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## MINIREVIEW

### Solid-State Chemical Stability of Proteins and Peptides

M. C. LAI<sup>†</sup> AND E. M. TOPP\*

Contribution from *Department of Pharmaceutical Chemistry, The University of Kansas, 2095 Constant Ave., Lawrence, Kansas 66047.*

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**Abstract** □ Peptide and protein drugs are often formulated in the solid-state to provide stabilization during storage. However, reactions can occur in the solid-state, leading to degradation and inactivation of these agents. This review summarizes the major chemical reactions affecting proteins and peptides in the solid-state: deamidation, peptide bond cleavage, oxidation, the Maillard reaction,  $\beta$ -elimination, and dimerization/aggregation. Physical and chemical factors influencing these reactions are also discussed. These include temperature, moisture content, excipients, and the physical state of the formulation (amorphous vs crystalline). The review is intended to serve as an aid for those involved in formulation, and to stimulate further research on the determinants of peptide and protein reactivity in the solid-state.

#### Introduction

In the last two decades, proteins and peptides have become an important class of potent therapeutic drugs. However, their susceptibility to chemical degradation in solution presents a challenge in the development of stable protein pharmaceuticals.<sup>1</sup> As a result, many polypeptide drugs are formulated as lyophilized or freeze-dried products to prolong their shelf life.<sup>2-4</sup> While a "dry" formulation is generally more stable than the corresponding aqueous formulation, chemical degradation reactions can still occur.<sup>2-4</sup> In some cases, protein stability in the solid state is less than or comparable to that in solution.<sup>5,6</sup>

Factors that may impact the chemical stability of proteins and peptides in the solid-state include residual

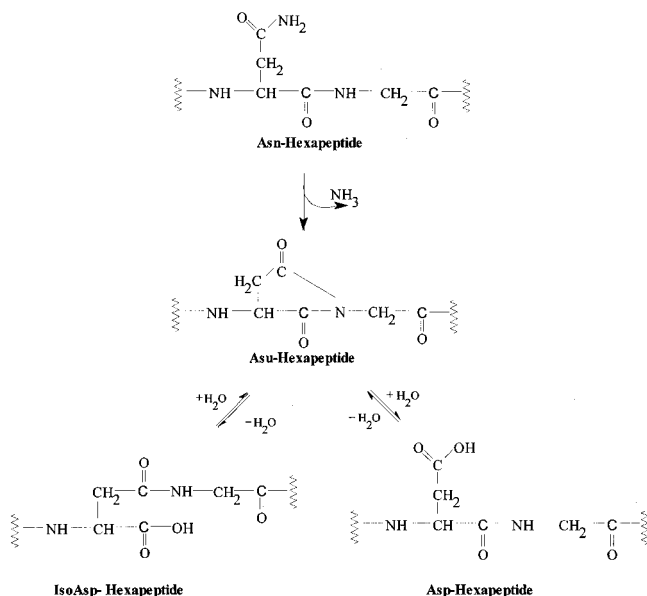
moisture and the excipient(s) used in a formulation. Excipients, such as polymers, are often included in protein and peptide formulations to protect the drug from degradation during processing and/or storage or to act as a matrix for controlled release. This review presents an overview of the chemical degradation reactions common to proteins and peptides in the solid state, and of our current knowledge regarding the effects of formulation and storage factors on peptide and protein stability in these systems.

The degradation pathways of proteins in the solid state can be classified into two types: chemical and physical. Chemical instability involves covalent modification of a protein or amino acid residue to produce a new molecule via bond cleavage, bond formation, rearrangement, or substitution. These chemical processes include such reactions as deamidation at asparagine (Asn) and glutamine (Glu) residues,<sup>7</sup> oxidation of sulfur atoms at cysteine (Cys) and methionine (Met) residues, disulfide exchange at Cys, and hydrolysis of aspartate (Asp) and glutamate (Glu) residues.<sup>8</sup> Physical instability refers to changes in the three-dimensional conformational integrity of the protein and does not necessarily involve covalent modification. These physical processes include denaturation, aggregation, precipitation, and adsorption to surfaces.<sup>1</sup> Chemical instabilities, such as deamidation and disulfide bond cleavage, may lead to physical instabilities, and vice versa. The physical instabilities of proteins will not be discussed in detail here, since the focus is chemical instability. The reader may refer to a recent article on the physical instability of proteins for further discussion.<sup>9</sup> Instead, this review will discuss reactions and factors that contribute to the chemical instability of proteins and peptides in the solid-state.

