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Transition metals enhance prebiotic depsipeptide oligomerization reactions involving histidine†

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Biochemistry exhibits an intense dependence on metals. Here we show that during dry-down reactions, zinc and a few other transition metals increase the yield of long histidine-containing depsipeptides, which contain both ester and amide linkages. Our results suggest that interactions of proto-peptides with metal ions influenced early chemical evolution.

Around half of all known proteins associate with metal ions or organometallic cofactors.[1–4] Metals stabilize protein structure (*e.g.*, zinc fingers) and mediate catalysis (nitrogenases), electron transfer (cytochromes), ligand transport (hemoglobin), and signalling (calmodulin). Metals stabilize nucleic acids; around 500 divalent metal cations associate with a single ribosome.[5] The dependence of biochemistry on metals appears ancient and rooted in chemical evolution, preceding emergence of life on Earth.[6,7] Long-standing questions about the origins of life might be answered by understanding how metals interact with ancestral biopolymers. For example, metals could have affected oligomerization reactions of early proto-polymers, and could have conferred stability and function, in analogy with their roles in extant biochemistry.

Depsipeptides, containing mixtures of ester and amide linkages, are plausible ancestors of polypeptides.[8–14] During drying of hydroxy acids and amino acids at mild temperatures (*i.e.*, 65 °C) ester bonds form first and are converted to peptide bonds by ester–amide exchange. Hydroxy acids and amino acids are thought to have been abundant on the prebiotic earth.[15–19]

Here we tested the hypothesis that interaction with Zn^{2+} or other metal ions with the amino acid histidine (His) might affect rates and extents of depsipeptide formation in dry-down reactions. We observed that Zn^{2+} and other selected transition metals increase yields of long His-containing depsipeptides. The increase in yield is specific for imidazole-containing amino and hydroxy acids and metals that interact directly with them.

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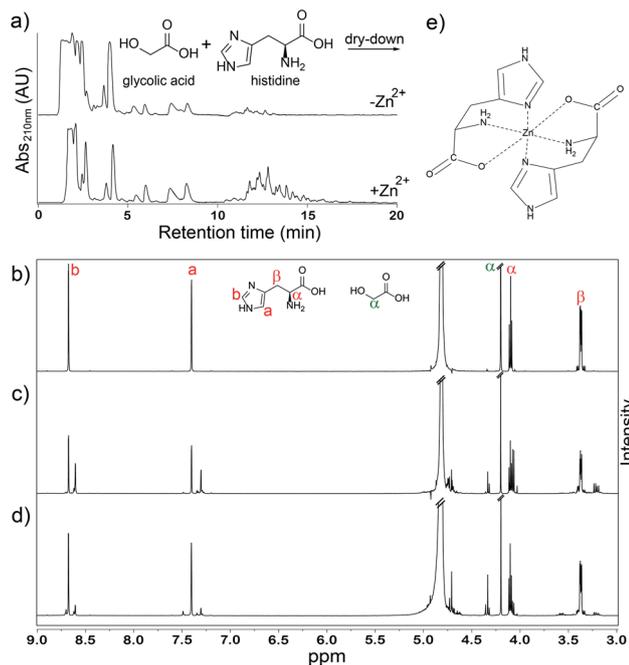
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We previously showed that His is readily incorporated into depsipeptides during dry-down reactions under mildly acidic conditions (pH ~3) at 85 °C.[12] These conditions are known generally to promote oligomerization in mixtures of hydroxy acids and amino acids into depsipeptides.[8–11] Here, mixtures of glycolic acid (glc) and L-His were reacted under these known reaction conditions in the presence or absence of various metals.

Addition of Zn^{2+} led to an increase in the average lengths of His-containing depsipeptides. Depsipeptide oligomers are readily detected by high-performance liquid chromatography (HPLC) using a C18 column (Fig. 1a). Longer oligomers exhibit longer retention times[20] allowing us to compare various dry-down reactions. The yield of products with a higher retention times on HPLC is increased following addition of Zn^{2+} to the reaction mixture (Fig. 1a). ^{1}H NMR analysis confirmed that the distribution of oligomeric species changes with addition of Zn^{2+} to the dry-down reaction (Fig. 1b–d). MS analysis verified the increased abundance of longer His-containing depsipeptides following dry-down with Zn^{2+} (Fig. S1†). On the other hand, Zn^{2+} decreases the extent of conversion of His into oligomers. While 42% of His monomer converted into oligomers in the absence of Zn^{2+}, only 22% of His monomer converted into oligomers in its presence (Fig. 1b–d). Oligomerization is indicated by shifts in the β-proton resonance envelope centered at ~3.37 ppm and in the imidazole proton envelopes at ~7.40 ppm and ~8.68 ppm (Fig. 1b–d). Extent of conversion to oligomers was calculated based on the integrals of residual nonreacted imidazole proton resonances (Fig. 1b–d).

