Polymer Radicals

9.1
General Remarks

Linear man-made polymers and also some biopolymers may have only one repeating unit, but often there are more than one repeating unit which do not follow one another in a regular way. With its four nucleotides as repeating units, DNA is a typical example. In solution, neutral linear polymers attain a coil-like conformation. In charged polymers, the charges repel each other, and the conformation of the polymer becomes rod-like. The local density of the repeating units and the conformation of the polymer chain have a dramatic effect on some of the properties of the free-radical chemistry of the polymer (Ulanski et al. 1997). Quite a number of the properties of DNA radicals can be understood if it is taken into account that DNA is a highly charged polymer.

9.2
Rate of Formation of Polymer Radicals

The rate of reaction of neutral free radicals such as $^{\bullet}OH$ with a polymer or an equal concentration (in g dm^{-3}) of its subunits is generally much lower for the polymer than that of the low molecular weight compound. The low molecular weight molecules are randomly distributed throughout the solution, while the polymer chains do not fill equally well the whole space. Thus, the average distance that a reactive free-radical has to travel to reach the target molecule is much longer in the case of the polymer. Experimentally, this has been shown with many synthetic polymers (Behzadi et al. 1970; Ulanski et al. 1995), and the rate of reaction of DNA with $^{\bullet}OH$ is also much lower (2.5×10^8 dm^3 mol^{-1} s^{-1}; Udovicic et al. 1994; for corresponding data on polynucleotides see Michaels and Hunt 1973) than that with nucleotides ($\sim 3 \times 10^9$ dm^3 mol^{-1} s^{-1}; for a compilation see Chap. 10.3). The rate constants of $^{\bullet}OH$ are often determined in competition with SCN^-. With charged polymers such as DNA or poly(A) (Loman and Ebert 1968), this may lead to complications and eventually to erroneous results due to a repulsion of SCN^- from the highly charged polymer (Ulanski and von Sonntag 2000).

The rate of reaction of e_{aq}^- with charged polymers such as polynucleotides is much lower than that of parent bases (Shragge et al. 1971). An electrostatic repulsion of e_{aq}^- by the negatively charged polymer adds to the effect discussed above. These much lower rates of polymers as compared to their subunits also allows one to determine the binding constants of drugs, e.g., ethidium bromide to DNA (Greenstock et al. 1977).

Competitive scavenging of reactive free radicals, such as $^{\bullet}OH$, by DNA and other substrates, is a very important aspect of DNA free-radical chemistry. This situation has been modeled by various approaches (van Rijn et al. 1985; Lafleur and Loman 1986; Verberne et al. 1987). The most recent model has been developed by Udovicic et al. (1991).

Increasingly, Monte-Carlo calculations become available, which try not only to describe the general rate of reactions but also the sites of attack within the

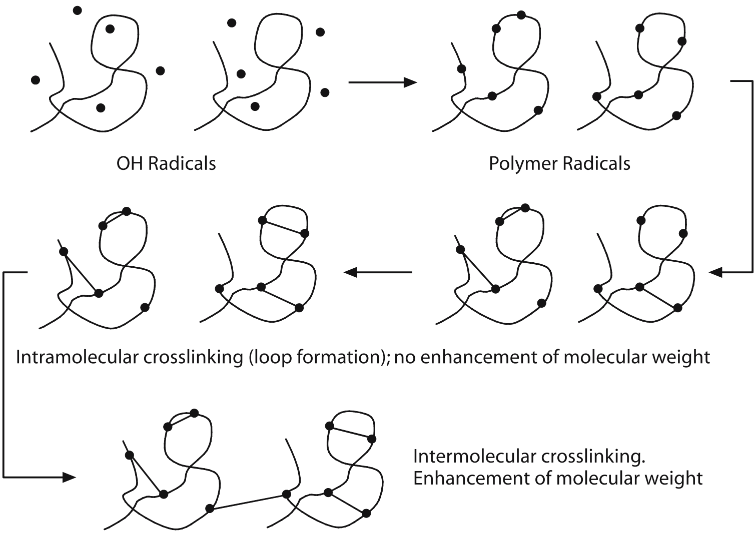


Fig. 9.1. Schematic description of the $^{\bullet}$OH-induced formation of polymer radicals and their subsequent decay

DNA (Chatterjee and Magee 1985; Wright et al. 1985; Valota et al. 2003). Chapter 12.2 refers to these studies.