The different types of chemical reactions that contribute

\* To whom correspondence should be addressed. Phone: (785) 864-3644. Fax: (785) 864-5736. e-mail: topp@ukans.edu.

<sup>†</sup> Current address: Bristol Myers Squibb, New Brunswick, NJ.



Scheme 1—Deamidation.

to protein and peptide instability in the solid-state are first presented. These include deamidation, peptide bond cleavage, oxidation, the Maillard reaction,  $\beta$ -elimination, and covalent dimerization or aggregation. In the next section, formulation factors that affect chemical stability, such as temperature, moisture, and excipients, are discussed. The review concludes with a summary and a discussion of the implications for future research.

## Solid-State Reactions of Peptides and Proteins

**Deamidation**—Chemical instability in the solid state due to deamidation has been observed for human growth hormone (hGH),<sup>4,10</sup> recombinant human interleukin-1 receptor antagonist,<sup>11</sup> recombinant bovine somatotropin (growth hormone),<sup>12</sup> and insulin.<sup>13,14</sup> While there have been numerous mechanistic studies of protein and peptide deamidation in solution,<sup>7,15–19</sup> few such studies have been reported for deamidation in the solid state. Two studies which provide a mechanistic perspective on deamidation in solids are summarized below.

The stability and mechanism of degradation of the Asn-hexapeptide (Val-Tyr-Pro-Asn-Gly-Ala) were studied in solid formulations lyophilized from acidic solutions ranging from pH 3–5. The main degradation pathway for Asn-hexapeptide in the pH 3 formulation is deamidation via hydrolysis of the Asn side chain to produce the Asp-hexapeptide, which is further hydrolyzed at the Asp-Gly amide bond to generate a small quantity of tetrapeptide (Scheme 1).<sup>18</sup> As the pH of the solution prior to lyophilization increases from 3 to 5, intramolecular attack of the carbonyl center of the Asn side chain by the amide nitrogen of the succeeding amino acid to form a cyclic imide intermediate becomes more prominent, as evidenced by an increase in the cyclic imide in the product distribution (Scheme 1).<sup>18</sup> In solution at pH 5, the cyclic imide is hydrolyzed to form the isoAsp-hexapeptide, which is the dominant degradation product;<sup>15</sup> however, the isoAsp-hexapeptide was not observed in the solid state.<sup>18</sup> The absence of the isoAsp-hexapeptide in the product distribution may be due to the low level of water available for hydrolysis in the solid state. The mechanism of deamidation for the Asn-hexapeptide in the solid state was found to be similar to that in solution.<sup>18</sup> In an extension of this work, we have recently investigated the deamidation of this

peptide in solid poly(vinyl alcohol) and poly(vinyl pyrrolidone) matrices.<sup>20–22</sup> As in the lyophilized peptide, the mechanism of deamidation appears to be similar to that in solution, but the kinetics and product distribution are altered, particularly in matrices of low water content.

