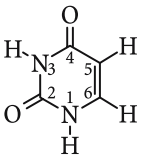
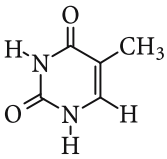
Nucleobases, Nucleosides and Nucleotides

10.1 General Remarks

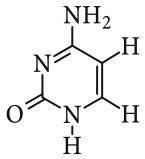
In DNA, there are four different nucleobases, the pyrimidines Thy and Cyt, and the purines Gua and Ade. In RNA, Ura replaces Thy[1].



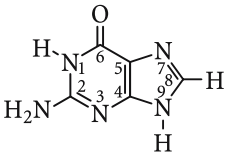
Uracil (Ura)



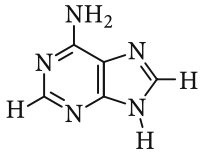
Thymine (Thy)



Cytosine (Cyt)



Guanine (Gua)



Adenine (Ade)

In their free-radical chemistry, these nucleobases have many properties in common. There are, however, also considerable differences which strongly affect the various reaction pathways. In nucleosides and nucleotides, free-radical attack mainly occurs at the base moiety. These reactions largely involve addition reactions. Only the sugar moiety and the methyl group in Thy can act as H-donors. The *C*(2′)-position is the least likely to be attacked because of the stronger BDEs of these hydrogens (Miaskiewicz and Osman 1994; Steenken et al. 2001), but this reaction can become of importance when favored by steric conditions.

10.1.1 pK_a Values

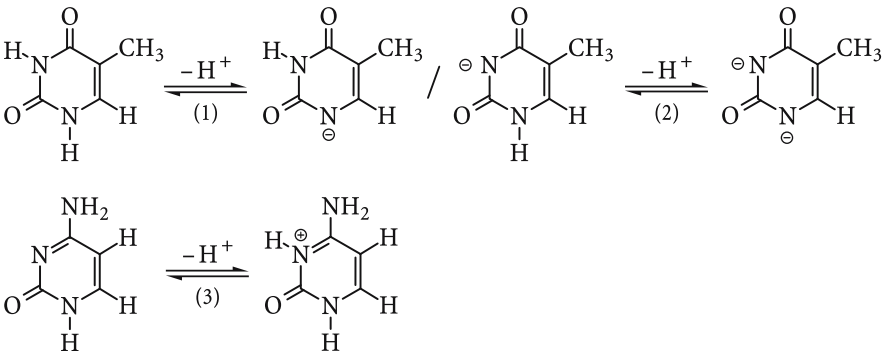
Ura, Thy and Gua deprotonate at pH < 10 [reaction (1)], but are not protonated at pH > 3. On the other hand, Cyt and Ade and their nucleosides already become protonated around pH 4 [e.g., reaction (3)], but, with the exception of Ade itself, they only deprotonate at very high pH (Table 10.1). The deprotonation of nucleosides at pH > 12 is often due to a deprotonation at the sugar moiety (Velikyan et

[1] In this chapter, the three-letter abbreviations (Fasman 1975) are used, and a few examples are given below. Nucleobases and its derivatives: adenine (**Ade**), guanine (**Gua**), cytosine (**Cyt**), thymine (**Thy**), uracil (**Ura**), 5-bromouracil (**5BrUra**), 1,3-dimethyluracil (**1,3Me$_2$Ura**), 5,6-dihydrouracil (**H$_2$Ura**), 5,6-dihydro,5,6-dihydroxythymine, thymine glycol, [**(OH)$_2$Thy**], 6-hydroxy-5,6-dihydrothymine (**6OHH$_2$Thy**). Nucleosides: adenosine (**Ado**), guanosine (**Guo**), Cytidine (**Cyd**), uridine (**Urd**), 2′-deoxyadenosine (**dAdo**), 2′-deoxyguanosine (**dGuo**), 2′-deoxycytidine (**dCyd**), thymidine (**Thd**), 2′-deoxy-5-bromouridine (**5BrdUrd**). Nucleotides: adenosine-3′-phosphate (**Ado-3′-P**), 2′-deoxyadenosine-5′-phosphate (**dAdo-5′-P**).

Table 10.1. pK_a values of nucleobases and nucleosides at the base moiety

Compound	Basic	Acidic
Ura	–	9.5/> 13
Urd	–	9.2
Thy	–	9.9/> 13
Thd	–	9.8
Cyt	4.6	12.2
dCyd	4.3	> 13
Ade	4.15	9.8
dAdo	3.8	–
Gua	< 0/3.2	9.6/12.4
dGuo	2.5	9.3

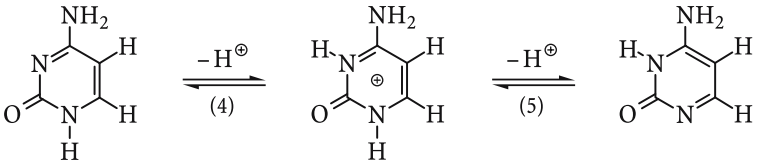
al. 2001). Double deprotonation [e.g., reaction (2)] only occurs at very high pH values an can be largely neglected.



The kinetics of the free-radical chemistry of the nucleobases has been studied by using mainly the pulse radiolysis technique (Chap. 13.3). For this reason, it is important to mention that short-lived transients are also observable in the case of Ura and Thy (Fielden et al. 1970; Greenstock et al. 1973b) as well as with Cyt (Greenstock et al. 1973b; Hissung and von Sonntag 1979; Schuchmann et al. 2005) even if all the water radicals are scavenged by other additives and thus are prevented from reacting with the nucleobase. The reason for this effect is the formation of H^+ and OH^- during the pulse (Chaps 2.2 and 13.3).

The pK_a values of Thy and Ura are close to 9.5. Thus, near neutrality they are deprotonated by OH^- formed in the pulse. Due to the low pK_a values, the reprotonation of the anions by water is sufficiently slow (~ 3×10^5 s^{-1}) to allow the anions to build-up to higher than steady-state concentrations. Of the two anions that are formed upon deprotonation [e.g., reaction (1)] only the one deprotonated at *N*(1) absorbs at longer wavelengths than the neutral molecules (Morita et al. 1981). This explains, why with the nucleosides which have the same pK_a values as the nucleobases no such intermediates are formed, although deprotonation by OH^- occurs as well.

With Cyt, the situation is quite different. The pK_a value of Cyt is 12.2. Hence, reprotonation of the Cyt anion by water is very fast (~10^8 s^{-1}), and the intermediate Cyt anion cannot reach a sufficiently high concentration to be observable under the conditions of such an experiment. On the other hand, Cyt is readily protonated, the pK_a value of the protonated Cyt being 4.6. The protonated Cyt absorbs at longer wavelengths than Cyt itself, and hence a short-lived intermediate is observed. This also applies to Cyd. However, while the subsequent deprotonation of the protonated Cyt by OH^- just reverts back to Cyd, this is not the case with Cyt (Schuchmann et al. 2005). There, a new absorption builds up due to the formation of its isomer, isocytosine, which has an absorption maximum at 296 nm (Dreyfus et al. 1976), i.e. at considerable longer wavelengths compared to Cyt (λ_{max} = 267 nm). Of the two isomers, Cyt is the thermodynamically favored species and isocytosine (richer in Gibb's free energy by 14 kJ mol^{-1}) eventually reverts to Cyt [reactions (4) and (5)].



Cytosine **Isocytosine**

10.1.2 Reduction Potentials

Gua has the lowest reduction potential among the four nucleobases (Table 10.2), and hence it is preferentially oxidized to its radical cation (for the calculation of ionization potentials of the DNA bases see Close 2004; Crespo-Hernández et al. 2004), and this property makes Gua and its derivatives to stick out of the other nucleobases with respect to its different free-radical chemistry. In contrast, Thy and Cyt are good electron acceptors, while the purines are only poor ones in comparison (for the calculation of electron affinities, see Richardson et al. 2004). This is of special importance in the effects caused by the absorption of ionizing radiation by DNA.

The reduction potential of Guo and Ado, determined pulseradiolytically (Steenken and Jovanovic 1997), corrects earlier much lower values (Jovanovic and Simic 1986, 1989), but is only slightly higher than the value of 1.47 V deter-

Table 10.2. Reduction potentials of nucleobases in nucleosides. (Steenken et al. 1992; Steenken and Jovanovic 1997; for further studies see text)

Compound	Reduction	Oxidation
Cyd	–1.15	
dCyd		$E_7 \approx 1.6$
Thd	–1.2	$E_7 \approx 1.7$
Ado		$E_7 = 1.56$
Guo		$E_7 = 1.29$

mined in acetonitrile by cyclic voltammetry (Seidel et al. 1996). Hydrogen bonding to Cyt reduces the reduction potential of Gua by 100 mV (Kawai et al. 2000; for further data including the reduction potentials of the nucleobases and some related compounds see Faraggi et al. 1996; for quantum mechanical calculations of electron affinities and ionization potentials of nucleobases see Faraggi and Klapper 1993; Russo et al. 2000).

The reduction potentials of all the nucleobase radical cations (and their deprotonated forms) are all higher than that of tryptophan ($E_7 = + 1.0$ V; Merényi et al. 1988; DeFelippis et al. 1989; Jovanovic et al. 1991), and in DNA repair of such intermediates by ET from surrounding proteins is thermodynamically feasible (for the reactions with other reducing agents see below). The DNA-binding bisbenzimidazole derivatives (such as *Hoechst 33258*) are expected to have even lower reduction potentials, and these compounds undergo efficient ET not only to one-electron oxidized purines on the model level (Adhikary et al. 1997b, 2000; Martin and Anderson 1998) but also when bound to DNA (Adhikary et al. 1997a).

Among the nucleobases, Thy and Cyt are most readily reduced (Table 10.2). Electron attachment energies have been determined in the gas phase (Aflatooni et al. 1998), and they confirm this view. Theoretical vertical attachment energy calculations rank the nucleobases in the order Ura < Thy < Cyt < Ade < Gua (Sevilla et al. 1995).

10.2 Radical Cations and their Conjugate Bases, the Heteroatom-Centered Radicals

10.2.1 Formation of Radical Cations

In the direct effect of ionizing radiation on DNA, radical cations are the primary products (Chap. 12). For this reason, their reactions are of considerable interest. Obviously, photoionization (e.g., at 193 nm) and laser multi-photon excitation leads to such species (e.g., Candeias and Steenken 1992b; Malone et al. 1995; Chap. 2.2). Base radical cation electron pairs have been proposed to be the first observable intermediates with a lifetime of 10 ps for Ade and four times longer for the other nucleobases (Reuther et al. 2000). Radical cations are also assumed to be intermediates in the reactions of photosensitization reactions with quinones, benzophenone, phthalocyanine and riboflavin (Cadet et al. 1983a; Decarroz et al. 1987; Krishna et al. 1987; Ravanat et al. 1991, 1992; Buchko et al. 1993; Douki and Cadet 1999; Ma et al. 2000). Nucleobase radical cations may be produced by electrochemical oxidation (Nishimoto et al. 1992; Hatta et al. 2001) or with strongly oxidizing radicals (for a compilation of their reduction potentials see Chap. 5.3). Rate constants are compiled in Table 10.3.

One-electron oxidation of dGuo to its radical cation, $G^{\bullet+}$, is achieved by strong oxidants such as Tl^{2+}, $SO_4^{\bullet-}$ and $Br_2^{\bullet-}$ (Table 10.3; for its EPR spectrum generated by $SO_4^{\bullet-}$ see Bachler and Hildenbrand 1992) as well as the heteroatom-centered radicals derived from the other nucleobases (e.g., Shi et al. 2000a). Weaker oxidants such as $N_3^{\bullet}$ and the dimeric tetramethylthiourea radical cation are capable of oxidizing dGuo only at high pH, i.e. in its anionic form thereby producing the guanyl radical, $G^{\bullet}$ (Schuchmann et al. 2000). Depending on the nature of the oxidant, oxidation may take place by direct ET as well as by addition-elimination. Kinetic deuterium isotope effects of 1.5-2 are observed in the (reversible) oxidation of Gua by 2-aminopurine radicals, and it has been concluded that this redox equilibrium can be considered in terms of a proton-coupled ET (Shafirovich et al. 2000). Such a proton-coupled ET step leads to a lowering of the overall free energy of reaction thus favoring ET (Rehm and Weller 1970; Atherton and Harriman 1993; for theoretical calculations see Cho and Shin 2000 and references cited therein).

Short-lived adducts may be formed as intermediates in the reactions of the oxidizing inorganic radicals with the nucleobases, and it is therefore not always fully excluded that processes observed at very short times and attributed to the reactions of radical cations are in fact due to such intermediates. It may be mentioned that, for example, a long-lived $SO_4^{\bullet-}$-adduct is observed in the reaction of $SO_4^{\bullet-}$ with maleic acid (Norman et al. 1970). It has been suggested that $SO_4^{\bullet-}$ in its reactions with the pyrimidines forms only an adduct and does not give rise to radical cations (Lomoth et al. 1999). The observation of heteroatom-centered radicals by EPR from the nucleobases Ura, Thy and Cyt (Catterall et al. 1992) as well as dCyd (Hildenbrand et al. 1989) (see below) has been taken as evidence that in the reaction of $SO_4^{\bullet-}$ with pyrimidines radical cations are likely, albeit

Table 10.3. Compilation of rate constants (unit: $dm^3\ mol^{-1}\ s^{-1}$) of oxidizing radicals with nucleobases and related compounds

Substrate	Radical	Rate constant	Reference
Ade	$SO_4^{\bullet-}$	4.6×10^9	Vieira and Steenken (1987a)
9MeAde	$SO_4^{\bullet-}$	4.1×10^9	Vieira and Steenken (1987a)
dAdo	$SO_4^{\bullet-}$ $Br_2^{\bullet-}$	3.2×10^9 4×10^5	Steenken (1989) von Sonntag (1994)
dAdo/H^+ (pH 2.4)	$SO_4^{\bullet-}$	4.4×10^9	Steenken (1989)
Ado	$SO_4^{\bullet-}$ Tl(II)	2.7×10^9 6.3×10^7	Vieira and Steenken (1987a) Al-Sheikhly (1994)
N^6,$N^6$$Me_2$Ado	$SO_4^{\bullet-}$	3.9×10^9	Vieira and Steenken (1987a)
dCyd	$SO_4^{\bullet-}$	2.5×10^8 1.6×10^9	O'Neil and Davies (1987) Aravindakumar et al. (2003)
Cyd	$SO_4^{\bullet-}$	3×10^9	Aravindakumar et al. (2003)
Cyt anion	$SO_4^{\bullet-}$	7.5×10^8	Hazra and Steenken (1983)
Cyt/H^+ (pH 2)	$Cl_2^{\bullet-}$	1.0×10^7	Patterson et al. (1972)
dCyd/H^+ (pH 2)	$Cl_2^{\bullet-}$	4×10^6	Patterson et al. (1972)
Gua anion	$^{\bullet}N_3$	4×10^9	Faraggi and Klapper (1994)
dGuo	$SO_4^{\bullet-}$ $SeO_3^{\bullet-}$	2.3×10^9 4.1×10^9 1.2×10^9	O'Neill and Davies (1987) Steenken (1989) Martin and Anderson (1998)
dGuo anion	$^{\bullet}N_3$ $(Me_4Thiourea)_2^{\bullet+}$	4×10^9 1.2×10^8	Faraggi and Klapper (1994) Schuchmann et al. (2000)
dGMP	$Br_2^{\bullet-}$	4×10^7	Willson et al. (1974)
Guo	Tl(II)	1.26×10^9	Al-Sheikhly (1994)
Thy	$SO_4^{\bullet-}$ $Cl_2^{\bullet-}$ $HPO_4^{\bullet-}$	3.1×10^9 7.0×10^7 9.6×10^7	Fujita et al. (1988) Patterson et al. (1972) Nakashima and Hayon (1979)
Thd	$SO_4^{\bullet-}$	2.1×10^9	Deeble et al. (1990)
3MeThd	$SO_4^{\bullet-}$	3.5×10^9	Deeble et al. (1990)
TMP	$SO_4^{\bullet-}$	1×10^9	Deeble et al. (1990)
1MeThy	$SO_4^{\bullet-}$	5×10^9	Deeble et al. (1990)
1,3Me_2Thy	$SO_4^{\bullet-}$	4.6×10^9	Deeble et al. (1990)
Ura	$Cl_2^{\bullet-}$ $HPO_4^{\bullet-}$ $H_2PO_4^{\bullet}$	3.5×10^7 9.7×10^7 6×10^8	Patterson et al. (1972) Nakashima and Hayon (1979) Nakashima and Hayon (1979)
1,3Me_2Ura	$SO_4^{\bullet-}$	5.5×10^9	Schuchmann et al. (1987)
1,3,6Me_3Ura	$SO_4^{\bullet-}$	3.5×10^9	Deeble et al. (1990)

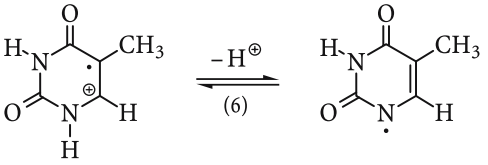
possibly very short-lived, intermediates. Yet, concerted release of sulfate ion and a proton would lead to the same heteroatom-centered radicals without free radical cations as intermediates (Aravindakumar et al. 2003). Once the heteroatom-centered radicals are formed, their protonation will lead to the formation of radical cations. Thus, such intermediates may play a role in the subsequent chemistries even if not formed in the primary step. This may, for example, be the reason for the formation of the allylic radical in the reaction of $SO_4^{\bullet -}$ observed with Thy (Deeble et al. 1990).

$Br_2^{\bullet -}$ can also be used to oxidize good electron donors, but at least with the pyrimidines its rate of reaction is too slow to be of any importance. Instead, degradation may occur by Br_2, the product of the disproportionation of $Br_2^{\bullet -}$, as has been shown for Thd (Cadet et al. 1983b).

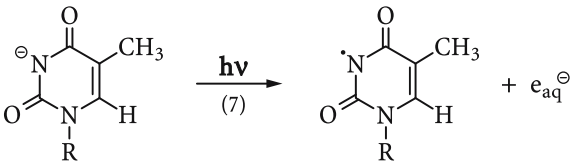
10.2.2 pK_a Values of Radical Cations and Heteroatom-Centered Radicals

Usually, radical cations have much lower pK_a values than their parent compounds. A typical examples is phenol, whose pK_a value is at 10 while that of its radical cation is at -2 (Dixon and Murphy 1976). Thus in this case, ionization causes an increase in acidity by 12 orders of magnitude. It is hence expected that also the nucleobase radical cations should be much stronger acids than their parents. This has indeed been found in all systems where equilibrium conditions are established, and the consequences for DNA base pairs have been discussed (Steenken 1992).

Pyrimidines. Photoexcited anthraquinone-2,6-disulfonate undergoes ET with Thy and its methyl derivatives as indicated by Fourier transform EPR (Geimer et al. 1997). These pyrimidine radical cations deprotonate at *N*(1) thereby giving rise to the corresponding *N*-centered radicals [reaction (6)].

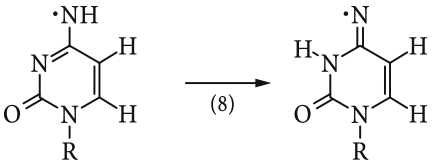


This view is been confirmed by an electrochemical product study (Hatta et al. 2001) that is discussed below. The pK_a value of the Thy radical cation has been determined at 3.2 (Geimer and Beckert 1998). When the position at *N*(1) is substituted by a methyl group and deprotonation of the radical cation can no longer occur at this position, deprotonation occurs at *N*(3) (Geimer and Beckert 1999; for spin density calculations using density functional theory (DFT) see Naumov et al. 2000). This *N*(3) type radical is also produced upon biphotonic photoionization of *N*(1)-substituted Thy anions [reaction (7)] in basic 8 molar $NaClO_4$–D_2O glasses which allowed to measure their EPR spectra under such conditions (Sevilla 1976).

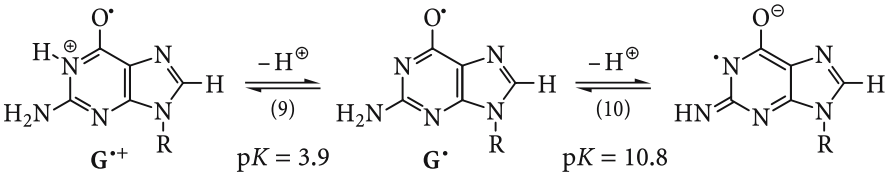


From a pulse radiolysis study on the $SO_4^{\bullet -}$-induced reactions of Thd (Deeble et al. 1990), it has been concluded that the pK_a of the Thd radical cation (deprotonation at *N*(3)) should be near 3.5, i.e. close to that at *N*(1) in Thy. It is noted that also in the parent, Thy, the pK_a values at *N*(1) and at *N*(3) are quite close. A Fourier-transform EPR study using photoexcited anthraquinone-2,5-disulfonic acid to oxidize Cyt and 1MeCyt shows that the radical cation of the former deprotonates rapidly at *N*(1) while that of the latter deprotonates at the exocylic amino group (Geimer et al. 2000). The EPR evidence for the formation of heteroatom-centered radicals by $SO_4^{\bullet -}$ in its reactions with some other pyrimidines (Bansal and Fessenden 1978; Hildenbrand et al. 1989; Catterall et al. 1992) is in agreement with a marked acidity of such radical cations. It is re-emphasized that this conclusion does not require that radical cations are formed in the primary step.

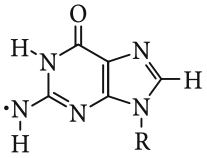
The primary exocyclic *N*-centered dCyd radical is only observed at very short times and is converted into another radical which has been attributed (Naumov et al. 2001) to its tautomer [reaction (8)]. This tautomerization has been calculated to be exothermic by 10.5 kJ mol^{-1}.



Purines. The Gua radical cation, $G^{\bullet +}$, is an acid (pK_a = 3.9; Willson et al. 1974; Asmus et al. 1978) and readily deprotonates at a heteroatom. In water, the deprotonation product identified by pulse radiolysis is the *N*(1) radical [denoted as $G^{\bullet}$; equilibrium (9); Candeias and Steenken 1989].



The radical that is formed upon deprotonation at *N*(2), *N*(2)$G^{\bullet}$, is very close in energy.

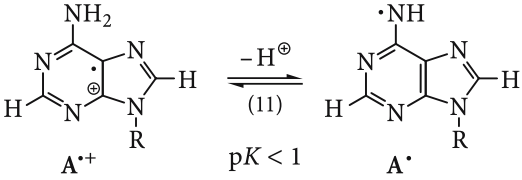


N(2)G•

In fact, calculations show that in the gas phase *N*(2)G• is more stable than G• (Mundy et al. 2002; Naumov et al., unpubl. results; in Wetmore et al. 1998a apparently an energy-richer rotamer (local minimum) has been calculated). The cross-over in stability from *N*(2)G• to G• would occur in a solvent having a DK like MeOH, and in γ-irradiated crystals of dGMP and cyclo-GMP *N*(2)G• (and not G•) is the stable species formed upon deprotonation of $G^{\bullet+}$ (Hole et al. 1987, 1989, 1992a,b; Close et al. 1985; Nelson et al. 1988). The reason for a change-over in stability as a function of solvent (environment) polarity is the marked difference of the dipole moments of G• and *N*(2)G• which has been calculated at 5.5 Debye (in water; Naumov et al., unpubl. results). This may now also explain the results obtained when GMP is oxidized in aqueous solution by photoexcited tris(1,4,5,8-tetraazaphenanthrene)ruthenium(II) (Jaquet et al. 1995). After deprotonation of $G^{\bullet+}$ in the solvent cage, the resulting *N*(2)G• adds to the ligand of the Ru-complex forming a well-characterized product. Since all these reactions are believed not to occur in the bulk but in the solvent cage where the partners, GMP and the Ru-complex with its aromatic ligands provide an environment whose effective DK will be considerably below that of water, *N*(2)G• is the stable species under such conditions.

At high pH, G• deprotonates further [equilibrium (10), $pK_a(G^{\bullet}) = 10.8$; Candeias and Steenken 1989]. $G^{\bullet+}$ ($pK_a = 3.9$) is a weaker acid than the protonated parent ($pK_a = 2.4$) but a stronger acid than its corresponding neutral parent ($pK_a = 9.4$). Based on the redox potential and the pK_a value, the *N*(1)–H binding energy in dGuo has been calculated at 380 kJ mol^{-1} (Steenken et al. 2001).

Ade has a considerably higher reduction potential than Gua (Table 10.2), and for this reason it is not as readily oxidized, even by strongly oxidizing radicals, $SO_4^{\bullet-}$ excepted. The pK_a of the dAdo radical cation, $A^{\bullet+}$, lies at less than 1 [equilibrium (11); Steenken 1989; for gas phase data see Hwang et al. 1999].

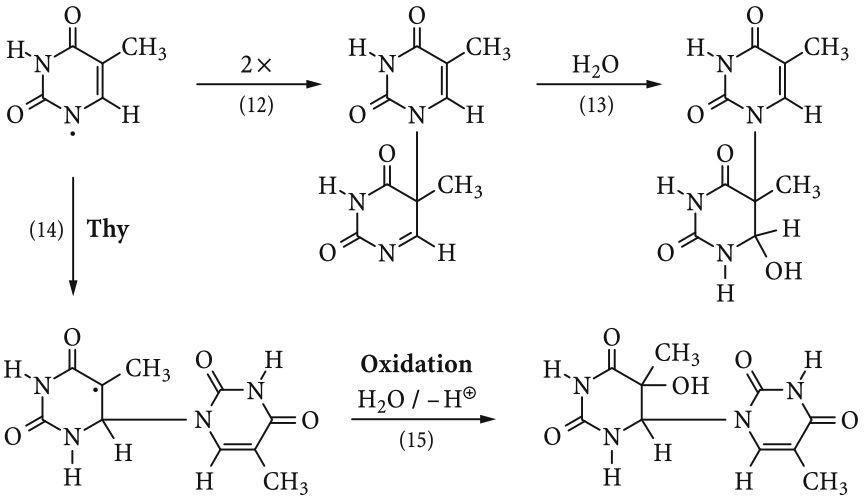


$A^{\bullet+}$ $\quad pK < 1$ $\quad A^{\bullet}$

10.2.3 Reactions of $SO_4^{\bullet -}$/$PO_4^{\bullet 2-}$-Adduct Radicals, Radical Cations and Heteroatom-Centered Radicals

Radical cations are strongly oxidizing intermediates, but also after deprotonation at a heteroatom (in the present systems at nitrogen) some of this oxidizing property remains. Thus a common feature of these intermediates is that they are readily reduced by good electron donors. Since the heteroatom-centered radicals and the radical cations are always in equilibrium, it is, at least in principle, possible that such intermediates react with water at another site (canonical mesomeric form), that is at carbon. This reaction leads to •OH-adduct radicals. Although deprotonation at a heteroatom is usually faster (but also reversible) than deprotonation at carbon, the latter reaction is typically "irreversible". This also holds for a deprotonation at methyl (in Thy).

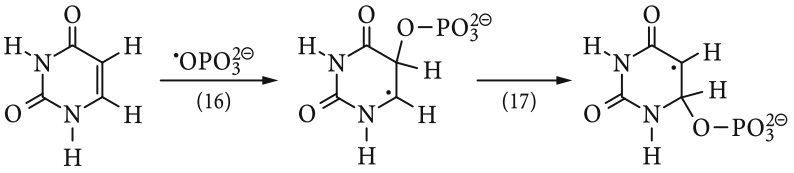
Pyrimidines. Reaction of Thy with photoexited menadione or its electrochemical oxidation yields mainly to the *N*(1)-*C*(5)-linked dimer (Hatta et al. 2001). This can be accounted for if the precursor radical cation deprotonates at *N*(1) (see above). For this *N*(1)-centered radical a second mesomeric form with the spin at *C*(5) can be written. Head-to-tail recombination leads to the isopyrimidine-type dimer [reaction (12)]. Isopyrimdines are unstable (see below) and add rapidly water [reaction (13)]. This dimer is also formed in the reaction with $SO_4^{\bullet -}$, albeit with a lower yield.



Upon electrochemical oxidation, dimers resulting from a recombination at *C*(5) are formed as well. Whether this route is mediated by the electrode surface or due to a recombination of a radical cation with an *N*-centered radical (note that there is a high radical density at the electrode surface and that the radical cation (pK_a = 3.2) has a lifetime of ~0.5 µs), must remain speculation. To a smaller extent, a further dimer is also observed. It may arise by an addition/oxidation

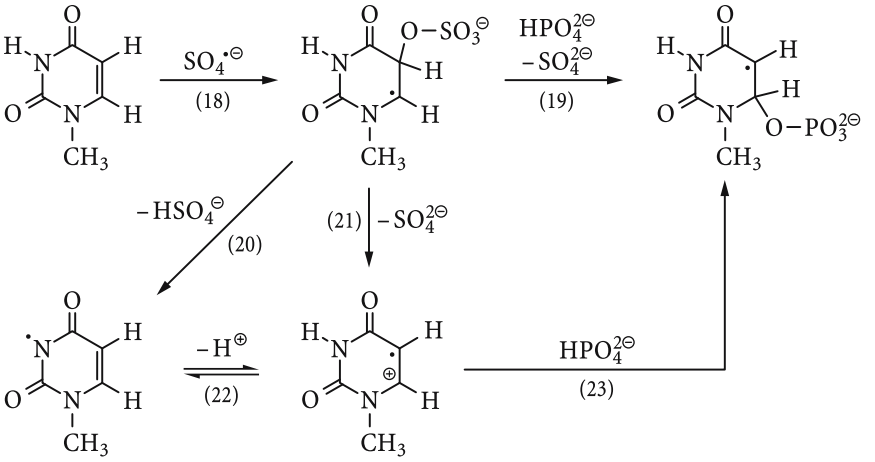
mechanism [reactions (14) and (15); a similar sequence has also been envisaged for the formation of the major dimer; Hatta et al. 2001]. An alternative route to this minor dimer would be a reaction of the radical cation with water (in competition with its deprotonation) yielding the *C*(5)OH-*C*(6)-yl radical and its recombination with the major radical. Since the addition of water to the radical cation would only be a minor route, it may easily have escaped detection by EPR. The formation of dimers have also been observed by electrochemical oxidation of 5FUra and 5ClUra, but 5BrUra and 5IUra did not afford any dimers (Hatta et al. 2001).

The electrophilic $SO_4^{\bullet -}$ preferentially adds to an electron-rich position of the substrate, *C*(5) in the case of pyrimidines. This must also hold for the phosphate radical [reaction (16)]. Here, however, the radical observed by EPR is the *C*(6)-adduct radical, and it has been concluded that a rapid 1,2-shift leads to this thermodynamically more stable radical [reaction (17); Behrens et al. 1988]. At pH > 6.5, the transformation reaction (17) is sufficiently slow to be intercepted by a spin trap, and the adduct to the primary radical formed in reaction (16) is indeed observed (Hildenbrand 1995).



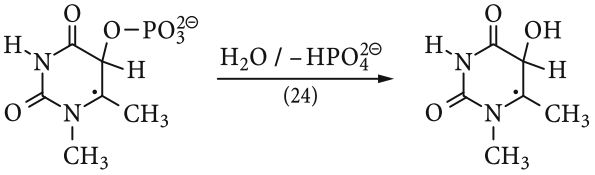
For a mechanistic interpretation of the EPR data, one must keep the possibility in mind that the reducing *C*(5)-adduct radical may have been oxidized by peroxodiphosphate in the free-radical chain reaction (see below) and that only the oxidizing *C*(6)-adduct radical remains in this sequence of reactions, although formed in small amounts, and is eventually detected by EPR as the only radical.

The phosphate-adduct radical is also formed, when the reaction is initiated by $SO_4^{\bullet -}$ [reaction (18)] in the presence of phosphate ions (Behrens et al. 1988). This may either be due to an S_N2 substitution reaction [reaction (19)] or a reaction of the phosphate ion with the radical cation [reaction (17)] formed either by an elimination of SO_4^{2-} plus H^+ [reaction (20)] and subsequent protonation of the *N*(3)-centered radical [equilibrium (22)] or by SO_4^{2-} elimination [reaction (21)], as envisaged originally. The reaction of the radical cation with phosphate would then give rise to the observed radical [reaction (23)].



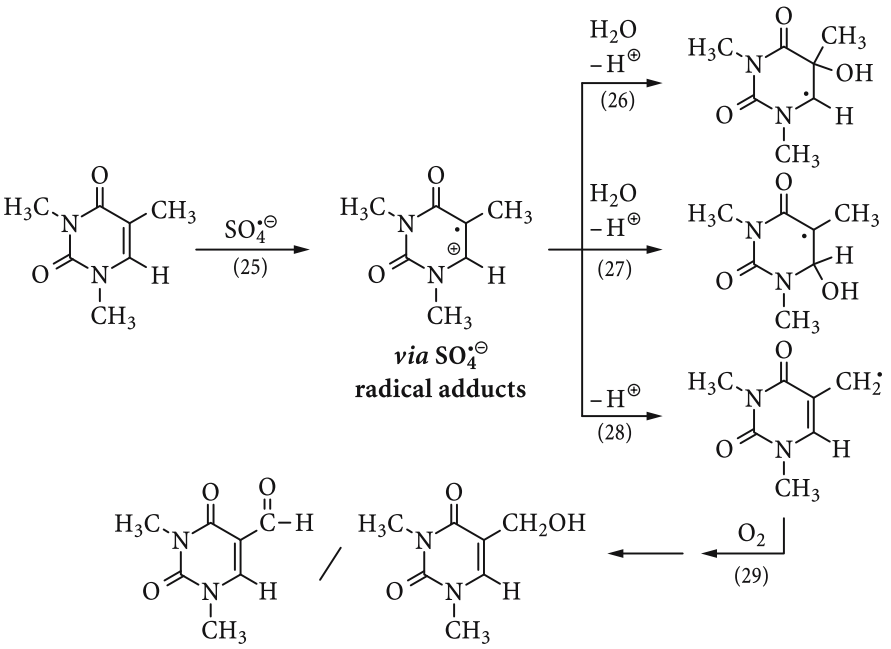
From the competition of phosphate and water for the intermediate(s) formed by $SO_4^{\bullet -}$, it has been concluded that the rate constant of reaction with phosphate must be $\geq 4 \times 10^8$ dm^3 mol^{-1} s^{-1}. The transformations of intermediates that play a role in this system by OH^- and by phosphate were followed by EPR techniques (Hildenbrand et al. 1989; Geimer and Beckert 1999).

When the electron-donating methyl substituent is introduced at *C*(6), the *C*(6)-phosphate-adduct radical is no longer stable on the EPR time scale, and



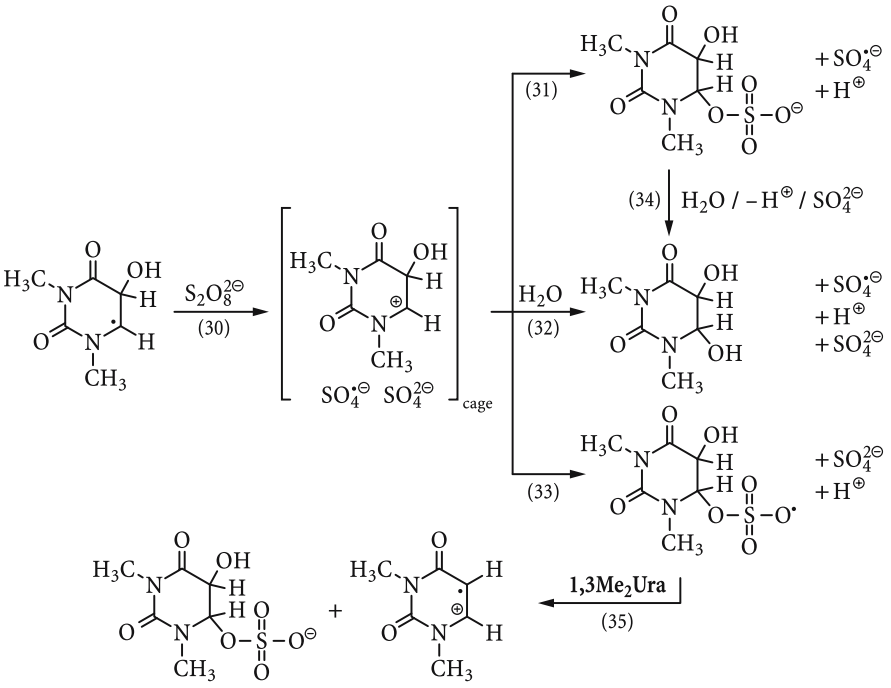
only its hydrolysis product is observed [reaction (24); Behrens et al. 1988]. The reason for the greater stability of the phosphate radical-adduct compared the sulfate radical-adduct is due to effects discussed in Chapter. 6.9.

