CH}_3\text{O}-\underset{\text{OH}}{\text{CH}}-\underset{\text{Cl}}{\dot{\text{C}}}$ 100%	
$\text{CH}_3\text{O}-\underset{\text{CH}_2-\text{Cl}}{\dot{\text{C}}}-\text{CH}_2-\text{L}(\text{Cl})$	$\text{CH}_3\text{O}-\underset{\text{CH}_2-\text{OH}}{\dot{\text{C}}}-\text{CH}_2-\text{OH}$ 100%	
	 80%	 20%
$\text{L}-\text{CH}_2-\text{O}$ 	$\text{HO}-\text{CH}_2-\text{O}$  100%	

Table 6.8. Stabilization energies of some cations and radicals relative to the corresponding methyl species. (According to G. Koltzenburg, compiled in von Sonntag 1987)

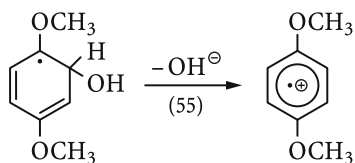
Cation	kJ mol^{-1}	Radical	kJ mol^{-1}
$^+\text{CH}_3$	0	$^{\bullet}\text{CH}_3$	0
$^+\text{CH}_2\text{CH}_3$	630	$^{\bullet}\text{CH}_2\text{CH}_3$	71
$^+\text{CH}_2\text{CH}_2\text{CH}_3$	685		
$^+\text{CH}_2\text{CH}(\text{CH}_3)_2$	825		
$^+\text{CH}(\text{CH}_3)_2$	965	$^{\bullet}\text{CH}(\text{CH}_3)_2$	122
$^+\text{C}(\text{CH}_3)_3$	1195	$^{\bullet}\text{C}(\text{CH}_3)_3$	193
$^+\text{CH}_2\text{OCH}_3$	1160		
$^+\text{CH}(\text{OCH}_3)_2\text{CH}_3$	1350		
$^+\text{CH}(\text{OCH}_3)_2$	1490		
$^+\text{C}(\text{OCH}_3)_3$	1580		



The observation of this γ -elimination reaction has raised the question, whether in DNA the related $\text{C}(1')$ radical can also lead to strand breakage. However due to the negative charge at the phosphate group in 3'-position, the rate of the γ -elimination reaction (54) should be considerably slower than that of reaction (53).



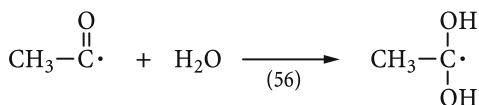
Aromatic radical cations are readily formed and have a measurable lifetime when they are stabilized by electron-donating substituents [e.g., reaction (55); O'Neill et al. 1975].



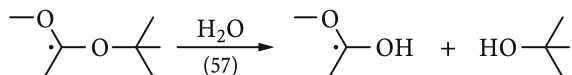
They may be produced by biphotonic excitation or by a strong oxidant such as $\text{SO}_4^{\cdot-}$. The radical cations of methyl-substituted benzenes react with water forming mainly hydroxycyclohexadienyl radicals and deprotonate at methyl only to a small extent yielding benzyl-type radicals (Sehested and Holcman 1978; Russo-Caia and Steenken 2002). As expected, the lifetime of these radical cations increases with increasing methyl substitution (toluene: $k > 5 \times 10^7 \text{ s}^{-1}$, *p*-xylene: $k \approx 2 \times 10^6 \text{ s}^{-1}$, 1,2,4,5-tetramethylbenzene: $k \approx 4 \times 10^4 \text{ s}^{-1}$). In strongly acidic solution, the reaction becomes reversible, and aromatic radical cations can also be generated via $\cdot\text{OH}$ under such conditions. Since the deprotonation at methyl is irreversible, benzyl-type radicals are the final products in acid solutions (Sehested et al. 1975, 2002). Aromatic radical cations also undergo oxidation of substituents in the side chain (Wang et al. 1993; Baciocchi et al. 1996, 1997, 1998, 1999).

6.10 Hydration and Hydrolysis of Radicals

In principal, all steps in these water-elimination reactions are reversible. Because in the reactions discussed above the final products are thermodynamically more stable, the equilibrium lies fully on the right side (i.e., the reverse rates are very slow). However, there are also cases where hydration of a radical is a fast process. For example, reaction (67) occurs at a rate of $2 \times 10^4 \text{ s}^{-1}$ (Schuchmann MN and von Sonntag 1988), i.e., a million times faster than the rate of hydration of its non-radical parent, acetaldehyde.