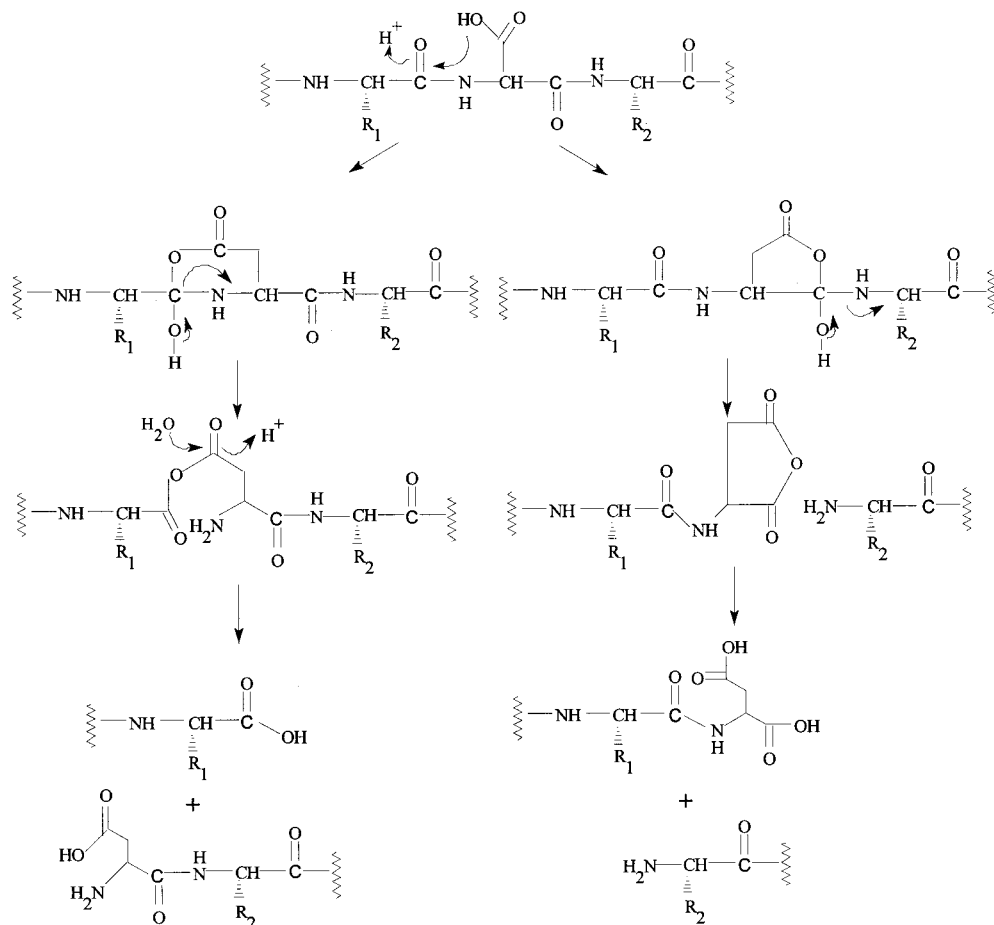
Human insulin has also been observed to undergo deamidation in the solid-state via a mechanism similar to that in solution.<sup>13</sup> In insulin formulations lyophilized from acidic solutions (pH 3–5), the rate-determining first step involves intramolecular nucleophilic attack of the C-terminal Asn<sub>A21</sub> carboxylic acid onto the side-chain amide carbonyl to release ammonium and to form a reactive cyclic anhydride intermediate, which can further react with various nucleophiles.<sup>13</sup> The cyclic anhydride intermediate may react with water to form [desamido<sub>A21</sub>] insulin,<sup>13</sup> and may also react with another molecule of insulin to form covalent dimers.<sup>13</sup> While the cyclic imide intermediates formed during Asn-hexapeptide deamidation in the solid state were observed to accumulate,<sup>23</sup> the cyclic anhydride intermediate formed during insulin deamidation did not.<sup>13</sup> Strickley and Anderson were able to verify that insulin deamidation proceeds via formation of a cyclic anhydride by using aniline trapping of the intermediate.<sup>13</sup> Consistent with these findings, Pikal and Rigsbee observed that the deamidation of human insulin occurs predominantly at Asn<sub>A21</sub>, except at high relative humidity when deamidation at Asn<sub>B3</sub> is more prevalent.<sup>14</sup>