It has been mentioned above that the pyrimidine radical cations are reasonably strong acids and rapidly deprotonate at a heteroatom. As all protonation/deprotonation reactions at heteroatoms are reversible [e.g., equilibrium (22)], the radical cations are regenerated upon reprotonation. Deprotonation at carbon or reaction with water yield the final free-radical products. For the 1,3Me$_2$Thy system, where the deprotonation/reprotonation equilibria such as reaction (22) fall away, reactions (25)-(28) have been postulated to account for the fact that in the presence of O_2 1,3Me$_2$5HOMeUra and 1,3Me$_2$5(CHO)Ura [reaction (29)] are formed in a combined yield of 80% of primary $SO_4^{\bullet -}$ radicals (Rashid et al. 1991). The formation of these products has been taken as evidence that a free radical cation must be an intermediate. It is, however, also possible that the allylic radical is formed in a concerted reaction HSO_4^- elimination. For such a process, a six-membered transition state can be written.



The allylic Thy radical is observed by EPR in Thd (Catterall et al. 1992) and TMP (Hildenbrand 1990). The identification of the *C*(6)-OH-5-yl radical by EPR supports the view (Deeble et al. 1990) that reaction with water competes with a deprotonation at methyl. Due to the ready oxidation of the (reducing) *C*(5)-OH-6-yl radicals by peroxodisulfate, this type of radical is only observed at low peroxodisulfate concentrations in these systems, i.e. the (oxidizing) *C*(6)-OH-5-yl radicals may be correspondingly enriched (Schulte-Frohlinde and Hildenbrand 1989) (note that the nucleobases themselves are not oxidized at a reasonable rate unless deprotonated; Moschel and Behrman 1974). These reducing *C*(5)-OH-6-yl radicals are capable of reacting with peroxodisulfate and thus induce chain reactions which in the case of 1,3Me$_2$Ura shows some very interesting properties (Schuchmann et al. 1987). It is nearly independent of the peroxodisulfate concentration, but shows a marked dependence on the 1,3Me$_2$Ura concentration. From this, it immediately follows that the mechanism is *not* characterized by the reaction of the reducing *C*(5)-OH adduct radical with peroxodisulfate as the rate determining step [reaction (30), $k = 2.1 \times 10^5$ dm^3 mol^{-1} s^{-1}], yielding *exclusively* SO_4^{2-}, the glycol [via the carbocation and water, reaction (32)]. This would be the trivial case of an $SO_4^{\bullet-}$-induced chain reaction (cf. Schuchmann and von Sonntag 1988; Ulanski and von Sonntag 1999). One rather has to consider that in this reaction the 1,3Me$_2$Ura carbocation, $SO_4^{\bullet-}$ and SO_4^{2-} are formed within the cage [reaction (30)]. There, the carbocation may recombine with either of the two anions or react with water [reactions (31)–(33)]. When the carbocation reacts with $SO_4^{\bullet-}$ [reaction (33)], a new oxidizing species is formed which, however, is not as reactive as $SO_4^{\bullet-}$. It propagates the chain with only a slow rate

[reaction (35), $k = 1.2 \times 10^4$ dm^3 mol^{-1} s^{-1}], and thus the chain length becomes dependent on the 1,3Me$_2$Ura concentration.



The same type of chain reaction is observed in the case of 1,3,6Me$_3$Ura with one minor difference: while with 1,3Me$_2$Ura the only chain product is the glycol, there are two chain products in 1,3,6Me$_3$Ura, its glycol and 1,3,6-trimethylisobarbituric acid, formed in a ratio of 2:1 (Rashid et al. 1991). The latter is believed to arise from the sulfate by an elimination of sulfuric acid. A deprotonation at methyl does not take place. This is quite in contrast to the situation in 1,3Me$_2$Thy and other Thy systems discussed above.

A chain reaction is also apparent in the reaction of $SO_4^{\bullet -}$ with Thy, since the quantum yield of Thy destruction exceeds $\Phi = 2.0$ in the photolysis of peroxodisulfate in the presence of Thy (Sudha Sawargara and Adinarayana 2003).

In pulse radiolysis studies of Urd and its derivatives (but not with dUrd), spectral changes are observed after the completion of the $SO_4^{\bullet -}$ reaction [$k = 3 \times 10^5$ s^{-1}; Bothe et al. 1990] that are not typical for $SO_4^{\bullet -}$ reactions with pyrimidines. On the basis of EPR experiments (Hildenbrand 1990; Catterall et al. 1992), these observations can be interpreted by an (overall) intramolecular H-transfer giving rise to a radical at the sugar moiety. This requires that considerable amounts of Ura are released which is indeed observed (Fujita et al. 1988; Aravindakumar et al. 2003; Table 10.4). Chain reactions occur as with the other pyrimidine/peroxodisulfate systems. This increases the Ura yield beyond that expected for a non-chain process, but when corrections are made for this by carrying out experiments at the very high dose rates of electron-beam irradiation, a

Table 10.4. *G* (base release) (unit: 10^{-7} mol J^{-1}) from some pyrimidine nucleosides and 2′-deoxynucleosides induced by the $SO_4^{\bullet-}$ radical [$G(SO_4^{\bullet-}) = 3.3 \times 10^{-7}$ mol J^{-1}) at different dose rates: pulsed electron-beam irradiation (~6 Gy per 2 µs pulse, high dose rate) and γ-irradiation (0.013 Gy s^{-1}, low dose rate; Aravindakumar et al. 2003)

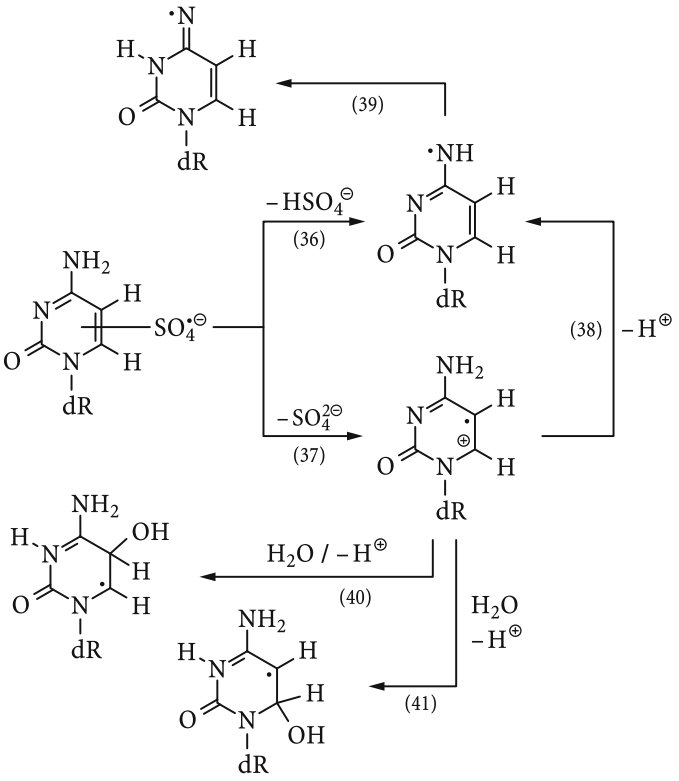
Nucleoside/2′-deoxynucleoside	Electron beam	γ-Radiolysis
Cyd	2.8	7.5
Urd	0.72	4.5
5MeUrd	n.d.	<0.05
dCyd	0.14	1.64
dUrd	0.06	0.6
Thd	0.2	1.0[a]

n.d., Not determined
[a] 0.7×10^{-7} mol J^{-1} at 1.3 Gy s^{-1}, 0.85×10^{-7} mol J^{-1} at 0.1 Gy s^{-1}

substantial part (22% of primary $SO_4^{\bullet-}$) of Ura release must be due to this radical transfer from the base to the sugar moiety.

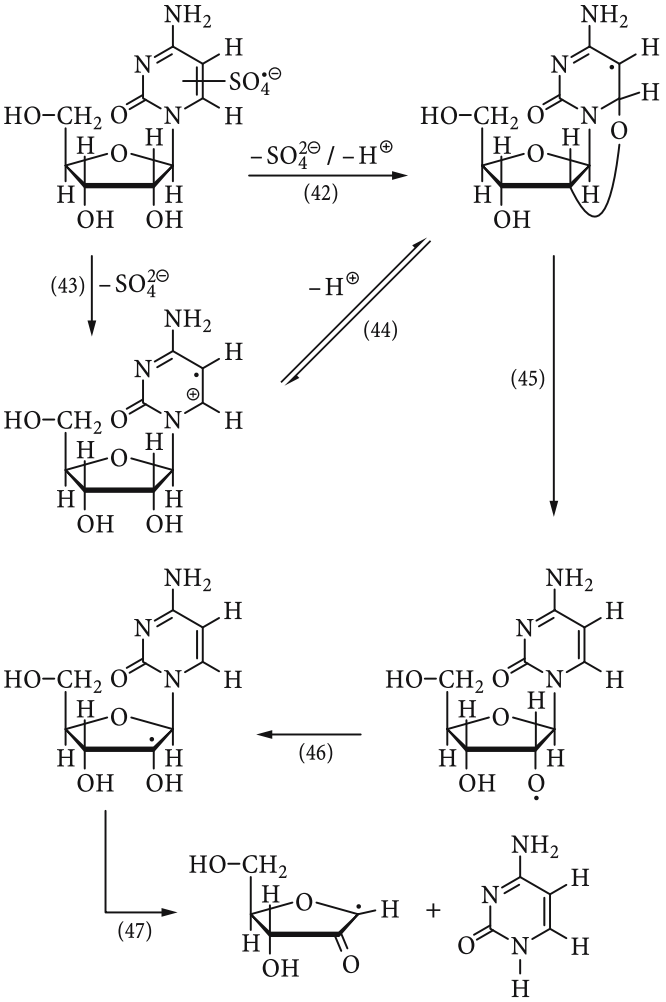
Mechanistic details will be discussed below, since the Urd seems to be analogous to the Cyd system, and the latter has been investigated in more detail (Schulte-Frohlinde and Hildenbrand 1989; Hildenbrand 1990; Catterall et al. 1992; Naumov et al. 2001; Aravindakumar et al. 2003). Interestingly, 5MeUrd does not undergo base release (Table 10.4), indicating that in this system the pathways dominating the reactions of Urd and Cyd are not followed. Whether the oxidation at methyl is the competing reaction is not yet known. A detailed mechanistic study would be required to shed light into this interesting phenomenon.

dCyd and Cyd differ dramatically in their reactions with $SO_4^{\bullet-}$. dCyd gives rise to a base-centered radical [reactions (36)–(41); Hildenbrand et al. 1989] which is formed in the tautomerization reaction (39) (Naumov et al. 2001).



In the original mechanistic concept, a free radical cation, reaction (37), has been postulated (Catterall et al. 1992). Based on circumstantial evidence, the concomitant release of HSO_4^- is now favored [reaction (36); Aravindakumar et al. 2003].

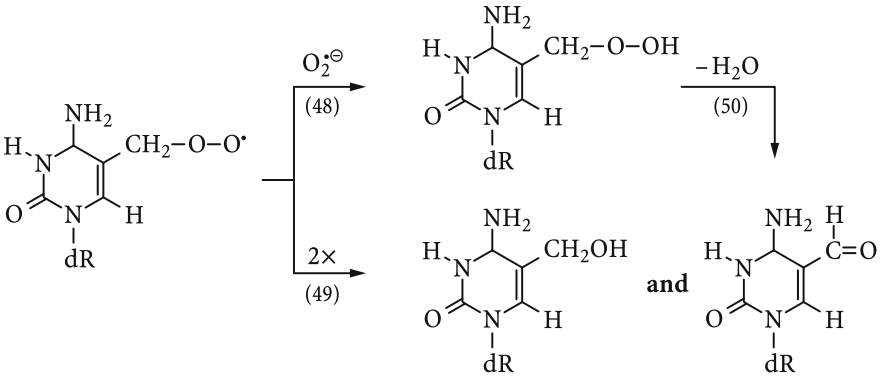
Cyd, in contrast, gives rise to a sugar-centered radical. The mechanism proposed by (Catterall et al. 1992) has been modified by Aravindakumar et al. (2003) [reactions (42)–(47)] insofar as route (42) is now favored over (43) followed by (44).



The S_N2 reaction (42) involving the *C*(2′)OH group competes successfully with the analogous reactions of water [cf. reactions (40) and (41)]. The ensuing radical rapidly decays by β-fragmentation [reaction (45), $k = 6 \times 10^4\ s^{-1}$; Schulte-Frohlinde and Hildenbrand 1989; Aravindakumar et al. 2003]. The 1,2-H-shift of the oxyl radical [reaction (46)] will be fast (Chap. 7.2). The radical that is detected by EPR requires that reaction (47) is also relatively fast. The Cyt yield is 85% of the primary $SO_4^{\bullet-}$ yield (cf. electron beam experiments in Table 10.4). Phosphate interferes with this sequence of reactions, and the same type of base radical as observed with dCyd now predominates (Niehaus and Hildenbrand 2000). The interference occurs twice, once by deprotonating the primary $SO_4^{\bullet-}$-adduct radical [enhancing the rate of reaction (42)] and also by protonating the cyclized radical [reaction (45)], i.e. it also shortens the lifetime of the latter (Aravindakumar et al. 2003).

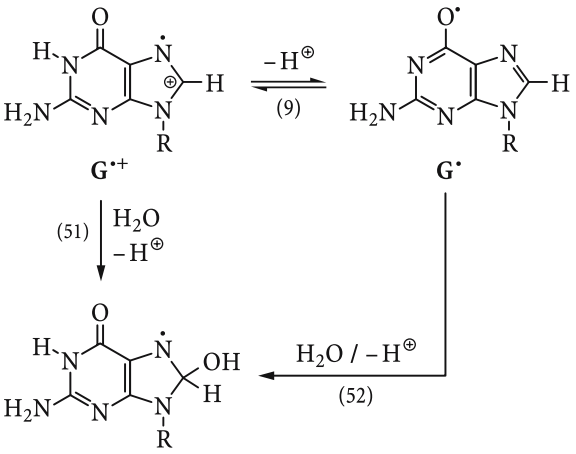
The menadione-sensitized oxidation of dCyd leads to the formation of the four *cis* and *trans* diasteroisomers of $(OH)_2$dUrd and to ring-opened products, and it has been concluded that the major reaction of the dCyd radical cation is its reaction with water yielding the •OH-adduct radical (Decarroz et al. 1987). However, *N*-centered radicals could well be their precursors. The formation of Cyt and 2-dRL has also been noticed.

The corresponding reaction with 5MedCyd leads mainly to an oxidation of the methyl group via a deprotonation of the radical cation at methyl (Bienvenu et al. 1996). Evidence for such a reaction has been obtained by EPR at 77K using biphotonic excitation to generate the radical cation (Malone et al. 1995). Mechanistically, this is analogous to the situation of Thy and its derivatives [reaction (28)]. In the presence of O_2, the 5MedCyd-derived allylic radical gives rise to the corresponding peroxyl radical. Upon its bimolecular decay, 5-hydroxymethyl-dCyd and 5-formyl-dCyd are formed [reaction (49)]. Moreover, $HO_2^•/O_2^{•-}$ (resulting from the reaction of the menadione radical anion with O_2) reduce the peroxyl radical to the hydroperoxide [reaction (48)] which decays into 5-formyl-dCyd with a half-life of 9.2 h by water elimination [reaction (50); Bienvenu et al. 1996].



For a study on the reaction of pyrimidine bases with the phosphate radical in the presence of peroxodiphosphate see Kumar et al. (2000); Kumar and Adinarayana (2001).

Purines. According to DFT calculations, the reaction of $G^{•+}$ with water [reaction (51)] is exothermic by 315 kJ mol^{-1}, while a corresponding reaction of the G• formed upon deprotonation of $G^{•+}$ is endothermic by 123 kJ mol^{-1}, and thus reaction (52) is no longer possible (Reynisson and Steenken 2002). Similarly, the reaction of $A^{•+}$ with water is exothermic by 325 kJ mol^{-1}, while A• formed upon deprotonation can no longer undergo such an reaction due to a calculated endothermicity of 183 kJ mol^{-1}.



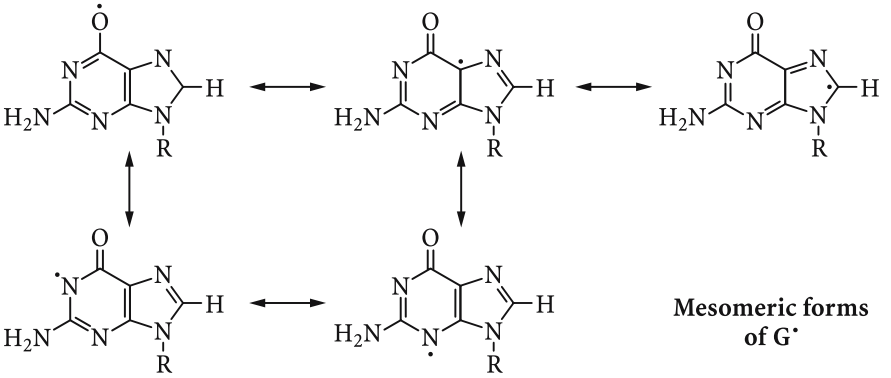
In the nucleoside and in ssDNA, $G^{\bullet+}$ ($pK_a = 3.9$) is expected to loose the proton rapidly to the water phase, but in dsDNA pairing with Cyt will prolong its lifetime and reaction (51) may proceed with a higher efficiency. The resulting *C*(8)-$^{\bullet}$OH-adduct is the precursor of the 8-oxo-G and other well-documented lesions (see below). The same type of reaction is expected to occur with $A^{\bullet+}$ (see below), but in dsDNA Ade binding to Thy will not prevent its deprotonation at N^6. This may be one of the reasons why the 8-oxo-G lesion is of a higher importance than the 8-oxo-A lesion (Chap. 12.9).

$G^{\bullet}$ is readily reduced by electron donors such as TMPD, ascorbate, ABTS (O'Neill and Chapman 1985), phenolic compounds (Jiang et al. 1999a,b; Shi et al. 1999b) or bisbenzimidazole derivatives (the *Hoechst* group of fluorescent dyes; Adhikary et al. 1997b; Martin and Anderson 1998). The good linear relationship between the logarithm of the ET rate with the reduction potential of the donor is evidence (O'Neill and Chapman 1985), but not proof [cf. Jagannadham and Steenken 1988a; Steenken 1988] that this reaction proceeds *via* an outer-sphere ET. At high pH, when $G^{\bullet}$ is deprotonated, poorer reductants are no longer capable of reducing this intermediate (O'Neill and Chapman 1985). The reaction of $^{\bullet}G$ with NO_2^- is noticeably slower [$k = 2.6 \times 10^6$ dm^3 mol^{-1} s^{-1}; Shafirovich et al. 2001] than the above reactions which are close to diffusion controlled. Yet, cellular levels of NO_2^- that are normally $<2 \times 10^{-4}$ mol dm^{-3} may be increased to $>1 \times 10^{-3}$ mol dm^{-3} under certain conditions. The product of this reaction, $^{\bullet}NO_2$, oxidizes 8-oxo-G (see below).

The fate of $G^{\bullet}$ in the absence of any additive is as yet unknown. It decays bimolecularly with a rate constant of some 10^8 dm^3 mol^{-1} s^{-1} (Faraggi et al. 1996), but there is increasing evidence that in competition, at least at elevated pH [$pK_a(G^{\bullet}) = 10.8$], its radical anion also decays unimolecularly [$k = 5 \times 10^3$ s^{-1} at pH 11 in the case of Guo and dGuo; Faraggi and Klapper 1994; Faraggi et al. 1996]. The nature of this unimolecular transformation is as yet unknown.

Unless a water-assisted disproportionation (cf. Wang et al. 1996) or a disproportionation by ET takes place, $G^{\bullet}$ has to dimerize. These dimers have escaped identification, but the various canonical mesomeric forms shown below indicate

that there can be quite a number of potential dimers. A potential product of the disproportionation is 8-oxo-G. Its yield in •OH-induced reactions is that low that this process must be of minor importance (see below).



G• does not react with O_2 on the pulse radiolysis time scale due to its high spin density at heteroatoms (von Sonntag 1994). This is further supported by the observation that even at the low dose rates of γ-radiolysis there is very little O_2-uptake [$G(-O_2) = 0.7 \times 10^{-7}$ mol J^{-1}] when G• is generated by Tl(II) in N_2O/O_2-saturated solutions (Al-Sheikhly 1994). From these data, the rate contant of G• with O_2 must be $\leq 10^2$ dm^3 mol^{-1} s^{-1}.

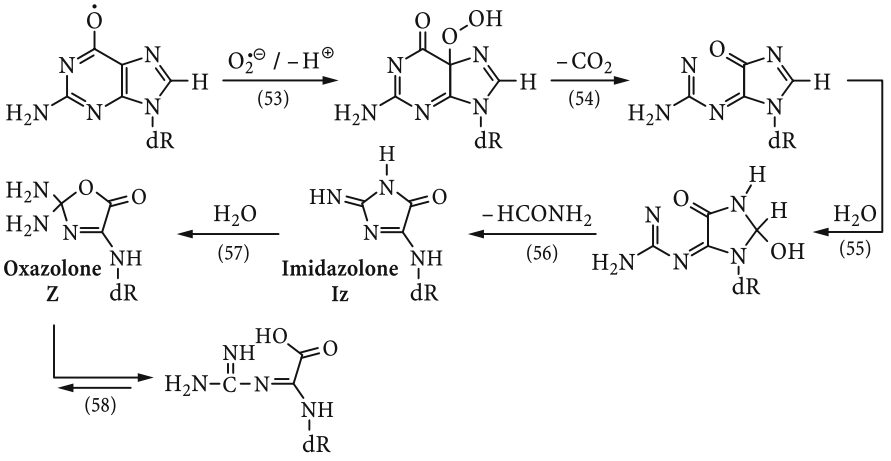
An important dGuo oxidation product is imidazolone (Iz), which decomposes into oxazolone (Z) and/or its ring-open guanodino acid form (Ravanat et al. 1991; Raoul et al. 1996; Gasparutto et al. 1999; for kinetic data see Table 10.5). At high pH, these compounds release guanidine for which an assay is available (Kobayashi et al. 1987) (Chap 13.3).

The proposed (Buchko et al. 1993; Cadet et al. 1994; Raoul et al. 1996) mechanism of the guanidine-releasing products formed in the •OH-induced (30% of •OH yield in the γ-radiolysis of air-saturated dGuo solutions; Douki and Cadet 1996), benzophenone- and riboflavin-sensitized oxidation of dGuo and also in the case of the oxidation of DNA by *tert*-butoxyl radicals (Adam et al. 1998) requires the reaction of $G^{\bullet+}/G^{\bullet}$ with O_2. This is in poor agreement with the data mentioned above. In fact, the formation of guanidine releasing products is due to a reaction of G• and $O_2^{\bullet-}$ [reactions (53)-(58); Misiaszek et al. 2004; in competition with ET that reformes G; see also Chap. 12.3]. On the nucleoside level, reaction (53) is very fast [$k = 4.4 \times 10^9$ dm^3 mol^{-1} s^{-1}; von Sonntag 1994], while it is an order of magnitude slower in ss- and dsODNs (Misiaszek et al. 2004). This drop may be due to an electrostatic repulsion of $O_2^{\bullet-}$ in the case of the negatively charged ODNs.

Table 10.5. Half-lives of Iz, the Z and 8-oxo-G at various conditions of temperature and pH (Raoul et al. 1996)

pH	Temp / °C	Iz	Z	8-oxo-G
7	20	24 h	Stable	Stable
	37	147 min	Stable	Stable
10	65	5.0 (11.2)[a] min	21.8 min	Stable
13	20	68.6 min	20.2 (58.5)[a] min	n.d.
	37	26.7 min	5.1 (23.8)[a] min	n.d.
	65	3.1 min	3.3 min	38.6 min

n.d., Not determined.
[a] Second component



Not all photooxidation pathways can be attributed to radical cations as the only intermediate. For example, in the benzophenone-sensitized reaction, some and β→α and α→β isomerization (in the case of α-dGuo) is observed (Vialas et al. 1999). while no such isomerization occurs upon the Mn-TMPyP-mediated oxidation by $KHSO_5$ (Vialas et al. 1999). Here, Iz is the only detected product [90% yield; Vialas et al. 1998] which points to different intermediates in these two systems. Ascorbate or cysteine, may intercept G•, and in their presence the oxazolone yield is strongly reduced (Douki et al. 1999).

The redox potential of A• is higher by 0.27 V than that of G• (Table 10.2), and thus reductants capable of reducing G• also reduce A• (Jiang et al. 1999a). In ODNs, it also undergoes ET from a neighboring G (Bamatraf et al. 2000).

Table 10.6. Compilation of rate constants for the reactions of $^{\bullet}OH$, $H^{\bullet}$ and e_{aq}^{-} with the nucleobases and related compounds. (Buxton et al. 1988)

Substrate	$^{\bullet}OH$	$H^{\bullet}$	e_{aq}^{-}
Ade	6.1×10^9	1.0×10^8	9.0×10^9
dAdo	4.6×10^9	–	8.2×10^9
Ado	5.8×10^9	2.0×10^8	1.1×10^{10}
AMP	4.1×10^9	1.9×10^8	3.8×10^9
Cyt	6.3×10^9	9.2×10^7	1.3×10^{10}
dCyd	6.0×10^9	–	–
Cyd	5.8×10^9	–	1.3×10^{10}
Gua	–	–	1.4×10^{10}
Gua anion	9.2×10^9	–	2.0×10^9
dGuo	4.1×10^{9a}	–	1.7×10^{10}
dGMP	4.7×10^9	–	6.0×10^9
Guo	7.8×10^9	5.0×10^8	6.0×10^9
Thy	6.4×10^9	6.8×10^8	1.8×10^{10}
Thd	4.7×10^9	3.2×10^8	–
Ura	5.7×10^9	4.7×10^8	1.5×10^{10}
Urd	5.2×10^9	–	1.4×10^{10}

[a] Steenken (1989)

10.3 Reactions Induced by $^{\bullet}OH/O^{\bullet-}$ and $^{\bullet}H$

10.3.1 Rate Constants

The nucleobases and related compounds react with $^{\bullet}OH$ at close to diffusion-controlled rates. A compilation of rate constants is given in Table 10.6. In nucleosides and nucleotides, $^{\bullet}OH$ attacks mainly at the base moiety, but some H-abstraction also occurs at the sugar moiety (Chap. 3.3). It is recalled that the high reactivity of $^{\bullet}OH$ results in a very low $^{\bullet}OH$ steady-state concentration, and reactions with substrates, even when present at rather low concentrations, predominate over the their reactions with $^{\bullet}OH$-induced substrate radicals. Thus,

Table 10.7. Reactions of $^{\bullet}OH$ with some pyrimidines. Yields of addition at *C*(5) and *C*(6). H-abstraction where applicable. (Fujita and Steenken 1981; Al-Sheikhly and von Sonntag 1983; Hazra and Steenken 1983)

Pyrimidine	Addition at C(5)	Addition at (C6)	H-Abstraction
Ura	82	18	–
Thy	60	30	10
6MeUra	88	12	Little
Isoorotic acid	63	37	–
Orotic acid	86	14	–
$1,3Me_2Ura$	78	17	Little
poly(U)	70	23	7
Cyt	87	10	–
1MeCyt	87	8	–
2MeCyt	92	10	–
5MeCyt	65	22	13
5CarboxyCyt	82	24	–

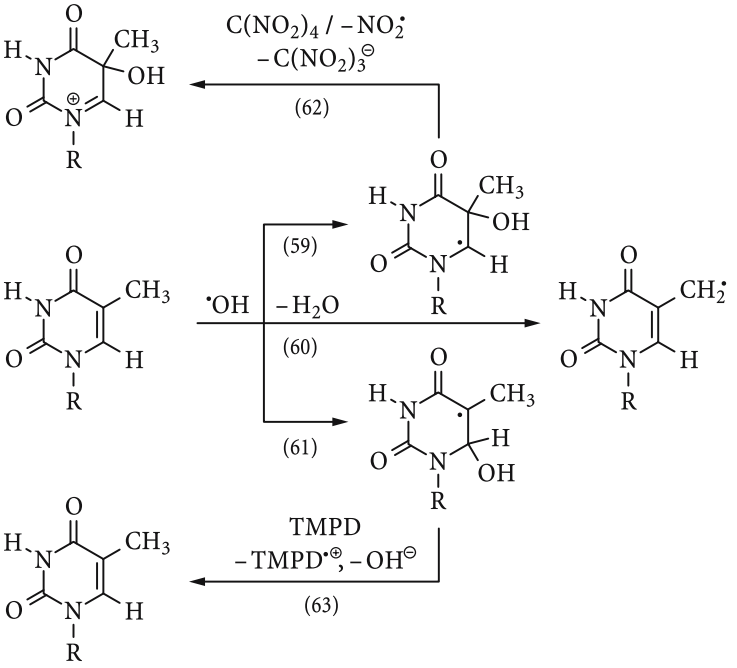
mechanisms involving consecutive additions of two $^{\bullet}OH$ that still continue to be considered in the literature [e.g., Jaussaud et al. 2000] have to be rejected.

The basic form of $^{\bullet}OH$, $O^{\bullet-}$ [$pK_a(^{\bullet}OH) = 11.8$], reacts much more slowly with the nucleobases (Ioele et al. 1998) that are all deprotonated at the pH where $O^{\bullet-}$ predominates (Table 10.11). It will be shown below that $^{\bullet}OH$ and $O^{\bullet-}$ differ substantially in their reactions.

10.3.2 Determination of the Site of $^{\bullet}OH$-Attack

Pyrimidines. When $^{\bullet}OH$ reacts with the pyrimidines, it adds to the *C*(5)–*C*(6) double bond, and in the case of Thy it also abstracts to a minor extent an H-atom from the methyl group [reactions (59)–(61)]. A radical at *C*(6) is formed upon addition at *C*(5) [reaction (59); for EPR studies see, e.g., Hildenbrand et al. 1989; Schulte-Frohlinde and Hildenbrand 1989; Catterall et al. 1992; for DFT calculations, see Wetmore et al. 1998b]. This radical has reducing properties due to the interaction with the electron pair at the neighboring nitrogen, and in a pulse radiolysis experiment its yield can be determined by its rapid reaction with TNM which yields the strongly absorbing nitroform anion [reaction (62); $\varepsilon(350nm) = 15{,}000\ dm^3\ mol^{-1}\ cm^{-1}$].

On the other hand, the *C*(6)-•OH-adduct formed in reaction (61) has oxidizing properties (note its mesomeric form with the radical at oxygen; quantum-mechanical calculations indicate that it is the most oxidizing radical among all conceivable •OH- and •H-adducts of the nucleobases; Colson and Sevilla 1995). The yield of this oxidizing radical can be determined with the help of a strong reductant such as TMPD [reaction (63); the TMPD radical cation is monitored; ε(565 nm) = 12,500 $dm^3\ mol^{-1}\ cm^{-1}$].



The allylic radical formed upon H-abstraction from the methyl group [reaction (60)] has neither reducing nor oxidizing properties, and its yield may be deducted from the difference of the sum of reducing and oxidizing radicals with respect to the total •OH yield. A series of such experiments has been carried out (Fujita and Steenken 1981; Al-Sheikhly and von Sonntag 1983; Hazra and Steenken 1983), and their results are compiled in Table 10.7.

The yield of 1,4-benzosemiquinone anions in the presence of 1,4-benzosemiquinone (Hayon and Simic 1973; Simic and Hayon 1973; Bamatraf et al. 1998) has been taken as a measure for the yield of reducing radicals formed upon •OH attack. The values reported for Cyt (83% by Bamatraf et al. 1998, 75% by Simic and Hayon 1973) and Thy (63% by Bamatraf et al. 1998, 35% by Simic and Hayon 1973, 41% by Hayon and Simic 1973) do not agree well with one another and only approximately with the data in Table 10.7. The values for dCyd (75%) and Thd (47%) (Bamatraf et al. 1998) are surprisingly low in comparison, especially since nearly all sugar derived radicals should also react with 1,4-benzoquinone by reduction. However, in this context it is recalled that an addition which is the more

Table 10.8. π-Electron densities of the HOMO in some pyrimidines at the relevant carbons as calculated by the DFT B3LYP/6-31G(d)//SCRF=PCM method in water (Naumov and von Sonntag, unpublished results). Values of the percentage of •OH-attack (in parentheses) are taken from Table 10.7

Nucleobase	C(5)	C(6)
Thy	0.204 (60%)	0.082 (30%)
Ura	0.222 (82%)	0.063 (18%)
6MeUra	0.236 (88%)	0.062 (12%)
Cyt	0.205 (87%)	0.045 (10%)

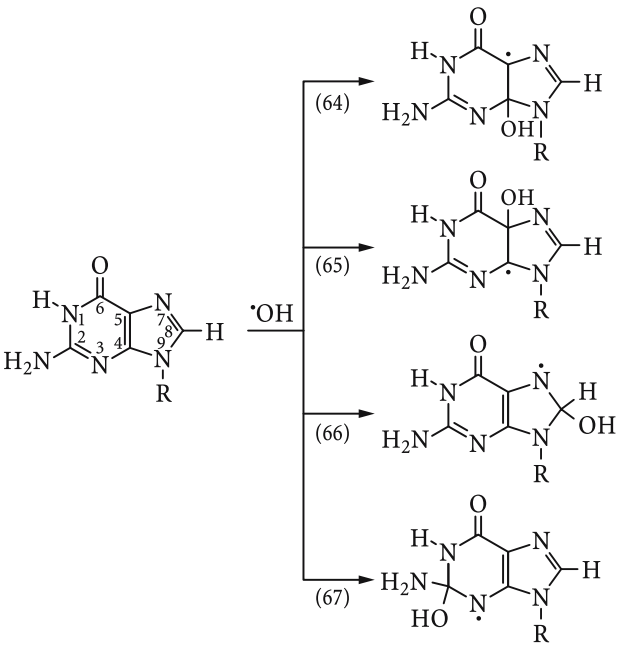
general reaction of radicals with 1,4-benzoquinone (Veltwisch and Asmus 1982; Schuchmann et al. 1998), is also given, at least to some extent, by other reducing radicals such as •CH_2OH (Simic and Hayon 1973; von Sonntag et al. 2004).

The rate of the oxidation of the reducing *C*(5)-•OH-adduct by Cu(II) varies between 10^6 dm^3 mol^{-1} s^{-1} and 10^8 dm^3 mol^{-1} s^{-1} depending on the complexing agent (Chabita et al. 1996; Fujita et al. 1996).

The strongly electrophilic •OH is very regioselective when adding to polarized C–C double bonds. The reaction is goverened by kinetics rather than thermodynamics. For the H-abstraction reaction (60), ΔG_{aq} = -112.2 kJ mol^{-1} has been calculated, while for the addition reactions (59) and (61) -42.6 kJ mol^{-1} and -85.5 kJ mol^{-1}, respectively, were obtained (Wu et al. 2004). As is seen from Table 10.7, the preference for •OH-attack does not correlate with the exothermicity of the reaction. In Table 10.8, calculated electron densities are given. In the pyrimidine series, they reflect well the experimental data obtained by redox titration (Table 10.7). In the purine series (see below), the situation seems to be more complex. The π-electron density does not sufficiently reflect the preferred site of attack, and more elaborate calculations that take the Mulliken charge into consideration as well are required (Naumov and von Sonntag, unpubl. results).

Purines. In general, •OH readily adds to double bonds but undergoes ET reactions only very reluctantly (Chap. 3.2). This also applies to purines despite their relatively low reduction potentials (Table 10.2). Thus, G• which is formed in the reaction of •OH with dGuo has a short-lived •OH-adduct rather than $G^{\bullet+}$ as precursor (Candeias and Steenken 2000), and the H-abstraction that could also lead to G• (for theoretical calculations see Mundy et al. 2002) does not occur to any significant extent.