9.3
Lifetime of Polymer Radicals

In general, radicals have to terminate bimolecularly. Polymer radicals may react *intra*molecularly with another radical situated at the same polymer molecule or *inter*molecularly with a radical at another polymer molecule. With a large number of radicals at the same macromolecule, such as are produced at the high dose rate of pulse radiolysis and at low polymer concentrations, the former process is usually favored (Fig. 9.1).

The kinetics of the bimolecular decay of poly(vinyl alcohol) (Ulanski et al. 1994) and poly(vinyl methyl ether) radicals (Janik et al. 2000b) have been studied in some detail (cf. Fig. 9.2). The $^{\bullet}$OH radicals formed during the pulse generate on the (coil-shaped) polymer a non-random distribution of radicals. First, the radicals which are very close to one another recombine. The intrinsic bimolecular rate constant for such a process can be much faster than that of the decay of an equal concentration of randomly distributed low molecular weight radicals. As the number of close-by radicals decreases, the intrinsic rate constant drops, and the lifetime of the polymer radicals increases considerably. Now, the bimolecular decay of the polymer radicals becomes much slower than that of the corresponding low molecular weight radicals. While in the case of low molecular weight radicals the bimolecular rate constant is independent of the

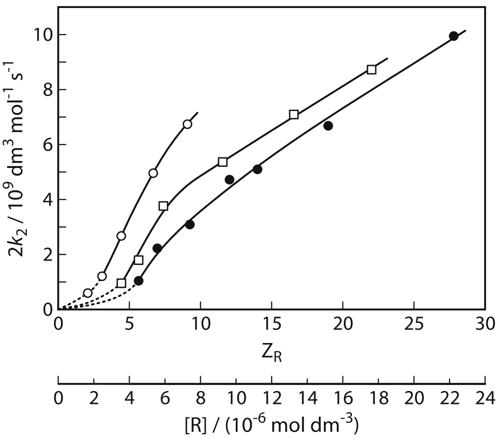


Fig. 9.2. Pulse radiolysis of poly(vinyl alcohol) (10^{-3} mol dm^{-3}) in N_2O-saturated aqueous solutions at pH 5.5. Incremental second-order rate constants as a function of a given radical concentration ([R]; *upper scale*) or radicals per macromolecule (Z_R; *lower scale*). *Open circles* 20 Gy; *open squares* 65 Gy; *filled circles* 120 Gy. Source: Ulanski et al. (1994), with permission

radical concentration, in polymer radicals it strongly depends on the number of radicals per polymer molecule (for a theoretical treatment of this phenomenon see Raap and Gröllmann 1983). With only a few radicals on the polymer chain, the lifetime of the radicals can become considerable, and due to the slowness of the motion of macromolecules, intermolecular reactions with radicals situated at other polymers is usually a rare event.

When the polymer is charged, the repulsive forces of the charges prevent an approach of the radicals, and the lifetime of the radicals increases dramatically. In the case of poly(acrylic acid), for example, the decay of the poly(acrylic) acid radicals is fast and follows the same kinetics as any radical derived from neutral polymers as long as the polymer is fully protonated (low pH) (Ulanski et al. 1996c). With increasing pH and concomitant dissociation of the polymer, however, the polymer assumes a rod-like shape, its segments become less flexible, and repulsive forces increasingly prevent their approach. Some radicals survive even for hours under such conditions.

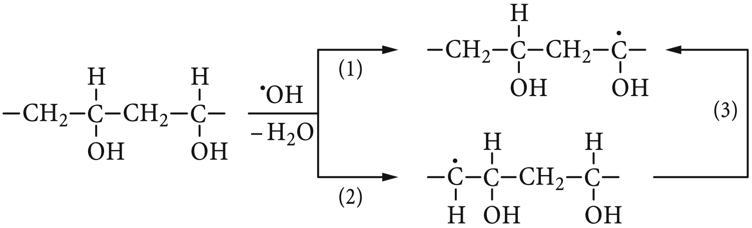
Interestingly, the corresponding peroxyl radicals have a noticeably shorter lifetime (Ulanski et al. 1996c). This has been explained by the fact that these radicals do not have to approach one another as closely, and thus the repulsive forces are less effective (Ulanski et al. 1997).