Similar to the degradation of the Asn-hexapeptide discussed previously, the solid-state degradation of a model Asp-hexapeptide (Val-Tyr-Pro-Asp-Gly-Ala) is dependent on the pH of the bulk solution prior to lyophilization. This value is often referred to as the “pH” of the solid, since the true hydrogen ion activity is difficult to measure and pH is technically undefined in the solid-state. Under acidic conditions (“pH” 3.5 and 5.0), the Asp-hexapeptide mainly decomposes to produce a cyclic imide intermediate via base-catalyzed intramolecular cyclization.<sup>23</sup> Hydrolysis of the Asp-Gly amide bond also occurs but to a lesser extent. Under neutral and basic conditions (“pH” 6.5 and 8.0), the Asp-hexapeptide degrades exclusively via intramolecular cyclization to produce the Asu-hexapeptide, which is further hydrolyzed to form the isoAsp-hexapeptide.<sup>23</sup> At “pH” 8, the isoAsp-hexapeptide is the dominant degradation product,<sup>23</sup> similar to that observed in solution.<sup>24</sup>

**Peptide Bond Cleavage**—A second common degradation pathway for peptides and proteins involves cleavage of the peptide bond. Representative pathways of peptide bond cleavage are shown in Scheme 2. Lyophilized human relaxin formulated with glucose can undergo hydrolytic cleavage of the C-terminal serine (Ser) residue on the B-chain (Trp<sub>28</sub>-Ser<sub>29</sub>-COOH) upon storage at 40 °C.<sup>25</sup> This observation was supported by a reduction in molecular mass corresponding to the loss of Ser from fragment T5-T9 of relaxin, as verified by liquid chromatography/mass spectroscopy (LC/MS) and tryptic digest.<sup>25</sup> Li et al. proposed that this cleavage involved an initial reaction of the Ser hydroxyl group with glucose followed by subsequent hydrolysis of the Trp-Ser bond via a cyclic intermediate.<sup>25</sup>

In the solid state, the major degradation pathway of aspartame ( $\alpha$ -aspartylphenylalanine methyl ester, APM) is intermolecular cyclization to form exclusively diketopiperazine (DKP) with the elimination of methanol.<sup>26</sup> In solution, the degradation of aspartame at neutral and basic pH also occurs mainly via cyclization to form diketopiperazine (DKP) or hydrolysis at the ester linkage to form  $\alpha$ -aspartylphenylalanine (AP) and methanol.<sup>27</sup> Since water was absent in the aspartame solid-state study, no hydrolysis products were observed.<sup>26</sup>

The instability of the undecapeptide substance P (SP) in the solid state also proceeds through diketopiperazine



Scheme 2—Proteolysis.

formation. The main pathway of decomposition consists of the sequential release of N-terminal dipeptides via their diketopiperazines, cyclo(Arg-Pro) and cyclo(Lys-Pro).<sup>28</sup> Under the conditions studied, the release of N-terminal dipeptides dominates over other possible routes of spontaneous modification, such as oxidation and deamidation.<sup>28</sup>

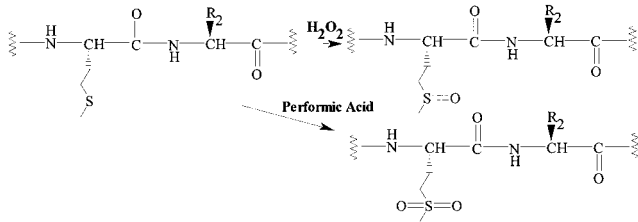
**Oxidation**—The side chains of His, Met, Cys, Trp, and Tyr residues in proteins are potential sites for oxidation (Scheme 3).<sup>1</sup> A major chemical decomposition pathway for human growth hormone (hGH) in the solid state is methionine oxidation at Met<sub>14</sub> to form the sulfoxide.<sup>10</sup> Even with minimal oxygen (~0.05%) in the vial headspace, decomposition via oxidation is comparable to or greater than that due to the alternative reaction of deamidation.<sup>4</sup> Storage of lyophilized hGH in an oxygen atmosphere results in greater decomposition than storage in a nitrogen atmosphere.<sup>29</sup> As in solution, atmospheric oxygen can easily oxidize Met residues in the solid state, leading to chemical instability and loss of biological activity.