The reactions of •OH with dGuo are shown in reactions (64)–(67).

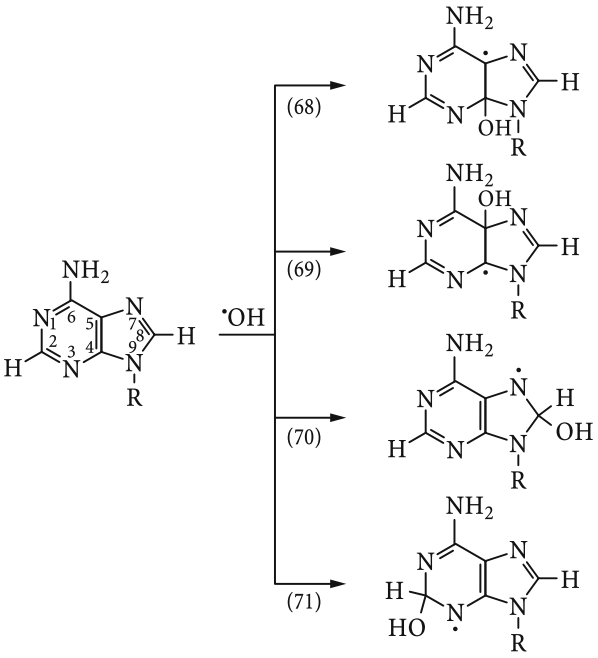


Of these radicals, 60–70% have oxidizing properties (for the reactions of purine-•OH-adducts with a number of reductants see, e.g., O'Neill 1983, 1984; O'Neill et al. 1985; Shi et al. 1999a; Candeias and Steenken 2000). This includes the •OH-adducts that eliminate rapidly water yielding G• (Steenken 1989). Its main precursor has been has been suggested to be the *C*(4)-•OH-adduct (~60-70%; Vieira et al. 1993; Candeias and Steenken 2000). This radical eliminates water leading to the even more strongly oxidizing G• [cf. reaction (77)].

The *C*(8)-•OH-adduct has reducing properties, and from its rapid reaction with $Fe(CN)_6^{3-}$ or methylviologen its yield has been determined at 17% (Candeias and Steenken 2000). It is the precursor of FAPY-dGuo and 8-oxo-dGuo whose combined yields have been determined after radiolysis in N_2O-saturated solutions at ~10% (Berger and Cadet 1985; lower limit for the *C*(8)-•OH-adduct). The maximum yield of 8-oxo-dGuo in the presence of $Fe(CN)_6^{3-}$ as oxidant and in the acid pH range has been found to be 23% (von Sonntag and Schuchmann 2001). This must be taken as an upper limit, since under these conditions reaction (51) may contribute to the formation of the *C*(8)-•OH-adduct.

The *C*(2)-•OH-adduct is likely to eliminate ammonia, and from the low ammonia yield it seems not to exceed 1.5% (von Sonntag and Schuchmann 2001). With dGuo, some H-abstraction occurs also at the sugar moiety. Among others, this is indicated by an isomerization of dGuo (in low yields, see Table 10.13). Nearly all sugar-derived radicals must have reducing properties, and, based on the pulse radiolysis data mentioned above, the upper limit of their yield must be much less than the total of 17%.

The reactions of •OH with dAdo/Ado are depicted in reactions (68)–(71).

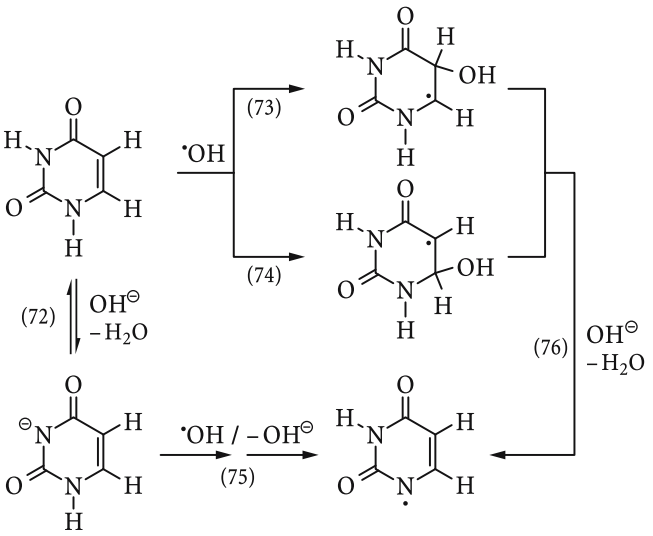


With Ado, only 32% of the radicals have oxidizing properties (O'Neill et al. 1985). It has been suggested that 37% add to the *C*(8) position [reaction (70)] and 50% to the *C*(4) position [reaction (68)] and <5% to *C*(5) [reaction (69)] with some H-abstraction at the sugar moiety (Vieira and Steenken 1990; Vieira et al. 1993).

The yield of 8-oxo-Ade from Ade has been reported to be the same in the absence of O_2 or in air-saturated solution, but is increased in the presence of small amounts of $Fe(CN)_6^{3-}$ (saturation level already at 4×10^{-6} mol dm^{-3}; Dias and Vieira 1997a,b), putting a question mark behind the suggestion (Vieira and Steenken 1991; Dias and Vieira 1997a) that in the presence of O_2 this product is formed by the elimination of $O_2^{\bullet -}$ from the *C*(8)-·OH-adduct peroxyl radical.

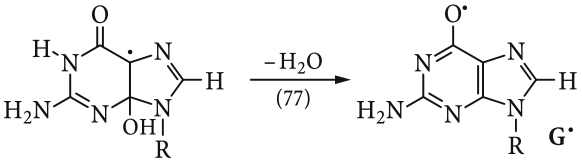
10.3.3 Water Elimination and Rearrangements

In basic solution, Ura and Thy undergo a series of reactions as depicted in reactions (72)–(76) for Ura as an example (Fujita and Steenken 1981). Ura dissociates at high pH [equilibrium (72); for pK_a values see Table 10.11]. Its ·OH-adducts can also be deprotonated at nitrogen leading to an oxidizing heteroatom-centered radical [reaction (76)].



Cyt has no pK_a in the basic pH range below 12 (Table 10.1). A number of transformations at pH <11 were observed by pulse radiolysis (Hissung and von Sonntag 1978). In Cyt and 5MeCyt, there is an OH^--induced reaction ($k = 1.4 \times 10^8$ dm^3 mol^{-1} s^{-1}) that is not observed with dCyd, indicating that the *N*(1)-H must be involved in this reaction, but the rate of reaction is somewhat too slow for a deprotonation at a heteroatom. EPR and product data that could shed some light on these reactions are missing. It is, hence, premature to suggest mechanistic details.

The *C*(4)-•OH-adduct of dGuo has oxidizing properties (note the mesomeric form with spin density at *O*(6)). It eliminates water yielding the even more strongly oxidizing G• [reaction (77); $k = 6 \times 10^3$ s^{-1} in the absence of buffer; Candeias and Steenken 2000].



A similar reaction has been suggested for the of dAdo that gives rise to A• [reaction (78); $k = 1.9 \times 10^4$ s^{-1}]. Again, the *C*(4)-•OH-adduct is less oxidizing than A• and reacts with TMPD with 2.3×10^7 dm^3 mol^{-1} s^{-1}, while A• reacts with 2×10^9 dm^3 mol^{-1} s^{-1} (Vieira and Steenken 1990).

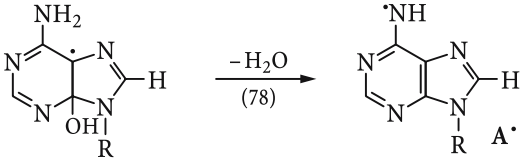


Table 10.9. γ-Radiolysis of N_2O-saturated aqueous solutions of Ura. Products and their *G* values (unit: 10^{-7} mol J^{-1}) at different pH values. (Idris Ali and Scholes 1980)

Product	pH 2	pH 4	pH 6	pH 8
Dimers	1.35	3.3	4.38	1.65
5,6-Dihydro-5,6-dihydroxyuracil (Ug; *cis* and *trans*)	0.68	0.32	0.30	0.18
5,6-Dihydro-5(and 6)-hydroxyuracil	0.31	0.44	0.29	0.18
Isobarbituric acid	0.29	0.12	0.52	0.16
Ura consumption	2.68	4.25	5.51	2.11

10.3.4 Products in the Absence of Oxygen

Pyrimidines. Detailed studies concerning the products that are formed upon $^{\bullet}OH$-attack (radiolysis of N_2O-saturated solutions) are available for Ura, Thy, Cyt and 1,3Me_2Ura (Tables 10.9-10.12).

In addition, the radiolysis of Ura in deoxygenated solutions (in the absence of N_2O) has also found attention (Infante et al. 1974; Shragge et al. 1974). Under such conditions, however, not only the $^{\bullet}OH$-induced reactions play a role, but also the electron-adduct radical with all the ensuing mechanistic complications contributes to the products.

The *N*(1)-H of the nucleobases can take part in disproportionation reactions leading to the formation of isopyrimidines (for their reactions see below). This crucial hydrogen is not available in nucleosides which are a much closer model for DNA. No detailed studies are available for pyrimidine nucleosides so far. A compound which has no hydrogen at *N*(1) is 1,3Me_2Ura. It still shows the major aspects of the base moiety of Ura- and Thy-containing nucleosides but is much more easy to handle analytically than nucleosides. Thus, results from a study on the γ-radiolysis of 1,3Me_2Ura in N_2O-saturated solutions (Table 10.12) may be a good guide for the reactions that one might have to envisage in the nucleosides and also in DNA. As has been discussed before, $^{\bullet}OH$ adds mainly at *C*(5) (~78%) and to a lesser extent at *C*(6) (~17%). Some H-abstraction at the methyls occurs as well. The major reaction of the dominating *C*(6)-yl radical is its recombination [reaction (79)].

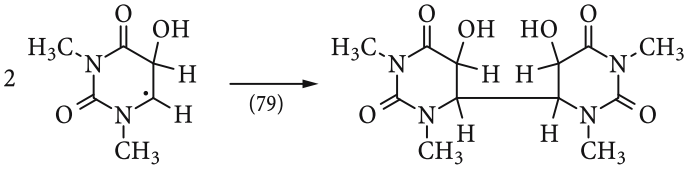


Table 10.10. γ-Radiolysis of N_2O-saturated aqueous solutions of Thy. Products and their *G* values (unit: 10^{-7} mol J^{-1}). *A* Infante et al. (1973), *B* Nishimoto et al. (1983a)

Product	A	B
5,6-Dihydro-5,6-dihydroxythymine (Tg; *cis* and *trans*)	2.4	0.35
5-Hydroxy-5,6-dihydrothymine	–	0.09
6-Hydroxy-5,6-dihydrothymine	0.15	0.1
5,6-Dihydrothymine	0.1	0.2
5-Hydroxymethyluacil	0.25	0.3
5-Hydroxy-5-methylbarbituric acid	0.11	–
5-Methylbarbituric acid	–	0.06
Formylpyruvylurea	0.12	–
Dimers	0.27	n.d.
Unknown	0.11	–
Thy consumption	4.05	2.8

n.d., Not determined

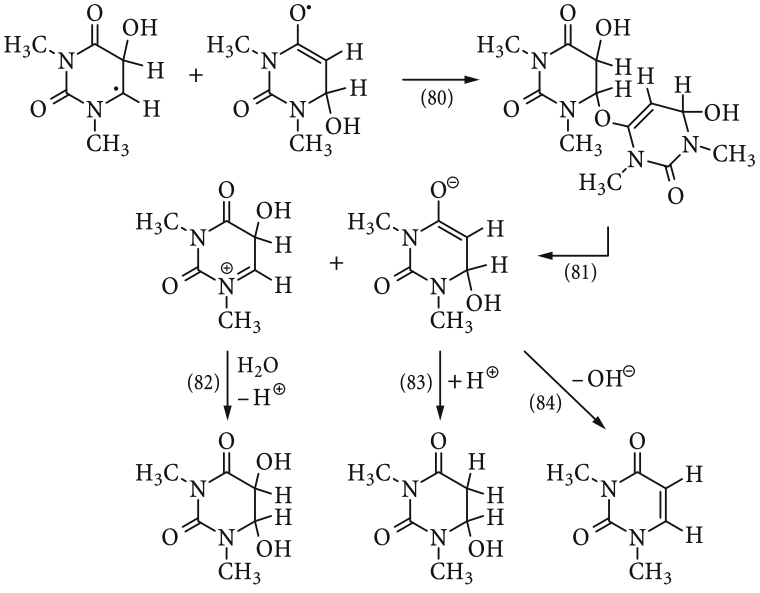
Table 10.11. γ-Radiolysis of N_2O-saturated aqueous solutions of Cyt. Products and their *G* values. (Dizdaroglu and Simic 1984b)

Product	G/10^{-7} mol J^{-1}
Dimers	3.3
5-Hydroxycytosine	1.5
5,6-Dihydroxycytosine	0.2
5,6-Dihydro-5,6-dihydroxyuracil (Ug)	0.15
6-Hydroxycytosine	0.08
5,6-Dihydro-5,6-dihydroxycytosine (Cg)	0.05
Ura	0.02
Cyt consumption	5.8

Table 10.12. γ-Radiolysis of N_2O-saturated aqueous solutions of 1,3Me_2Ura. Products and their *G* values (unit: 10^{-7} mol J^{-1}; Al-Sheikhly and von Sonntag 1983)

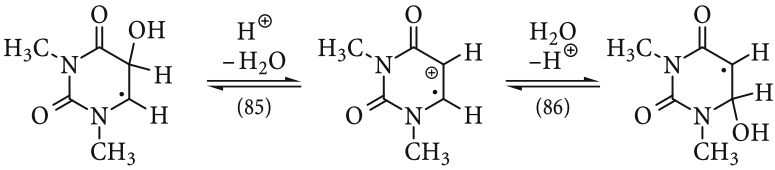
Product	pH 3	pH 6.5	pH 10.4
5,6-Dihydro-5-hydroxy-1,3-dimethyluracil	0.4	0.8	0.6
5,6-Dihydro-6-hydroxy-1,3-dimethyluracil	<0.1	0.2	<0.1
1,3-Dimethylisobarbituric acid	0.15	0.1	≤0.1
5,6-Dihydro-5,6-dihydroxy-1,3-dimethyluracil	1.6	0.9	0.85
Dimers (of 6-yl radicals, in monomer units)	1.8	3.5	3.3
Dimers (involving H-adduct radicals)	<0.1	0.2	<0.1
1,3Me_2Ura consumption	4.0	5.9	5.3

In competition, the C(6)-yl and C(5)-yl radicals may disproportionate, possibly via an adduct [reactions (80) and (81)]. This yields the hydrate via an enol [reaction (83)]. The other product is the glycol [reaction (82)]. In the original paper (Al-Sheikhly and von Sonntag 1983), it has been proposed that it may be formed in an ET reaction. Due the considerable rearrangement energies involved in ET reactions as compared to radical recombination reactions, it is now considered that this ET reaction might occur via an addition/elimination process [reactions (80) and (81)] such as has also been found for other systems.



In this context, it should be mentioned that the glycols derived from Thd (Tg) are now also very well characterized (Jolibois et al. 1996).

As can be seen from Table 10.12, there are practically no changes in the product yields when neutral and basic solutions are compared. However, the yield of the dimers is drastically reduced in acid solutions, while that of the glycol is enhanced. Altogether, the *G* value of consumption is also reduced which points to an increase of the importance of disproportionation reactions. This has been explained by an acid-catalyzed transformation of the reducing *C*(6)-yl radical into the oxidizing *C*(5)-yl radical [reactions (85) and (86); Al-Sheikhly and von Sonntag 1983].

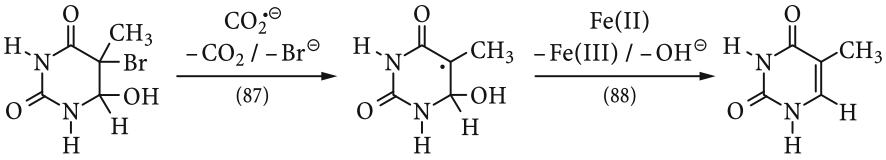


This interpretation indicates that the oxidizing radical is thermodynamically favored over the reducing radical. This is confirmed by quantum mechanical calculations (Naumov and von Sonntag, unpubl. results; Wu et al. 2004), and when low-temperature sulfuric acid glasses containing Ura or Thy are X-irradiated, the dominant radical seen by EPR is the 5-yl radical (Riederer and Hüttermann 1982).

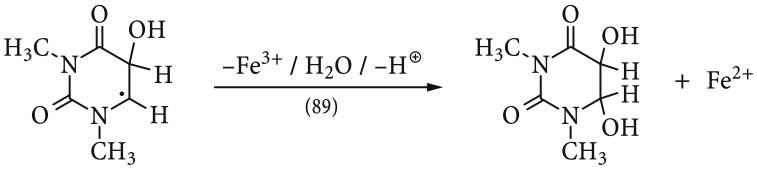
With d(TpA), a number of products were separated by HPLC, and two of them (the dinucleoside with a Tg lesion (four stereoisomers) and one with a 6-hydroxy-5,6-dihydrothymine lesion (two isomers)) were characterized by NMR (Belfi and Box 1985). Further identified products were Thy, Ade and dAMP. With d(GpC) and d(CpG) γ-irradiated in N_2O-saturated solutions, the corresponding Ug (deamination products of the Cg) and the 5- and 6-hydroxy dCyd substitution products were detected (Paul et al. 1987b). In addition, dinuclosides with intact dCyd and a 8-oxo-G moiety were observed. With d(TpA) and d(ApT), Tg, the free bases and the monophosphates were detected (Paul et al. 1987a).

The *C*(5)-•OH-adduct radicals of pyrimidines can be reduced by thiols (Barvian and Greenberg 1992) or by cylohexa-1,4-diene (Barvian et al. 1996). The rate of reduction by thiols seems to be slow. Otherwise, the formation of thioethers (the recombination product of a cysteamine-derived thiyl radical with a TMP-derived •OH-adduct; $G = 1.55 \times 10^{-7}$ mol J^{-1}) in the radiolysis of N_2O-saturated solution of TMP in the presence of 5% cysteamine (Grachev et al. 1983, 1986) are difficult to explain.

The UV spectrum of the (oxidizing) *C*(6)-•OH-adduct of Thy has been obtained (Deeble and von Sonntag 1985) and its reactions were studied (Nishimoto et al. 1983c) by generating it specifically via the reaction of 5-bromo-6-hydroxythymine with $CO_2^{\bullet-}$ [reaction (87)]. In the presence of transition metal ions in their low oxidation states and with the more reducing ones such as Fe(II), Pt(II) or Cu(I), Thy in high yields [reaction (88)] and only traces of 6-hydroxy-5,6-dihydrothymine were observed. This indicated that a potential enolate must eliminate an OH^- rather than protonates at *C*(5) (ketonization).



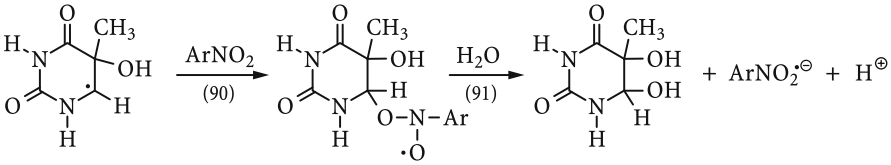
When •OH is generated by the Fenton reaction, i.e. in the presence of H_2O_2 and Fe^{2+}/Fe^{3+}, the transition metal ions (and possibly H_2O_2; in fact, photolysis of H_2O_2 in the presence of Ura and Thy is a very convenient way of preparing their glycols in good preparative yields; Hahn and Wang 1977) undergo redox reactions with the radicals that are formed by •OH-attack. In the case of 1,3Me_2Ura, the otherwise dominating product, the dimers (Table 10.12), are no longer formed. Instead, the 1,3Me_2Ura glycol is now practically the only product (Theruvathu et al. 2001). It is formed in a short chain reaction; 2.7 mol 1,3Me_2Ura are consumed and glycol formed for 1 mol of Fe^{2+} consumed. The major radical, the reducing *C*(5)-•OH-adduct is oxidized by Fe^{3+} [reaction (89)] thereby regenerating Fe^{2+} which give rise to further •OH upon its reaction with H_2O_2 (Chap. 2.5).



The glycol is also the most important product when Ura is γ-irradiated in aqueous solution in the presence of Fe^{3+} (Bhattacharyya and Mandal 1983).

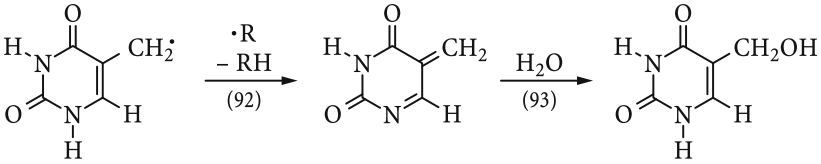
In •OH-induced reactions of Thy, Tg and 5-hydroxymethyluracil yields are markedly enhanced in the presence of nitroxyl radicals such as TEMPO (Kagiya et al. 1983). Adducts may be the intermediates. In the case of the nitroxyl radical TAN and for the Thd system, such adducts have been characterized (Berger et al. 1985).

The Tg yield is also substantially enhanced in the presence of electron-affinic sensitizers, and in the radiolysis of N_2O-saturated solutions its yield has been reported to increase from $G = 0.32 \times 10^{-7}$ mol J^{-1} in the absence to $G = 1.6 \times 10^{-7}$ mol J^{-1} in the presence of misonidazole (Nishimoto et al. 1983a). It has been emphasized that electron-afficinic sensitizers do not necessarily undergo an outer-sphere ET, but may react by addition (Wardman 1987). This type of reaction has been investigated in detail using nitroaromatics as oxidants (Jagannadham and Steenken 1984, 1988a,b; Steenken and Jagannadham 1985). When the adducts hydrolyze (possibly in competition with other reactions, since the Tg yield depends on the oxidant; Nishimoto et al. 1983a), the products are identical to the ones expected to be formed by ET [reactions (90) and (91)].



When an *N*(1)-H is avalable as in free-base systems, deprotonation at *N*(1) speeds up the hydrolysis (Steenken and Jagannadham 1985). For example, the corresponding *p*-nitroacetophenone Ura adduct decays with $2.4 \times 10^5\ s^{-1}$ when deprotonated at *N*(1). The *N*(1)-alkylated pyrimidines also hydrolyze, but slower (e.g., $k = 4.5 \times 10^3\ s^{-1}$ in the case of uridylic acid) when deprotonated at *N*(3). In neutral solution, the rate of hydrolysis must be considerably slower, possibly that slow that other reactions may compete.

It has been mentioned above that •OH abstracts from Thy also to a minor extent a hydrogen at methyl. Indeed, 5-hydroxymethyluracil has been detected to be formed in about 5% yield (Nishimoto et al. 1983a). It is suggested here that the introduction of the OH group may have occurred via an isopyrimidine-type intermediate as depicted in reactions (92) and (93).



It is interesting that in the presence of misonidazole the 5-hydroxymethyluracil yield is reduced to one quarter (Nishimoto et al. 1983a). Addition of misonidazole to the allylic radical which has no marked reductive power (note that this radical is also not oxidized by the more reactive oxidant TNM, see above) must thus give products other than 5-hydroxymethyluracil.

In the case of Cyt, the expected glycols, Cg, have only been detected in low amounts; instead, major amounts of 5OHCyt and the deamination product, Ug, were reported (Table 10.11, see also Table 10.16). The dCyd glycols are now, however, well characterized (Tremblay et al. 1999). They readily undergo water elimination ($t_{1/2}$ = 50 min at 37 °C). This may have been the reason, why in earlier studies only low yields of these products were detected. It may be mentioned here, that in DNA the lifetime of the Cg lesion is much longer ($t_{1/2}$ = 20 h), and thus this product stands a good chance to be involved in the repair processes.

In the reaction of Cyt (Mandal and Yamamoto 1985) and dCyd (Yamamoto and Mandal 1988) with •OH fluorescent products are formed; their chemical structures are as yet unknown.

Purines. Product studies on the reactions of •OH with the purines are not at the same level as those of the pyrimidine series. Only the products that can be traced back to an •OH-attack at *C*(8) and involve the sugar moiety were detected with the presently available analytical techniques. Yet, •OH attack at *C*(8) is only around 17% in Guo/dGuo and ~30% in Ado/dAdo (see above). Attack at the

Table 10.13. γ-Radiolysis of dGuo (5×10^{-3} mol dm^{-3}) in deaerated and N_2O-saturated solutions. Products and their *G* values (unit: 10^{-7} mol J^{-1}; Berger and Cadet 1985)

Product	N_2	N_2O
N^6-(2′-Deoxy-α-D-*erythro*-pentopyranosyl)-2,6-diamino-5-formamidopyrimid-4-one (α-FAPY-G)	0.27	0.26
N^6-(2′-Deoxy-β-D-*erythro*-pentopyranosyl)-2,6-diamino-5-formamidopyrimid-4-one (β-FAPY-G)	0.09	0.1
5′-8-Cyclo-2′,5′-dideoxyguanosine	0.05	0.06
8-oxo-G	–	0.25
Gua	0.2	0.4
9-(2′-Deoxy-α-D-*erythro*-pentopyranosyl)guanine	0.02	0.03
9-(2′-Deoxy-β-D-*erythro*-pentopyranosyl)guanine	0.01	0.02
9-(2′-Deoxy-α-D-*erythro*-pentofuranosyl)guanine	0.02	0.02
9-(2′-Deoxy-α-L-*threo*-pentofuranosyl)guanine	0.02	0.02
9-(2′-Deoxy-β-D-*erythro*-pento-1,5-dialdo-1,4-pyranosyl)-guanine	0.07	0.08
2-Deoxyribonolactone, 2-dRL	[a]	[a]
dGuo consumption	0.83	1.6

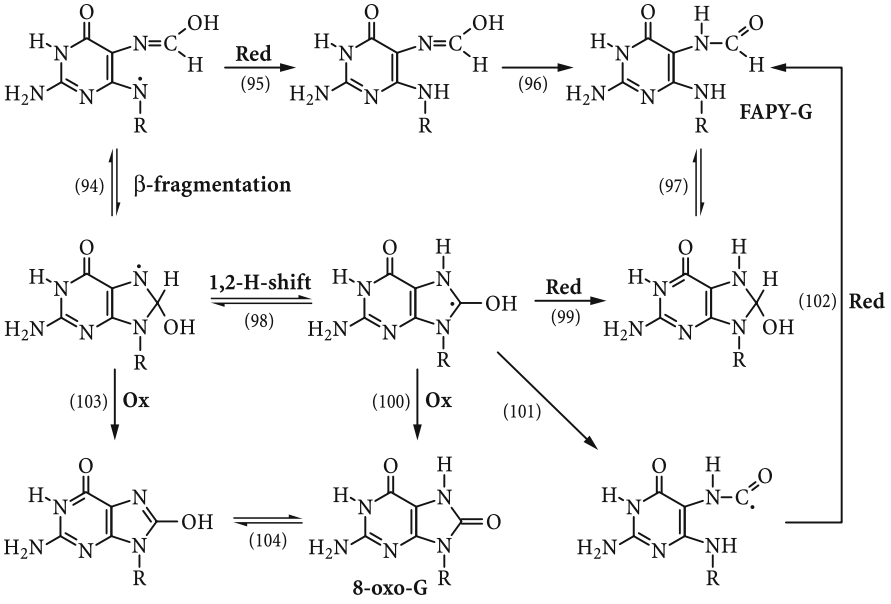
[a] Observed, but not quantified

Table 10.14. γ-Radiolysis of Ade (2×10^{-3} mol dm^{-3}) in N_2O-saturated solutions. Products and their *G* values (unit: 10^{-7} mol J^{-1}; van Hemmen and Bleichrodt 1971; see also van Hemmen 1971)

Product	*G* value
4,6-Diamino-5-formamidopyrimidine (FAPY-A)	0.2
8-Hydroxyadenine (8-oxo-A)	0.35
6-Amino-8-hydroxy-7,8-dihydropurine	0.1
Ade consumption	1.0

sugar moiety will also not exceed 10-15%. Product yields of the reaction of •OH with dGuo and Ade are compiled in Tables 10.13 and 10.14. It is re-emphasized that the material balance with respect to •OH formed under the given conditions is very poor.

Based on a pulse-radiolytic study, it has been concluded that 17% of •OH add to the *C*(8)-position of dGuo (see above). The ensuing reactions are complex and seem to involve a number of equilibria, β-fragmentation and 1,2-H-shift reactions as depicted in reactions (94)–(104).



Final products then arise from subsequent reduction/oxidation (H-transfer) reactions. The *C*(8)-•OH-adduct undergoes rapid ring-opening [reaction (94), $k = 2 \times 10^5\ s^{-1}$]. The *C*(8)-•OH-adduct and its ring-opened successor radical are reducing radicals and readily react with $Fe(CN)_6^{3-}$ or methylviologen. The oxidation product of the ring-opened radical has not yet been identified, but the oxidation product of the *C*(8)-•OH-adduct is a well-known product, 8-oxo-G. With 9MeGua, the formation of 8-oxo-9MeGua increases to about 20% in the presence of $Fe(CN)_6^{3-}$ [reactions (103) and (104); Candeias and Steenken 2000]. Interestingly, the $Fe(CN)_6^{3-}$ concentration required to oxidize fully the precursor radical is much lower than suggested by the rate constant assigned to the ring-opening process, and it has hence been assumed that reaction (94) must be reversible. The yield of 8-oxo-G depends also on the pH. In the presence of $Fe(CN)_6^{3-}$, the maximum yield of $G = 1.3 \times 10^{-7}$ mol J^{-1} is reached at an $Fe(CN)_6^{3-}$ concentration of 5×10^{-4} mol dm^{-3} in acid solution (von Sonntag and Schuchmann 2001; see also Vieira et al. 1993). This *G* value corresponds to the yield of the *C*(8)-•OH-adduct, i.e. there seem to be no side reactions that compete with this oxidation.

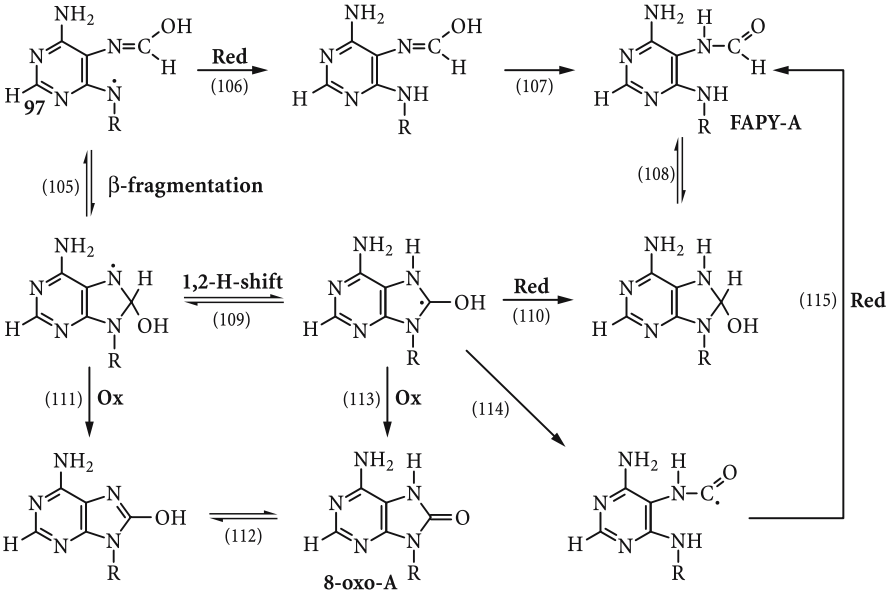
The ring-opened radical may also be reduced in, for example, disproportionation reactions to yield FAPY-G [reactions (95) and (96)]. A 1,2-H-shift [reac-

tion (98)], typical for heteroatom-centered radicals, may also contribute to the formation of 8-oxo-G [reaction (100)] and FAPY-G [reactions (99) and (97)]. In Table 10.13, the formation of two isomers is reported. With dAdo, considerable isomerization and even the hydrolysis of FAPY-A is observed (see below). Equilibrium (97) would not account for the isomerization of β-FAPY-G into α-FAPY-G. Thus it is likely that this isomerization occurred during work-up.

In this context it is worth mentioning that there is evidence (Candeias and Steenken 2000) that neither $G^{\bullet+}$ nor $G^{\bullet}$ react with water at an appreciable rate ($k = < 0.1\ s^{-1}$) forming the *C*(8)-•OH-adduct, that is, the precursor of 8-oxo-G. This seems to be in contradiction to a later suggestion by this group that at least the reaction of $G^{\bullet+}$ with water is highly exothermic (306 kJ mol^{-1}; Reynisson and Steenken 2002) and may undergo this reaction, [reaction (57)] quite readily unless kinetically disfavored.

8-oxo-G is typically synthesized according to Kasai and Nishimura (1984) by an Udenfriend-type reaction (Chap. 2.5), but in this synthesis a steady-state concentration of only about 6% (with respect to remaining dGuo) is reached (Wager, Schuchmann and von Sonntag, unpubl.). Mere competition for •OH would result in a much higher yield. 8-oxo-G is much more readily oxidized than dGuo itself (see above), and in the sequence of events there must be an oxidant other than •OH which is responsible for this low yield. Despite a more recent study of this reaction (Hofer 2001), mechanistic details remain unresolved.

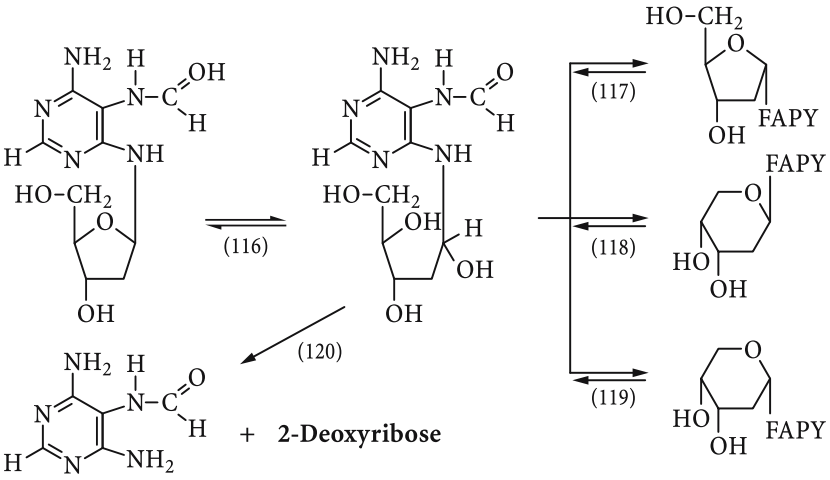
The *C*(8)-•OH-adduct of Ade and its derivatives shows the same reaction pattern [reactions (105)–(115)] as discussed above for Gua and its derivatives.



There are only minor differences. Its yield is higher (~30-37%). With N^6,N^6Me$_2$dAdo, the ring opening reaction (105) occurs at a rate of $9.5 \times 10^4\ s^{-1}$, and its rate is enhanced by OH^- (Vieira and Steenken 1987a,b). The yield of

FAPY-A has been found at 2% of •OH and that of 8-oxo-A at 5% (Vieira and Steenken 1990; Vieira et al. 1993). In the presence of $Fe(CN)_6^{3-}$, the 8-oxo-A yield is raised to 18% and that of FAPY-A is now < 0.2%. It is not yet understood why the balance (based on ~30% *C*(8)-•OH-adduct) is that poor.

FAPY-A is not stable in aqueous solution. It rapidly isomerizes and eventually is fully hydrolyzed [reactions (116)–(122); Raoul et al. 1995].



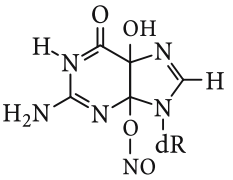
With FAPY-A derived from dAMP, where the pyranose forms cannot play a role, an anomeric ratio of $\beta/\alpha = 1.33$ develops after 6 h, while the deglycosylation half-life is 103 h at 37 °C (Greenberg et al. 2001). The deglycosylation of FAPY-G derived from dGMP is even slower.