9.4
Radical Transfer

A polymer usually has more than one functional group, more than one type of radical is formed upon $^\bullet$OH-attack. These radicals may undergo radical transfer either by H-abstraction from a position where the H-atom is more loosely bound, or add to double bonds. The polymer radical experiences a very high local concentration of these functional groups as long as the polymer chains are flexible, and the rate of this (*intra*molecular) reaction will be much higher than an equivalent *inter*molecular reaction of low molecular weight models at the same concentration. In a charged polymer, the rate of this process decreases with increasing charge of the polymer due to a lower flexibility of segments. On the other hand, since this process is kinetically of first order while radical recombination processes are of second order, such a process may only become prominent when the polymer is highly charged, that is, when the bimolecular termination becomes slow. Two competing processes are discussed here, H-transfer and β-fragmentation. In DNA, there is also the possibility that radicals may add intramolecularly to a double bond at one of the bases. Evidence for such a reaction is not yet on firm ground, but this possibility should be kept in mind.

9.4.1
Intramolecular H-Transfer

In poly(vinyl alcohol), $^{\bullet}OH$ abstracts preferentially a hydrogen in α-position to the hydroxyl group (forming the tertiary radical, 70%) but also from the methylene group (forming the secondary radical, 30%) [reactions (1) and (2)]. The C-H BDE of the secondary hydrogen is somewhat higher than that of the tertiary hydrogen in the -CHOH- group, and thus the secondary radicals undergo the H-abstraction reaction (3) ($k_3 = 460\ s^{-1}$; von Sonntag et al. 1999; see also Chap. 6.5). Whether the reaction occurs with the first available hydrogen [five-membered transition state as depicted in reaction (3)] or over a larger distance, is as yet unknown. The rate of this H-transfer is only that fast, because it occurs as an *intra*molecular process. In order to compare this first-order rate with known second-order processes, one may take the concentration of neighboring -CHOH- groups in the polymer as 10 mol dm^{-3}, that is, the second-order rate constant should not exceed 50 dm^3 mol^{-1} s^{-1} by much. For comparison, the somewhat more exothermic H-transfer from 2-PrOH to the $^{\bullet}CH_2$-CHOH-CH_3 radical [H-abstraction by a primary alkyl radical as compared to a secondary one as in reaction (3)] has a rate constant of 430 dm^3 mol^{-1} s^{-1} (Burchill and Wollner 1972).



In poly(acrylic acid), two radicals are also formed upon $^{\bullet}OH$-attack. Again, the secondary radical undergoes *intra*molecular H-abstraction, leading to the tertiary radical [reaction (4); Ulanski et al. 1996c].

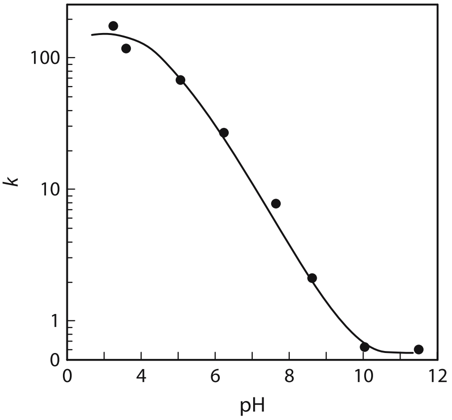
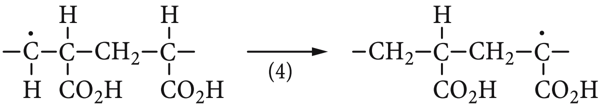


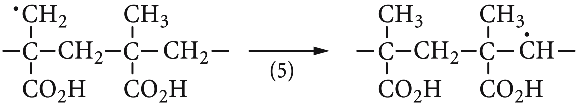
Fig. 9.3. Pulse radiolysis of N_2O-saturated solutions of poly(acrylic acid). First-order rate constant of the β- to α-radical conversion as a function of pH. Source: Ulanski et al. (1996c), with permission



$$-\overset{\bullet}{\underset{H}{C}}-\overset{H}{\underset{CO_2H}{C}}-CH_2-\overset{H}{\underset{CO_2H}{C}}- \xrightarrow[(4)]{} -CH_2-\overset{H}{\underset{CO_2H}{C}}-CH_2-\overset{\bullet}{\underset{CO_2H}{C}}-$$