Human insulin-like growth factor I (hIGF-I), lyophilized from phosphate buffer, also undergoes oxidation at its Met residue.<sup>30</sup> There were no significant differences in reaction rates (second-order kinetics) between solution and solid states.<sup>30</sup> However, Met oxidation in the solid-state constitutes a greater fraction of the total protein modification than in solution.<sup>30</sup> Both oxygen content and light exposure affect the oxidation rate.<sup>30</sup> Exposure to light increases the oxidation rate by a factor of 30.<sup>30</sup> This increase in oxidation rate with exposure to light and oxygen suggests that photooxidation and molecular oxygen may be involved in the generation of radicals. However, no further experiments were conducted to determine the nature of the radicals involved or the mechanism of Met oxidation in the solid state.

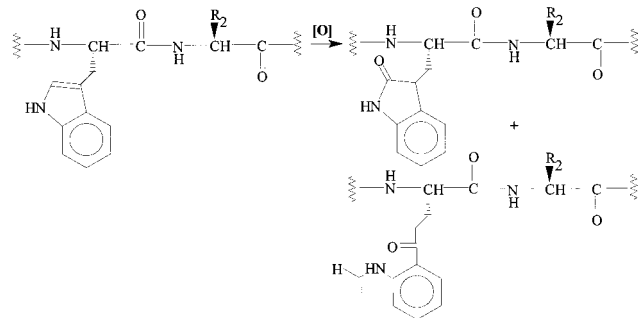
The oxidative deamidation of a cyclic hexapeptide, acetylcysteine-asparagine-(5,5-dimethyl-4-thiazolidinecarbonyl)-(4-(aminomethyl)phenylalanine)-glycine-aspartic acid-cysteine cyclic disulfide, in a lyophilized mannitol formulation does not appear to depend on molecular oxygen as a reactive species.<sup>31</sup> The oxidation reaction occurs at the aminomethyl phenylalanine moiety to form a benzaldehyde derivative.<sup>31</sup> This oxidative degradant is not detected in the neat solid drug stored under atmospheric oxygen, suggesting that oxygen is not involved in the reaction.<sup>31</sup> Instead, the decomposition of the heptapeptide may be due to a reaction with reducing sugar impurities in the mannitol excipient.<sup>31</sup> The proposed mechanism involves (1) formation of a Schiff base from the peptide primary amine reacting with the carbonyl of the aldehydic group on the reducing sugar, (2) tautomerization to a more stable configuration, conjugated with the phenyl group, and (3) hydrolytic cleavage of the new Schiff base to generate the observed aldehyde derivative.<sup>31</sup> The first part of this proposed reaction, the formation of the Schiff base, proceeds via a mechanism similar to the Maillard reaction, discussed below.

**Maillard Reaction**—The food industry has studied extensively the nonenzymatic browning of food due to the Maillard reaction, which results from reducing sugars reacting with either amino or free amine groups in proteins, leading to changes in both the chemical and physiological properties of the proteins (Scheme 4).<sup>32</sup> The first phase of the Maillard reaction involves a condensation reaction between the carbonyl of a reducing sugar and an amino group to form an N-substituted glycosylamine, which then converts to a Schiff base and a molecule of water.<sup>33</sup> Subsequent cyclization and isomerization (Amadori rearrangement) result in derivatives which cause discoloration