The observed increase in depsipeptide length upon addition of Zn^{2+} might result from direct association between Zn^{2+} and His monomers (Fig. 1e)[21] because the effect is Zn^{2+} dose-dependent and is maximal at a 1 : 1 molar ratio of Zn^{2+} to His (Fig. S2†). Specific interaction of Zn^{2+} with His monomer has been reported previously.[22] The increased production of long His-containing depsipeptides with increasing Zn^{2+} is reversed when the number of Zn^{2+} equivalents exceeds that of His. Three
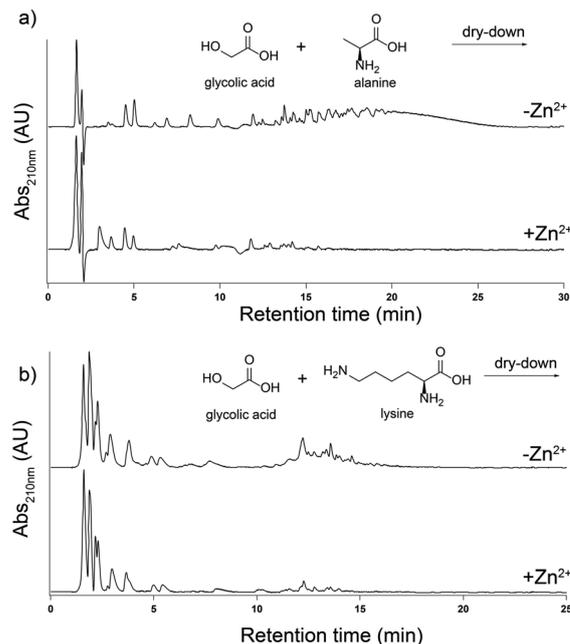
Fig. 1 Zinc increases the yield of long His-containing depsipeptides in dry-down reactions. (a) His monomer was dried with glycolic acid (glc) at a 1 : 1 molar ratio at 85 °C for seven days in the presence or absence of Zn^{2+}, at a 1 : 1 molar ratio (His : Zn^{2+}). Analysis of samples via C18-HPLC showed a dramatic increase in the yield of longer oligomers in the presence of Zn^{2+}. (b and d) ^{1}H NMR spectrum of a mixture of glc and His in D_2O before (b) and after (c and d) dry-down at 85 °C for seven days in the absence (c) or presence (d) of 1 eq. of Zn^{2+}. (e) A possible coordination complex between Zn^{2+} and two His monomers.

Fig. 2 Zinc does not increase extent of polymerization or length of oligomers of Ala- or Lys-containing depsipeptides in dry-down reactions. Alanine (a) or lysine (b) were dried with glc at a 1 : 1 molar ratio, for one week at 85 °C under unbuffered conditions, in the presence or absence of Zn^{2+}, at a 1 : 1 molar ratio of amino acid to Zn^{2+}. The addition of Zn^{2+} hindered depsipeptide formation for both amino acids tested, as opposed to the reverse trend observed with His.

equivalents of Zn^{2+} completely inhibited oligomerization reactions (Fig. S3†). The effect of Zn^{2+} on reactivity of His during the dry-down conditions might arise from either a locked chelate conformation or increased electrophilicity of the carbonyl. Importantly, Zn^{2+} did not cause polymerization of His in the absence of glycolic acid (Fig. S4†).
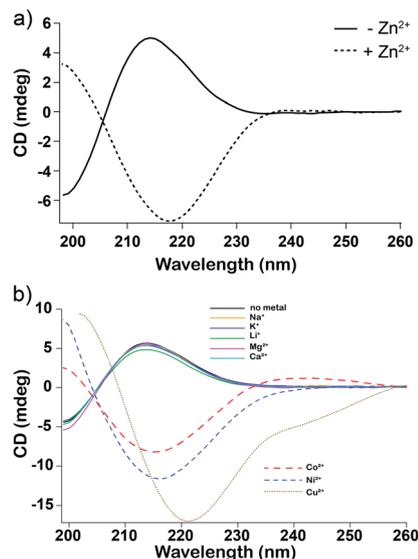
The effect of Zn^{2+} on depsipeptide formation is not a generic effect and is specific to His. We dried-down mixtures of glc with either alanine (Ala) or lysine (Lys). The addition of Zn^{2+} to a 1 : 1 molar ratio with these amino acids does not increase the yield of products in any length range. In fact, Zn^{2+} inhibited depsipeptide formation for both Ala and Lys (Fig. 2).