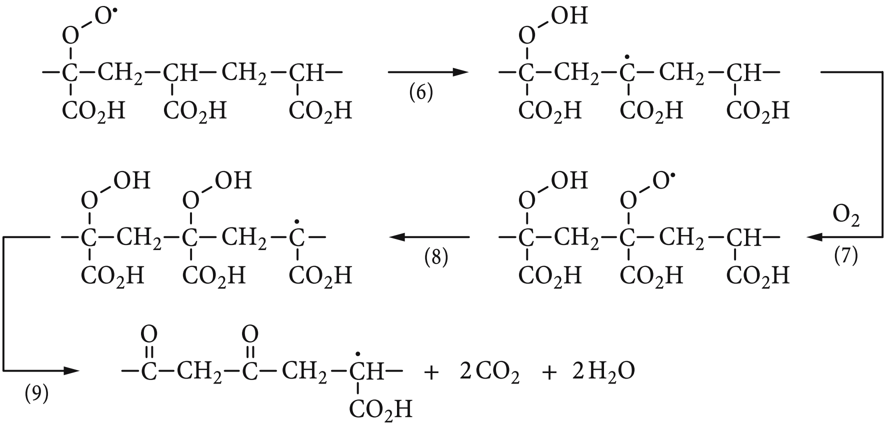
The rate of this reaction strongly depends on the pH (Fig. 9.3), i.e., the protonation state of the polymer. With increasing pH, the rate of reaction slows down considerably, an indication that the flexibility of the polymer chain is of importance for this reaction to occur efficiently. Whether this implies that H-abstraction mainly occurs from distant sites and not from a neighboring subunit [as shown in reaction (4)], cannot be decided yet on the basis of the existing data.

A similar H-abstraction takes place in poly(methacrylic) acid, converting the primary radical into a secondary one [reaction (5); $k = 350\ s^{-1}$ at pH 7.5; Ulanski et al. 1999b].



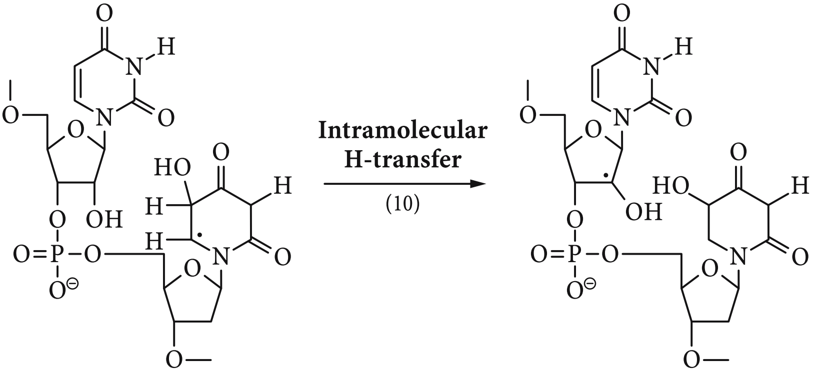
$$-\overset{^{\bullet}CH_2}{\underset{CO_2H}{C}}-CH_2-\overset{CH_3}{\underset{CO_2H}{C}}-CH_2- \xrightarrow[(5)]{} -\overset{CH_3}{\underset{CO_2H}{C}}-CH_2-\overset{CH_3}{\underset{CO_2H}{C}}-\dot{C}H-$$

When in the poly(acrylic acid) system radical the tertiary radical is converted by O_2 into the corresponding peroxyl radical, a chain reaction sets in which yields CO_2 and a acetylacetone-like product [reactions (6)–(9); Ulanski et al. 1996a; for the formation of acetylacetone in the model system 2,4-dimethylglutaric acid, see Ulanski et al. 1996b].



The CO_2 yield considerably exceeds that of the acetylacetone-like product, and although CO_2 is certainly also formed in other reactions (cf. the low molecular weight model; Ulanski et al. 1996b), this observation may be taken as a hint that the H-abstraction reaction does not proceed with neighboring groups only (via a favorable six-membered transition state) but also with more distant sites. A chain-type autoxidation has also been observed with poly(vinyl methyl ether) and a related model compound (Janik et al. 2000a,b).