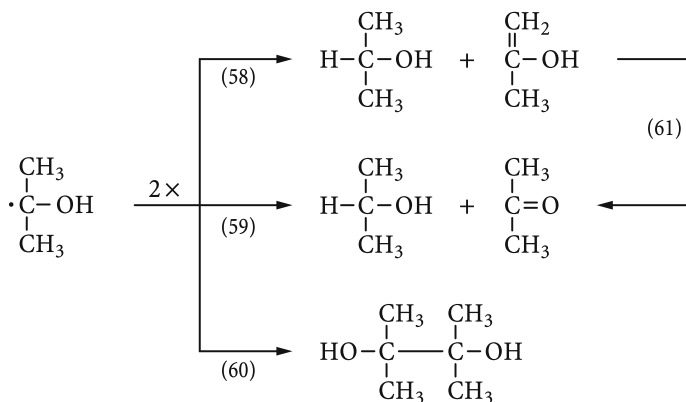
The hydrolysis of the glycosidic linkage in disaccharides is usually a slow and acid-catalyzed process. It is remarkably speeded up, when at the site of the glycosidic linkage the hydrogen has been replaced by a lone electron [reaction (68)] (for reviews see von Sonntag 1980; von Sonntag and Schuchmann 2001).



Details have not been investigated. Whether in DNA such a reaction plays also a role in the elimination of the nucleobases from the $C(1')$ radical, is as yet not known.

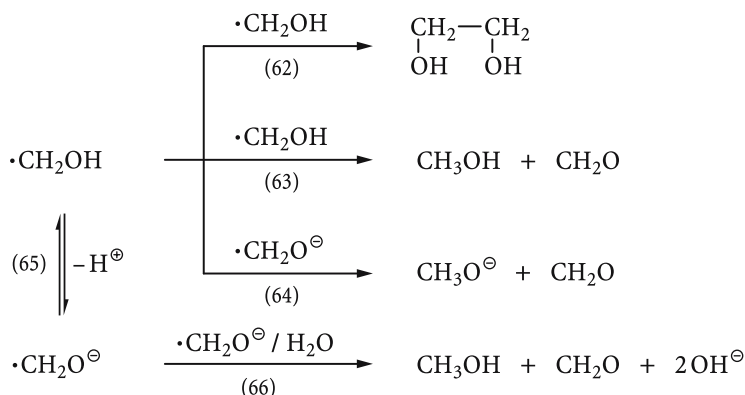
6.11 Bimolecular Termination Reactions

In general, carbon-centered radicals disappear by recombination and disproportionation (when β -hydrogens are available). The rate of reaction is usually somewhat below diffusion-controlled and may require some activation energy (e.g., $\sim 19 \text{ kJ mol}^{-1}$ for $\cdot\text{C}(\text{CH}_3)_2\text{OH}$; Mezyk and Madden 1999). Although recombination is usually the preferred reaction, disproportionation plays an increasing role, when the number of hydrogens in β -position is increased. A case in point is the series of α -hydroxyalkyl radicals. With the hydroxymethyl radical, where only one hydrogen (that at oxygen) is available for the disproportionation reaction, the disproportionation/recombination ratio is 0.17 (Wang et al. 1996) [cf. reactions (62) and (63)]; this ratio increases to ~ 2.3 in the case of the α -hydroxyethyl radical (Seddon and Allen 1967; four hydrogens available for disproportionation) and with the 2-hydroxyprop-2-yl this ratio is about 10 (Lehni and Fischer 1983). In the latter case seven hydrogens, six at the methyl groups and one oxygen-on, now facilitate disproportionation which is now the preferred mode of radical termination.. Although the formation of acetone [reaction (59)] is thermodynamically much favored over the formation of its enol [reaction (58)], the latter reaction is kinetically chosen preferentially (von Sonntag 1969; Blank et al. 1975; see also Laroff and Fischer 1973; Bargon and Seifert 1974).



The hydroxymethyl radicals display an interesting feature. Their neutral forms largely dimerize [reaction (62)], but their radical anions disproportionate [reaction (66)], although there are no longer any hydrogens available for disproportionation (Wang et al. 1996). It has been suggested that this surprising disproportionation reaction may be due to a head-to-tail combination of the hydroxymethyl radical anions or it may proceed by a water-assisted reaction.

In termination reactions, all mesomeric structures may contribute. Cases in point, where one would not immediately expect this to play a significant role are the α -carboxymethyl radicals (Wang et al. 2001). For some of the nucleobase radicals also more than one mesomeric structure may be written (Chap. 10), and it is not unlikely that also here this aspect has to be taken into account.



The rates of these bimolecular termination reactions are usually close to diffusion controlled except for equally charged radicals (Ulanski et al. 1997), notably polymeric radicals (Chap. 9.3). DNA belongs to this group.

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