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Review

Metal assisted peptide bond hydrolysis: Chemistry, biotechnology and toxicological implications

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Abbreviations: 1:1 Zr(IV)-Ld POM, Zr(IV)-substituted Lindqvist type polyoxometalate $(Me_4N)_2[W_5O_{18}Zr(H_2O)_3]$; 1:2 Ce(IV)-Kg POM, Ce(IV)-substituted Keggin-type polyoxometalate $[Ce(\alpha\text{-}PW_{11}O_{39})_2]^{10-}$; 1:2 Zr(IV)-Kg POM, Keggin type polyoxometalate $(Et_2NH_2)_{10}[Zr(PW_{11}O_{39})_2]\cdot 7H_2O$; 1:2 Zr(IV)-WD POM, Wells–Dawson type polyoxometalate $K_{15}H[Zr(\alpha_2\text{-}P_2W_{17}O_{61})_2]_{25}H_2O$; 2:2 Zr(IV)-Kg POM, Keggin type polyoxometalate $(Et_2NH_2)_8[\{\alpha\text{-}PW_{11}O_{39}Zr\text{-}(\mu\text{-}OH)(H_2O)\}_2]\cdot 7H_2O$; 2:2 Zr(IV)-Ld POM, Lindqvist-type polyoxometalate $(n Bu_4N)_6[\{W_5O_{18}Zr(\mu\text{-}OH_2)\}]\cdot 2H_2O$; 4:2 Zr(IV)-WD POM, tetrazirconium(IV)-substituted Wells–Dawson polyoxometalate, $Na_{14}[Zr_4(P_2W_{16}O_{59})_2(\mu_3\text{-}O)_2(OH)_2(H_2O)_4]\cdot 57H_2O$; AAT, human α-1-antitrypsin; ATCUN/NTS, square planar complexes of peptides or proteins containing the N-terminal R1a-R2a-His sequence; BSA, bovine serum albumin; CoPA, pentaammineaquacobalt(III); COPD, chronic obstructive pulmonary disease; CoTA, tetraamminediaquacobalt(III); Cp, η^5-cyclopentadienyl; Cu[9]aneN$_3$)Cl$_2$, 1,4,7-triazacyclononane dichloride; Cyc, cyclen; DFT, density functional theory; dtco-3-OH, dithiacyclooctan-3-ol; EDTA, ethylenediaminetetraacetic acid; en, ethylenediamine; FRET, fluorescence resonance energy transfer; Gly-pNA, glycine-*p*-nitroanilide; GSH, reduced glutathione; GSMe, S-methylglutathione; H_3bcmga, bis-*N*,*N*-carboxymethyl-L-glutamic acid; H_3bcmpa, bis-*N*,*N*-carboxymethyl-L-phenylalanine; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HEWL, hen-egg-white lysozyme; h-IAPP, human islet amyloid polypeptide; HL[1], 2-[(bis(pyridylmethyl)amino)methyl]-4-methyl-6-formylphenol; HSA, human serum albumin; H(tdp), 2-[(2-(2-hydroxyethylamino)ethylimino)methyl]phenol; IP, intermediate product; L, 2-[bis(2-aminoethyl)amino]ethanol; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; Mb, horse heart myoglobin; MIIA domain, metal ion-inducible autocleavage domain; PNA, peptide nucleic acid; POMs, polyoxometalates; PS, polystyrene; pz, pyrazine; SPI-2, serine protease inhibitor 2; tren, triaminotriethylamine; trien, triethylenetetraamine; tmp, 3,4,7,8-tetramethyl-1,10-phenanthroline; Tris, tris(hydroxymethyl)aminomethane.

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ABSTRACT

Metal-assisted hydrolysis of peptide bond is a promising alternative for enzymatic cleavage of proteins with prospective applications in biochemistry and bioengineering. Many metal ions and complexes have been tested for such reactivity with a number of targets, from dipeptides through oligopeptides through proteins. The majority of reaction mechanisms reported so far is based on the Lewis acidity of a given metal ion. In the alternative hydrolysis reaction the metal ion, Cu(II), Ni(II) or Pd(II), plays a structural role by forming a square planar complex with Ser/Thr–His or Ser/Thr–Xaa–His sequence, which enables a N → O rearrangement of the acyl moiety in the peptide bond downstream from the Ser/Thr residue. Both Lewis acid and N → O acyl rearrangement reaction types are discussed in detail, including molecular mechanisms, the chemical character of hydrolytic agents, reaction conditions, and the origins of differences between the results obtained for peptide and protein models. Toxicological implications and practical applications of metal assisted peptide bond hydrolysis are also presented, with a focus on the Ni(II) assisted N → O acyl rearrangement in Ser/Thr–Xaa–His sequences.