A polymer much closer to DNA is poly(U). With this polymer, base radicals and base peroxyl radicals abstract an H-atom sugar moiety of the neighboring or a close-by nucleotide [e.g., reaction (10); Deeble and von Sonntag 1984, 1986; Deeble et al. 1986].



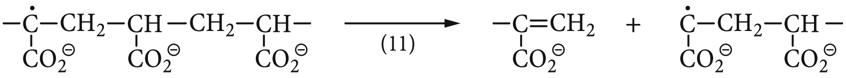
Compared to DNA, this H-transfer to the sugar moiety is especially favored in poly(U) or poly(C) (Chap. 11.2) by the low C(2′)-H BDE induced by the OH group in α-position (Chap. 6.5).

9.4.2
Intermolecular H-Transfer

In charged polymers, a strong influence of charge on the rate of H-abstraction is also observed with external thiols as hydrogen donors. A case in point is poly(U) (Fahey et al. 1991). As mentioned above, base-centered radicals can abstract an H atom from the sugar moiety, and the resulting radical undergoes chain scission (see below). This reaction can be prevented by thiols which donate an H-atom to the base radical. Since poly(U) is a charged polymer, the rate of H-transfer to the polymer strongly depends on the charge of the thiol (Chap. 11.2).

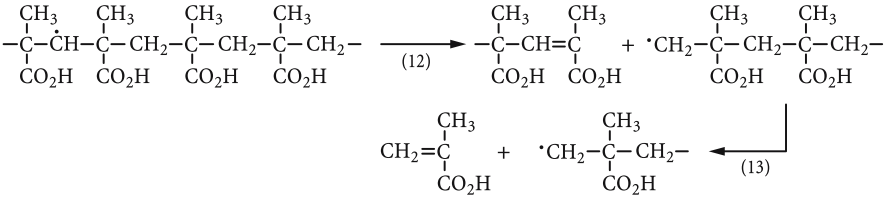
9.4.3
Homolytic β-Fragmentation and Hydrolysis

Homolytic β-fragmentation is a common process in free-radical chemistry. It is the reverse of the better known polymerization. Although β-fragmentation is often rather slow and has to compete with the bimolecular termination reaction of free radicals, it can become of considerable importance in long-lived radicals such as the poly(acrylic acid) radicals (charged at high pH), where this reaction leads to chain scission [reaction (11); von Sonntag et al. 1995; Ulanski et al. 1996c].



$$-\underset{CO_2^{\ominus}}{\dot{C}}-CH_2-\underset{CO_2^{\ominus}}{CH}-CH_2-\underset{CO_2^{\ominus}}{CH}- \xrightarrow[(11)]{} -\underset{CO_2^{\ominus}}{C}=CH_2 + \underset{CO_2^{\ominus}}{\dot{C}}-CH_2-\underset{CO_2^{\ominus}}{CH}-$$

In poly(methacrylic acid), where this type of reaction is ~50 times faster (von Sonntag et al. 1995; Ulanski et al. 1999a), even at room temperature subsequent depolymerization occurs as a very efficient process [reactions (12) and (13); Ulanski et al. 1999a,b].

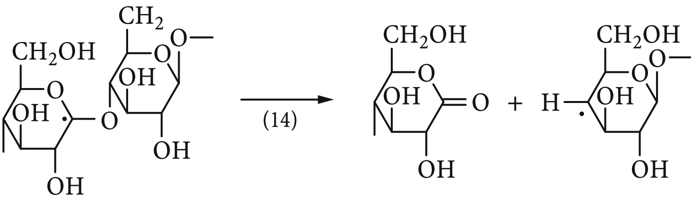


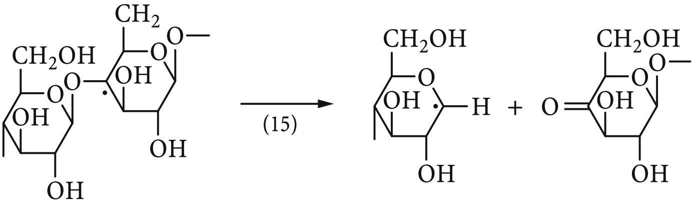
$$-\underset{CO_2H}{\overset{CH_3}{C}}-\dot{C}H-\underset{CO_2H}{\overset{CH_3}{C}}-CH_2-\underset{CO_2H}{\overset{CH_3}{C}}-CH_2-\underset{CO_2H}{\overset{CH_3}{C}}-CH_2- \xrightarrow[(12)]{} -\underset{CO_2H}{\overset{CH_3}{C}}-CH=\underset{CO_2H}{\overset{CH_3}{C}} + {}^{\bullet}CH_2-\underset{CO_2H}{\overset{CH_3}{C}}-CH_2-\underset{CO_2H}{\overset{CH_3}{C}}-CH_2-$$