The reactions of •OH-induced radicals of purine deoxyribonucleosides with nitroxyl radicals (for rate constants, see Brustad et al. 1972) have been studied with, for example, TAN, and it has been observed that the FAPY-products are no longer formed to a significant extent, and in the case of dAdo the formation of 8-oxo-A is enhanced (Berger and Cadet 1983b). This further supports the oxidizing properties of the nitroxyl radicals, although the formation of an adduct as an intermediate is very likely, considering that in the case of pyrimidine-derived radicals stable adducts have been observed (Cadet et al. 1979).

The attack of •OH at the *C*(2) position of dAdo is of little importance (see above), and it is thus not surprising that 2-hydroxy-dAdo is only a minor product (Frelon et al. 2002).

Fluorescent material is formed in the reaction of •OH with Ade, and it as been suggested that dimers may contribute to the as yet not fully characterized material (Yamamoto et al. 1985).

In the reaction of peroxynitrite with dGuo 4,5-dihydro-5-hydroxy-4-(nitrosooxy)-2′-deoxyguanosine has been reported to be formed (Douki et al. 1996) besides 8-oxo-G and Z (Douki and Cadet 1996) as well as 8-nitroguanine (Douki et al. 1996; Burney et al. 1999).



4,5-Dihydro-5-hydroxy-4-(nitrosooxy)-2'-deoxyguanosine

While 8-oxo-A is formed in the peroxynitite reaction with dAdo (Douki and Cadet 1996), 8-oxo-G (from dGuo) is not detected (Douki and Cadet 1996; Uppu et al. 1996) due to its much faster reaction with this reagent (Uppu et al. 1996).

Unless a non-radical mechanism accounts for the formation of 4,5-dihydro-5-hydroxy-4-(nitrosooxy)-2′-deoxyguanosine, $^{\bullet}NO_2$ must add to the 2′-deoxyguanosine $^{\bullet}OH$-adduct via its *O*-centered mesomeric form in contrast to the nitration of tyrosine, where $^{\bullet}NO_2$ reacts as an *N*-centered radical (van der Vliet et al. 1994; Lymar et al. 1999).

10.3.5 Products in the Presence of Oxygen

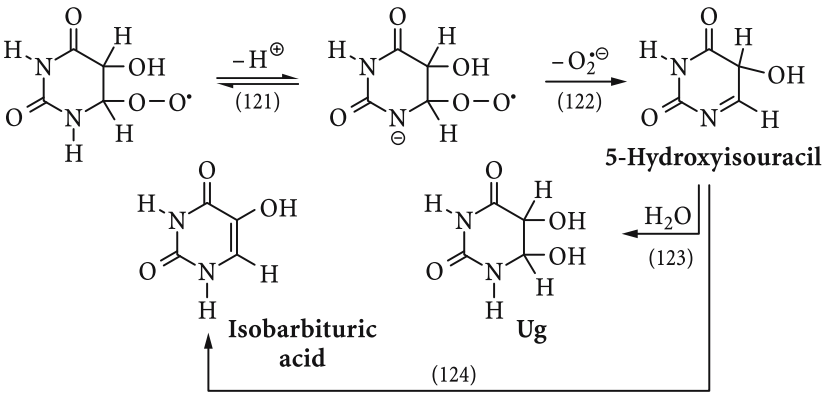
In the presence of O_2, most radicals are converted into the corresponding peroxyl radicals with the notable exception of heteroatom-centered radicals which do not react with O_2 at an appreciable rate (Chap. 8.2). However, even though peroxyl radical reactions may dominate in the reactions induced by the autoxidation of Fe(II)EDTA or Fe(II)NTA (Chap. 2.5), in the case of 2′-deoxynucleosides the subsequent reactions seem to be considerably modified by the presence of the transition metal ion, i.e. product ratios are found in these reactions which are different from those observed by ionizing radiation in the absence of Fe(II)/Fe(III) (Murata-Kamiya et al. 1998). A basis for understanding these differences may be the various redox reactions that the peroxyl radicals will undergo with Fe(II)/Fe(III) (cf. Yurkova et al. 1999; Theruvathu et al. 2001; see also Chaps 2.5 and 8.3).

Pyrimidines. The pyrimidine-$^{\bullet}OH$-adducts react with O_2 at close to diffusion-controlled rates yielding the corresponding peroxyl radicals ($k \approx 2 \times 10^9$ dm^3 mol^{-1} s^{-1}; Willson 1970). In basic solutions, but also in neutral solutions as long as the (dominating) *C*(6)-peroxyl radical has a sufficiently long lifetime, it undergoes $O_2^{\bullet-}$-elimination after deprotonation at *N*(1) [reactions (121) and (122)] (Schuchmann and von Sonntag 1983). Details of this kind of $O_2^{\bullet-}$-elimination, including the determination of the pK_a value of the peroxyl radical, has been studied for a very similar system, glycine anhydride (Mieden et al. 1993). In reaction (122) an isopyrimidine (5-hydroxyisouracil) is formed. This product is only short-lived and undergoes a rearrangement into isobarbituric acid [reaction (124)] and hydration yielding Ug [reaction (123)]. Such reactions which will be discussed in more detail below.

Table 10.15. γ-Radiolysis of N_2O/O_2-saturated solutions of Ura (2×10^{-4} mol dm^{-3}). Products and their *G* values (unit: 10^{-7} mol J^{-1}; Schuchmann and von Sonntag 1983)

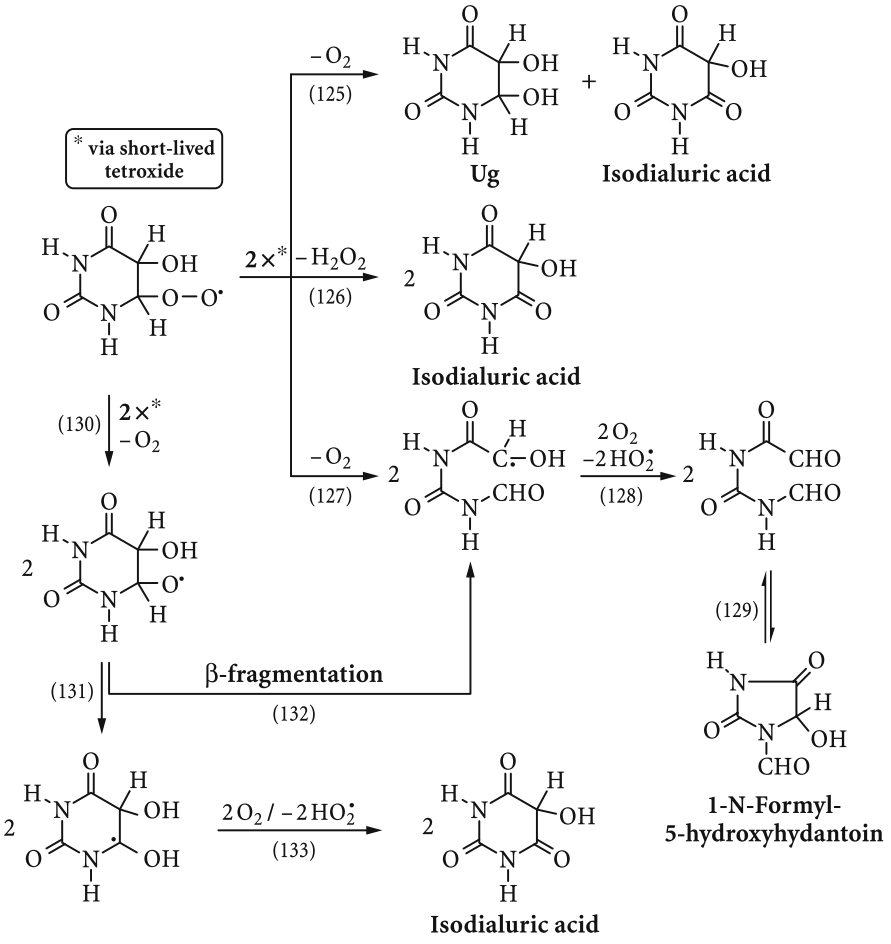
Product	pH 3.0	pH 6.5	pH 10.0
5,6-*cis*-Dihydroxy-5,6-dihydrouracil (Ug)	0.6	0.9_5	1.4_5
5,6-*trans*-Dihydroxy-5,6-dihydrouracil (Ug)	0.5	1.1	1.0
Isobarbituric acid	0	0.2	1.2_5
1-*N*-Formyl-5-hydroxyhydantoin	1.6_5	1.4_5	0.2
Dialuric acid	0.9_5	0.4	0.2
Isodialuric acid	0.1	0.2	0.1
5-Hydroxyhydantoin	0.4	0.4	0.3
Unidentified products	0.9_5	0.6	0.9_5
Hydrogen peroxide	n.d.	3.0	n.d.
O_2 consumption	n.d.	5.0	n.d.
Ura consumption	5.1	5.5	5.4

n.d., Not determined



In acid solutions, but also in neutral solutions at a high steady-state radical concentration, $O_2^{\bullet -}$-elimination becomes too slow to be of importance as compared to the bimolecular decay of the peroxyl radicals. This leads to a very different product distribution (Table 10.15).

Typical decay pathways, with tetroxides as short-lived intermediates (Chapter 8.8), lead to Ug, dialuric acid and O_2 [reaction (125)], as well as to two mol dialuric acid and H_2O_2 [reaction (126)].



Elimination of O_2 with concomitant fragmentation yields 1-*N*-formyl-5-hydroxyhydantoin [reactions (127-129]. The peroxyl radicals also give rise to oxyl radicals upon their bimolecular decay [reaction (130)], an alternative route to 1-*N*-formyl-5-hydroxyhydantoin [reactions (132), (128) and (129)]. In competition, these oxyl radicals may also undergo a 1,2-H-shift [reaction (131)], and after addition of oxygen eliminate $HO_2^{\bullet}/O_2^{\bullet -}$ [reaction (133)]. Thus also under such conditions, $O_2^{\bullet -}$ are likely intermediates. They are expected to react with other peroxyl radicals present to yield the corresponding hydroperoxides. Such hydroperoxides are abundant intermediates in the radiolysis of air-saturated pyrimidine solutions (Cadet and Teoule 1975; Wagner et al. 1987, 1990a).

A detailed kinetic study is still missing for Cyt and its derivatives, but for dCyd product data are available (Wagner et al. 1999). They are compiled in Table 10.16 together with the products observed upon menadione photosensitization.

Table 10.16. Product yields (%) in the γ-radiolysis and menadione-sensitized oxidation of aerated aqueous solutions of dCyd (Wagner et al. 1999)

Product	γ-Radiolysis	Photosensitization
5,6-Dihydroxy-5,6-dihydro-2′-deoxyuridine (Ug)	28	27
5-Hydoxy-2′-deoxycytidine	12	7
N_1-(dR)-Hydroxyhydantoine	3	2
N_1-(dR)-Formamide (Fo)	12	2
N_1-(dR)-1-Carbamoyl-3,4-dihydroxy-2-oxoimidazolidine	17	6
Aminocarbonyl[2-dR)-amino]-2-oxomethylcarbamic acid	3	2
N_1-(dR)-Biuret	3	2
5′,6-Cyclo-5-hydroxy-5,6-dihydro-2′-deoxyuridine	2	Not detected
dUrd	Not detected	36
Cyt	12	4
2-Deoxyribono-1,4-lactone, 2-dRL	Traces	4

In the γ-radiolysis, similar reactions are expected to occur as discussed above for the Ura system. Here, however, about equal amounts of $^{\bullet}OH$ and $O_2^{\bullet -}$ are formed initially and thus the latter will play an even larger role on the way to the products, and thus it is even more difficult to come up with a well-substantiated reaction scheme. An interesting product is 5′,6-cyclo-5-hydroxy-5,6-dihydro-2′-deoxyuridine. Its formation is discussed below in the context of the reactions of alkyl radicals.

Photooxidation and γ-radiolysis agree in their products reasonably well as long as the base is damaged. The reason for this may be that in the photooxidation a dCyd radical cation / menadione radical anion pair is the first intermediate. The reaction of the dCyd radical cation with water could give rise to $^{\bullet}OH$-adducts (as in radiolysis). The most important product, however, is dUrd, that is, deaminated dCyd (Table 10.16) which is not, and cannot be, formed upon radiolysis. The mechanism of its formation is not discussed in the original paper, but it is not unlikely that it results from an unstable intermediate (adduct?) formed in the reaction of the dCyd radical cation / menadione radical anion pair in the solvent cage.

With d(GpC) and d(CpG) γ-irradiated in N_2O/O_2-saturated solutions, the corresponding Ug and 1-carbamoyl-2-oxo-4,5-dihyroxyimidazolidine deriva-

tives were detected (Paul et al. 1987b). Dinuclosides with intact dCyd and an 8-oxo-G moieties were also observed. With d(TpA) and d(ApT), the Fo derivatives are the prominent products, but products with an aldehyde group at the free 5′-end were also detected (Paul et al. 1987a).

With d(TpA) and d(GpC) the same products as observed to be formed by ionizing radiation were detected upon autoxidation induced by ascorbate plus phosphate buffer (low amounts of transition metal ions are omnipresent; Arakali et al. 1988).

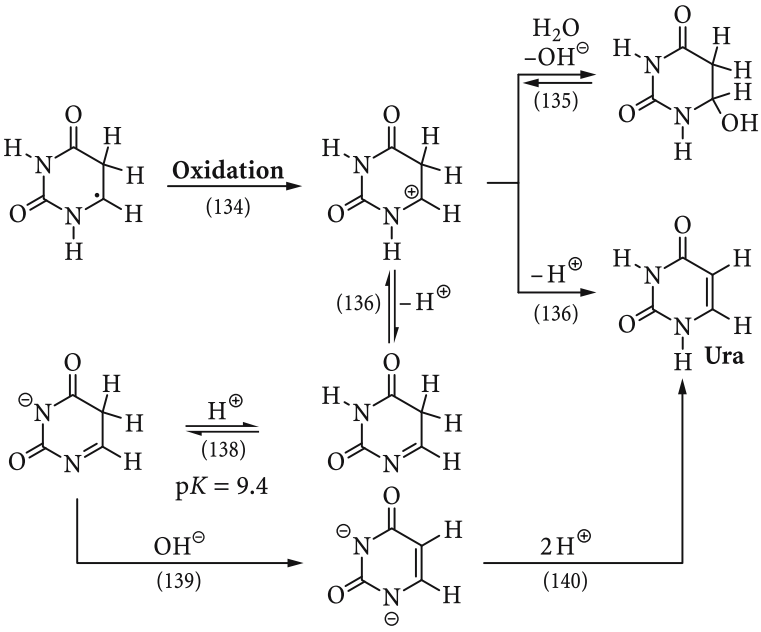
Purines. The reactions of the $^{\bullet}OH$-adduct radicals of the purines in the presence of O_2 are still very poorly understood. The dGuo *C*(8)-$^{\bullet}OH$-adduct is reported to react very fast with O_2 ($k = 4 \times 10^9$ dm^3 mol^{-1} s^{-1}; Candeias and Steenken 2000). There is no agreement as to the yield of 8-oxo-G under such conditions. In one report, its *G* value is given as 0.84×10^{-7} mol J^{-1} (Vieira et al. 1993), but a lower value of 0.3×10^{-7} mol J^{-1} has also been measured (von Sonntag and Schuchmann 2001). An even much lower value has been found in the γ-radiolysis of air-saturated dGuo solutions ($G = 0.0038 \times 10^{-7}$ mol J^{-1}; Svoboda and Harms-Ringdahl 1999). The latter group reports that in DNA *G*(8-oxo-G) is markedly higher (0.077×10^{-7} mol J^{-1}). Thus, considerably more work will be required not only to establish the yield of this crucial product, but also to shed some light on the mechanism of its formation in the presence of O_2. When Gua was oxidized with the Fenton reagent (0.15×10^{-3} mol dm^{-3} Fe^{2+} and 50×10^{-3} mol dm^{-3} H_2O_2) the 8-oxo-G yield "oscillated" over a time range of 20 min with very little 8-oxo-G to start with (White et al. 2003). This cannot be attributed to the Fenton reaction proper, since under these experimental conditions this reaction is completed after a few seconds (Chap. 2.5). Similar findings were reported for DNA. There is no mechanistic explanation yet for these intriguing observations.

10.3.6 Formation and Properties of Isopyrimidines

Isopyrimidines have been postulated (Haysom et al. 1972, 1975; Al-Yamoor et al. 1977; Asmus et al. 1978; Al-Sheikhly et al. 1984; Schuchmann et al. 1984a; Garner and Scholes 1985) or are likely to be involved (Holian and Garrison 1966; Teoule and Cadet 1974; Cadet 1980) as short-lived intermediates formed upon oxidation of pyrimidine-6-yl radicals carrying an H-atom at *N*(1) [reactions (134) and (137)]. Isopyrimidines are also intermediates in the photohydration reaction (Al-Yamoor et al. 1977; Garner and Scholes 1985). In the Ura system, for example, the carbocation (immonium ion) is the first intermediate which either deprotonates at *C*(5) yielding Ura [reaction (136)] or reacts with water giving rise to the hydrate [reaction (135)]. The latter reaction is reversible in acid solution. Mechanistically, reaction (–137) accounts for the well-known water elimination of the photohydrate (for its stabilty in near-to-neutral solutions see Carter and Greenberg 2001; the other isomer with the OH group at *C*(5) is not acid labile, and these two hydrates may be distinguished based on their different behavior in acid solution).

Table 10.17. Rate constants of isopyrimidine → pyrimidine rearrangements at 20 °C. (Schuchmann et al. 1984a)

Isopyrimidine	Neutral spont. s^{-1}	Neutral H^+-catal. dm^3 mol^{-1} s^{-1}	Neutral OH^--catal. dm^3 mol^{-1} s^{-1}	Anion spont. s^{-1}	Anion OH^--catal. dm^3 mol^{-1} s^{-1}
Isouracil	3000	1.8×10^7	Absent	50	4.9×10^5
3-Methyl-isouracil	2500	1.1×10^7	2.7×10^7	Absent	Absent
5-Hydroxy-isouracil	2000	2.6×10^7	Absent	< 50	$\times 10^5$



Deprotonation of the carbocation at *N*(1) [reaction (137)] is kinetically favored over the deprotonation at *C*(5) [reaction (136)]. Thus, isouracil is an important intermediate in these reactions. It is sufficiently long-lived to follow its reactions by pulse radiolysis. Isouracil is in equilibrium with its anion [equilibrium (138)]. This allows reactions (139) and (140) to proceed as well. However, when *N*(3) is substituted such as in 3MeUra, this additional pathway is no longer possible. For a compilation of rate constants see Table 10.17.

Table 10.18. Sites of H•-attack (in %) in Ura and some of its derivatives. (Das et al. 1985)

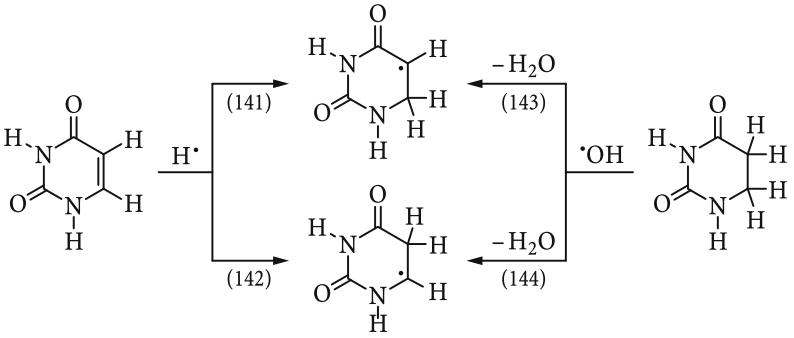
Substrate	*C*(5)	*C*(6)	Methyl group and sugar moiety
6MeUra	87	13	nil[a]
1,3Me$_2$Ura	71	29	nil[a]
Ura	69	31	–
poly(U)	60	40	nil[a]
Thy	37	59.5	3.5
Thd	32	62.5	5.5
1,3Me$_2$Thy	25	73	2.0

[a] Within experimental error

10.3.7 Reactions of the Hydrogen Atom

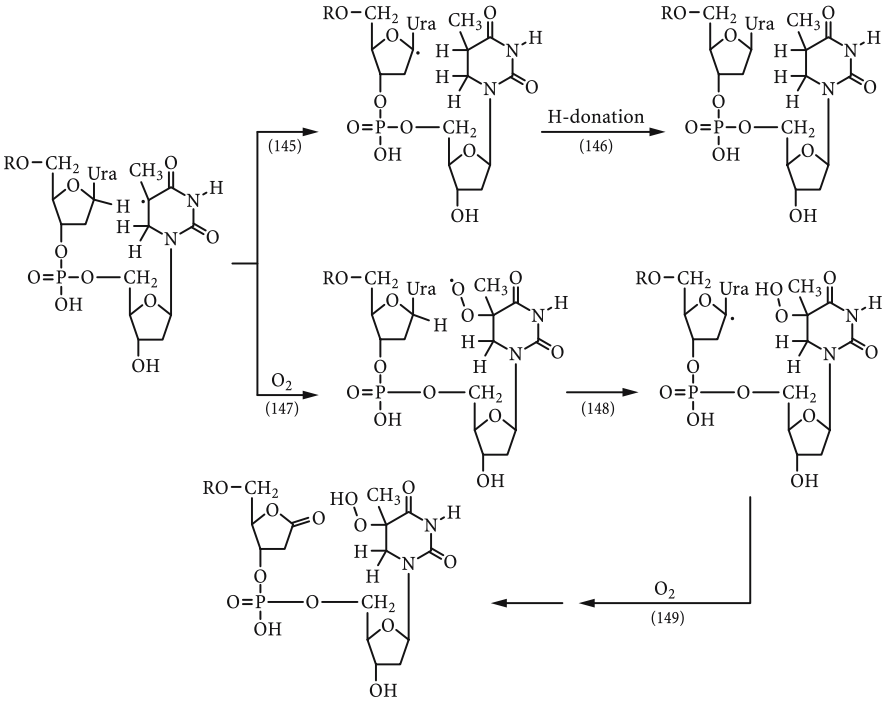
Similar to •OH, H• is an electrophilic radical (Chap. 4.4), and in its additions to C–C double bonds it has a strong preference for electron-rich sites (Das et al. 1985; Table 10.18). Thus, the *C*(5)-position is the preferred site of addition in the pyrimidine series as depicted here for Ura [reaction (141)].

The *C*(6)-yl radical is also formed upon the reaction of •OH with dihydropyrimidines [reaction (144); Schuchmann et al. 1984b], as can be seen from the data compiled in Table 10.19. For a quantum-mechanical study of their structure and EPR coupling constants see Jolibois et al. (1998).



Due to the much lower rate of H-abstraction by H• as compared to •OH, H-abstraction is generally of much lower if any importance (Table 10.18).

The 5,6-dihydrothymid-5-yl radical has been produced independently by photolyzing an adequately substituted derivative (Barvian and Greenberg 1995). This radical has a rather low H-abstracting power, and very good H-donors such as 1,4-dihydrocycloexadiene are required to afford substantial yields of H_2Thd beyond simple disproportionation. The latter has been shown to proceed both by H-transfer to *C*(5) as well as to *O*(4). In the case of the dinucleotide dUrdpThd, the 5,6-dihydrothymid-5-yl abstracts the *C*(1′)-H of the neighboring dUrd unit [reaction (145); Tallman and Greenberg 2001]. The rate constant for this intramolecular H-transfer has been estimated to range between 115 and 400 s^{-1}. In the presence of O_2, an interesting selective intramolecular *C*(1′)-H abstraction by the 5*S*-diastereoisomer of the *C*(5) peroxyl radicals takes place. This leads to a damage amplification (tandem lesion) with a 2′dRL and a 5OOH6HThy lesion [reactions (147)-(149)].

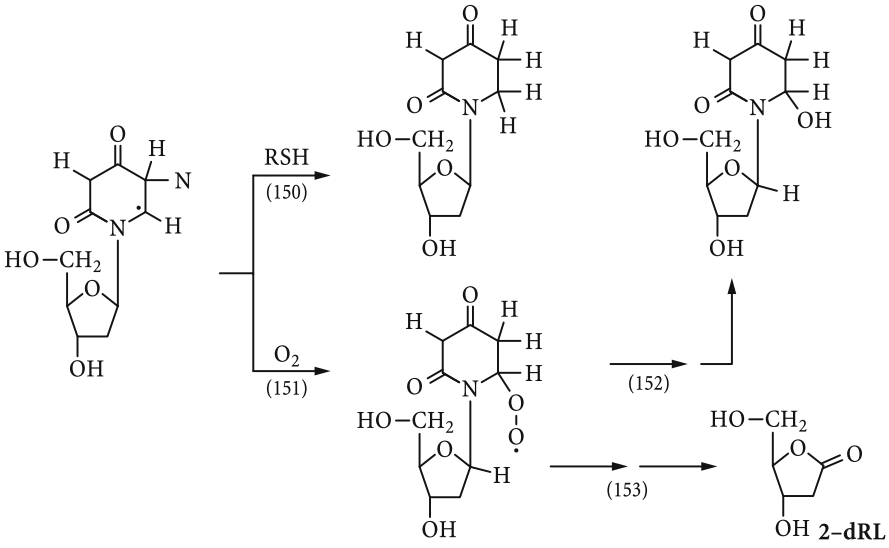


The 5,6-dihydro-2′-deoxyuridin-6-yl was generated specifically by photolyzing the respective tertiary butyl ketone (Carter and Greenberg 2003). It reacts fast with 2-mercaptoethanol [reaction (150); $k = 8.8 \times 10^6$ dm^3 mol^{-1} s^{-1}] and noticeably slower with 2,5-dimethyltetrahydrofurane (31 dm^3 mol^{-1} s^{-1}). In the presence of O_2, 6-hydroxy-5,6-dihydro-dUrd is the major product [reactions (151) and (152)]. Interestingly, 2-dRL is also formed under such conditions which is believed to be formed by an intramolecular *C*(1′)-H abstraction via a six-membered transition state [reaction (153); for this type of reaction see also Chap. 8.6].

Table 10.19. Pattern of $^{\bullet}OH$-radical attack (in %) on H_2Ura and some of its methyl derivatives. The $^{\bullet}OH$-balance is sometimes significantly below 100%, partly due to the inefficiency of the method for the detection of oxidizing *C*(5)-yl radicals. (Schuchmann et al. 1984b)

Substrate	*C*(5)	*C*(6)	Methyl	Total
H_2Ura	5	90	–	95
$1MeH_2Ura$	≈ 2	61	29	92
$3MeH_2Ura$	≈ 2	72	10	84
$1,3Me_2H_2Ura$	≈ 2	≈ 62	30[a]	94
H_2Thy	4	74	6	84
$6MeH_2Ura$	≈ 2	84	6	92

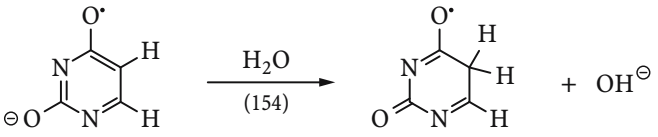
[a] ≈ 22% at *N*(1)CH_3 and 8% at *N*(3)CH_3



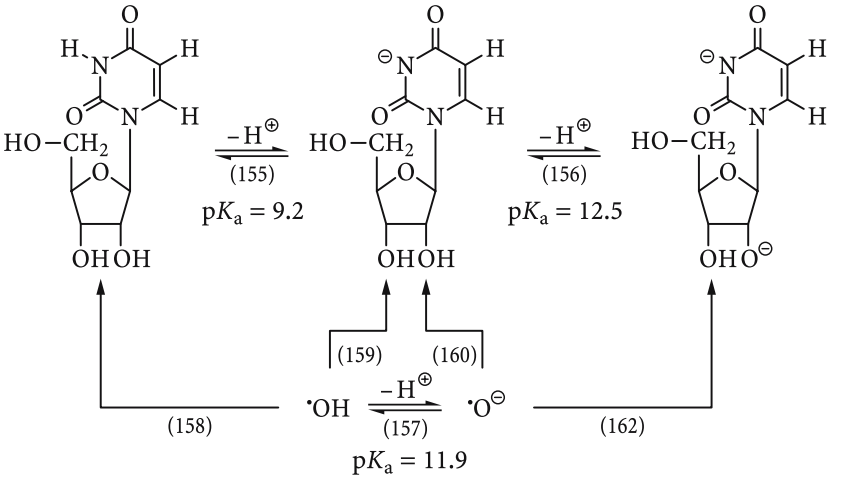
In DNA, the *C*(1′)-H is hidden in the minor groove and hence difficult to access by reactive free radicals such as $^{\bullet}OH$ (Chap. 12.2). If the above type of reaction would occur within DNA, it would lead to a tandem lesion (for their biological importance see Chap. 12.5).

10.3.8 Reactions of $O^{\bullet-}$

At very high pH, $^{\bullet}OH$ deprotonates ($pK_a(^{\bullet}OH) = 11.9$), and the reactions that are observed are due to that of $O^{\bullet-}$. The reactions of $O^{\bullet-}$ are typically one order of magnitude lower than those of $^{\bullet}OH$. In some of the studies reported below, experiments have been carried out at pH 13. This pH is not high enough to exclude major contributions of $^{\bullet}OH$. This has to be taken into account when consulting these papers. In contrast to $^{\bullet}OH$, $O^{\bullet-}$ only very reluctantly adds to C-C double bonds, but it is a good H-abstractor and has also a considerable oxidation power (Chap. 3.1). At pH 13, all nucleobases are deprotonated, and their reduction potentials are quite low (ranging between 0.63 V (Gua) and 0.88 (Ura); Jovanovic and Simic 1986). For Ura, Cyt, Ade and Gua, it has been suggested that the reaction of $O^{\bullet-}$ with their anion and dianions occurs by ET, a reaction that is also given by $Br_2^{\bullet-}$ under these conditions (Ioele et al. 1998). In the case of Cyt, an H-abstraction from the amino group has also been considered as an alternative. With Thy, 1MeUra and 1MeCyt H-abstraction at methyl dominates (Ioele et al. 1998), and this is also reported for other methyl-substituted pyrimidines (Luke et al. 2003). The one-electron oxidized nucleobase (di)anions of Ura, Thy (formed via $Br_2^{\bullet-}$) and Ade decay unimolecularly with rate constants near $10^4\ s^{-1}$. Two alternatives are envisaged, nucleophilic substitution at *C*(6) by OH^- or protonation at carbon by water [reaction (154)]. Since the rate of reaction does not depend on the OH^- concentration, the second alternative may be favored. It is analogous to the also slow protonation at carbon of the radical anion that is discussed in the next paragraph.



In nucleosides, *G*(base release) increases dramatically at high pH (Fujita 1984). This has been suggested to be due to an OH^--induced transformation of a base $^{\bullet}OH$-adduct radical into a sugar-centered radical that releases the base. However, it has been subsequently shown that this effect is due to the involvement of the basic form of $^{\bullet}OH$, the $O^{\bullet-}$ radical [Scholes et al. 1992; reactions (160) and (162)]. The $O^{\bullet-}$ radical undergoes H-abstraction from the sugar moiety rather than addition to the base (for rate constants see Chatgilialoglu et al. 2005). Some of these sugar-derived radicals will release the base (see below). Reactions (155)-(162) show the various pK_a values that are involved in the Urd system given as an example. The deprotonation of ribonucleosides at the 2′-position at high pH has recently been substantiated (Velikyan et al. 2001).



10.4 Radical Anions and their Protonated Forms

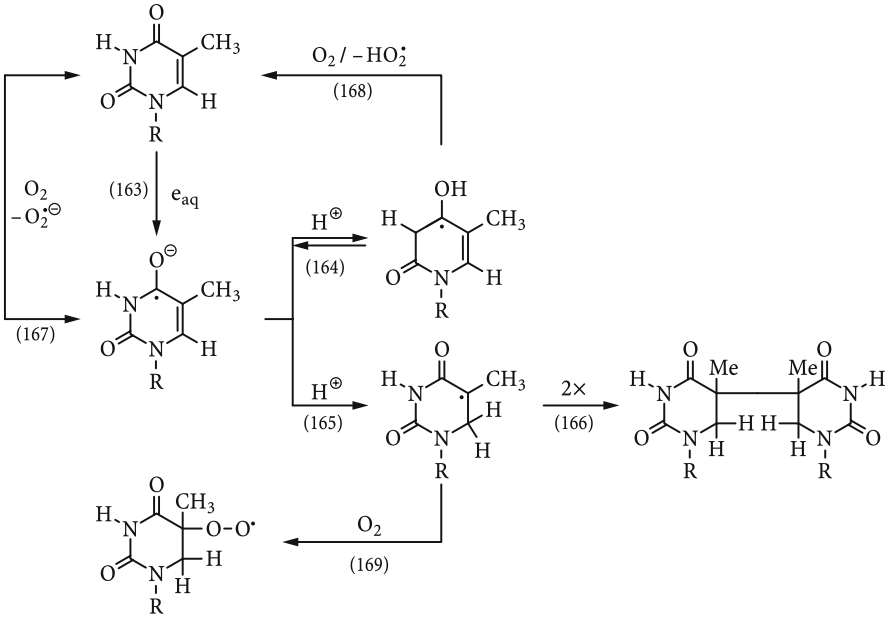
The radical anions may be formed by reacting the nucleobases with e_{aq}^- which may be either generated radiolytically or in a two-step reaction, e.g., in the laser flash photolysis of anthraquinonedisulfonate in the presence of pyrimidines (yielding the pyrimidine radical cation and an anthraquinonedisulfonate radical anion) and subsequent photoionization of the anthraquinonedisulfonate radical anion (Lü et al. 2001). The latter approach, combined with Fourier transform EPR spectroscopy, yielded detailed information as to the conformation of the radical anions of Ura and Thy in aqueous solution (for a discussion see Close 2002; Naumov and Beckert 2002). Similarly valuable EPR information has been obtained from γ-irradiated single crystals (cf. Box and Budzinski 1975; Box et al. 1975; Sagstuen et al. 1998).

Pyrimidines. The pyrimidines react with e_{aq}^- at practically diffusion-controlled rates (Table 10.6). The ensuing reactions of the radical anions of Ura and Thy are very well understood, while with that of Cyt some open questions still remain.

Thy and Ura behave like typical carbonyl compounds, and the first intermediate is a radical anion [reaction (163), in the case of Thy/Thd] which is in equilibrium with its *O*-protonated conjugate acid [equlibrium (164)].

Table 10.20. Rate constants for protonation of the pyrimidine radical anion at *C*(6) by $H_2PO_4^-$ using various approaches of evaluating the data (Deeble et al. 1985)

Pyrimidine	pK_a	$k/10^7$ dm^3 mol^{-1} s^{-1}
1,3Me$_2$Thy	7.2	1.6/0.74 /0.95
Thy	7.2	0.32/0.33
Thd	7.2	0.19/0.21
1MeUra	7.0	0.14/0.25
Ura	7.3	~0.1
Urd	7.2	~0.05/~0.05
6MeUra	7.3	<0.01



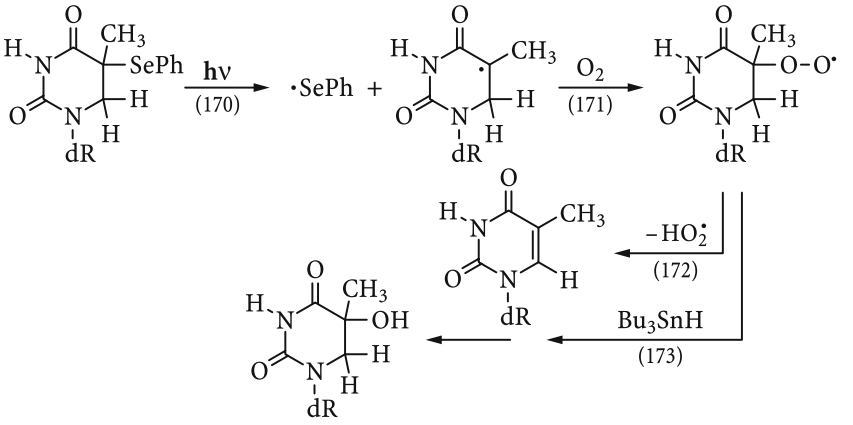
The other functional groups, especially the second carbonyl function, withdraws considerable electron density, and hence the pK_a values of these *O*-protonated radical anions are much lower than those of the simple α-hydroxyalkyl radicals (Thy: pK_a = 6.9 (Hayon 1969); Ura: pK_a = 7.2 (Shragge and Hunt 1974); the value of 4.3 reported for the pK_a for the protonated 5,6Me$_2$Ura radical anion (Aravindakumar et al. 1998) is surprising low and difficult to explain on the basis of the effects of methyl substituents on the pK_a values of α-hydroxyalkyl radi-

cals; Chap. 6.2). In contrast to a protonation at the heteroatom [reaction (164)], protonation at carbon [reaction (165)] is connected with some conformational changes, and thus the conversion into this thermodynamically more stable (for DFT calculations see Naumov and von Sonntag, unpublished results) isomer can only be observed on the pulse radiolysis time scale, when buffer is added to speed up the protonation/deprotonation reactions (Das et al. 1984; Deeble et al. 1985; for rate constants see Table 10.20; for an EPR study see Novais and Steenken 1986).