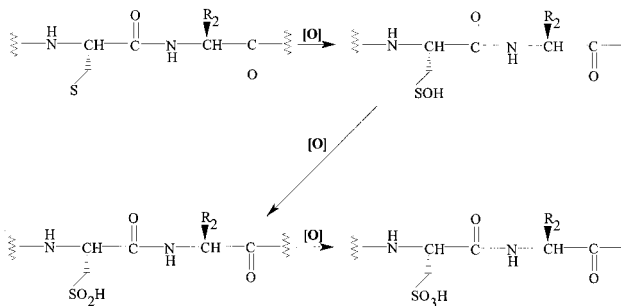
**A. Met**



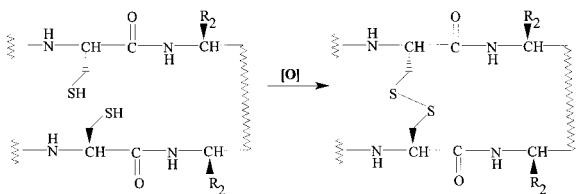
**B. Trp**



**C. Cys**



**D. Disulfide Bond**

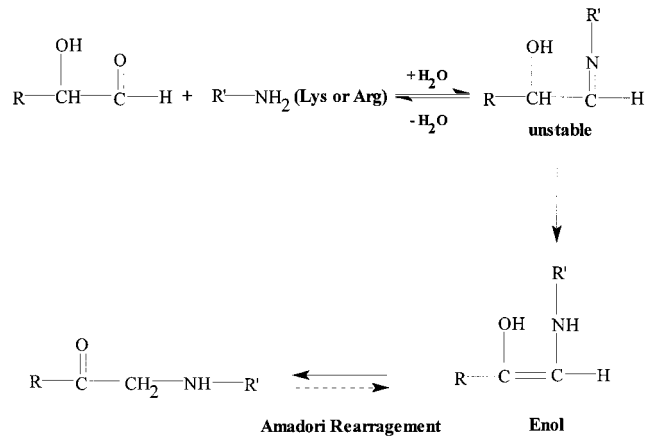


Scheme 3—Oxidation.

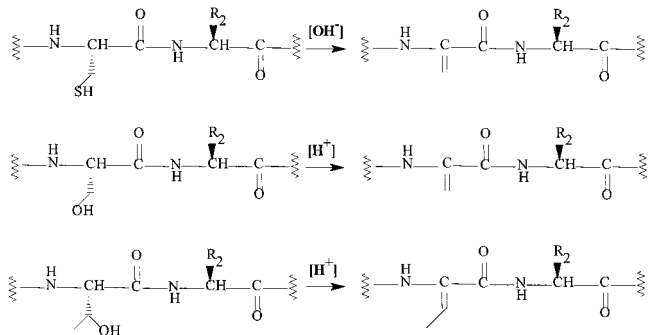
(nonenzymatic browning) of the formulation.<sup>33</sup> This type of covalent modification is a problem in the solid state because the initial aminocarbonyl condensation reaction to form the Schiff base is accelerated in the low moisture range.<sup>25,34</sup>

Lyophilized human relaxin (Rlx) formulated with glucose was observed to degrade via the Maillard reaction to form adducts with glucose.<sup>25</sup> The resulting adducts were shown by liquid chromatography/mass spectroscopy (LC/MS) to contain up to four glucose molecules covalently attached to Rlx.<sup>25</sup> With tryptic digestion, the individual reaction sites on Rlx were identified as including Lys<sub>A9</sub>, Lys<sub>B9</sub>, and Arg<sub>B17</sub>.<sup>25</sup> The fourth reaction site was hypothesized to be either Lys<sub>A17</sub> or Arg<sub>B13</sub> on the T2-T7 fragment, which showed a broadened peak on the tryptic map, but positive identification was not possible using mass spectroscopy.<sup>25</sup>

A review of the food literature prior to 1966 by Goldblith and Tannenbaum revealed that lysine loss in foods is



Scheme 4—Maillard Reaction.



Scheme 5— $\beta$  Elimination.

primarily due to the Maillard reaction.<sup>35</sup> Lysine is usually lost more rapidly than the other amino acids because of its free  $\epsilon$ -amino group, which will react easily with the carbonyl of reducing sugars.<sup>33</sup> However, other residues, such as arginine, asparagine, and glutamine, have been observed to react with reducing sugars also.<sup>25,34</sup>

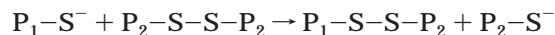
**$\beta$ -Elimination**—Lyophilized bovine insulin has been observed to degrade rapidly with increased water content to produce both covalent and noncovalent aggregates after incubation at 50 °C at various relative humidities.<sup>36</sup> Costantino et al. hypothesized that the reducible covalent interactions were due to thiol-catalyzed disulfide exchange.<sup>36</sup> They speculated that these free thiol groups resulted from the  $\beta$ -elimination of intact disulfide bonds in insulin.<sup>36</sup> The proposed mechanism for  $\beta$ -elimination involves hydroxide ion catalyzed cleavage of a carbon-sulfur bond (cysteine) (Scheme 5A), resulting in two new residues, dehydroalanine and thiocysteine.<sup>36</sup> Dehydroalanine can then react with lysine to form a lysinoalanine cross-link, while thiocysteine can undergo further decomposition to form thiol-containing products, such as hydro-sulfide ions (free thiols).<sup>36</sup> A 5-fold increase in the level of free thiols was measured in lyophilized insulin after incubation at 50 °C and 96% relative humidity.<sup>36</sup> The free thiols formed during solid state aggregation were predominantly low molecular weight (<3000 Da), perhaps hydro-sulfide ions.<sup>36</sup>