$$\xrightarrow[(13)]{} CH_2=\underset{CO_2H}{\overset{CH_3}{C}} + {}^{\bullet}CH_2-\underset{CO_2H}{\overset{CH_3}{C}}-CH_2-$$

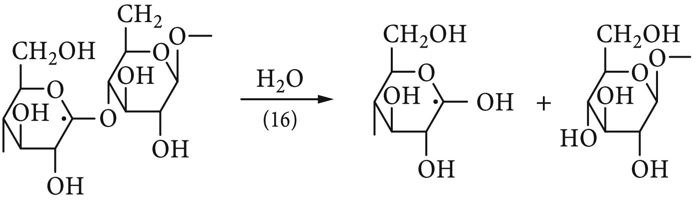
Because of a ready addition of the methacrylic acid released in reaction (13) to all radicals in this system, the situation of equilibrium polymerization is approached even at room temperature (Ulanski et al. 2000).

In carbohydrates, β-fragmentation of radicals adjacent to the glycosidic linkage [e.g., reactions (14) and (15)] will also lead to chain scission.





These reactions are in competition with a fast hydrolysis of the glycosidic linkage [e.g. reaction (16)] which can be many orders of magnitude faster than that of the parent.

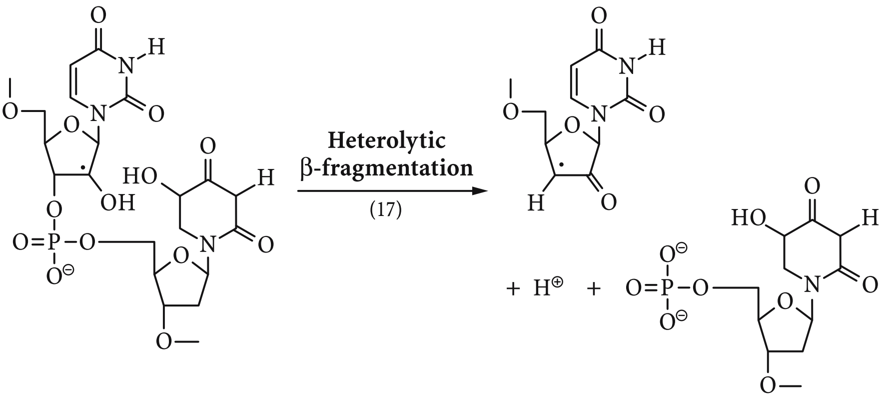


These reactions are that fast that they occur at the time scale of pulse radiolysis (Deeble et al. 1990, 1991; Ulanski and von Sonntag 2000). In DNA, such reactions will not lead immediately to a stand break, but they may well contribute to base release.

9.4.4

Heterolytic β-Fragmentation

Radicals can also eliminate an anion in β-position thereby forming a radical cation. This reaction becomes only fast, when the ensuing radical cation is stabilized by electron donating substituents and the leaving group has a good nucleofugacity. In DNA, this kind of reaction leads to strand breakage from the *C*(4′) radical (Dizdaroglu et al. 1975). In poly(U), such reaction also occurs from the *C*(2′) radical [reaction (14); Hildenbrand and Schulte-Frohlinde 1989a,b]. Mechanistic details are discussed in Chapters 6.9 and 11.2.