Together with this transformation, the redox properties of the radicals change dramatically. While the radical anion and its *O*-protonated conjugate acid are good reducing agents has the *C*(6) protonated tautomer oxidizing properties. This is also reflected in their reactions with O_2. The former two give rapidly rise to $HO_2^{\bullet}/O_2^{\bullet-}$ thereby restoring the pyrimidine [reactions (167) and (168); Deeble and von Sonntag 1987]. On the other hand, when O_2 reacts with the *C*(6) protonated tautomer [reaction (169)], the pyrimidine chromophore is destroyed in the subsequent reactions of the ensuing peroxyl radical. In the absence of O_2, the 5,5′-dihydrodimer is formed [reaction (166); Ito et al. 2002].

The radical anion can also be repaired by polyphenols such as rutin or quercitin (Shi et al. 2000b; Zhao et al. 2003). Yet, this repair is not related to their phenolic functions but is rather due to an ET to their carbonyl (flavone) functions.

Photolysis of 5,6-dihydro-5-selenophenyl-dTyd (Tallman et al. 1998) also affords the *C*(6)H$^{\bullet}$-adduct, and in the presence of O_2 the corresponding peroxyl radical [reactions (170) and (171)]. The latter may undergo $HO_2^{\bullet}$-elimination giving rise to Thd [reaction (172)] or, in the presence of tributyltinhydride, yields 5,6-dihydro-5-hydroxy-dTyd [reaction (173)]. The ratio of these two products depends on the tributyltinhydride concentration, and from such data the ratio of the rate constants of reactions (172) and (173) has been calculated at 1.3×10^{-2} mol dm^{-3}.

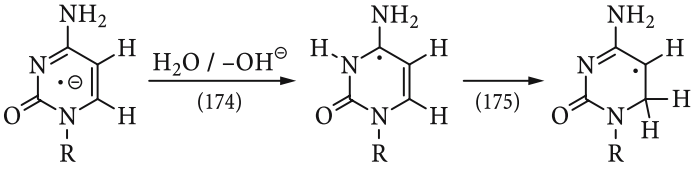


The rate of reaction (173) has been estimated at ~65 s^{-1} assuming a reactivity of tributyltinhydride similar to that of a thiol. For the latter a rate constant was taken from the work of Schulte-Frohlinde et al. (1986) that later had to be revised to a much lower value (Hildenbrand and Schulte-Frohlinde 1997; Lal et al. 1997).

Thus the rate of $HO_2^{\bullet}$-elimination must be considerably slower (nearer to 1 s^{-1}), but still fast enough to play a role in DNA free-radical chemistry. Reaction (172) is reminescent of the $HO_2^{\bullet}$-elimination from β-hydroxycyclohexadienylperoxyl radicals (derived from the reaction of $^{\bullet}OH$ with benzene in the presence of O_2; Chap. 8.4). In this system, the reaction is much faster (k = 800 s^{-1}; Pan et al. 1993b); possibly due to the gain in energy in the course of the re-aromatization].

In this context it is worth considering that in the free-radical chemistry of DNA the *C*(6)-$^{\bullet}$OH-adducts radicals are certainly of a greater importance than the *C*(6)-H-adduct radicals investigated here. If the benzene system is a good guide $HO_2^{\bullet}$-elimination from hydroxycyclohexadienylperoxyl radicals is noticeably slower than that from cyclohexadienylperoxyl radicals (Pan et al. 1993a), i.e., the rate of $HO_2^{\bullet}$-elimination from 5,6-dihydro-6-hydroxy-thymidine-5-peroxyl radicals may even be slower.

The Cyt electron adduct is rapidly protonated by water [reaction (174); $t_{1/2}$ < 200 ns, Hissung and von Sonntag 1979; $t_{1/2}$ < 20 ns, Visscher et al. 1988] most likely at *N*(3) at or at the amino group (Symons 1990; Hüttermann et al. 1991; Podmore et al. 1991; Barnes and Bernhard 1994).



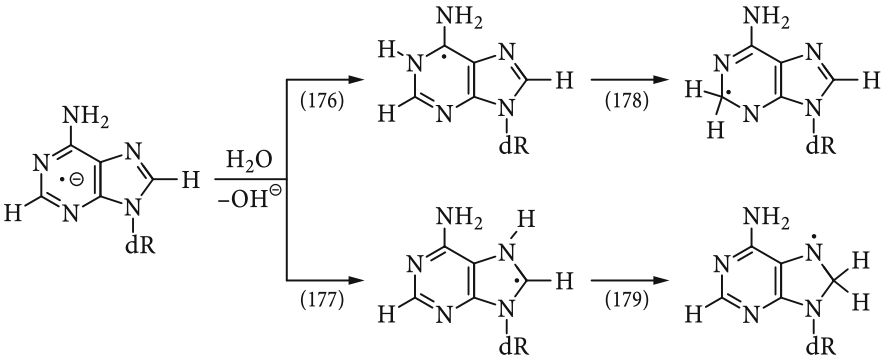
The resulting neutral radical must have a pK_a value ≥ 11, as shown by conductance measurements in pulse radiolysis (Hissung and von Sonntag 1979). The absence of any noticeable changes in the absorption spectrum of the radical derived from Cyd in the pH range 6-13 suggests that its pK_a value is even >13 (Steenken et al. 1992). Like the situation in the corresponding Thy system, the heteroatom-protonated species is not thermodynamically favored and subsequent (irreversible) protonation seems to occur at carbon [reaction (175)], albeit with a rate constant (estimated at 2.5 × 10^3 s^{-1}; Nese et al. 1992) too slow to be measured by pulse radiolysis.

For studies on the formation of the Ura-H$^{\bullet}$-adducts at *O*(4) and *C*(5) in the gas phase see Syrstad et al. (2001) and Wolken and Turecek (2001).

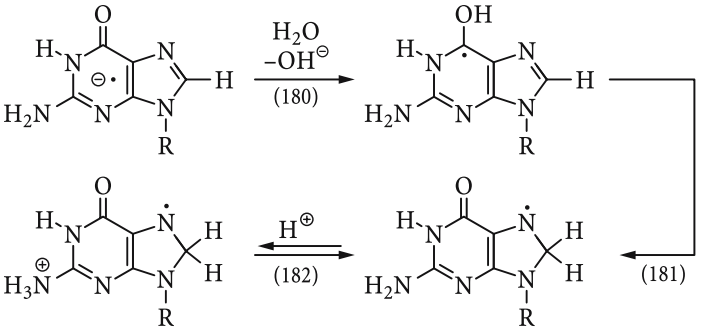
Purines. With the purines, H$^{\bullet}$ and e_{aq}^- react at close to diffusion-controlled rates. Besides that, very little is known about the reactions of H$^{\bullet}$. However, H$^{\bullet}$ and $^{\bullet}$OH being both electrophilic radicals (Chaps 3.2 and 4.4), the position-specificity for the addition of H$^{\bullet}$ should be very similar to that of $^{\bullet}$OH.

The properties of the purine radical anions formed by their reaction with e_{aq}^- resemble those of the Cyt radical anion. Because the pK_a values of the heteroatom-protonated conjugate acid of the purine radical anions are very high, the purine radical anion are rapidly protonated by water (Hissung et al. 1981a; Visscher et al. 1987; von Sonntag 1991; Candeias and Steenken 1992a; Candeias et al. 1992; Aravindakumar et al. 1994). For example, the dAdo radical anion

is protonated by water with a rate of ≥1.4 × 10^8 s^{-1} (Visscher et al. 1987). Such a rapid protonation reaction occurs typically at a heteroatom [reactions (176) and (177); note that protonation can also occur at other nitrogen atoms]. The radical anion and also their heteroatom-protonated conjugate acids have reducing properties. Thus, the latter react readily with oxidants such as *p*-nitroacetophenone [k = 5 × 10^9 dm^3 mol^{-1} s^{-1}; Hissung et al. 1981a) and methylviologen [k = 2.5 × 10^9 dm^3 mol^{-1} s^{-1}; Candeias and Steenken 1992a]. Interestingly, the oxidation by *p*-nitroacetophenone does not fully restore dAdo, but a product is formed which has a pK_a value of 8.8, and it has been suggested that this product might contain the elements of water. Alternatively, the carbocation at *N*(6) formed upon oxidation may deprotonate at *N*(6) yielding the imino analog of 2'-deoxyinosine [pK_a(inosine = 8.8)] in competition to a deprotonation at *N*(1) that restores dAdo. The considerable change at high pH in the recorded UV absorption spectra which occurs at approximately pH 10.5 (Moorthy and Hayon 1975) is not due to a deprotonation reaction, but a rearrangement of heteroatom protonated radicals into carbon-protonated ones [reactions (178) and/or (179); Hissung et al. 1981a].

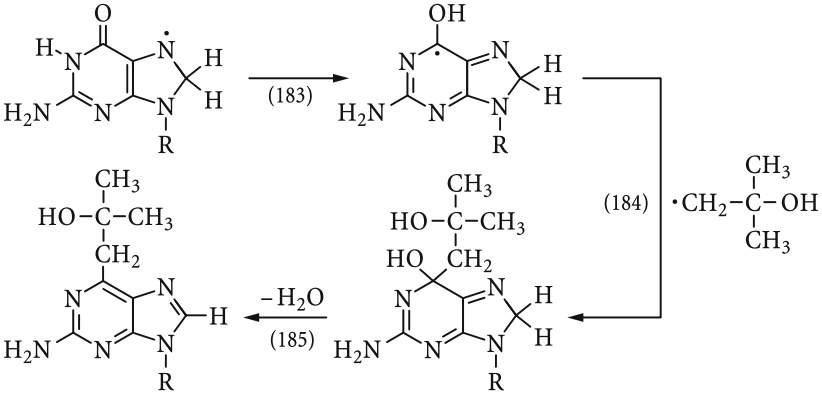


In Guo, after the very fast protonation of the electron adduct by water at the heteroatom [$k \geq 10^7$ s^{-1}, von Sonntag 1991; Candeias et al. 1992; at *O*(6), *N*(3) or *N*(7), cf. reaction (180)], a rapid transformation occurs [reaction (181); k(in H_2O) = 1.2 × 10^6 s^{-1}, k(in D_2O) = 1.5 × 10^5 s^{-1}] which is also catalyzed by phosphate buffer (k = 5.9 × 10^7 dm^3 mol^{-1} s^{-1}) which has been attributed to a protonation at *C*(8) (Candeias et al. 1992). This assignment is based upon solid-state EPR data, where *C*(8)-H•-adduct is the thermodynamically most stable H•-adduct radical (Rakvin et al. 1987; for DFT calculations see Naumov and von Sonntag, unpubl. results). The high solvent kinetic isotope effect of k_H/k_D = 8 is a strong indication that a proton is transferred in the rate-determining step. The magnitude of the rate of phosphate buffer catalysis points to a protonation at carbon (for a similar reaction observed with the Thy radical anion see Table 10.20). The *C*(8)-H•-adduct has a pK_a value of 5.4 [equilibrium (182)].



The *C*(8)-H$^{\bullet}$-adduct is only a weak oxidant. It does not react with methylviologen (E = -0.44 V/NHE; $k \leq 10^7$ dm^3 mol^{-1} s^{-1}), but it is quite readily oxidized by $Fe(CN)_6^{3-}$ (E = 0.35 V/NHE; $k = 5.6 \times 10^8$ dm^3 mol^{-1} s^{-1}).

When dGuo radical anion and the *t*BuOH-derived radical are generated side by side, a highly fluorescent product is formed [reactions (183)–(185); Yamamoto et al. 1995; Mandal and Yamamoto 1986].

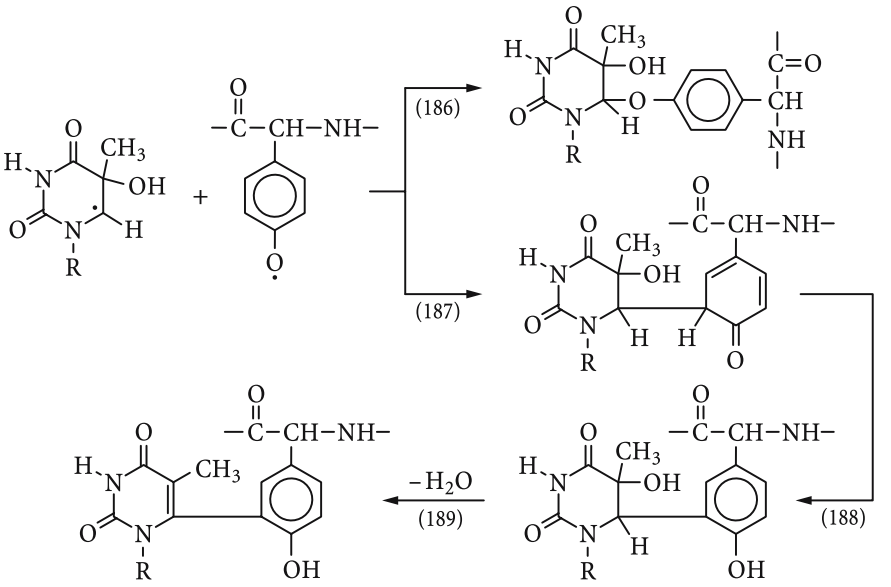


The mechanism presented here is somewhat at variance with that proposed by the authors (Yamamoto et al. 1995) who suggested that the *t*BuOH-derived radical adds to the primarily formed electron-adduct radical. Since this has been shown above to have only a very short lifetime, it will not be capable of undergoing bimolecular recombination reactions. An isomerization of *C*(8)-H$^{\bullet}$-adduct [reaction (183)] followed by an addition of the *tert*-butanol-derived radical and water elimination [reactions (184) and (185)] is not in conflict with the above pulse radiolysis results [note that the tautomerization reaction (183) cannot be excluded on the basis of the pulse radiolysis data].

10.5 Reactions with Alkyl and Thiyl Radicals

The question as to the reactions of alkyl radicals with nucleobases is a very important one. For example, α-hydroxyalkyl radicals, generated in the reaction of reactive free-radicals with alcohols, are capable of inactivating biologically active DNA (Nabben et al. 1983). Moreover, alkyl-type radicals are formed when reactive radicals such as •OH and H• add to the nucleobases or abstract an H atom from the sugar moiety of DNA. Thus, in principle, these DNA radicals thus generated could add to a neighboring nucleobase if the rate of reaction is sufficiently high and steric conditions allow the reaction to proceed. In DNA, this kind of reaction may lead to an intramolecular cross-link, e.g. by forming a small loop. Furthermore, DNA histone cross-linking may occur if a protein-derived radical would add to one of the DNA bases. Mechanistically, one has to clearly distinguish such addition reactions from the trivial case, where two base radicals or a base radical and a protein radical recombine. This trivial case is well documented (Yamamoto 1973; Grachev et al. 1983, 1986; Dizdaroglu and Simic 1984a,b; Dizdaroglu and Simic 1985a,b; Simic and Dizdaroglu 1985; Karam et al. 1986; Gajewski et al. 1988; Margolis et al. 1988; Dizdaroglu and Gajewski 1989; Dizdaroglu et al. 1989; Gajewski and Dizdaroglu 1990; Gajewski et al. 1990).

A case in point is the combination of a Thy •OH-adduct with a tyrosine-derived phenoxyl radical [reaction (186); Simic and Dizdaroglu 1985].



Apparently, the phenoxyl radical reacts also at carbon [reaction (187); the typical site for self-termination; Jin et al. 1993, 1995]. The resulting product undergoes an H-shift and eliminates water [reactions (188) and (189)]. The first step is certainly very fast and is expected to occur on the sub-ms time scale (cf. Capponi

et al. 1986). The second step will be much slower and may only occur during the work-up (cf. the slow – and proton-catalyzed – water elimination of bis(hydroxy cyclohexadienyl) into biphenyl; Mark et al. 2003).

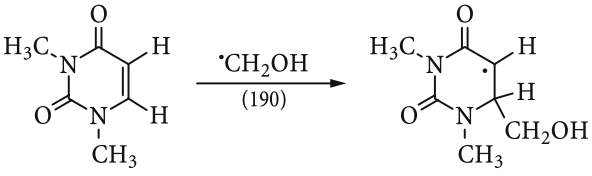
These reactions are only trivial as far as their chemistry is concerned (recombination of radicals and subsequent water elimination). This does not mean, however, that these reactions are of little importance in cellular-DNA free-radical chemistry.

It will be shown below that alkyl radicals add predominantly at the *C*(6)-positions of the pyrimidines and, when products as shown above are found after •OH-attack in very complex systems such as nucleohistones (e.g., Gajewski et al. 1988; Dizdaroglu and Gajewski 1989; Dizdaroglu et al. 1989; Gajewski and Dizdaroglu 1990) or Thy dimers in polydeoxythymidylic acid (Karam et al. 1986), it cannot be fully excluded that they are formed via the trivial two-radical recombination mechanism.

One of the first •OH-induced purine damage detected was in the 5′,8-cyclonucleotides. This lesion was later also observed in DNA (Chap. 12.5). In the following, the non-trivial case, the reactions of organic radicals with pyrimidines and purines will be discussed, and a special section will devoted to 5′,8-cyclonucleosides and nucleotides whose mechanism of formation has been found to be very complex.

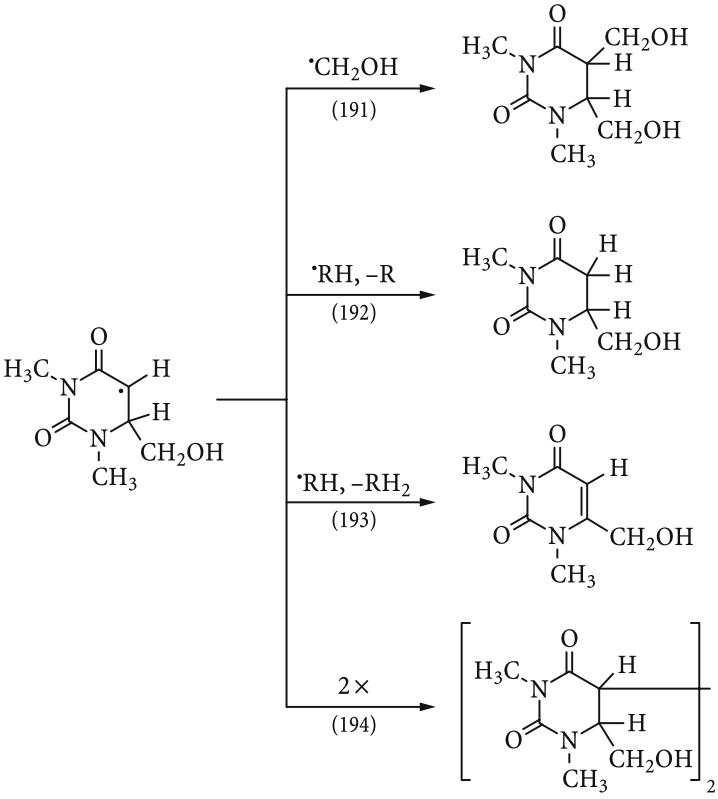
Pyrimidines. Alkyl radicals are nucleophilic radicals and add to the *C*(6)-position of pyrimidines rather than to the *C*(5)-position as the electrophilic •OH and H• do. The reactions of pyrimidines with α-hydroxyalkyl radicals that can be readily generated photolytically or radiolytically have been investigated intensively (Brown et al. 1966; Zarebska and Shugar 1972; Leonov et al. 1973; Frimer et al. 1976; Shetlar 1976, 1979, 1980; Ekpenyong and Shetlar 1979; Cadet et al. 1981; Ishida et al. 1985, 1986; Schuchmann et al. 1986). In the earlier radiolytic studies (Brown et al. 1966; Zarebska and Shugar 1972; Cadet et al. 1981), e_{aq}^- had been scavenged by the pyrimidines, and thus the pyrimidine electron adducts took part in the reactions. This has been avoided in a later study on the reactions of $^{\bullet}CH_2OH$ with $1,3Me_2Ura$ and $1,3Me_2Thy$ (Schuchmann et al. 1986), and the subsequent discussion is based on these results.

In the case of $1,3Me_2Ura$, all products (Table 10.21) can indeed be accounted for if in the primary step $^{\bullet}CH_2OH$ adds to the *C*(6) position [reaction (190)].



There is a considerable effect of the *G* values on the dose rate, and from this dose rate dependence it has been calculated that the rate constant of the addition of $^{\bullet}CH_2OH$ to $1,3Me_2Ura$ must be about 1×10^4 dm^3 mol^{-1} s^{-1}. Thus, the rate of this reaction is five orders of magnitude lower than that of •OH. Even at

the lowest dose rate used, not all $^{\bullet}CH_2OH$ were scavenged by the pyrimidine but also reacted with one another and with the 1,3Me$_2$Ura $^{\bullet}CH_2OH$-adduct [reactions (191)-(194)].



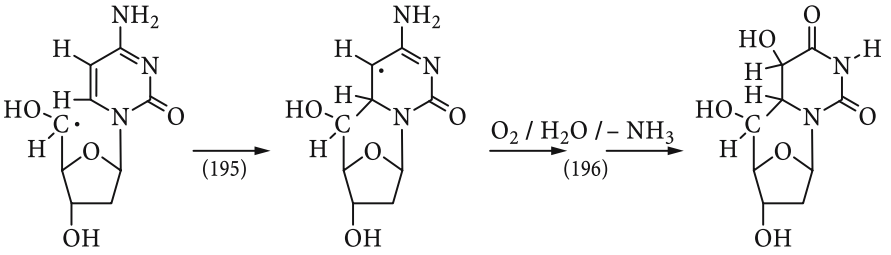
In this context, it may be of interest that hydroxymethylation of 1,3Me$_2$Ura (and its derivatives) by the Eu(III)/Eu(II) photoredox system in MeOH affords 5,6-dihydro-1,3-dimethyl-6-hydroxymethyluracil in close to 100% yield (Ishida et al. 1985). Apparently, the one-electron-reduced 1,3Me$_2$Ura, the *O*(4)-protonated 1,3Me$_2$Ura-4-yl radical, does not undergo sufficiently rapid isomerization into the thermodynamically more stable 1,3-dimethyl-5-hydro-uracil-5-yl radical under these conditions. Otherwise, 5,6-dihydro-1,3-dimethyl-5-hydroxymethyluracil would have been observed.

In dCyd, the α-hydroxyalkyl radical formed upon $^{\bullet}OH$ attack at the 5′-position must add to *C*(6) [reaction (195)] that fast that it is not scavenged effectively by O_2. An oxidation of the ensuing *C*(5) radical by O_2 and deamination are further likely steps [reaction (196)] to the observed product (Wagner et al. 1999; for its yield see Table 10.16).

Table 10.21. γ-Radiolysis if N_2O-saturated aqueous solutions of MeOH (0.5 mol dm^{-3}) in the presence of 1,3Me_2Ura (5×10^{-4} mol dm^{-3}). Products and their *G* values (unit: 10^{-7} mol J^{-1}) at different dose rates (unit: Gy s^{-1}; Schuchmann et al. 1986)

Product	0.18	0.026	0.0028
1,3-Dimethyl-6-hydroxymethyl-uracil	0.2	0.2	0.2
5,6-Dihydro-1,3-dimethyl-6-hydroxymethyluracil	0.85	1.7	2.1
5,6-Dihydro-5,6-di(hydroxymethyl)-1,3-dimethyluracil	0.95	0.7	0.6
5,5′-Bi-(5,6-dihydro-6-hydroxymethyl-1,3-dimethyl)uracilyl	0.45[a]	0.68[a]	0.95[a]
Formaldehyde	0.7	1.1	n.d.
Ethylene glycol	0.95	0.8	ND
1,3-Dimethyluracil consumption	2.4	3.2	4±1

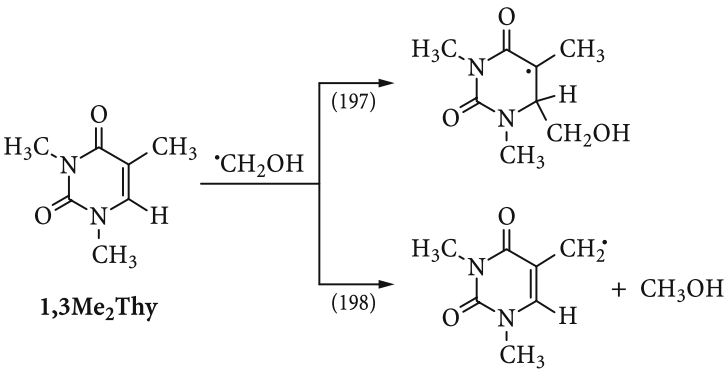
n.d., Not determined
[a] G values in monomer units



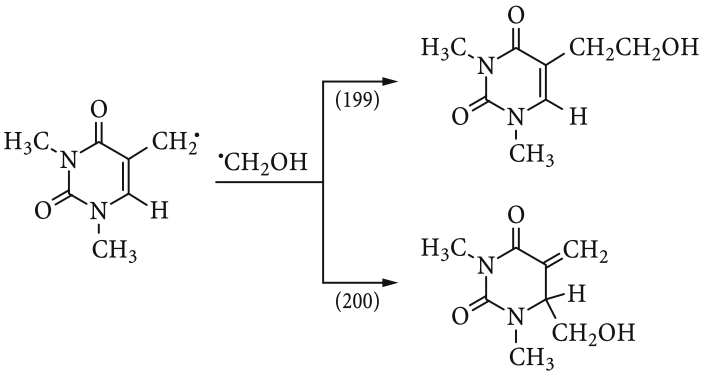
Although the O_2 concentration prevailing under the experimental conditions and other details such as products of competing reactions are not known exactly, one can estimate that the rate of the *C*(5′)→*C*(6) addition must be around 10^5 s^{-1}. This is the same order of magnitude as the addition of the *C*(5′) radical to the *C*(8) position in purines (see below).

The cyclonucleoside shown above has been synthesized and some of its properties such as piperidine stability were studied (Muller et al. 2002).

An interesting additional aspect offers the reaction of $^{\bullet}CH_2OH$ with 1,3Me_2Thy (Schuchmann et al. 1986). Here, not only is an addition to the *C*(6) position [reaction (197)] observed, but as much as 25% of $^{\bullet}CH_2OH$ abstract an H atom from the methyl group [reaction (198); see also Leonov et al. 1973; Livneh et al. 1982].



The allyl radical can react with another $^{\bullet}CH_2OH$ to form either the hydroxyethyl derivative [reaction (199)] or its isomer with an exocyclic double bond [reactions (200)].



The latter appears to be much more reactive towards $^{\bullet}CH_2OH$ than 1,3Me$_2$Thy itself, and reaches only such a low steady-state. Instead, its addition products (compiled in Table 10.22) are found to increase linearly with dose [for the first steps to these products see reactions (201)–(203)].

Table 10.22. γ-Radiolysis if N_2O-saturated aqueous solutions of MeOH (0.5 mol dm^{-3}) in the presence of 1,3Me_2Thy (5×10^{-4} mol dm^{-3}). Products and their *G* values (unit: 10^{-7} mol J^{-1}) at a dose rate of 0.19 Gy s^{-1}. (Schuchmann et al. 1986)

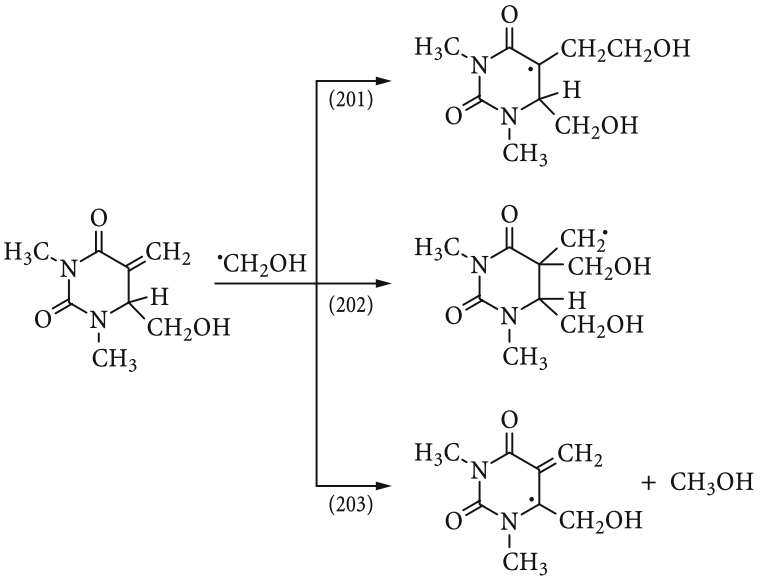
Product	*G* value
5,6-Dihydro-1,3-dimethyl-6-hydroxymethylthymine	1.6
5,6-Dihydro-5,6-di(hydroxymethyl)-1,3-dimethylthymine	0.3
1,3-Dimethyl-6-hydroxymethylthymine	0.08
1,3-Dimethyl-5-(2-hydroxyethyl)uracil	0.12
5,6-Dihydro-1,3-dimethyl-5-(2-hydroxymethyl)-6-hydroxymethyluracil	0.25
5-(2-Hydroxyethyl)-6-hydroxymethyluracil	0.03
5,6-Dihydro-5,6-di(hydroxymethyl)-1,3-dimethyl-5-(2-hydroxyethyl)uracil	0.09
5,6-Dihydro-5-(2-(1,3-dihydroxy)propyl)-1,3-dimethyl-6-hydroxymethyluracil	0.04
5,6-Dihydro-5-(5′,6′-dihydro-1′,3′,5′-trimethyluracil-6′-yl)-6-hydroxymethyl-1,3.5-trimethyluracil	0.01
5,5′-Bi-(5,6-dihydro-6-hydroxymethyl-1,3-dimethyl)thyminyl	0.12[a]
Formaldehyde	0.6
Ethylene glycol	n.d.
1,3-Dimethylthymine consumption	2.5

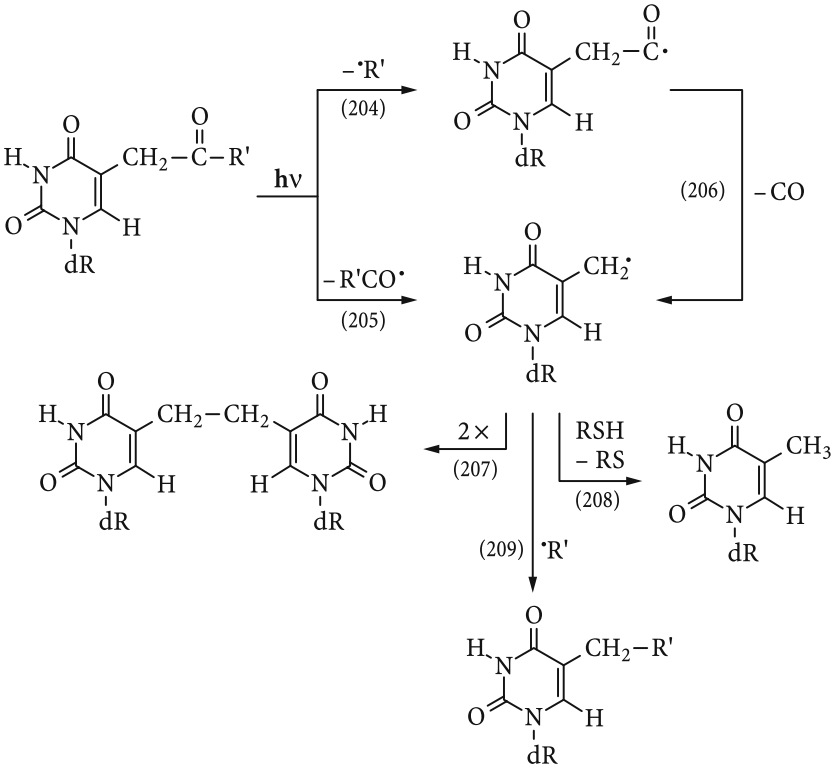
n.d., Not determined
[a] *G* value in monomer units

The allylic Thd radical has been generated photolytically [reactions (204–206); Anderson et al. 2000].

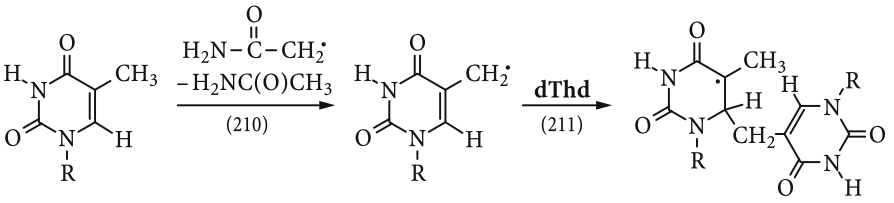
With R′ = benzyl and in the absence of O_2, the major product (73%) is the decarbonylation product [reaction (209); possible formed to a large extent within the solvent cage], and the dimer of the allylic radical [reaction (207)] is formed only in small amounts. Addition of a thiol increases the yield of Thd [reaction (208)]. If an evaluation of the data reported for the reduction of the allylic •OH-adduct to 1,3-cylohexadiene by a thiol (Pan et al. 1988), estimated at ~10^4 dm^3 mol^{-1} s^{-1}, is a good guide the rate constant for reaction (208) should be similar. This would revise an *assumed* rate constant of 10^6 dm^3 mol^{-1} s^{-1} and the conclusions as to the repairability of allylic Thy in DNA radicals by cellular thiols (Anderson et al. 2000).

The allylic radical has also by abstraction of the allylic hydrogen by the $H_2NC(O)CH_2$• radical in Thd [reaction (210] and its isomer has been produced from 6-chloromethyluracil by dissociative electron capture and also in low-tem-


(201)
(202)
(203)
+ CH3OH


hν
(204)
(205)
(206)
– CO
2×
(207)
RSH
– RS
(208)
(209)

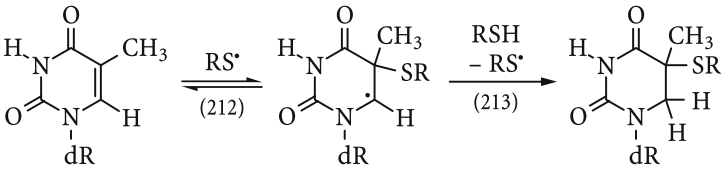
perature EPR experiments (Wang et al. 1997). Under such conditions the allylic radicals adds to the *C*(6)-position [reaction (211)], but there is no evidence for *C*(1′)-H abstraction. Thus, this observation may be of some importance regarding potential DNA-DNA cross-linking reactions.



In contrast, with dCMP as a substrate that lacks the weakly-bound allylic hydrogens, $H_2NCOCH_2^{\bullet}$ abstracts the *C*(1′)-H which is the most weakly-bound among the hydrogens of the sugar moiety (Wang et al. 1997).

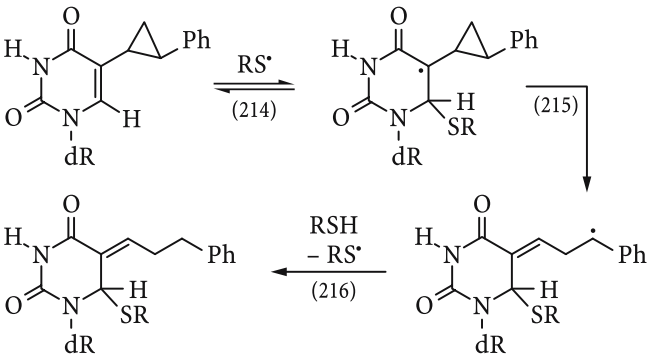
Addition of the (reducing) $CO_2^{\bullet-}$ radical to Thy (products not fully elucidated) shows that this radical behaves similar to other alkyl radicals, and reduction of Thy is certainly not its only reaction (Wada et al. 1982). Similar studies on Thd yielded the 5,5′-dihydrodimer ($G = 0.75 \times 10^{-7}$ mol J^{-1}) and H_2Thd ($G = 1.4 \times 10^{-7}$ mol J^{-1}; Nishimoto et al. 1983b). This does not yet fully account for the total $CO_2^{\bullet-}$ yield ($G \approx 6 \times 10^{-7}$ mol J^{-1}), but is a strong indication that reduction of Thd by $CO_2^{\bullet-}$ takes place in competition to addition.

