



Figure 3.9 Main degradation products resulting from oxidation of Tyr. Blue and red helices represent the main polypeptide chains.

form and only half of that of Trp at 290 nm so that photooxidation of Tyr appears to proceed mainly by the ionized Tyr. Most Tyr residues have pKa values above 10, and since many therapeutic protein formulations are well below pH 10 the Tyr photooxidation is less common than other photosensitive amino acid residues. Thus, the rates of photooxidation in proteins are generally His > Trp > Met > Tyr (Matheson & Lee, 1979), and examples of Tyr oxidation of proteins are much more sparse than for the other susceptible amino acid residues. Tyr residues can also be oxidized with chemical oxidants or metal-catalyzed reactions. One example is the oxidation of Tyr in superoxide dismutase and human serum albumin via the well-known Fenton reaction where Fe^{2+} is oxidized to Fe^{3+} in the presence of H_2O_2 generating free radical $\text{OH}\cdot$ (Dubinina et al., 2002). The subsequent one-electron oxidation of Tyr results in long-lived Tyr radicals, which can then form dityrosine cross-links that may disrupt secondary and tertiary structure of the proteins. In another study, several proteins (horseradish peroxidase, crystalline insulin, bovine pancreatic insulin, bovine serum albumin, and collagen) and L-tyrosine are shown to form dityrosine cross-links after oxidation with peroxidase and H_2O_2 at pH 9.5 (Aeschbach, Amado, & Neukom, 1976).

Tyr oxidation in mAbs

The literature has some examples of Tyr oxidation of proteins but there are few, if any, reports of oxidation of Tyr in mAbs. Although many of the product inserts for therapeutic mAbs state that exposure to light should be avoided, generally there are no data available that show whether Tyr residues are oxidized. This is not surprising since photooxidation proceeds mainly via the ionized Tyr, and as