9.4.5

$HO_2^\bullet/O_2^{\bullet-}$-Elimination Reactions and β-Fragmentation of Oxyl Radicals

In peroxyl-free-radical chemistry, $HO_2^\bullet/O_2^{\bullet-}$ elimination reactions play a major role (Chap. 8.4). In polymer free-radical chemistry, these reactions are of special interest, because they lead to a conversion of slowly diffusing polymer-derived radicals into the readily diffusing $HO_2^\bullet/O_2^{\bullet-}$ radicals. The $HO_2^\bullet/O_2^{\bullet-}$-elimination typically proceeds from an α-hydroxyalkylperoxyl radical [reaction (22)]. In poly(vinyl alcohol), for example, such an structural element is formed by H-abstraction and subsequent O_2 addition [reactions (18) and (19)]. The same structural element may also be formed during the bimolecular decay of peroxyl radicals which carry an H-atom in β-position [reactions (20) and (21)].

$$\text{–HC(OH)-CR}_2\text{–} + {}^\bullet\text{OH} \rightarrow \text{–}^\bullet\text{C(OH)-CR}_2\text{–} + \text{H}_2\text{O} \tag{18}$$

$$\text{–}^\bullet\text{C(OH)-CR}_2\text{–} + \text{O}_2 \rightarrow \text{–}^\bullet\text{OOC(OH)-CR}_2\text{–} \tag{19}$$

$$2\,\text{–C(H,OO}^\bullet\text{)-CR}_2\text{–} \rightarrow 2\,\text{–C(H,O}^\bullet\text{)-CR}_2\text{–} + \text{O}_2 \tag{20}$$

$$\text{–C(H,O}^\bullet\text{)-CR}_2\text{–} \rightarrow \text{–}^\bullet\text{C(OH)-CR}_2\text{–} \tag{21}$$

$$\text{–C(OH,OO}^\bullet\text{)-CR}_2\text{–} \rightarrow \text{–C(O)-CR}_2\text{–} + \text{HO}_2^\bullet \tag{22}$$

$$\text{–C(OH,OO}^\bullet\text{)-CR}_2\text{–} + \text{OH}^- \rightarrow \text{–C(O}^-\text{,OO}^\bullet\text{)-CR}_2\text{–} + \text{H}_2\text{O} \tag{23}$$

$$\text{–C(O}^-\text{,OO}^\bullet\text{)-CR}_2\text{–} \rightarrow \text{–C(O)-CR}_2\text{–} + \text{O}_2^{\bullet-} \tag{24}$$

$$\text{–C(H,O}^\bullet\text{)-CR}_2\text{–} \rightarrow \text{–C(O)H} + {}^\bullet\text{CR}_2\text{–} \tag{25}$$

The $HO_2^\bullet$ elimination at reaction (22) is often slow, and at a high concentration of peroxyl radicals this reaction may compete with the bimolecular decay of the peroxyl radicals (leading to chain scission; Ulanski et al. 1994). However in the presence of base, deprotonation speeds up the $O_2^{\bullet-}$ elimination [reactions (23) and (24)]. Thus, under certain conditions, small changes in pH can have a dramatic effect on product yields in such systems.

It is noted that the 1,2-H shift [reaction (21)] always competes with the β-fragmentation reaction of oxyl-radicals [reaction (25)]. In the main chain of polymers, β-fragmentation causes a chain break. The ratio of the importance of reaction (21) vs. reaction (25) is determined by the stabilization of the radical that is released in the β-fragmentation process (25) (Gröllmann and Schnabel 1980; Schuchmann and von Sonntag 1982).

In DNA, the peroxyl radicals at *C*(3′)-*C*(5′) could, in principle, give rise to oxyl radicals that may lead to strand breakage through β-fragmentation. In contrast to the *C*(4′)-mechanism in the absence of O_2, details are, however, not yet established. For developing mechanistic concepts, we still fully rely on model systems such as those described above.

9.5
Oxidation and Reduction of Polymer Radicals

The reduction and oxidation of radicals are discussed in Chapter. 6.3–6.5. That in the case of radicals derived from charged polymers the special effect of repulsion can play a dramatic role was mentioned above, when the reduction of poly(U)-derived base radicals by thiols was discussed. Beyond the common oxidation and reduction of radicals by transition metal ions, an unexpected effect of very low concentrations of iron ions was observed in the case of poly(acrylic acid) (Ulanski et al. 1996c). Radical-induced chain scission yields were poorly reproducible, but when the glass ware had been washed with EDTA to eliminate traces of transition metal ions, notably iron, from its surface, results became reproducible. In fact, the addition of 1×10^{-6} mol dm^{-3} Fe^{2+} reduces in a pulse radiolysis experiment the amplitude of conductivity increase (a measure of the yield of chain scission; Chap. 13.3) more than tenfold and also causes a significant increase in the rate of the chain-breaking process. In further experiments, this dramatic effect of low iron concentrations was confirmed by measuring the chain scission yields by a different method. At present, the underlying reactions are not yet understood. These data are, however, of some potential relevance to DNA free-radical chemistry, since the presence of adventitious transition metal ions is difficult to avoid.