The thiyl radical ($RS^{\bullet}$) is electrophilic and hence with pyrimidines its preferred site of attack is *C*(5) and to a lesser extent *C*(6) (Jellinek and Johns 1970; Varghese 1973, 1974; Shetlar and Hom 1987). Addition of $RS^{\bullet}$ to C-C double bonds is highly reversible [reaction (212), $k_{212} \approx 10^7$ dm^3 mol^{-1} s^{-1}, $k_{-212} \approx 10^5$ s^{-1} (Woijik et al. (2005); see also Chap. 7.4], and for fixing the $RS^{\bullet}$-adduct a fast subsequent reaction is required [reaction (213)].

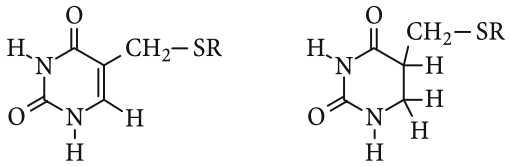


Considering that the equilibrium concentration of the *C*(6)-yl radical should be low, the major reaction should be a dimerization of $RS^{\bullet}$, but data confirming this are not available.

In reaction (214), the addition of $RS^{\bullet}$ to the *C*(6) position is followed by a very rapid and irreversible cyclopropyl carbinyl radical rearrangement [reaction (215); Carter et al. 2000]. The resulting radical is comparatively long-lived and can be reduced by the thiol [reaction (216)]. Thus in this example, the minor pathway is detected, while the other, being reversible, remains unobserved.



The acetone-sensitized photolysis of Thy in the presence of L-cysteine (R = cysteinyl), yields mainly 5-*S*-L-cysteinyl-5,6-dihydrothymine (see above), but also minor amounts of 5-*S*-L-cysteinylmethyluracil and 5-*S*-L-cysteinylmethyl-5,6-dihydrouracil are formed (Shetlar and Hom 1987; for an earlier study see Varghese 1973).



5-cytsteinyl-methyluracil

5-cytsteinyl-5,6-dihydro-methyluracil

The formation of 5-*S*-L-cysteinylmethyluracil may be taken as an indication that under these conditions photoexcited acetone also abstracts an H-atom from the methyl group of Thy or (less likely) that RS• is also capable of undergoing this reaction. The observation of 5-*S*-L-cysteinylmethyl-5,6-dihydrouracil is less easily explained. An exomethylene precursor as discussed above for the reaction of •CH_2OH with Thy could, in principle, account for it. Detailed mechanistic studies are, however, missing.

Purines. The reactions of purines with α-hydroxyalkyl and α-alkoxyalkyl radicals have been most intensively investigated (Elad et al. 1969; Steinmaus et al. 1969, 1971; Elad and Salomon 1971; Leonov et al. 1973; Salomon and Elad 1973; Leonov and Elad 1974a,b; Moorthy and Hayon 1975; Frimer et al. 1976; Aravindakumar et al. 1994), but the reactions of radicals derived from amino acids (Elad and Rosenthal 1969; Elad et al. 1969; Elad and Salomon 1971; Poupko et al. 1973; Salomon and Elad 1974) and amines (Elad and Salomon 1971; Salomon and Elad 1973) and of the methyl radical (Maeda et al. 1974) are also reported (for a review of the older work see Elad 1976).

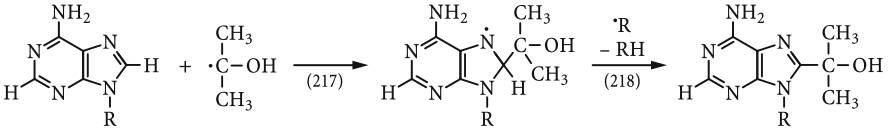
Alkyl radicals are nucleophilic radicals, and for this reason protonated purines react faster with alkyl radicals than the purines themselves (Table 10.22). Their rate also increases with increasing nucleophilicity of the radical, and hence •$C(CH_3)_2OH$ reacts much faster than •CH_2OH (Table 10.23). In fact, the

Table 10.23. Rate of reaction (unit: $dm^3\ mol^{-1}\ s^{-1}$) of α-hydroxyalkyl radicals with purines. (Aravindakumar et al. 1994)

Substrate	pH	$^{\bullet}C(CH_3)_2OH$	$^{\bullet}CH(CH_3)OH$	$^{\bullet}CH_2OH$
$HypH^+$	0.4	7.8×10^7	2.2×10^7	$\sim 5 \times 10^6$
Hyp	6.5	$\sim 4 \times 10^6$	n.d.	n.d.
$InoH^+$	0.4	3.2×10^7	3.0×10^7	$\sim 6 \times 10^6$
Ino	6.5	6.4×10^6	$\sim 5 \times 10^6$	n.d.
Ino anion	11.2	$\sim 10^6$	n.d.	n.d.
$AdoH_2^{2+}/AdeH^+$	0.4	1.2×10^8	4.3×10^7	4.4×10^6
$AdoH^+$	0.4	4.7×10^{7a}	1.5×10^7	$\sim 3 \times 10^6$
Ado	7	$< 10^{6a}$	n.d.	n.d.
Ado anion	13.6	$< 10^{6a}$	n.d.	n.d.
$dAdoH^+$	0.4	1.3×10^8	3.1×10^7	5.5×10^6
$GuoH^+$	0.4	4.3×10^7	1.8×10^7	5.7×10^6
$1MeGuoH^+$	0.5	8.0×10^{7a}	n.d.	n.d.
$dGuoH^+$	0.4	7.1×10^7	1.4×10^7	$\sim 4 \times 10^6$

n.d., Not determined
[a] From Moorthy and Hayon (1975)

reactivity of $^{\bullet}CH_2OH$ is so low, that its reaction is barely noticed, even at low steady-state concentrations of these radicals (Table 10.23). The product which is typically observed is the *C*(8)-alkylated purine, [e.g., reactions (217) and (218)].



As can be seen from Table 10.24, the consumption of the purines is noticeably higher than is accounted for by the *C*(8)-alkylated product. Thus, other, as yet not established, reactions must take place as well. It is recalled that the *C*(8) position rates among the sites preferred by electrophilic radicals and thus is possibly not the most preferred one for an attack by the nucleophilic alkyl radicals. Yet the EPR spectra of the intermediates formed in the reactions of the $H_2NCOCH_2^{\bullet}$ radical with Ade and Gua derivatives have also been interpreted as being mainly due to the *C*(8)-adduct radicals (Wang et al. 1997). Methyl radicals, generated in

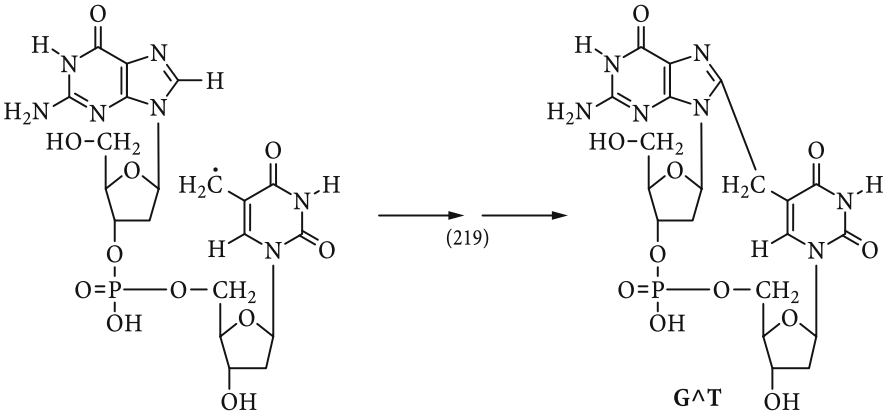
Table 10.24. Reactions of $^{\bullet}CH_2OH$ and $^{\bullet}C(CH_3)_2OH$ with Ade and Ino. Products and their *G* values (unit: 10^{-7} mol J^{-1}) determined under steady-state γ-radiolysis conditions (dose rate 0.28 Gy s^{-1}) at pH 6.5. (Aravindakumar et al. 1994)

Substrate	Radical	CH_2O	$(CH_2OH)_2$	$(CH_3)_2CO$	Ade consumption	Addition product
Ade	$^{\bullet}CH_2OH$	0.93	2.2	-	1.2	< 0.2[a]
Ade	$^{\bullet}C(CH_3)_2OH$	-	-	0.3	4.5	1.9
Ino	$^{\bullet}C(CH_3)_2OH$	-	-	3.8	-	n.d.

n.d., Not determined
[a] Structure not identified, assumed to be the *C*(8)-hydroxymethyl-substituted Ade

the photolysis of *N-tert*-butyoxy-2-pyridone in aqueous solution in the presence of dGuo, yielded 2.3% 8MedGuo and 0.27% 7MedGuo (Adam et al. 2002c). These yields are again very low, and the full product spectrum still awaits elucidation.

In Thy-Gua and Thy-Ade dinucleosides, the allylic Thy-derived radical gives rise to a tandem lesions denoted as G^T, T^G, A^T and T^A [e.g., reaction (219); Bellon et al. 2002].



In a GTG-containing 15-mer exposed to γ-irradiation in deaerated aqueous solutions, the G^T lesion strongly dominates over the T^G lesion, and in a ATA-containing 15-mer A^T dominates over T^A.

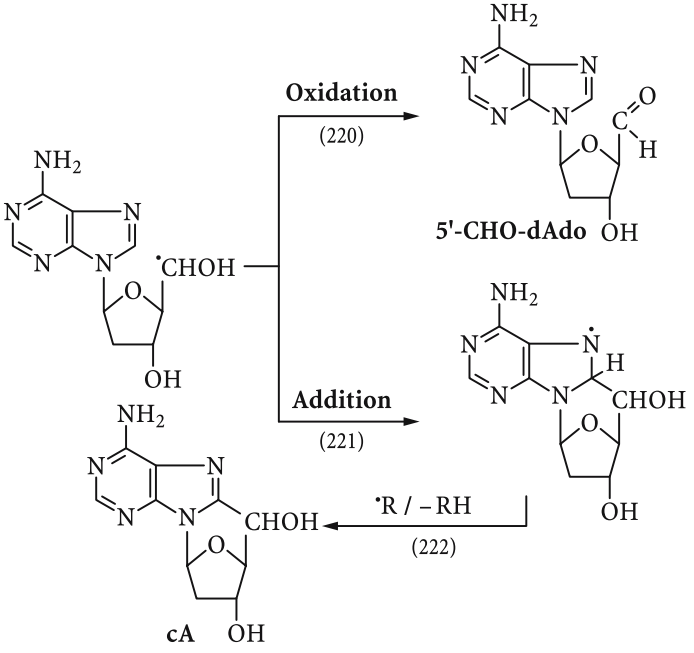
In the DNA of mammalian cells, Cyt at CpG sites is methylated (5MeCyt, mC). The radical at methyl in mCpG has been specifically generated upon photolysis of the corresponding SPh derivative. Cross-linking to C(8) of the neighboring Gua was found to be a major reaction both in d(mCpG) and d(GpmC) (Zhang and Wang 2003). Besides this cross-linking, an oxidation of MeCyt moi-

ety to $5CH_2OHCyt$ and 5CHOCyt in the absence of O_2 is observed but not yet understood.

An additional product, <d(TpG)>, that is formed in the benzophenone and menadione-sensitized oxidation of d(TpG), where the allylic Thy radical must have added to the *C*(4) position of the neighboring Gua moiety, is discussed below.

Purine-5′,8-cyclonucleosides and -cyclonucleotides. With purine nucleosides/nucleotides, cyclonucleosides/cyclonucleotides, cA and cG, have been observed as products formed upon •OH-attack (Hagen et al. 1965; Keck et al. 1966; Raleigh et al. 1976; Mariaggi et al. 1976; Raleigh and Blackburn 1978; Haromy et al. 1980; Berger and Cadet 1983a; Raleigh and Fuciarelli 1985; von Sonntag 1994). Reference material has been synthesized (Romieu et al. 1999a), and a method for their site-specific introduction into an ODN has been devised (Romieu et al. 1999c).

It is usually assumed that an H-abstraction at *C*(5′) by •OH (see, however, below) leads to the *C*(5′) radical which adds to *C*(8) [e.g., reaction (221); for details of this reaction see below, where experiments that lead to the specific generation of this radical are discussed]. In a disproportionation reaction with other radicals, the cyclonucleoside (cyclonucleotide) is formed [reaction (221)]. In competition, the *C*(5′) radical may be oxidized giving rise to the 5′-aldehyde [reaction (220)].



With AMP as substrate, *G*(cA) strongly depends on the pH. This has originally been explained by a variation of the rate constant of the H-abstraction reaction by •OH from the *C*(5′)-position as a function of the charge at the base and the

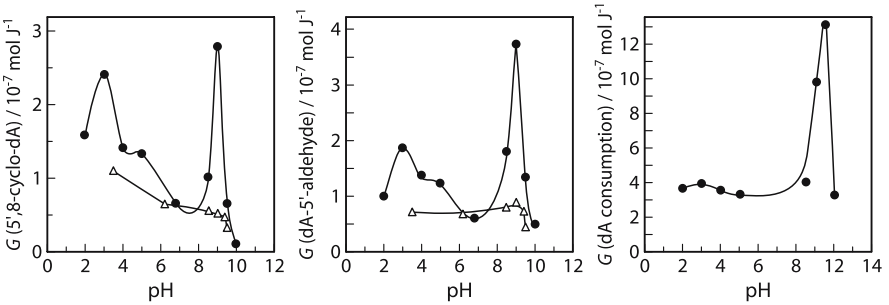


Fig. 10.1. γ-Radiolysis (*filled circles*) and electron-beam irradiation (*open triangles*) of N_2O-saturated solutions of dAdo. *G* values of the formation of the sum of the two isomers of cA (*left*), dAdo-5′-aldehyde (*middle*) and dAdo consumption (*right*) as a function of pH. Source: Wagner et al. (1999)

phosphate group (Raleigh and Fuciarelli 1985). Arguments have been put forward that this explanation is not adequate (von Sonntag 1987a). As it now turns out, the situation must indeed be much more complex. In the case of dAdo the same kind of pH dependence is observed (von Sonntag 1994). While the yield of the sum of the two AMP-derived cyclonucleotide isomers reaches a *G* value as high as 0.65×10^{-7} mol J^{-1} at its maximum (Raleigh and Fuciarelli 1985), the yield of the corresponding dAdo products is even 2.85×10^{-7} mol J^{-1} (Fig. 10.1). In addition, another product which has the *C*(5′) radical as a precursor, the dAdo-5′-aldehyde [reaction (220)], shows the same pH dependence, and their combined yields reaches a *G* value of 6.6×10^{-7} mol J^{-1} at the maximum close to pH 9.5. In fact, we deal here with a damage amplification reaction, since under the same conditions *G*(dAdo consumption) reaches a value of 13×10^{-7} mol J^{-1}, that is, twice the $^{\bullet}OH$ yield (Fig. 10.1). It is generally accepted that $^{\bullet}OH$ adds mostly to the base moiety, and thus these high values clearly rule out $^{\bullet}OH$-attack at the *C*(5′) position as the main primary process. This, however, requires that base radicals are capable to induce the formation of the *C*(5′) radicals which are the precursors of cA and 5′-CHO-dAdo. In accordance with this, the formation of cA can also be induced by $Br_2^{\bullet-}$ which is known to oxidize only the base moiety (von Sonntag 1994). Thus, besides a very small fraction of $^{\bullet}OH$ that attack the *C*(5′) position, there must be a major contribution of base radicals involved in the formation of these products.

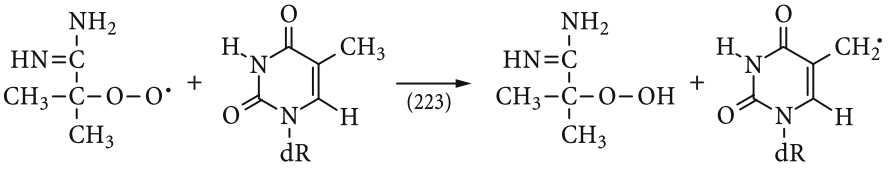
Mechanistically, this damage amplification reaction is not yet understood. Obviously, a second dAdo molecule is required for the reaction to proceed. When the termination of the radicals becomes very fast, this reaction no longer can proceed efficiently. As a consequence, the yields of 5′,8-cyclo-dAdo and 5′-CHO-dAdo drop dramatically at very high dose rate, i.e., under the conditions of pulse radiolysis (Fig. 10.1, triangles; Wagner et al. 1999). This is one of the reasons, why this reaction cannot be studied with this technique.

cG and the dGuo-5′-aldehyde are also major products in the dGuo system, but they never reach yields as high as those found with dAdo (preliminary results from the author's group), and cG is only formed in reasonable yields under

acidic conditions. At pH 3.5 where 10% of the dGuo is protonated, the cG yield is approximately halved in the presence of 5×10^{-4} mol dm^{-3} $Fe(CN)_6^{3-}$. Under such conditions, oxidation of the *C*(5′) precursor radical should be fast ($k \approx 2 \times 10^9$ dm^3 mol^{-1} s^{-1}; cf. Adams and Willson 1969), and from this observation one estimates that the intramolecular addition should be in the order of 10^6 s^{-1}. In less acidic solutions practically only the 5′-aldehyde is formed under such conditions. This is in agreement with a much lower rate of addition of α-hydroxyalkyl radicals to neutral purines (Table 10.23).

10.6 Reactions with Peroxyl Radicals

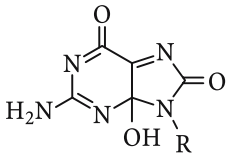
The general reactions of peroxyl radicals are discussed in Chapter 8. Here, it is recalled that peroxyl radicals are comparatively inert radicals. The reduction potential of simple alkylperoxyl radicals (~0.8 V) is considerably lower that that of Gua (1.29 V) which has the lowest reduction potential of all the nucleobases (Table 10.2). Yet, there are considerably more strongly oxidizing peroxyl radicals such as acylperoxyl radicals whose oxidation power is as high as 1.6 V, and such peroxyl radicals may stand a much better chance of reacting with the purines, notably Gua by ET. The ROO-H BDE is lower than that of typical C-H bonds, and H-abstraction reactions are therefore endothermic and thus very slow. For this reason, peroxyl radical reactions can be very selective. For the study of their reactions with substrates, it is required to reduce their bimolecular termination reactions to a minimum. This can be partly achieved by producing a very low steady-state concentration. This seems to have been realized by the slow (reaction time 25 h) thermal decomposition of 2,2′-azobis(2-methylpropinonamidine) at 40 °C (Chap. 2.4) in oxygenated solutions (Martini and Termini 1997). With Thd, these peroxyl radicals react mainly by abstracting the (most weakly bound) allylic hydrogen [reaction (223)], and in subsequent reactions the 5-methyl group is oxidized to hydroxmethyl, aldehyde and carboxylate functions.
In fact, 5-hydroxymethyluracil is a major oxidative DNA lesion, and is excreted into the urine in rather large amounts (Bianchini et al. 1996).



The same reaction has been carried out with dGuo in the context of a study of mutagenic effects of peroxyl radicals on DNA (Valentine et al. 1998). Some products have been recognized by HPLC but were not identified. Gua is not released, and there was no evidence that 8-oxo-G is among the products.

The thermolysis of dioxetanes in the presence of O_2 also yields peroxyl radicals (alkylperoxyl and acetylperoxyl), and these generate upon their reaction with dGuo mainly Z and 4-HO-8-oxo-G with only small amounts of 8-oxo-G

(Adam et al. 2001). It seems that 4-HO-8-oxo-G is not a primary product and results from an oxidation of 8-oxo-G (it is noted that the reduction potential of 8-oxo-G is only 0.74 V; Steenken et al. 2000).

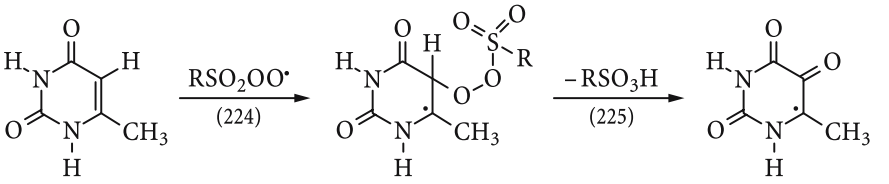


4-Hydroxy-8-oxo-guanosine (4-OH-8-oxo-G)

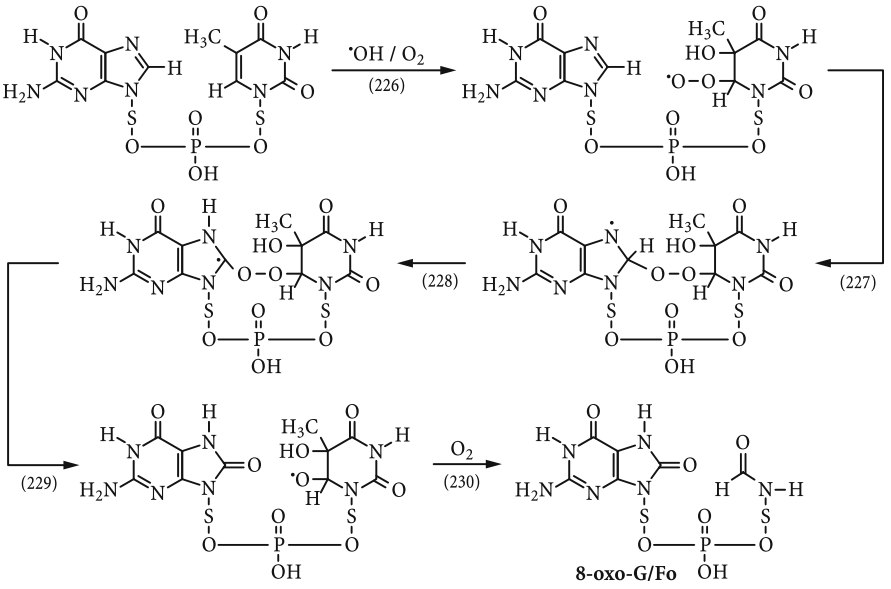
Similarly, Gua has been reported to yield 8-oxo-G albeit in only in 1% yield (relative to the peroxyl radical yield; Simandan et al. 1998). In the same study, the products from peroxyl radical reactions with other nucleobases are also reported. Ade gives rise to 8-oxo-A and 6-hydoxylaminopurine (in total 2%), while in the case of Cyt the formation of 5-hydroxy-Cyt (5%), 5,6-dihydroxyCyt (1%) and Cg (1%) are reported. Detected Thy products were the Tg (5%), $5CH_2OH$Ura (5%) and 5-hydroxy-5-methylhydantoin (1%). In this context, it is recalled that due to the slowness of the reaction of peroxyl radicals with substrates and the fast self-termination of peroxyl radicals product yields strongly depend on the rate of peroxyl radical generation. The in vivo generation of peroxyl radicals which may be much slower than typical rates of in vitro generation of peroxyl radicals could, in principle, result in higher product yields.

Mechanistically, it is difficult to see how some of these products that are well-known from $^{\bullet}$OH-induced reaction may be formed upon peroxyl-radical attack, for example, the glycols, and the question must be raised, whether these may arise from the thermal decomposition of hydroperoxides formed in preceding reactions such as reaction (223).

Alkylperoxyl radicals are not the only peroxyl radicals that react with DNA components. Sulphonylperoxyl radicals which are formed in the free-radical-induced oxidation of thiols (Chap. 7.4) also react readily with Thy by an abstraction of the allylic hydrogen (Razskazovskii and Sevilla 1996), analogous to reaction (223). With 6MeUra an interesting addition/elimination reaction has been proposed to occur [reactions (206) and (207); Razskazovskii and Sevilla 1996]. H-abstraction from the sugar moiety of nucleosides [notably *C*(1′), cf. Miaskiewicz and Osman (1994)] and in DNA from the more accessible *C*(4′)-position has also been considered.



A peroxyl-radical-induced reaction seems also to be the tandem lesion consisting of an 8-oxo-G and a formamido residue (8-oxo-G/Fo) observed upon the reaction of •OH with d(GpT) in the presence of O_2 [reactions (226)–(230); Box et al. 1993], and the same type of reactions were observed with d(GpC), d(TpG) and d(CpG) (Box et al. 1995). An ^{18}O-labeling study yielded some mechanistic information (Douki et al. 2002). The ^{18}O label is in the 8-oxo-G and to 50% also in the formamido residue. The first step is the addition of •OH to the Thy moiety with the formation of the *C*(5)- and the *C*(6)-peroxyl radicals [e.g., reaction (226)]. Upon their addition to the *C*(8)-position of the neighboring Gua moiety, an *N*-centered radical is formed [reaction (227)]. Such radicals do not react with O_2, but readily undergo 1,2-shift reactions (Chapter 7.2) [reaction (228)]. The resulting radical at *C*(8) is expected to undergo β-cleavage yielding the 8-oxoG lesion [reaction (229)]. The oxyl radical at the Thy residue will further degrade into the Fo lesion [reaction (230)]. According to this mechanism, the ^{18}O label will always be in the 8-oxo-G residue, but only in the Fo residue, when the *C*(6)-peroxyl radical is the precursor. Tandem lesions with a Z and a Fo moiety were not observed, and this may be taken as a support for the above mechanism.

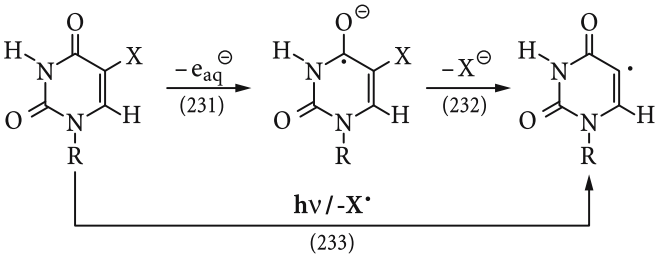


This type of damage amplification reaction is also observed in polynucleotides and in DNA (Chaps 11.2 and 12.5).

10.7 Halogenated Pyrimidines and Purines

Halogenated pyrimidines. There is a considerable interest in the reactions of 5-halourucils, notably 5BrUra. The latter can substitute Thy in DNA without

changing the viability of DNA significantly, since the van-der-Waals radii of -CH_3 and -Br are nearly identical. The incorporation of 5BrUra into DNA renders this DNA more sensitive towards ionizing and UV radiation (for reviews see Hutchinson 1973, 1985, 1987; Hutchinson and Köhnlein 1980; von Sonntag 1987a). The main reason for this sensitizing effect is thought to be due to the formation of the reactive uracil-5-yl radical formed under both conditions [reactions (231)-(233); for spin-trapping of this radical see Hedrick et al. 1982].



Upon photolysis, there are two reactive species formed side by side, the vinylic uracilyl radical and Br•. The latter has oxidizing properties (E^7 = 1.66 V; Wardman 1989), and in DNA it can oxidize neighboring G and A moieties (Wojcik et al. 2003). The quantum yield of photodecomposition of 5BrUra is only 1.8×10^{-3}, but increases dramatically upon deprotonation (Campbell et al. 1974). In the presence of MeOH as an H-donor, it also increases substantially above 2 mol/l MeOH. It has been speculated that above this concentration cage reactions come into play. Reported rate constants for the reaction of Br• with MeOH are 5×10^4 dm^3 mol^{-1} s^{-1} in water and 1×10^6 dm^3 mol^{-1} s^{-1} in acetonitrile (Neta et al. 1988).

The haloracil radical anion eliminates the halide ion [reaction (232); for a quantum mechanical calculation, albeit not taking solvation into account see Sommerfeld 2001]. In the case of 5IUra•$^-$ and 5BrUra•$^-$, this reaction is very rapid and occurs on the nanosecond time scale (Table 10.25), and protonation cannot intercept these species at pH 3 (Bhatia and Schuler 1973; Wagner et al. 1974). At 77 K, however, 5BrUra•$^-$ is sufficiently long-lived to be observed by EPR (Riederer et al. 1978), and only at 155 K it decays according to reaction (232) (Sevilla et al. 1974). The elimination of Cl^- from 5ClUra•$^-$ is already sufficiently slow for other reactions, e.g., a protonation reaction, to be able to compete (Wagner and Schulte-Frohlinde 1975; Burr et al. 1976). With 5FUra•$^-$ the rate of F^--elimination is now so slow that even at the low dose rates of γ-radiolysis F^--elimination remains incomplete (Bansal et al. 1972). Details are as yet not known, but it is conceivable that 5FUra•$^-$ is protonated at carbon (see above), and the subsequent combination reactions of the ensuing radicals no longer release F^-.

5BrUra•$^-$ is not only formed in the reaction of e_{aq}^- with 5BrUra, but other reducing radicals produce this intermediate as well (Zimbrick et al. 1969; Bansal et al. 1972; Görner 1993). Possibly, more important for the sensitizing effect in DNA is the fact that the radical anions of Thy and Ade can also transfer an electron to 5BrUra (Nese et al. 1992). In model systems this is no longer possible with Gua (for a study of the ET in 5BrUra-substituted oligonucleotides see Fuciarelli et al.

Table 10.25. Rate constants of halide elimination from the radical anions of 5-halouracils

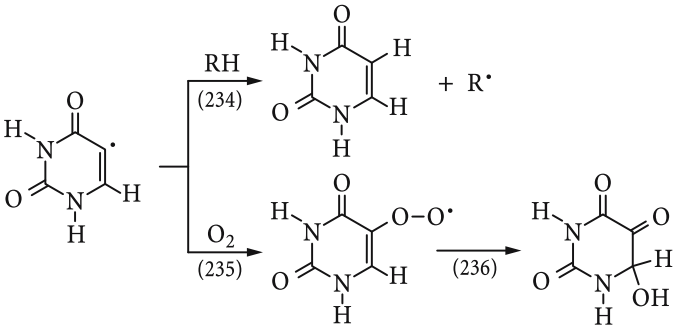
5-Halouracil	Rate constant/s^{-1}	Reference
5IUra	4×10^8	Rivera and Schuler (1983)
5BrUra	1×10^8	Rivera and Schuler (1983)
5ClUra	1.4×10^5 9×10^4	Rivera and Schuler (1983) Wagner and Schulte-Frohlinde (1975)
5FUra	Slow	Bansal et al. (1972)

Table 10.26. Compilation of rate constants of ET from electron adducts and their protonated forms of nucleobases and nucleosides. (Nese et al. 1992)

Substrate	Reaction	k/$dm^3\ mol^{-1}\ s^{-1}$	Reference
Thy	$Thy^{\bullet -}$ + 5BrUra	1.1×10^9	Adams and Willson (1972)
	$Thy^{\bullet -}$ + Cyt	1.7×10^9	Nese et al. (1992)
	$Thy^{\bullet -}$ + Guo	5.0×10^8	Nese et al. (1992)
		7.0×10^7	Nese et al. (1992)
Thd	$ThdH^{\bullet}$ + 5BrUra	2.3×10^7	Nese et al. (1992)
	$Thd^{\bullet -}$ + 5BrUra	7.2×10^8	Nese et al. (1992)
Ado	$AdoH^{\bullet}$ + 5BrUra	3.5×10^8	Adams and Willson (1972)
		2.0×10^8	Nese et al. (1992)
Cyt	$CytH^{\bullet}$ + 5rBrUra	$< 5 \times 10^7$	Adams and Willson (1972)
	$CytH^{\bullet}$ + Thy	2.0×10^7	Nese et al. (1992)
		2.0×10^6	Nese et al. (1992)
Guo	$GuoH^{\bullet}$ + 5BrUra	No transfer	Nese et al. (1992)

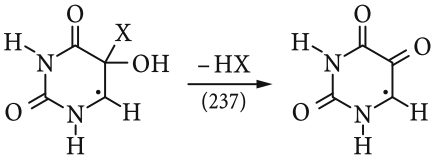
1994). It is discussed above that the nucleobase radical anions can be protonated at a heteroatom and/or carbon. Only the heteroatom-protonated species retains reducing properties, and thus the rate of protonation at carbon determines whether or not an ET to 5BrUra is observed under the given condition. Protonation at carbon is especially fast in the case of Guo, and for this reason an ET to 5BrUra was not observed (Nese et al. 1992). A compilation of the rate constants for such ET reactions is found in Table 10.26. As can be seen from this table, the radical anions transfer an electron to 5BrUra at practically diffusion-controlled rates, while the heteroatom-protonated species react two orders of magnitude more slowly.

The Ura-5-yl radical is a vinyl-type radical. It readily adds to, e.g., its parent, 5BrUra ($k = 2.7 \times 10^8$ dm^3 mol^{-1} s^{-1}; Rivera and Schuler 1983), but vinyl radicals are also good H-abstractors [cf. reaction (234)] and typically react with, e.g., 2-PrOH in the rage of 2×10^5 to 2.4×10^7 dm^3 mol^{-1} s^{-1}, depending on the substituent (Mertens 1994; Mertens and von Sonntag 1994a).



Their corresponding peroxyl radicals have the unusual property of absorbing strongly in the visible (Chap. 8.2). The Ura-5-peroxyl radical formed in reaction (235) also absorbs in the visible ($\lambda_{max} = 570$ nm), and it has been shown by pulse radiolyis that it decays rapidly (6×10^4 s^{-1}), apparently unimoleculary (Mertens and von Sonntag 1994a). The resulting product is isodialuric acid [Gilbert and Schulte-Frohlinde 1970; reaction (236)], and it had already postulated by these authors that a unimolecular process might be involved in the formation of this product.

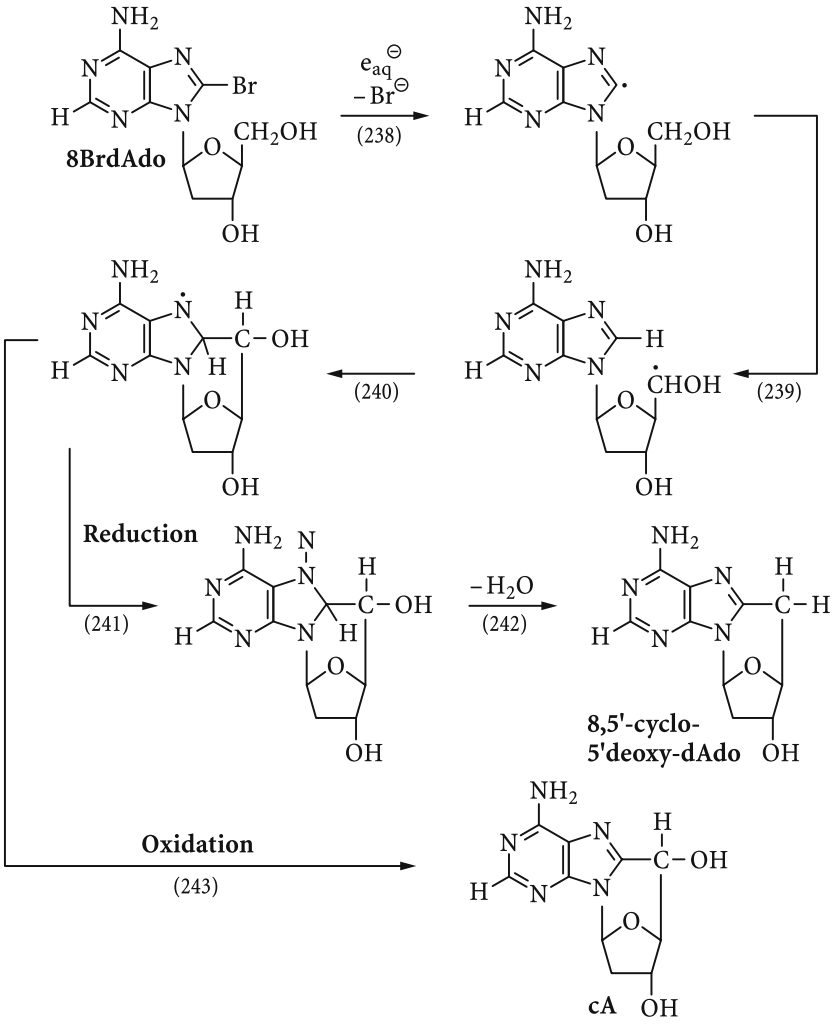
Addition of •OH to C(5) in 5-haloruacils leads to a rapid release of HX [reaction (237); $k \geq 10^6$ s^{-1}; Bansal et al. 1972; Neta 1972; Patterson and Bansal 1972; Mori et al. 2001] as is typical for geminal halohydrines (Köster and Asmus 1971; Mertens and von Sonntag 1994b; Dowideit et al. 1996).