In addition to Zn^{2+}, we investigated the effects of Na^+, K^+, Ca^{2+}, Mg^{2+}, Cu^{2+}, and Co^{2+} on the oligomerization of His in depsipeptides. We dried-down mixtures of glc and His in the presence or absence of various metals (1 : 1 molar ratio of M^+ or M^{2+} to amino acid). Analysis by HPLC showed that Zn^{2+}, Cu^{2+}, and Co^{2+}, but not Na^+, K^+, or Mg^{2+}, increased the production of longer His-containing depsipeptides (Fig. S5 and S6†). Ca^{2+} decreased the production of His-containing depsipeptides (Fig. S5†).

Circular dichroism spectroscopy (CD) supported our hypothesis that enhancement of oligomerization of His in the presence of Zn^{2+} results from direct association between monomeric His and Zn^{2+}. We added various concentrations of

Fig. 3 Circular dichroism analysis confirms that zinc and several other transition metals interact with His monomer. Glycolic acid (glc) and His were mixed, at a 5 : 1 molar ratio, in 50 mM Tris buffer (pH 7.2). Circular dichroism (CD) spectra were collected for the mixture in the absence or presence of 1 eq. (referring to the amount of His monomer) of (a) Zn^{2+} or (b) various other metals. CD spectra showed a clear shift in the signal of His following addition of Zn^{2+}, Ni^{2+}, Cu^{2+}, and Co^{2+}, but not for the other metals tested.

Zn^{2+} to monomeric glc plus His. The CD spectrum inverts at equal molar ratio of Zn^{2+} and His (Fig. 3a). We attribute the inversion to formation of His–Zn^{2+} complex in concert with a change in the conformation of His. An example of a possible complex is shown in Fig. 1e.

CD spectra of glc plus His only report conformational changes of His because glc is achiral. The conformational change upon Zn^{2+} binding is dose dependent; the change in the CD spectra increases with increasing concentrations of Zn^{2+} (Fig. S7†). Addition of Zn^{2+} to the dry-down product mixture of His-containing depsipeptides resulted in far more subtle changes in the CD spectra, which appears to arise from binding of Zn^{2+} to small amounts of remnant His monomer that was not converted into polymers during the dry-down reaction (Fig. S8†).[12] In accordance with the observed species-specific impact of metals on dry-down reactions (Fig. S5†), the inversion of the CD signal of His monomer was also observed for Co^{2+}, Cu^{2+}, and Ni^{2+}, but not for Na^{+}, K^{+}, Li^{+}, Mg^{2+}, or Ca^{2+}. Thus, it appears that low-lying d-orbitals of metals are important for interaction with His. The differences in the electron configuration between the different metals affect their metal coordination properties. Transition metals are more electronegative and have more oxidation states than alkaline and alkaline-Earth metals, and their valence electrons in the d-shell tend to promote stable coordination complexes. By contrast, Zn^{2+} inhibited oligomerization of Ala or Lys in dry-down reactions. This inhibition is consistent with recent thermodynamic calculations[23] that examined effects of metals on the monomer–oligomer equilibria of glycine. Metals shift the equilibria toward the monomer, particularly at neutral and alkaline pH.[23]

To determine if oligomerization of imidazole-containing monomers other than His is promoted by Zn^{2+}, we dried L-β-imidazole lactic acid (the hydroxy acid analog of His, herein termed his) with glc for one week at 85 °C. The reaction produced polyesters, co-polymers of his and glc (Fig. S9†). Addition of Zn^{2+} to his and glc dry-down reaction mixtures increased the yield of longer polyester oligomers (Fig. 4a). ^{1}H NMR analysis of these polyesters indicate that Zn^{2+} did not change the extent of conversion of his monomer into oligomers: 39% of his converted into oligomers in the absence of Zn^{2+} and 38% of his converted into oligomers in its presence (Fig. S10†).
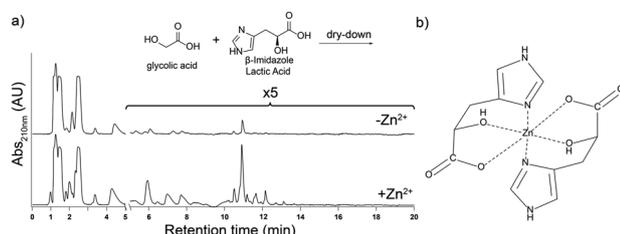

Fig. 4 Zinc increases lengths of his-containing polyesters in dry-down reactions. (a) L-β-Imidazole lactic acid (His) was dried with glycolic acid (glc) at a 1 : 1 molar ratio at 85 °C for seven days in the presence or absence of Zn^{2+}, at a 1 : 1 molar ratio of his to Zn^{2+}. Analysis of samples *via* C18-HPLC showed a dramatic increase in the yield of longer oligomers in the presence of Zn^{2+}. (b) Possible coordination complex between Zn^{2+} and his monomers.

Therefore, Zn^{2+} does not increase the overall oligomeric yield but rather the distribution of product oligomers, increasing the yield of longer oligomers (Fig. 4a and Fig. S10†). These results imply that a terminal alcohol can support a chelation complex with Zn^{2+}, in analogy with the suggested chelation complex of Zn^{2+} by His (compare Fig. 4b to Fig. 1e).