**Covalent Dimerization and Aggregation**—Dimerization and aggregation differ from the other types of degradation reactions discussed in this review in that they are not the result of a single chemical change. In fact, many different types of chemical or physical changes can induce the formation of dimers or aggregates. A brief description of chemically induced dimerization and aggregation is included here because of its importance in the pharmaceutical industry, and because much of the published literature on protein stability uses aggregate formation as



a key stability indicator. Dimerization or aggregation via covalent cross-linkage can be categorized into two types: reducible (via disulfide exchange) and nonreducible.

**Reducible Dimerization and Aggregation**—Lyophilized bovine serum albumin, ovalbumin, glucose oxidase, and  $\beta$ -lactoglobulin were observed to form covalent intermolecular disulfide linkages via a thiol–disulfide interchange reaction (Scheme 3D).<sup>37,38</sup> Liu et al. postulated that the intermolecular thiol–disulfide interchange results from the ionized thiol on one albumin molecule attacking the disulfide linkage of another albumin molecule:



where P1 and P2 are the first and second protein molecules.<sup>37</sup> Thiolate ions rather than thiols are the reactive species in this reaction, since a decrease in the initial solution pH resulted in a slower aggregation rate while an increase in pH led to a more rapid reaction.<sup>37</sup> Free thiols are both necessary and sufficient for the moisture-induced aggregation to occur, since S-alkylated BSA (no free sulfhydryl groups) does not undergo aggregation.<sup>37</sup>

Moisture-induced aggregation of bovine insulin occurred via both noncovalent and covalent interactions. The covalent interactions were reportedly due to intermolecular disulfide bonds as evidenced by the dissolution of 21% of the aggregates upon treatment with a reducing agent, 10 mM dithioerythritol, and 1 mM EDTA to prevent its autoxidation.<sup>36</sup> Costantino et al. postulated that  $\beta$ -elimination produced free thiols which can subsequently catalyze the reshuffling of intact protein disulfides and lead to intermolecular disulfide cross-linkage.<sup>36</sup>

Chemical instability in the solid state can also occur after proteins first experience physical instability, such as denaturation or unfolding. Lyophilized recombinant human keratinocyte growth factor (rhKGF) is prone to aggregation at elevated temperatures.<sup>39</sup> Its aggregation pathway is proposed to proceed initially with unfolding of the protein, leading to formation of large soluble aggregates, which can form disulfide bonds.<sup>39</sup> Finally, these precipitates are converted to scrambled disulfides and/or nondisulfide cross-linked oligomers. Recombinant human albumin (rHA) also undergoes intermolecular thiol–disulfide interchange.<sup>40</sup> The unfolding or loss of tertiary structure in lyophilized rHA is suspected to have initiated the covalent thiol–disulfide exchange.<sup>40</sup> The covalent aggregation of ovalbumin, glucose oxidase, and  $\beta$ -lactoglobulin have also been linked to initial protein physical instability, such as protein unfolding.<sup>37</sup>

**Nonreducible Dimerization and Aggregation**—Lyophilized human insulin can undergo covalent dimerization at the Asn<sub>A21</sub> site to form [Asp<sub>A21</sub>-Phe<sub>B1</sub>] and [Asp<sub>A21</sub>-Gly<sub>A1</sub>] insulin dimers.<sup>13</sup> This dimerization occurs after deamidation of the C-terminal Asn<sub>A21</sub> forms a reactive cyclic anhydride intermediate that further reacts with the free N-terminal amine of another insulin molecule to yield dimers.<sup>13</sup> Lyophilized tumor necrosis factor (TNF) is also susceptible to the formation of cross-linked aggregates consisting of dimers, trimers, and higher oligomers, which were nonreducible when treated with  $\beta$ -mercaptoethanol.<sup>41</sup>