9.6
Products of the Termination of Polymer Radicals

Polymer radicals may recombine upon bimolecular termination. When this cross-linking takes place between two polymer molecules the molecular yield increases. When there are more than one radical on the polymer chain, cross-linking between these two sites will form only a loop (Fig. 9.1), that is, no increase in the molecular weight ensues despite the fact that cross-linking has occurred. In competition to recombination, radicals may disproportionate, when at least one of the radicals carries a hydrogen in β-position. A disproportionation reaction does not lead to a change in molecular weight. The ratio of recombination to disproportionation depends considerably on the substituents next to the radical site (Chap. 6.11). Thus, a change from one kind of radical into another one (induced by an intramolecular radical transfer process, see above) must also have an influence on the recombination to disproportionation ratio and hence on the cross-linking yield. As a consequence, product yields (*inter*molecular cross-linking, loop formation, chain scission) strongly depend on the rate of radical generation and on the polymer concentration (at the same rate of radical generation but at lower polymer concentrations more radicals are formed per macromolecule and unit time than at a higher polymer concentration). Such a behavior is particular to polymers and usually not observed with low-molecular weight material.

Termination reactions of peroxyl radicals of polymers may eventually lead to chain scission (see above).

9.7
DNA

It has been discussed above that polymer radicals may have lifetimes different from those of their monomer units. These lifetimes have been shown to depend on various parameters such as charge and number of radicals per polymer chain. With respect to the lifetime of DNA radicals, not too many studies are available. In a very early pulse radiolysis study, it has been stated that very little UV/Vis absorption decrease of the DNA radicals over the time interval of 300-900 μs was detected (Scholes et al. 1969). Using Raleigh light-scattering for detection gave a somewhat complex picture (Lindenau et al. 1976). A relatively fast decrease in the signal with $t_{1/2} \approx 0.8$ ms was followed by a much slower one of $t_{1/2} \approx 8$ s. These changes were interpreted as being due to an detachment of DNA segments caused by DSBs and SSBs, respectively. If this interpretation is correct, these data would not lead to any information as to the lifetime of DNA radicals. In an experiment where a ~3×10^{-3} mol dm^{-3} calf thymus DNA solution was subjected to a short pulse of 350 Gy (equivalent to 2×10^{-4} mol dm^{-3} DNA radicals) and subsequently a tritiated nitroxyl radical (TAN) was added after some delay, a biphasic decay was observed, the slower part exhibiting a half-life of about 10 s (Brustad et al. 1971). It is evident that under these conditions quite a large number of radicals per DNA strand have been created (one per ten nucleotides, on average), and it is not unlikely that the rapid part has to be connected with the very fast early part of radical decay generally shown by polymers having a large number of radicals per polymer chain. In DNA, this fast decay will certainly slowed down by the repulsive forces of the phosphate groups.

For DNA in cells and in the absence of O_2, one has to take into account that the lifetime of the DNA radicals is not determined by their bimolecular decay but rather by their reaction with the cellular thiols, mainly GSH (Chap. 12.11). In the presence of O_2, the situation becomes more complex, and the lifetime of the DNA peroxyl radicals is as yet not ascertained. It is expected to be considerably longer than the lifetime of DNA radicals in the absence of O_2. Already in small DNA fragments (Box et al. 1993, 1995; Tallman and Greenberg 2001) but also in DNA (Maccubbin et al. 2000; Bourdat et al. 2000), damage amplification reactions induced by one $^{\bullet}OH$ (tandem lesions) have been observed to take place quite effectively. This can only happen when either the intramolecular radical reaction is fast or the bimolecular termination reaction is slow. The latter certainly plays an important role here. In the case of DNA, O_2-uptake followed upon γ-irradiation of its aqueous solution is much higher than that of an equivalent mixture of its nucleotides (Isildar et al. 1982). This clearly shows that in the polymer additional reactions occur that are not given by its subunits.

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