Several distinct non-exclusive mechanisms can explain why Zn^{2+} promotes formation of longer His-containing depsipeptides. Dry-down reactions are conducted under mildly acidic conditions (pH ∼ 3), in which the imidazole side chain (pK_a of ∼6) and the α-amino group (pK_a of ∼9) of monomeric His are protonated and the carboxylic acid (pK_a of ∼2) is deprotonated. Deprotonation of α-amino group would be promoted by His coordination of Zn^{2+} (Fig. 1), favoring an intermediate in formation of depsipeptides through ester–amide exchange. Zn^{2+} coordination by His might also lock His in a specific reactive conformation and/or increase the electrophilicity of the His carbonyl group. Zn^{2+} is expected to pull electron density from His and expose the carbonyl to nucleophilic attack (Fig. 1e). Dehydration would promote His coordination with Zn^{2+} by depleting competing water molecules.[21,24] In principle, it is possible that a complex is formed in which glc and His simultaneously chelate Zn^{2+}, or in which His and glc-based oligomers chelate Zn^{2+} such that a favored configuration for a nucleophilic attack is reached.

The effects of metals on oligomerization of amino acids by methods other than dry-down reactions has been investigated previously.[23,25–30] Concentrated sodium chloride (>3 M) promotes oligomerization in the presence of Cu^{2+}, to increase the yield of glycine (Gly)- and Ala-based peptides.[25] Various metals can affect oligomerization of chemically activated amino acids (*N*-carboxyanhydrides).[31,32] Chemical activation studies focused on Gly, the simplest and most reactive amino acid, but resulted in only low yields of very short peptides.[23,25–28,33–39] It has been proposed that minerals might catalyze dry-down oligomerization of amino acids.[33–39] McKee *et al.* observed that silica hinders the amidation of Gly in the presence of lactic acid, the hydroxy acid analog of Ala.[40] However, silica did lead to an enrichment of amide bonds over ester bonds.[40]

His may not be a prebiotic amino acid. It has been proposed that the prebiotic chemical ancestor of His might be imidazole-4-acetaldehyde,[41–44] which is produced by Strecker synthesis.[45,46] The His-containing depsipeptides produced here do not appear to bind to Zn^{2+} (Fig. S8†). This absence of chelation is consistent with the low number and density of His side chains, and the absence of backbone amines at ester linkages. Longer depsipeptides with greater number and density of His residues may bind Zn^{2+} and might lead to emergence of small metalloenzymes.

The importance of small proto-metalloproteins on the prebiotic Earth is supported by the cooperative interactions of metals and proteins in extant biology. Mulkidjanian proposed the zinc world theory, according to which the first metabolism was driven by zinc sulfide minerals that catalyzed photochemical reactions.[47–49] Primordial cooperation may have existed between metals and proto-peptides prior to the emergence of coded protein synthesis.[50–53] For instance, amyloidogenic

heptapeptides can function as Zn^{2+}-dependent esterases.[51] Zn^{2+} promotes fibril formation by His-containing peptides, acting as a catalytic cofactor. Short peptides with acidic residues, such as aspartic acid and glutamic acid,[52,53] could have protected short RNA molecules against Mg^{2+}-induced degradation.[54,55] Coordination of metal ions induces peptide conformational changes and supramolecular assembly.[56–60] In addition to effects on peptide self-assembly and function, metal–peptide interactions are utilized for fabrication of nanofiber materials for various applications, including three-dimensional cell culture and tissue engineering.[56,61,62]

It is generally accepted that Zn^{2+} concentration has remained fairly constant in seawater through time, whereas the concentrations of Co^{2+} and Ni^{2+} were higher in earlier stages of Earth history than in modern seawater.[63–72] If accumulation of metals occurred at shallow lakes or similar environments that were subjected to dry-wet cycling, they might have affected distribution of polymers that formed within these environments in a specific manner. Our results suggest that the close relationship between metals and biopolymers has roots in prebiotic chemistry and shaped their co-evolution.

Conclusions

We have partially characterized the interdependence between metals and amino acids that is thought to have roots in prebiotic chemistry and to have shaped the chemical evolution of biopolymers. Specifically, depsipeptides, containing both ester and amide linkages, have been proposed as ancestors of peptides. We examined the effects of metals on depsipeptide formation in dry-down reactions. We postulated that zinc might influence the formation of depsipeptides containing histidine (His). Here we show that through direct association with His, zinc and a few other transition metals dramatically increase the yield of long His-containing depsipeptide oligomers. By contrast, alkali and alkali earth metals do not show the same effect. The results here show that interactions of proto-peptides with metal ions could have influenced early chemical evolution.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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