The resulting radicals have only weakly oxidizing properties and react with TMPD with a rate constant of 2×10^8 dm^3 mol^{-1} s^{-1} (Mori et al. 2001).

Halogenated purines. 8BrdAdo has been used to study some of the steps in the cyclization reaction that yields the purine cyclonucleosides/tides (Flyunt et al. 2000; Chatgilialoglu et al. 2003). Upon the reaction of e_{aq}^-, the very reactive vinylic radical at *C*(8) is formed [reaction (238); $k = 1.6 \times 10^{10}$ dm^3 mol^{-1} s^{-1}] which undergoes rapid H-abstraction from the hydroxymethyl group at *C*(5′) [reaction (239)]. In neither of these reactions are radicals formed which strongly absorb in the accessible UV/Vis range. Upon addition of the *C*(5′) radical to *C*(8) [reaction (239); $k = 1.6 \times 10^5$ s^{-1}], an aminyl radical is formed whose UV/Vis spectrum is

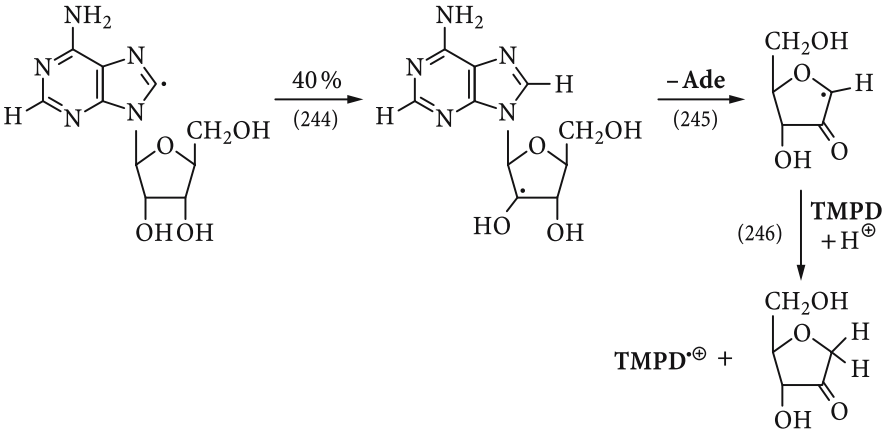
similar to that of the *C*-protonated electron adduct of dAdo. Subsequent redox reactions with $Fe(CN)_6^{4-}/Fe(CN)_6^{3-}$ gives rise to the observed products, cA and 8,5′-cyclo-5′-deoxy-dAdo [reactions (241)-(243)].



The rate constants for the *C*(5′) radical with O_2 ($k = 1.8 \times 10^9$ dm^3 mol^{-1} s^{-1}) and $Fe(CN)_6^{3-}$ ($k = 4.2 \times 10^9$ dm^3 mol^{-1} s^{-1}) are close to diffusion controlled. In contrast, the aminyl radical reacts with O_2 reversibly and is oxidized by $Fe(CN)_6^{3-}$ markedly slower ($k = 8.3 \times 10^8$ dm^3 mol^{-1} s^{-1}). With $Fe(CN)_6^{3-}$ as the oxidant, the (5′*R*):(5′*S*) diastereoisomeric ratio of cA is 6.

In the reactions of e_{aq}^- with 8BrAdo are markedly different (Chatgilialoglu et al. 2004). The first step is the same and equally fast, but the *C*(8) radical now not only abstracts the *C*(5′)-H (~60%) but also the *C*(2′)-H (~40%). The *C*(5′) radical adds considerably more slowly to the *C*(8)-position as compared to the

8BrdAdo system ($k \approx 2.3 \times 10^4$, von Sonntag 1987b; $k \approx 1 \times 10^4\ s^{-1}$, Chatgilialoglu et al. 2004), possibly due to conformational differences. Thus, the *C*(5′) radical has a much longer lifetime, and as a consequence high yields of the 5′-aldehyde are formed in the presence of an oxidant such as TNM or O_2 (von Sonntag 1987b). H-abstraction of the *C*(2′)-H leads to the release of Ade [reactions (244) and (245); Chatgilialoglu et al. 2004]. The oxidizing radical formed upon Ade release is monitored by TMPD [reaction (246)], and from a computer analysis of the data a rate constant of $k_{245} = 1.1 \times 10^5\ s^{-1}$ and $k_{246} = 4.6 \times 10^9\ dm^3\ mol^{-1}\ s^{-1}$ has been arrived at (in the original paper, it has been suggested that TMPD is oxidized by the precursor radical cation, but this will deprotonate too rapidly to undergo this reaction).



The Ado *C*(2′) radical has been generated separately in a photolytic experiment using an adequately substituted Ado derivative, and from a competition of Ade release and reduction by GSH $k_{GSH}/k_{245} = 4.3\ dm^3\ mol^{-1}$ has been arrived at. Based on the assumption that k_{GSH} should be around $10^6\ dm^3\ mol^{-1}\ s^{-1}$ a reasonable (within a factor of 2) agreement with the above k_{245} has been obtained. Considering, however, that α-hydroxyalkyl radicals react in aqueous solution at least 50 times faster with thiols (Chap. 7.4), the rate of Ade release may even be much faster then estimated from the above-mentioned computer analysis of the data.

A detailed study on the reaction of 8BrGuo with reducing radicals, notably e_{aq}^- but also with other reducing radicals, has shown that in these reactions it behaves differently from 5BrUra and 8BrdAdo (Ioele et al. 2000). In this case, a comparatively long-lived ($k = 5 \times 10^4\ s^{-1}$) intermediate absorbing at around 600 nm is formed, and in H_2O vs D_2O, there is a strong kinetic isotope effect of $k_H/k_D = 8.0$ in its decay. In the presence of *t*BuOH, equal amounts of Br^- and Guo are formed, and when the reaction is carried out in D_2O, deuteration occurs at *C*(8). Based on spectral similarities, it is suggested that on the way to these products the $G^{\bullet+}$ or $G^{\bullet}$ are intermediates, but it is difficult to see wherefrom the reduction equivalent should come. It is not expected that these intermediates are capable of abstracting an H atom from *t*BuOH with a rate constant of about $10^4\ dm^3\ mol^{-1}\ s^{-1}$ as would be required for a complete reduction of the inter-

mediate by *t*BuOH under the given conditions. Thus, the suggested mechanism must remain tentative. A way out of this dilemma would be if the radical anion first protonated at a heteroatom and subsequently at *C*(8) (these are typical purine reactions, see above, and the latter step would be connected with such a large KIE, see above). The resulting *N*(9) radical would have to undergo $Br^{\bullet}$ loss yielding the observed product Guo and the right isotope labeling. Elimination of $Br^{\bullet}$ in β-fragmentation reactions is common.

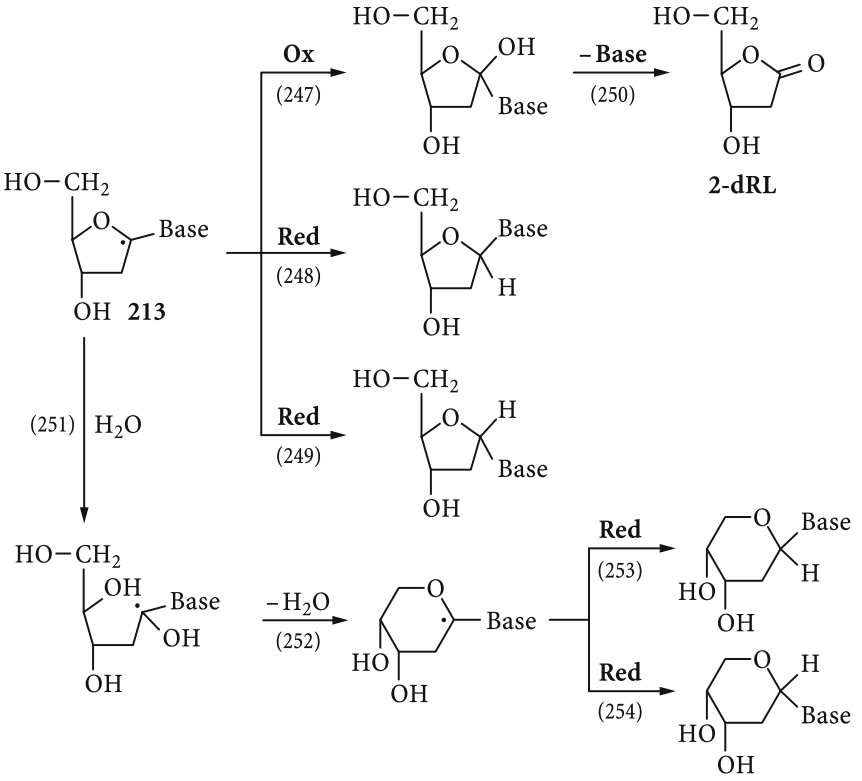
10.8 Reactions of Sugar-Derived Radicals in Nucleosides and Nucleotides

The bond dissociation energies of the various C–H bonds in the 2-deoxyribose moiety have been calculated on the basis of *N*(1)–H BDE in dGuo (380 kJ mol^{-1}; Steenken et al. 2001). They are compiled in Chap. 4, Table 4.6.

The *C*(1′)-H is the most loosely bound hydrogen, followed by *C*(4′)-H. In H-abstraction reactions, these positions are the most likely ones to be attacked be reactive free radicals, while those bound to *C*(2′) are the most unlikely ones. This argument only holds when other parameters, e.g. steric factors and acessibility as in DNA (Chap. 12.2), can be neglected. In the *ribo*-series, the *C*(2′)–H is, of course, again only loosely bound, and many striking differences between the free-radical chemistry of 2′-deoxynuleosides and nucleosides and more noticeably in the corresponding homopolymers may be due to this difference (Chap. 11.2).

10.8.1 Isomerization at *C*(1′) and *C*(4′)

The *C*(1′) radical assumes a close to planar conformation. Upon subsequent reduction the α- and β-isomers are likely to be formed in approximately equal yields [reactions (248) and (249)].



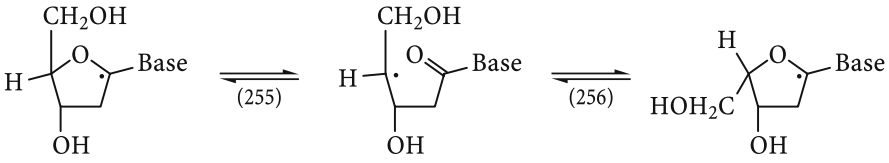
When the starting material is the nucleoside, the reformation of the β-form cannot be monitored, but in the case of dAdo (Mariaggi et al. 1979) and dGuo (Berger and Cadet 1985) the α-form as well as the pyranose forms have been detected. To account for the latter, one has to assume that during the radical lifetime hydrolysis of the *O*-glycosidic linkage occurs [reaction (251)] and reclosure to the pyranose forms takes place [reaction (252)] prior to a subsequent reduction [reactions (253) and (254)]. A rapid hydrolysis of the *O*-glycosidic linkage is a well-documented process in the free-radical chemistry of disaccharides (Kochetkov et al. 1965, 1968; Dizdaroglu and von Sonntag 1973; von Sonntag et al. 1976; Adam 1977; Zegota and von Sonntag 1977), but that the reverse reaction must also be fast has no reported analogy in these systems.

The *C*(1′) radical can also be produced upon UV-photolysis of the corresponding *tert*-butylketone (see below; Goodman and Greenberg 1996; Chatgilialoglu et al. 2000). In the presence of H-donors such as thiols or 1,4-cyclohexadiene, the dUrd-1′-yl radical is reduced into a 3:2 mixture of the β- and α-2′-deoxynucleosides [cf. reactions (248) and (249)]. The rate constant of H-donation by thiols varies only little (mercaptoethanol: 2.3×10^6; cystein: 2.9×10^6; glutathione: 4.4×10^6 $dm^3\ mol^{-1}\ s^{-1}$) and so does the anomeric ratio of the product, dUrd (Chatgilialoglu et al. 2000).

In the case of dGuo an isomerization at *C*(4′) has also been observed. In a preliminary communication this product had been assigned to the β-anomer

Table 10.27. γ-Radiolysis of Thd in N_2O- and N_2O/O_2-saturated solutions. *G* values (unit: 10^{-7} mol J^{-1}) of altered sugars and released Thy. (Dizdaroglu et al. 1976)

Product	N_2O	N_2O/O_2
2,5-Dideoxy-pentos-4-ulose	0.01	Absent
2,4-Dideoxy-pentadialdose	0.02	Absent
2,4-Dideoxy-pentos-3-ulose	0.03	Absent
2,3-Dideoxypentos-4-ulose	0.1	Absent
2-Deoxy-pentos-4-ulose	0.1	0.2
2-Deoxyribonolactone, 2-dRL	0.02	0.07
2-Deoxy-tetrodialdose	Absent	0.03
Thy	≤0.2	≤0.4



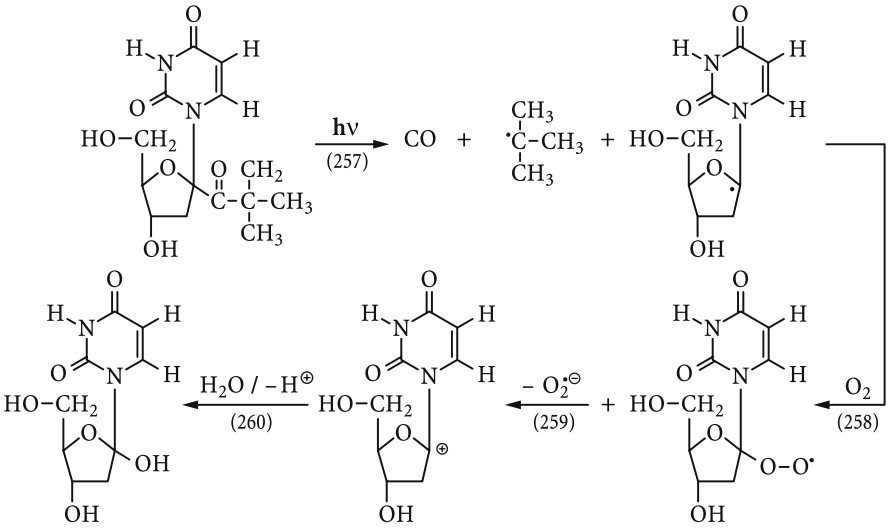
(Berger and Cadet 1983a), but later (Berger and Cadet 1985) to the α-anomer (Table 10.13). The formation of the α-anomer poses the question, how two centers can be isomerized in subsequent reactions. It is well established that in carbohydrates the *C*(1′)-type radical can undergo β-scission (for a review see von Sonntag 1980). If this reaction is reversible the isomerization of two centers is understood.

10.8.2 Oxidation at *C*(1′)

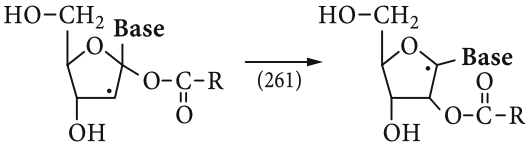
The •OH-induced oxidation of Thd at *C*(1′) leads to the formation of 2-dRL and the concomitant release of Thy [reactions (247) and (250); Dizdaroglu et al. 1976]. In the absence of an oxidant, 2-dRL is formed only in low yields (Table 10.27), and disproportionation reactions with other radicals present have to account for its formation. In the presence of O_2, its yield is considerably increased. This raises the question as to how these reactions may proceed.

This requires a specific generation of the *C*(1′) radical. To this end, the corresponding *tert*-butylketone derivative has been synthesized (Goodman and Greenberg 1996; Chatgilialoglu et al. 1998; Chatgilialoglu and Gimisis 1998). Upon UV photolysis, it looses CO and a *tert*-butyl radical [reaction (257); for

their EPR spectra see Chatgilialoglu et al. 1998]. In the absence of an oxidant, the radicals disproportionate and dimerize. Disproportionation yields α-/β-dUrd and Ura/2-dRL (via the hydrolysis of 1′,2′-dehydro-dUrd) in ~15% yields each pair (Goodman and Greenberg 1996). In a laser flash photolysis experiment, the reaction of the *C*(1′) radical with O_2 [reaction (258)] was determined at $k = 1 \times 10^9$ dm^3 mol^{-1} s^{-1} (Chatgilialoglu et al. 1998). In the presence of TNM, the nitroform anion is formed with a rate constant of 1.5×10^4 s^{-1} (Emanuel et al. 1999). This has been taken as evidence for the rapid release of $O_2^{\bullet -}$ from the *C*(1′)-peroxyl radical [reaction (259)]. In contrast, based on thiol scavenging experiments, it has been calculated that the rate of $O_2^{\bullet -}$ elimination can only be in the order of 1 s^{-1} (Tallman et al. 1998).



In this context, it is worth mentioning that the *C*(1′)-substituted *C*(2′) radical undergoes rapid β-(acyloxy)alkyl rearrangement [reaction (261)], whereby a *C*(1′)-type radical is also formed (Gimisis et al. 1995, 1998).

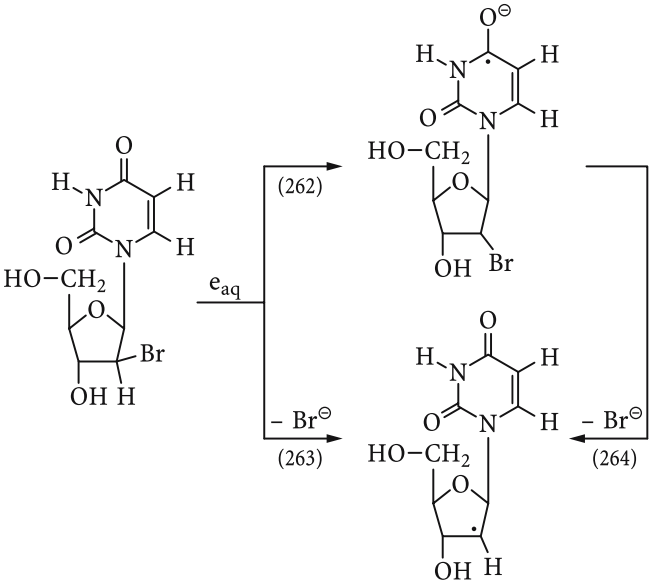


Being a strongly reducing radical, the *C*(1′) radical is also readily oxidized by Fe^{3+} and Cu^{2+}. Rate constants for these reactions have been determined at ~1×10^8 dm^3 mol^{-1} s^{-1} and 7.9×10^7 dm^3 mol^{-1} s^{-1}, respectively (Chatgilialoglu et al. 2000).

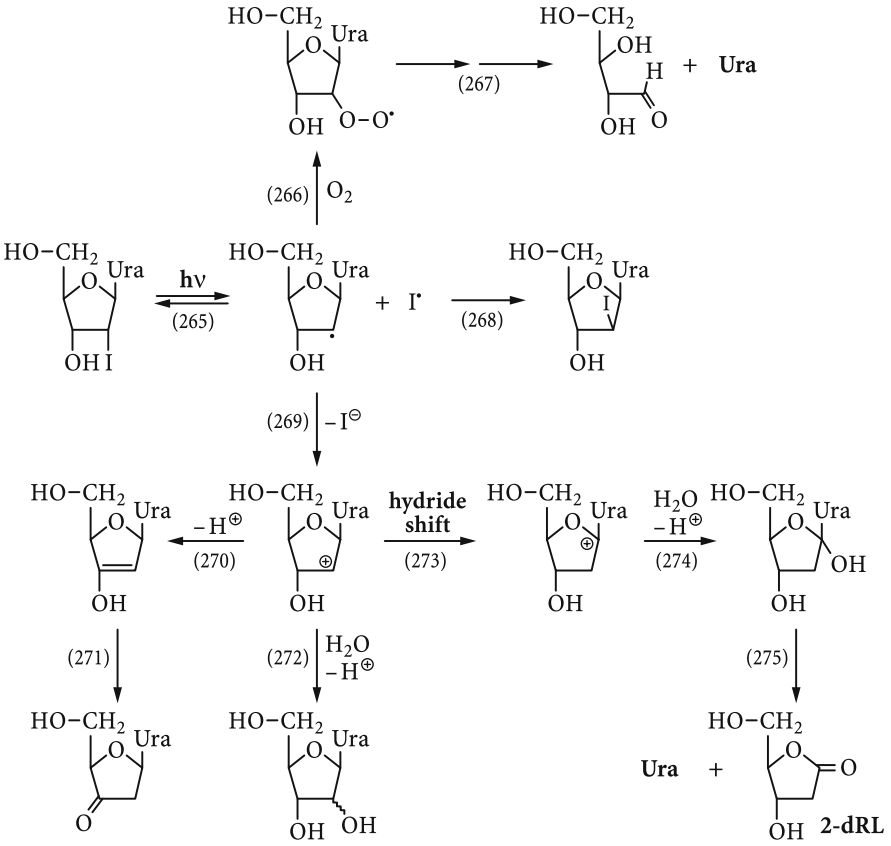
The *C*(1′)-radical is also an intermediate in the free-radical-induced cylisation of 6-(2,2-dibromovinyl)uridine (Gimisis and Chatgilialoglu 1996).

10.8.3
Oxidation at *C*(2′)

The *C*(2′) radical has been generated with some selectivity by reacting 2′BrdUrd with e_{aq}^- [reaction (263)-(264); Hissung et al. 1981b].



In the presence of O_2, it is converted into the corresponding peroxyl radical [reaction (266)]. The bimolecular decay of this peroxyl radical with the other peroxyl radicals present is this system leads to erythrose [reaction (267)] in 15% yield, i.e., the β-fragmentation reaction of a short-lived oxyl radical intermediate is of minor importance.

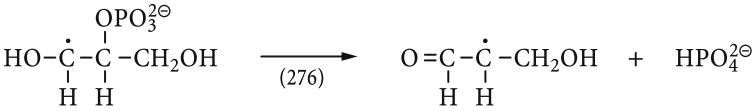


If the peroxyl radical chemistry of other alkyl radicals is any guide formation of hydroxyl and carbonyl functions at the *C*(2′) position are much more likely products (Chap. 8.8). This view is supported by the observation that in Z-form DNA intrastrand H-abstraction of the 2′β-hydrogen by the dUrd-5-yl radical results in 2′-hydroxylation in the presence of O_2 (Kawai and Saito 1999), but the above-mentioned erythrose lesion is also observed in DNA (Dizdaroglu et al. 1977), in dsODNs (Sugiyama et al. 1997) and may even become the major *C*(2′)-derived lesion (Sugiyama et al. 1993). Important information as to the fate of the *C*(2′) radical has been obtained from a study on the photolyis of 2′IdUrd (Sugiyama et al. 1995). The major products (for some additional products, see References) and the suggested pathways for their formation are shown in reactions (265)–(275).

The primary photolytic step is the homolytic scission of the C-I bond [reaction (265)]. The resulting radicals may recombine [reactions (–265) and (268)]. An ET within the solvent cage has also been suggested [reaction (269)]. Alternatively, one may consider the direct formation of the carbocation and iodide ion as a second photolytic pathway. Interestingly, there seems to be a rapid hydride shift [reaction (273)]. Deprotonation at *C*(1′), analogous to reaction (270), and

rapid hydrolysis of the ensuing enol ether [cf. Janik et al. (2000)] would be an alternative pathway. The observed pentose-nucleosides that are suggested to be formed in reaction (245) may also have peroxyl radicals as precursors (see the above discussion).

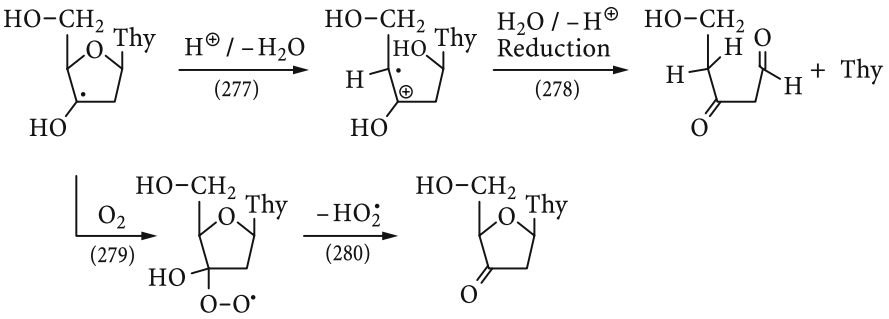
Attack at *C*(2′) in 3′-*ribo*-nucleotides is followed by a rapid release of phosphate as can be deduced from corresponding model systems such as the glycerophosphates (Samuni and Neta 1973; Steenken et al. 1974; Schuchmann et al. 1995) [reaction (276); $k > 10^6\ s^{-1}$; Schuchmann et al. 1995; see also Chap. 6.9].



In *ribo*-nucleosides, the *C*(2′) radical releases very rapidly the base (Chatgilialoglu et al. 2004). Details have been discussed in the paragraph on halogenated bases.

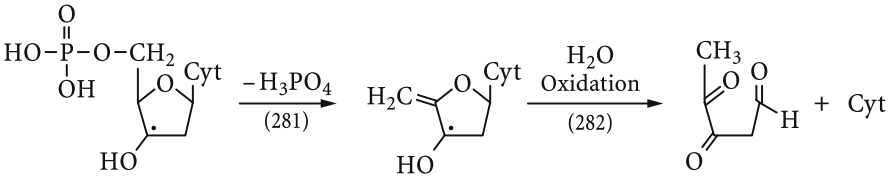
10.8.4 Oxidation at *C*(3′)

The Thd *C*(3′) radical is an α-hydroxyalkyl-β-alkoxyl radical that can rearrange and yields after reduction 2,4-dideoxy-pentos-3-ulose, whereby Thy is released (Dizdaroglu et al. 1976) [reactions (277) and (278); for the yield, see Table 10.27].

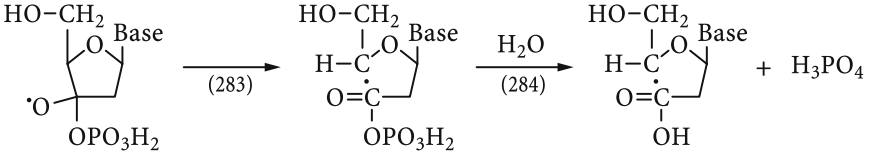


In the presence of O_2, formation of 3-keto-dThd is the most likely process [reactions (279) and (280)]. Since the peroxyl radical formed in reaction (279) is closely related to that derived from 2-PrOH, the rate of $HO_2^{\bullet}$-elimination is expected to be close to $650\ s^{-1}$ (cf. Bothe et al. 1977).

An interesting route has been observed with dCMP (Schuchmann et al. 1983). The formation of the allylic radical upon elimination of phosphoric acid seems to be the driving force for reaction (281). Cyt is released in the subseqent reactions (282). The suggested mechanism has been supported by experiments in D_2O.



H-abstraction at *C*(3′) in 3′-nucleotides gives rise to an α-phosphatoalkyl radical (the phosphatoalkyl group in α-position favors the rate of H-abstraction less than an OH group; Schuchmann et al. 1995). From a study on the •OH-induced reactions of trimethylphosphate, it has been concluded that a hydrolysis of the $^{\bullet}CH_2OP(O)(OCH_3)_2$ radical must be very slow at pH 7 and is just noticeable at high pH (von Sonntag et al. 1972). In the presence of O_2, the alkyl group is fully degraded (formation of dimethylphosphate in full yield; Schuchmann and von Sonntag 1984). The rapid formation of acids ($k = 0.3 + 2.3 \times 10^4$ [OH^-] s^{-1}) has been attributed to the hydrolysis of the anhydride of formic acid and dimethylphosphoric acid (for the hydrolysis of other anhydrides of formic acid see Leitzke et al. 2003). Much closer to the question of the potential reactions of the *C*(3′) radical is a study on triisopropyl phosphate (Schuchmann et al. 1984c). In the presence of O_2, ~50% of •OH gives rise to the formation of diisopropylphosphate, and acetic acid is an important product (Schuchmann et al. 1995). This points to the formation of the anhydride of acetic acid and diisopropylphosphoric acid as an intermediate whose precursor must be an oxyl radical. Translated to the *C*(3′)-O• formed upon the bimolecular decay of the *C*(3′)-OO• radicals of nucleotides, fragmentation of the *C*(3′)-*C*(4′) bond will occur [reaction (283)], and the anhydride function in will subsequently hydrolyze [reaction (284)]. Of course, there are further decay routes, but the reaction sequence shown here must certainly be of a major importance.



Oxidation of α-phosphatoalkyl radicals by TNM leads first to an adduct which subsequently decays thereby releasing NF^- (Schuchmann et al. 1995). Nitroaromatic sensistizers form also adducts albeit more slowly than TNM. Oxidation of α-phosphatoalkyl radicals by $Fe(CN)_6^{3-}$ is only moderately fast.

Phosphate release yields from some 3′- and 5′-mononucleotides are compiled in Table 10.28. The data in N_2O-saturated solutions indicate that phosphate release from the 3′-position is about twice as efficient than that from the 5′-position. Correcting for the fact that under O_2 the •OH yield is about halved, there is a protecting effect for 3′-AMP 3′-dAMP and 3′-GMP but an enhancement in the case of 3′-CMP and 3′-UMP. For the 5′-nucleotides, there is always an increase

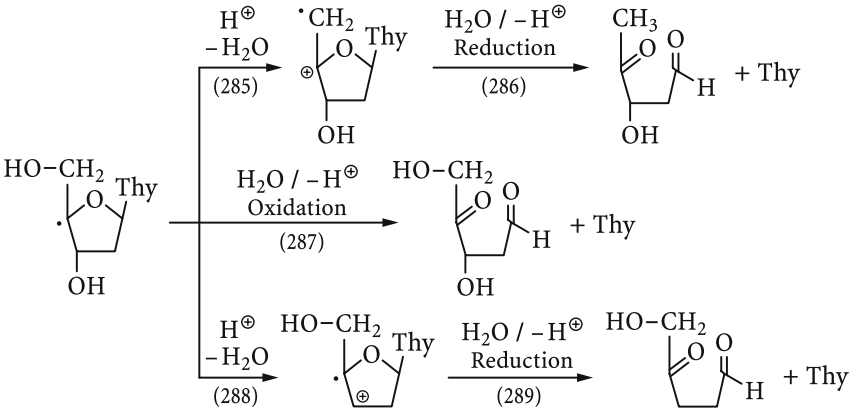
Table 10.28. *G* values (unit: 10^{-7} mol J^{-1}) of inorganic phosphate release in the γ-radiolysis of aqueous solutions of some 3′- and 5′-monoucleotides (Raleigh et al. 1974). Data from Greenstock and Shierman (1975) are given in brackets

Nucleotide	N_2O		O_2	
	3′	5′	3′	5′
AMP	1.02 (1.0)	0.36 (0.29)	0.22	0.29
GMP	0.45	0.24 (0.22)	0.14	0.22
CMP	0.70 (0.67)	0.37 (0.38)	0.72	0.43
UMP	0.75 (0.76)	0.44 (0.45)	0.80	0.48
TMP	0.86	0.37 (0.35)	–	–
dAMP	0.81	0.34 (0.34)	0.13	0.31
dGMP	(0.42)	(0.23)		
dUMP		(0.37)		
dCMP		(0.37)		

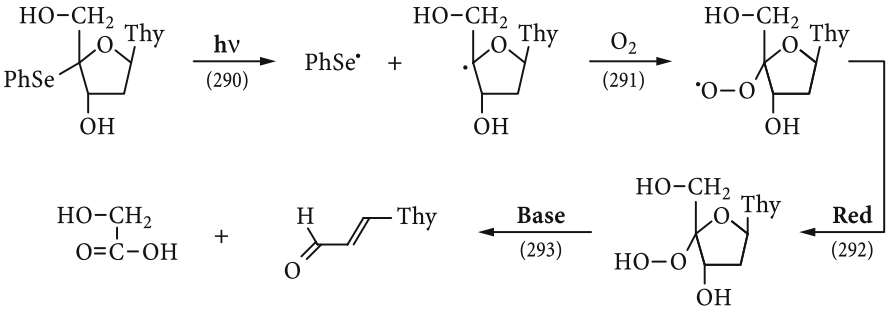
(per •OH) when O_2 is present. Lacking an obvious trend, it is premature to come up with a convincing mechanistic proposal. In the *ribo*-series, the *C*(2′) radicals certainly contribute to phosphate release as discussed above.

10.8.5 Oxidation at *C*(4′)

Some of the sugars that are formed in the radiolysis of Thd also have the *C*(4′) radical as precursor (Dizdaroglu et al. 1976) (for a quantum-chemical study of conformation of the *C*(4′) radical and hyperfine coupling constents see Parr and Wetmore 2004). The water elimination reactions as depicted in reactions (285) and (288) are generally proton-catalyzed. Yet, the ensuing products are also observed in neutral solution. Their yields are given in Table 10.27.

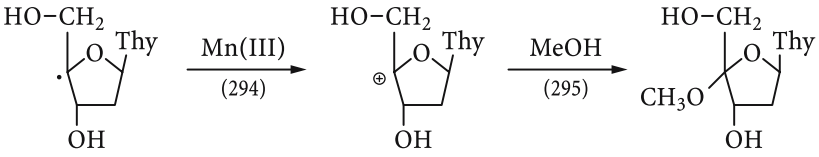


The *C*(4′) radical has been generated specifically photolytically in the presence of O_2 [reactions (290)–(293); Giese et al. 1995].



The hydroperoxide (two isomers) is formed in high yield under these conditions (the nature of the reduction equivalent that is required for this process is as yet not known), and subsequent treatment with a base gives rise to glycolic acid and the base propenal [Grob fragmentation; reaction (292); yields near 90%].

In the absence of O_2 and in the presence of Mn(III) acetate, the *C*(4′) radical is oxidized to the corresponding radical cation which in MeOH gives rise to the acetal [reactions (294) and (295); Beyrich-Graf et al. 1998].



To study the effect of a phosphate group at *C*(5′), D-ribose-5-phosphate has been investigated in some detail as a model system (Stelter et al. 1974, 1975a,b, 1976). The phosphate group is a much better leaving group than the OH group, and its elimination does not require proton catalysis. The data compiled in Table 10.29

Table 10.29. Products and their *G* values (unit: 10^{-7} mol J^{-1}) from γ-irradiated solutions of D-ribose-5-phosphate. (Stelter et al. 1976)

Product	N_2O	N_2O/Fe(II)	N_2O/Fe(III)	N_2O/H_2O_2	N_2O/O_2
Inorganic phosphate	1.35	n.d.	n.d.	1.45	0.62
Pentodialdose	0.23	0.47	0.65	0.38	0.10
2-Hydroxy-4-oxoglutaraldehyde	0.07	Absent	Absent	0.07	Absent
5-Deoxypentos-4-ulose	0.10	0.83	0.44	0.1	Absent
3-Oxoglutaraldehyde	0.06	Absent	Absent	0.06	Absent
Tetrodialdose	Absent	Absent	Absent	Absent	0.42
Formic acid	Absent	Absent	Absent	Absent	0.43
Minor phosphate-free products	0.1	Absent	0.12	0.06	0.09

n.d., Not determined

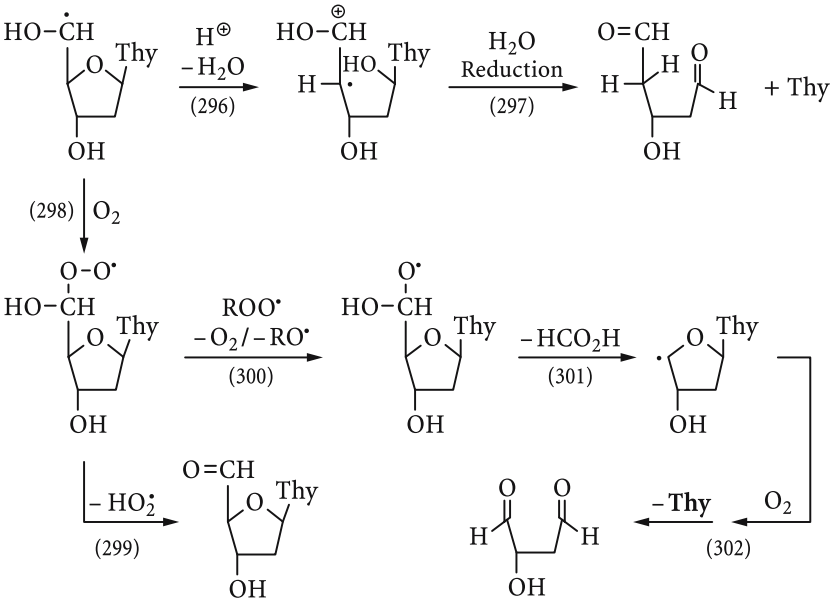
substantiate the view expressed above. They will not be discussed in more detail.