Another protein that forms nonreducible dimers in the solid state is recombinant bovine somatotropin (rbSt). When lyophilized rbSt was stored at 30 °C and 96% RH, the rate of loss of monomeric rbSt was greater than or equal to the rate of loss in solution.<sup>12</sup> Covalent dimers accounted for 80–90% of the total degradation products observed, with the remaining 20–10% attributed to deamidation/cleavage. The fractional amount of nonreducible dimers was only 23–26% in solution.<sup>12</sup> Most of the covalent dimers were not reducible with  $\beta$ -mercaptoethanol, indicating that

the covalent bonds were not disulfide bonds.<sup>12</sup> Hageman et al. hypothesized that such covalent interaction could be due to the condensation of a lysine  $\epsilon$ -amine and a carbonyl side chain of either Asp or Glu.<sup>12</sup>

A similar mechanism was proposed for the degradation of lyophilized ribonuclease A due to the formation of soluble and insoluble aggregates during storage at 45 °C. These aggregates were not dissociable using an anionic detergent (sodium dodecyl sulfate) and a reducing agent (2-mercaptoethanol), indicating that the aggregates were covalently attached but not through disulfide bonds.<sup>42</sup> Originally, protein oxidation was believed to be the cause of the aggregation since exposure to oxygen and light increased the solid-state aggregation rate of ribonuclease A.<sup>43</sup> Upon further investigation, Townsend et al. postulated that these covalent linkages did not result from an oxidation reaction but from the lysine residues reacting with asparagine or glutamine in a manner similar to the mechanism proposed by Hageman et al. for rbSt.<sup>44</sup> The loss of free lysine residues in the insoluble aggregates, as determined by amino acid analysis, is consistent with this mechanism.<sup>44</sup>

A loss of lysine and histidine residues also was observed by Schwendeman et al. in studies of the moisture-induced aggregation of tetanus and diphtheria toxoids.<sup>45</sup> In this case, however, aggregation was thought to be caused by formaldehyde-induced cross-linking of the proteins, since the aggregates were not soluble under either reducing (10 mM dithioerythritol, 1 mM EDTA) or denaturing (6 M urea) conditions, and since the toxoids had been treated with formaldehyde (“formalinized”) during production.<sup>45</sup> The authors proposed a mechanism for the formation of stable intermolecular cross-links in this system and established methods for stabilizing the toxoid formulation against this reaction. Effective stabilization methods included succinyl-ation, treatment with sodium borohydride, and addition of sorbitol.<sup>45</sup>

## Factors Influencing Protein and Peptide Chemical Instability in Solids

The importance of temperature, moisture, and formulation excipients in determining the solid-state stability of small molecule drugs has been widely reported and accepted.<sup>45–47</sup> However, the effects of these factors on the solid state chemical stability of proteins and peptides are not as widely reported or understood. In addition to these factors, there is a growing literature that suggests that the hydrogen ion activity in the solid-state may have a significant influence on peptide and protein stability, paralleling the influence of pH in the solution state. The physical state of the solid (e.g., glassy vs rubbery) also has been shown to affect protein reactivity in the solid state. This section reviews published reports of the effects of these factors on peptide and protein stability in the solid state: temperature, moisture, excipients, hydrogen ion activity, and the physical state of the solid.

**Temperature**—The exposure of solid protein and peptide formulations to elevated temperatures generally decreases chemical stability by accelerating almost all chemical degradation reactions. For example, the deamidation of the Asn-hexapeptide increases with increasing temperature in the solid-state, with the formation of the cyclic imide intermediate becoming more favored over the direct hydrolysis of the Asn side chain.<sup>18</sup> In general, the increase in degradation rates with temperature did not follow an Arrhenius relationship within the temperature range studied (40–70 °C).<sup>18</sup> This suggests that acceleration of chemical reaction kinetics due to temperature is not solely responsible for the rate increase.

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