1. Introduction

Peptide bond, the focus of this review, is one of the most important linkages in the realm of biomolecules. Its main function is to connect amino acid residues, forming peptide and protein chains. In Nature, the peptide bond is formed by the condensation reaction between the α-carboxylic group of one amino acid and the α-amino group of another one, resulting in the loss of a water molecule. In the cells the reaction is catalyzed by ribosome, a large protein/RNA structure which accelerates it by a factor of 10^7 [1,2]. One may say that the creative limitedness of protein structures results directly from properties of the peptide bond, especially from the partial double-bond nature of the C—N bond which imposes planarity in this structure, as shown in Fig. 1 [3]. It is however important to mention that in the reality of protein structures significant deviations from the planarity may occur for individual bonds, with significant consequences for their stability [4].

The peptide bond is very stable in water solution under physiological condition. Its half-life is estimated at 350–600 years at 25 °C and neutral pH [5]. This remarkable kinetic stability is required for its function, but presents a challenge when there is a physiological need to break it. There are three general types of peptide bond cleavage mechanisms: oxidative, photooxidative and hydrolytic [6–9]. The first two introduce covalent modifications into the cleaved moiety, being thus irreversible. They are also difficult to control, often causing "collateral damage" of covalent modifications of other functional groups in proteins. Only the hydrolysis reaction, reciprocal to the condensation reaction, can cleave the peptide bond by restoring the carboxylic and amine functional groups. This chemical strategy was adopted by living organisms, where several classes of peptidases, enzymes hydrolyzing the peptide bonds, evolved.

Enzymes catalyze peptide bond hydrolysis using two general strategies: either utilizing a one-step process in which the activated water molecule is a nucleophile attacking the amide bond, or in a two-step process with the participation of a nucleophilic residue. According to the former mechanism, a water molecule is activated by an aspartic acid residue or a metal ion, usually Zn(II). In the second case, a Ser, Thr, or Cys residue performs a nucleophilic attack, which results in the covalent binding of C-terminal part of the processed protein to the enzyme. The N-terminal part of the substrate is released simultaneously. In the second step of this reaction type the acyl-enzyme intermediate is hydrolyzed finally by an activated water molecule [10,11].

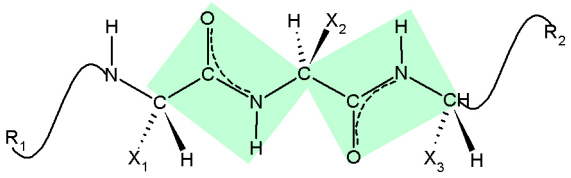

Fig. 1. The structure of the peptide bond in the context of the peptide chain. Planar fragments are marked with gray rectangles. The common *trans*-conformation is shown.

The proteolytic enzymes have different types of specificities, depending on their function. Some, like those responsible for post-translational processing of proteins or peptides, e.g., Angiotensin Converting Enzyme, are highly sequence specific [12]. Others, like Proteinase K, cleave all peptide bonds non-specifically [13]. This function can be reproduced chemically in a simple procedure of acid digestion at elevated temperatures [14]. Thus, current efforts in providing chemical tools for peptide bond hydrolysis focus on reactions that provide at least moderate sequence specificity. This goal cannot be really provided by simple non-enzymatic chemical agents, notably cyanogen bromide, which not only have poor specificity, but also usually require harsh reaction conditions, leading to unwanted side reactions [15,16].

Autocatalytic peptide bond hydrolysis mechanisms evolved for posttranslational modifications of proteins separately from enzymatic mechanisms. The most important of these mechanisms are N → O and N → S acyl transfer reactions, utilizing serine, threonine and cysteine residues. Under particular steric conditions enforced by specific protein domain fold, the Ser/Thr hydroxyl or Cys thiol group can attack the carbonyl carbon of the preceding amide bond results in an (thio)ester intermediate. The (thio)ester then splits into two separate molecules. At physiological conditions this reaction is not favored, but an acidification or an alkalization shifts the reaction equilibrium toward the products. Proteins which undergo such autoproteolysis facilitate the process by enhancing the deprotonation of catalytic —OH/—SH group, the amino group protonation and the destabilization of the hydrolyzed peptide bond by structural changes [17]. As mentioned above, the autoproteolysis process, while very clean in terms of side-reactions, requires large protein domains and cannot be easily used to cleave bonds in other proteins.

These circumstances encouraged the search for novel agents for peptide bond hydrolysis in the field of metal ion chemistry. The purpose of this review is to present the current stage of this research area and to sketch some perspectives for its further development. Some approaches described below are aimed to mimic or paraphrase metalloproteases, while other look for novel reactivities. Three general reaction mechanisms depicted in Fig. 2 are exploited in these studies.

Two of these mechanisms are based on Lewis acid properties of given metal ions. In this paradigm the metal ion can (i) activate a water molecule or (ii) activate/destabilize the peptide bond by engaging its carbonyl oxygen. These two mechanisms often occur