In DNA, H-abstraction at *C*(4′) leads to strand breakage and the same products as reported here are formed in the course of this process (Chap. 12.4). In this reaction, an alkene radical cation/phosphate anion pair is formed. The dynamics of this reaction has been studied in some detail with the help of adequately substituted model systems (Crich and Huang 2001).

10.8.6 Oxidation at *C*(5′)

The formation of purine 5′,8-cyclonucleosides and -cyclonucleotides and pyrimidine 5′,6-cyclco-nucleosides are a typical product of an oxidation at *C*(5′). Because it involves an addition of an alkyl radical to the base moiety, this reaction has already been discussed in Section 5.3.1. The dAdo *C*(5′) radical was generated specifically by reacting 8BrdAdo with e_{aq}^-. The ensuing reactions are discussed in Section 7.2.

According to the study on Thd already mentioned above (Dizdaroglu et al. 1976), the release of Thy is connected with the formation of 2,4-dideoxypentodialdose [reactions (262) and (263)].



In the presence of O_2, the *C*(5′) radical is converted into the corresponding peroxyl radical [reaction (298)]. Upon its bimolecular decay with other peroxyl radicals present, the oxyl radical is formed [reaction (296)]. An analogous oxyl radical has been produced by thermally decomposing the *tert*-butyl ester of thymidine-5′-carboxylic acid (Montevecchi et al. 2004). These oxyl radicals undergo ready β-fragmentation [reaction (301)], and the most pronounced products of this reaction are 2-hydroxytetrodialdose and Thy [reaction (302); Dizdaroglu et al. 1976]. Interestingly, the $HO_2^{\bullet}$-elimination [reaction (299)] is not sufficiently fast to compete effectively at pH 7. For yields, see Table 10.27.

10.8.7 Base Release

The release of unaltered bases is a general phenomenon of the free-radical-induced reactions of DNA and its constituents. The process is multi-phasic. Typically, a fraction is set free on the time-scale of the free-radical reactions or very shortly afterwards (Table 10.30). Mechanistically, this could mean that a base can already be eliminated at the free-radical stage (for an example see above) or that a resulting non-radical product is very unstable. The determination of the released bases (e.g., by HPLC) requires a couple of minutes. Thus, a fast hydrolyzing intermediate cannot be distinguished experimentally from processes occurring at the free-radical stage. However, the slow component is certainly due to unstable non-radical products. In the course of base release, the altered sugars that gave rise to this instability of the *N*-glycosidic linkage are set free. Their determination yields valuable information as to the structures of these labile products and may even provide a clue as to the mechanism of their formation.

Table 10.30. γ-Radiolysis of N_2O/O_2-saturated aqueous solutions of 2′-deoxynucleosides (2×10^{-3} mol dm^{-3}). *G*(base release) (unit: 10^{-7} mol J^{-1}) immediately after irradiation and after heating for 3h at 60 °C. (Wagner and von Sonntag, unpubl. results)

2′-Deoxynucleoside	Immediately	After 3 h at 60 °C
dAdo	0.37	0.57
dGuo	0.16	0.27
dCyd	0.20	0.51
Thd	0.14	0.45

Table 10.31. *G* (base release) from nucleosides and nucleotides γ-irradiated in aqueous solution

Substrate	Saturating gas	*G* value	Substrate	Saturating gas	*G* value
Thd	N_2O	0.2[a]	Urd	N_2O	0.66[b]
	N_2O	0.14[b]	UMP	Air	0.28[d]
	N_2O/O_2	0.4[a]	Ado	N_2O	1.2[b]
	N_2O/O_2	0.14[b]	ADP	Air	0.35[e]
dCyd	N_2O	0.79[b]	Ado-3′,5′-P	N_2O	0.2[b]
dAdo	N_2O	0.43[b]		N_2O/O_2	0.39[b]
	N_2O/O_2	0.54[b]	Inosine	N_2O	0.91[b]
dUrd	N_2O	0.34[b]		N_2O/O_2	0.46[b]
TMP	N_2O	0.1[b]	IMP	N_2O	0.77[b]
dThy-3′-P	N_2O	0.27[b]		N_2O/O_2	0.46[b]
dCCMP	N_2O	1.0[c]	dIMP	N_2O	0.35[b]
dAMP	N_2O	0.33[b]		N_2O/O_2	0.72[b]
	N_2O/O_2	0.64[b]			

[a] Dizdaroglu et al. (1976)
[b] Steenken and Schulte-Frohlinde, unpublished, reported in von Sonntag (1987a)
[c] Schuchmann et al. (1983)
[d] Ducolomb et al. (1971)
[e] Hems and Eidinoff (1958)

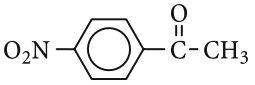
Typically, a mixture of such labile products are formed side by side, but more recently the precursor radicals of at least some of the labile products can be made quite specifically (e.g., the radical at *C*(1′), see above). In the future, this may al-

low an assignment of the various components to certain intermediates. Potential intermediates have been discussed in the preceding paragraphs.

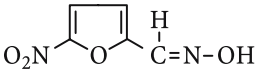
Further base release data are compiled in Table 10.31. There is a considerable spread in these values among the various nucleosides/nucleotides even under seemingly same experimental conditions. Part of this variation could be due to a change in the ratio of •OH attack at the base vs sugar moieties. The time elapsed between irradiation and work-up may also play a role (see Table 10.30). Compared to the 2′-deoxynucleosides, an additional site, *C*(2′), is likely to contribute. There is a dramatic difference between Ado and Ado-3′,5′-P. Phosphate release may here compete with base release. Further data are required to put this suggestion on a better footing.

10.9 Oxidation of Nucleobase/Sugar Radicals by Radiation Sensitizers

The oxidation of DNA radicals by hypoxic sensitizers, normally nitro compounds, has found considerable interest in the context of attempts to improve irradiation regimes in the radiotherapy of solid tumors (Chap. 12.11). Concomitantly, model studies have been undertaken in order to shed some light on potential mechanism of their reactions. *p*-Nitroacetophenone (PNAP) has often been used as a convenient model sensitizer.



PNAP



Nifuroxime

The radicals derived from 2-deoxyribose (ribose) upon •OH-attack yield 37% (23%) $PNAP^{\bullet -}$, and it has been concluded that ET only occurs from the *C*(1′) radicals (Michaels et al. 1976). With $^{\bullet}CH_2OH/CH_2O^{\bullet -}$ the rate of reaction with PNAP is only fast with the anion, $CH_2O^{\bullet -}$ (Adams and Willson 1973). Whether the radicals formed at the other sites in 2-deoxyribose and ribose give (slowly) rise to adducts cannot be deduced from the reported data. Yet, the fact that PNAP enhances the yield of free phosphate in the radiolysis of GMP (Greenstock et al. 1973a) is an indication that such adducts are likely to be formed, but the rate of reaction is very slow with α-phosphatoalkyl radicals ($< 5 \times 10^7$ dm^3 mol^{-1} s^{-1}; Schuchmann et al. 1995).

Practically no ET to PNAP occurs from the reducing Ura-6-yl Cyt-6-yl radicals, but the (protonated) Cyt electron adduct gives rise to $PNAP^{\bullet -}$ (Hissung and von Sonntag 1979). As mentioned above, the (protonated) electron adduct of dAdo is also rapidly oxidized by PNAP, but upon ET, dAdo is not reformed (Hissung et al. 1981a). Possibly, the resulting product retains the elements of water.

With a nitro compound that has a higher reduction potential than PNAP, e.g., nifuroxime, the rate of reaction with various radicals seems to be always near diffusion-controlled, and there is a competition between ET and adduct formation

(Greenstock and Dunlop 1973). The adducts are still radicals. As discussed in Chap. 6.3, they may decompose unimolecularly by releasing the sensitizer radical anion or undergo β-fragmentation yielding the nitroso compound and an oxyl radical (Nese et al. 1995). Although in its outcome the former reaction is equivalent to an ET, the branching (competition) occurs now at the level of the adduct.

Quinones are also strong oxidants, and their potential as radiation sensitizers has been investigated on the model level. Again, ET competes with addition (Simic and Hayon 1972, 1973; Hayon and Simic 1973). With carbon-centered radicals, a C-C bond is formed in the addition reaction, and subsequent reactions are different (von Sonntag et al. 2004) from the adducts formed with nitro compounds.

10.10 Irradiation in the Solid State

Experiments in the solid state, especially EPR studies, have supplemented our knowledge in the area of the free-radical chemistry of nucleobases and related compounds considerably. Here, only some salient points can be mentioned, and for more detailed information the reader is referred to the excellent reviews that have appeared on this topic (Wyard and Elliott 1973; Bernhard 1981; Hüttermann 1982, 1991; Close 1993; Sevilla and Becker 1994; Becker and Sevilla 1997) and to the book by Box (1977).

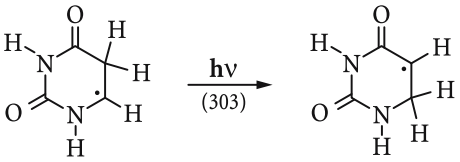
Mainly two types of experiments have been carried out, γ-irradiation in the solid state (mainly single-crystals) and in glassy matrixes at low temperatures. In addition, γ-irradiated solids may be dissolved in water containing spin traps, and the spin-trapped radicals identified by EPR afterwards (cf. Mossoba et al. 1981; Spalletta and Bernhard 1982; Zhang et al. 1983). While irradiation in a glassy matrix is very much related to the situation that prevails in aqueous solutions, that is, the radicals generated in the matrix react with the added substrates, irradiation in the solid state may cause radical formation via two different processes: ionization processes (formation of radical cation is and radical anions) and the decomposition of electronically excited states (which could also be formed upon recombination of a radical cation and an electron). It has often been tried to disentangle these two primary processes, but, of course, such assignments are not always straightforward. Sometimes, a confusing terminology persists which calls the electron-loss centers radical cations and the electron-gain centers radical anions, irrespective of their protonation state (i.e. charge sign).

Whenever H$^\bullet$-adducts are observed, they must not necessarily have H$^\bullet$ as precursor. Protonation of the radical anion must always be considered as an alternative/additional route. In crystals, the radical cations may serve as the proton source, while in frozen aqueous solutions the solvent will provide the proton.

Frozen solutions. In frozen aqueous solutions, the additive may not precipitate but accumulate in ice-free areas in a rather uncontrolled way. Upon irradiation, there are only a few radicals from the radiolysis of ice that reach the solute, and radical formation can occur by direct absorption of the energy of ionizing radia-

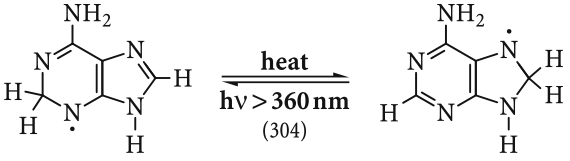
tion. In addition, erenkov radiation will photoexcite the solutes, and being aggregated they stand a chance of forming well-known photoproducts, e.g., in the case of Thd the cyclobutane dimers (Shaw et al. 1988). The long lifetimes of the radicals under these conditions make reactions possible that are not as readily observed in liquid water. For example, all conceivable 5′,6-5,6-dihydrocyclonucleosides were observed both for Thd and dUrd (Shaw and Cadet 1988), and the same cyclonucleoside as is formed with dUrd is also observed with dCyd (Shaw and Cadet 1996 or other Cyt deamination reactions; see above).

Single-crystals and powders. In Ura, the *N*(1)-centered radical is observed (Zehner et al. 1976). Based on our present knowledge, one may suggest that it arises most likely from the deprotonation of the radical cation. The radical anion is protonated at *O*(4). The *C*(5)-H•-adduct primarily formed is converted with light of $\lambda > 400$ nm into the thermodynamically more stable *C*(6)-H•-adduct [reaction (303)]. This is also observed with other pyrimidines (Flossmann et al. 1976).

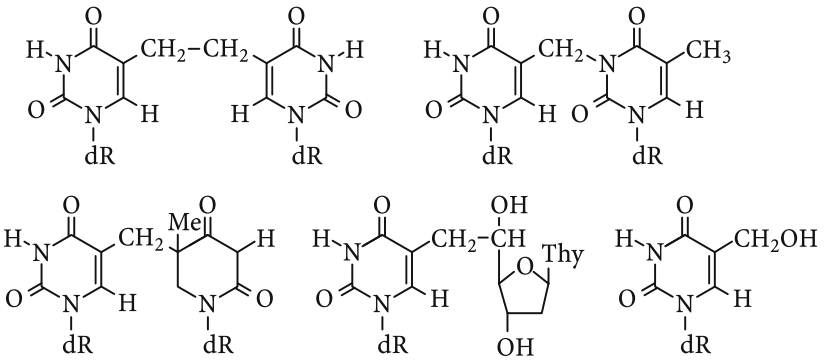


In 1MeUra, a predominating radical is the -CH_2• radical (Flossmann et al. 1973, 1975a,b). A -CH_2• radical (here, allylic) is also observed with Thy and 5MeCyt (Hüttermann 1970; Hüttermann et al. 1971; Dulcic and Herak 1973). Radical cations are likely precursors, while the precursor of the Thy *C*(6)-H•-adduct that is commonly observed (Henriksen and Snipes 1970) could be the Thy radical anion (Symons 1990; see above).

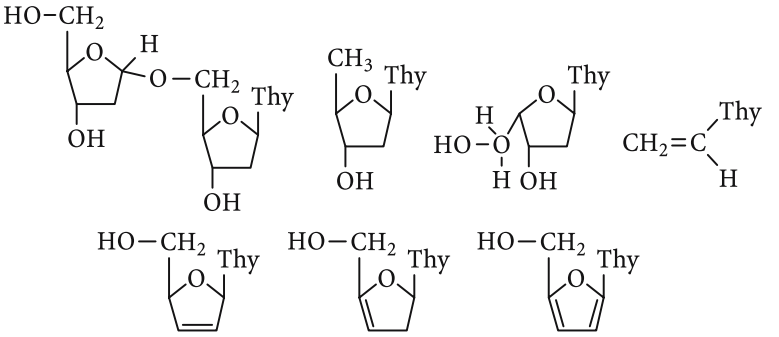
The ENDOR technique applied to an X-irradiated dAdo single-crystal allowed a complete analysis of the EPR parameters of the major radicals formed in that system (Nelson et al. 1998). The hole deprotonates at *N*(6) while the electron gain center protonates at *N*(3); •H-adducts are formed at *C*(2) and *C*(8). The thermodynamically more stable radical is the *C*(8) •H-adduct (see above), but in Ade light can convert the *C*(8) •H-adduct into the *C*(2) •H-adduct [Zehner et al. 1977; reaction (304)].



Photolysis of $G^{\cdot+}$ leads to the formation of sugar radicals (Adhikary et al. 2005). Product studies from solid state irradiation of Thd are also available (Gromova et al. 1999). As discussed above, the Thd radical cation is expected to deprotonate at *N*(3) and at methyl, and the ensuing structural elements indeed dominate the product spectrum parts of which is shown below.

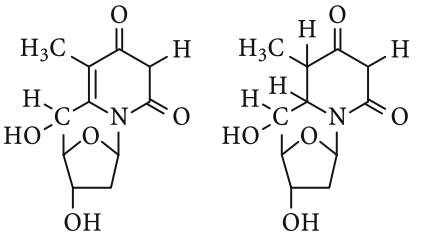


The release of free base (see also Hoffman and Hüttermann 2000) and the formation of 2-dRL results from a damage of the sugar moiety, but there are a host of



further products altered at the sugar moiety.

The formation of the cyclonucleosides shown below (for their synthesis see Romieu et al. 1999b) shows that the addition of the *C*(5′) radical can also add to the *C*(5)-*C*(6) Thy double bond [the corresponding Cyd case has been discussed



above in reactions (195) and (196)].

In the irradiation of solid Thd the formation of •H-adducts is established (see above), and it is thus not surprising that H_2Thd (and also H_2Thy; secondary product?) are also among the products.

Similar experiments have been carried out with dGuo (Gromova et al. 1998). The free base, 2-dRL sugar lesions of analogous to those reported above (now

Table 10.32. Photosensitized oxidation of Thd by benzophenone and menadione. Product yields after 44% conversion of the educt. (Delatour et al. 1998)

	HMdUrd	FordUrd	Tg
Benzophenone	7.5%	20%	19%
Menadione	7.5%	16%	55%

with Gua as the base) have again been observed. The 8,5′-deoxy-cyclonucleoside, cG and the 5′-aldehyde (mechanistically interesting is the formation of two isomers; is an enol the intermediate?) are the other products that have been detected.

10.11 Photosensitization and Singlet Dioxygen Reactions

Photoexcited anthraquinone-2,6-disulfonate undergoes ET with Thy and its methyl derivatives, and the EPR results (Geimer et al. 1997; Geimer and Beckert 1998, 1999) have been discussed above.

Thy and Thd quench triplet menadione giving rise to the menadione radical anion (Wagner et al. 1990b). The corresponding Thy product has been considered to be the Thy radical cation, based on the rapid oxidation of TMPD. However, this intermediate has been shown to deprotonate rapidly ($pK_a = 3.2$; Geimer and Beckert 1998), and it is more likely that this rapid oxidation is given by the *N*-centered radical formed upon deprotonation of the radical cation. The reactions of menadione- and benzophenone-sensitized oxidation of Thd in the presence of O_2 lead mainly to HMdUrd, FordUrd and Tg (Decarroz et al. 1986; Delatour et al. 1998; Table 10.32). It has been suggested that the reaction mainly proceeds via an ET (formation of the Thd radical cation), but H-abstraction at methyl has not been excluded as an additional pathway. Qualitatively, these two sensitizers yield the same products, but interestingly, the material balance is much better in the case of menadione sensitization. The reason for this is not yet known.

The products that are formed upon photosensitization of dCyd by menadione were already given in Table 10.16 together with those formed upon $^{\bullet}OH$-attack. It has again been suggested that the precursor of these products is the dCyd radical cation formed by ET to excited menadione (Decarroz et al. 1987).

The riboflavin triplet reacts with dGMP acid by ET ($k = 6.6 \times 10^9$ dm^3 mol^{-1} s^{-1}), and evidence for the formation of the (deprotonated) Gua radical cation has been obtained by laser flash photolysis (Lu et al. 2000). The photosensitized reactions of dGuo by TRP is thought to follow two pathways, the formation of Z has been attributed to an ET reaction (Type I), and the reaction of singlet dioxygen [$O_2(^1\Delta_g)$; Type II] leads to 4-OH-8-oxo-G and 8-oxo-G (Ravanat et al. 1998). The effect of D_2O and azide on the 4-OH-8-oxo-G yields shows that this

Table 10.33. Photosensitization of dGuo by various sensitizers. Ratio of product distribution. (According to Ravanat et al. 1998)

Photosensitizer	(4-OH-8-oxo-G + 8-oxo-G)/Z
Zn-TRP	5.6
Methylene blue	3.6
TRP	2.3
Riboflavin	0.4

TRP = μ[meso-5,10,15,20-tetra(pyridyl)porphyrin]tetrakis[bis(bipyridine)chloride ruthenium(II)]

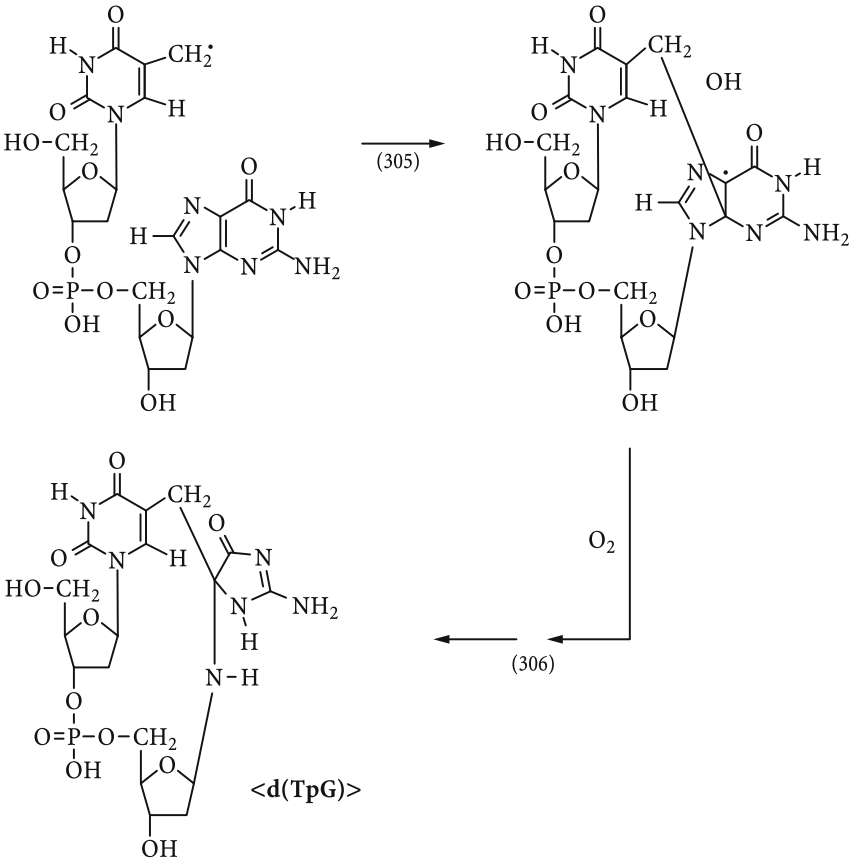
Table 10.34. Effect of photoexcited menadione, benzophenone and riboflavin on Thd, dGuo and d(TpG). Degradation (+ = observed, - = not observed) and specific products in the case of d(TpG). (Delatour et al. 1999)

	Menadione	Benzophenone	Riboflavin
Thd	+	+	–
dGuo	–	+	+
d(TpG)	+	+	+
T → HMdU/FordU	+	+	–
dG → dZ	–	+	+
<d(TpG)>	+	+	–

product results from the $O_2(^1\Delta_g)$ reaction (for the synthesis of oligonucleotides that contain this lesion see Romieu et al. 1999d). The products are very sensitive to further degradation, even at low conversions. In a mixture of dGuo and 8-oxo-G, the latter is practically fully degraded before dGuo starts to be consumed (Ravanat et al. 2003). This has been attributed to the rapid oxidation of 8-oxo-G by $G^{\bullet}$ ($k = 4.6 \times 10^8$ dm^3 mol^{-1} s^{-1}; Steenken et al. 2000). Moreover, the reaction of $O_2(^1\Delta_g)$ with 8-oxo-G readily yields as the major product 1-(2-deoxy-β-D-erythro-pentofuranosyl)cyanuric acid (Raoul and Cadet 1996), but Z is also among the products (Ravanat et al. 1998). In fact, methylene blue photooxidizes 8-oxo-G three times faster than dGuo (Buchko et al. 1995a). As a consequence, the ratio of the product yields, shown for various sensitizers in Table 10.33, may have a wide error bandwidth, but the data strongly indicate that sensitization by

riboflavin differs mechanistically from that of the other which mainly produce $O_2(^1\Delta_g)$.

These studies have been extended to the photooxidation of d(TpG) by riboflavin and methylene blue, and again Z and its precursor Iz have been characterized (Buchko et al. 1995b). When d(TpG) is photooxidized with benzophenone or menadione, an additional product, <d(TpG)>, is formed [reactions (305) and (305); Delatour et al. 1999]. It constitutes a tandem lesion.



The effects of the three sensitizers, menadione, benzophenone and riboflavin that have been investigated with respect to their reactivity towards Thd, dGuo and d(TpG) are compared in Table 10.34. Riboflavin is only capable of sensitizing dGuo and the Gua moiety of d(TpG), and thus does not give rise to <d(TpG)>. In contrast, menadione does not sensitize dGuo or the Gua moiety of d(TpG).

Mechanistically, it is likely that in the first step to <dTpG)> the allylic Thy radical is created. There are two possibilities: (a) ET from Thy to the sensitizer and deprotonation of $Thy^{\bullet+}$ or (b) H-abstraction of the allylic hydrogen by the sensitizer. The authors favor route (a). Yet $Thy^{\bullet+}$ should oxidize rapidly the neighboring Gua moiety. Moreover, it is difficult to see, why excited menadione

does not oxidize dGuo, although Gua is more easily oxidized than Thy. Another intriguing aspect is the report that the riboflavin triplet reacts rapidly with dUMP by ET (Lu et al. 2000), but no products that should be formed from this type of reaction are observed for Thd (Delatour et al. 1999) that should undergo that reaction as easily. For explaining the formation of the observed products, the allylic Thy radical has to add to *C*(4) of the neighboring Gua moiety [reaction (305)], and addition of O_2 to the Gua radical thus generated will convert in subsequent reaction this part of the molecule into Z [reaction (306)]. Reaction (306) is in competition with an O_2-addition to the allylic Thy radical that leads to the other observed product, the HMdU and FordU derivatives.

Photooxidation of the dGuo-5′-lysine ester leads to Z cross-linked to the lysine moiety (Morin and Cadet 1995), indicating that DNA-protein cross-links may also occur via such a process in case this amino acid happens to be in a proper position for the reaction to proceed.

Photooxidation of Ade by menadione results in a complex sequence of reactions to a formylation and acetylation of Ade at *N*(6) (Wang and Liu 2002). These groups stem from the sensitizer.

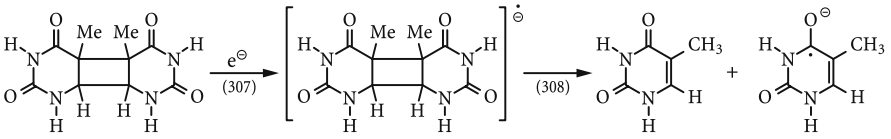
Photooxidation of purine nucleosides and also of Cyt by pyrimido[5,4-*g*]pteridine *N*-oxide under argon affords in high yields the 5′-*O*,8-cyclopurine nucleosides and 5′-*O*,6-cyclocytidne, whereby the *N*-oxide is reduced (Sako et al. 1986). Nucleobase radical cations are believed to be the intermediates in this surprising oxidation reaction.

10.12 Oxidation by Transition Metal Ions in their High Oxidation State

Transition metal ions in their high oxidation state have also been used to oxidize DNA components. These reactions may involve one-electron oxidation steps, i.e., free-radicals may also play a role. Oxoruthenium(IV) complexes oxidize GMP an order of magnitude faster (k = 6.1 - 15 $dm^3\ mol^{-1}\ s^{-1}$) at the base moiety than dCMP (0.24 - 0.47 $dm^3\ mol^{-1}\ s^{-1}$), where the sugar moiety is attacked (Farrer and Thorp 2000).

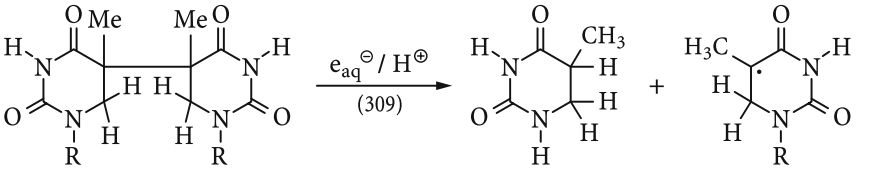
10.13 Free-Radical-Induced Transformations of Damaged Nucleobases

A number of studies are concerned with the free-radical reactions of typical nucleobase lesions. For example, the cyclobutane-type Thy dimer can be split by one-electron reduction [Heelis et al. 1992; reactions (307) and (308)], a process that is relevant to the repair of this typical UV-damage by the photoreactivating enzyme (photolyase, for a review see Carrell et al. 2001, for the energetics of the complex reaction sequence, see Popovic et al. 2002). At 77 K, the dimer radical anion is sufficiently long-lived to be detectable by EPR (Pezeshk et al. 1996).

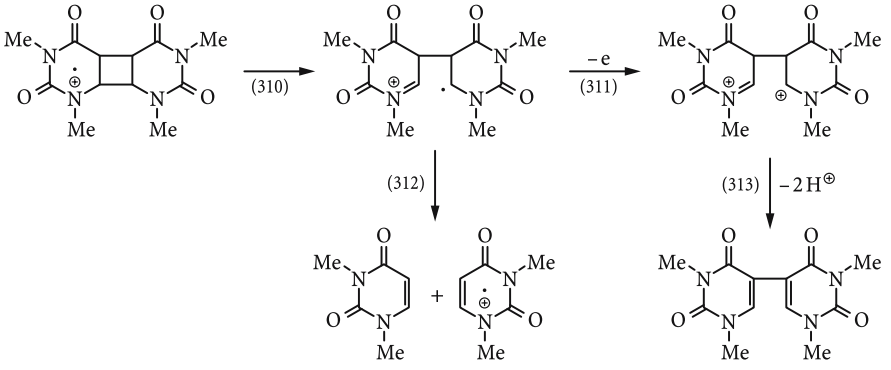


The dimer can be split by e_{aq}^- and by other reducing radicals such as $CO_2^{\bullet -}$ or $^{\bullet}C(CH_3)_2OH$, albeit with a much lower efficiency. The resulting Thy radical anion is also capable of transferring an electron to the Thy dimer, and this leads to a short chain reaction.

The *C*(5)-*C*(5′)-linked dihydrothymine dimers are also readily split by e_{aq}^- [reaction (309)] forming H_2Thy but also Thy in appreciable yields (Ito et al. 2000).



Reaction with $^{\bullet}OH$ also leads to the splitting of the dimer (~30% efficiency), and there is evidence that one-electron oxidants such as $SO_4^{\bullet -}$ may also induce the splitting of the dimer (Heelis et al. 1992). The $^{\bullet}NO_3$-radical-induced splitting of the tetramethyl-substituted Ura cyclobutane dimer has been investigated in acetonitrile (Krüger and Wille 2001). The $^{\bullet}NO_3$ radical has been generated photolytically from a Ce(VI) salt (Chap. 5.2). Under theses conditions, the 5-5′-linked intermediate is also trapped, possibly by a deprotonation or a Ce(IV)-mediated oxidation that competes with β-fragmentation [reactions (310)–(313)].

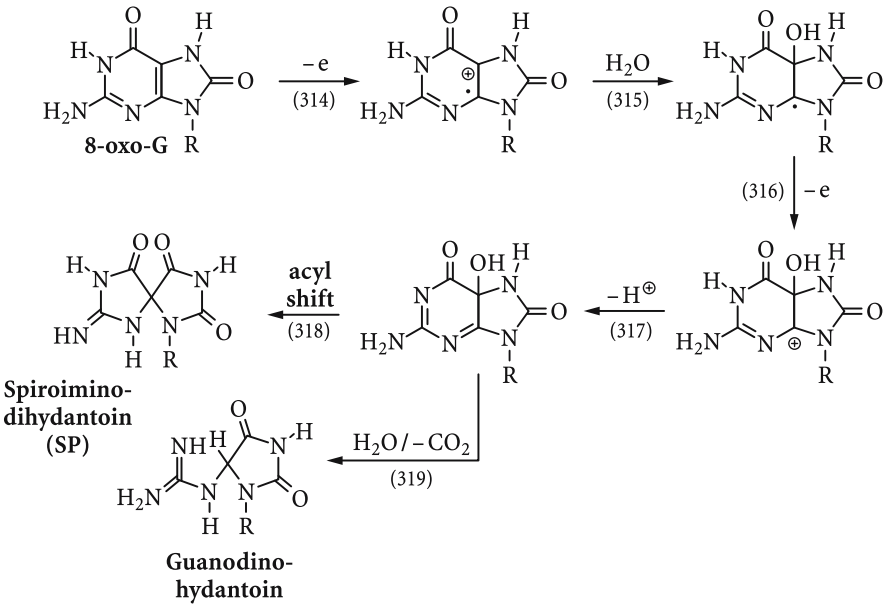


One-electron oxidation of the 5,5′-linked dihydrothymine dimer by $SO_4^{\bullet -}$, $N_3^{\bullet}$ or photoexcited anthraquinone-2-sulfonate also affords Thy together with H_2Thy (Ito et al. 1999).

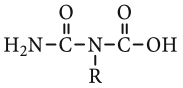
The reaction of $CO_2^{\bullet -}$ with Tg affords Thy, H_2Thy and 6OHH_2Thy (Nishimoto et al. 1985). The yield of the former two products is noticeably enhanced

in the presence of Fe^{2+}. Photoreduction of Tg by aromatic amines leads such as TMPD, leads to Thy (72%) and 6OHH$_2$Thy (27%) (Ide et al. 1985).

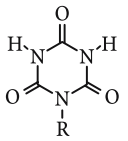
The reduction potential of 8-oxo-G is low [E^7 = 0.74 V/NHE (Steenken et al. 2000); +0.6 V (Berger et al. 1990)]. It is thus more easily oxidized than dGuo, and may act as a sink of oxidizing radicals (Doddridge et al. 1998), including $^{\bullet}NO_2$ ($k = 5.3 \times 10^6$ dm^3 mol^{-1} s^{-1}; Shafirovich et al. 2001). It is about 1000-fold more reactive towards peroxynitrite than dGuo (Burney et al. 1999; Niles et al. 1999; for a nitration product, see Niles et al. 2000; for a study in ODNs see Tretyakova et al. 1999; for the repair of such lesions see Duarte et al. 1999). With such a low reduction potential, it may even be oxidized by peroxyl radicals whose reduction potentials range between 0.77 and 1.6 V (Chap. 8.3). Upon its oxidation, spiroiminodihydantoin (Sp) is formed as the major product [reactions (314)–(318); Luo et al. 2000]. To a lesser extent some decarboxylation also occurs [reaction (319)]. This product has been characterized in some detail (Luo et al. 2001b).



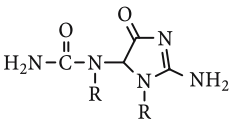
Sp is also a major (final) product in the oxidation of dGuo by triplet states (Luo et al. 2001a; Adam et al. 2002a,b; for an earlier study see Adam et al. 1996). Further reported oxidation products of 8-oxo-G are oxaluric acid (by $O_2(^1\Delta_g)$; Duarte et al. 2000), cyanuric acid, iminoallantoin, parabanic acid and 1,3,5-triazepane-2,4,6,7-tetrone (Hickerson et al. 1999). Oxaluric and parabanic acids may also be formed upon the reaction of the 8-oxo-G radical with $O_2^{\bullet-}$ (Misiaszek et al. 2005; Chap. 12.3).



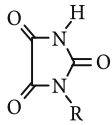
Oxaluric acid



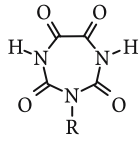
Cyanuric acid



Iminoallantoin



Parabanic acid



1,3,5-Triacepane-2,4,6,7-tetrone

$O_2(^1\Delta_g)$ not only oxidizes dGuo to 8-oxo-G, but the latter reacts even two orders of magnitude faster with this oxidant (Sheu and Foote 1995a), whereby the 4-hydroperoxide is formed via an unexpected rearrangement of the dioxetan intermediate (Sheu and Foote 1995b). The water-soluble endoperoxide derived from *N*,*N*′-di(2,3-diydroxypropyl)-1,4-naphthalenedipropanamide is a clean source of $O_2(^1\Delta_g)$, and can even prepared with an ^{18}O label. Using this approach, the oxygen label in the final products, Iz, Z, Sp and guanodinohydantoin was detected (Martinez et al. 2002).

The dCyd oxidation products 5-hydroxy-dCyd and 5-hydoxy-dUrd have low oxidation potentials (Wagner et al. 2004) and are hence likely to be oxidized further. For this reason the oxidation of 4-hydroxy-dUrd has been studied (Rivière et al. 2004). Using Br_2 or Na_2IrBr_6 but also menadione plus UV as oxidants, the main oxidation products were the isodialuric acid, dialuric acid and hydantoin derivatives.

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