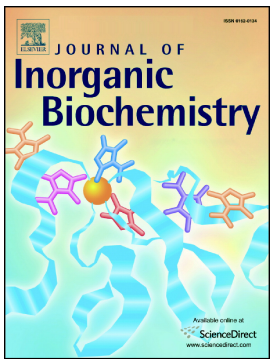

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Aluminum's preferential binding site in proteins: sidechain of amino acids versus backbone interactions.

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The interaction of aluminum ion Al(III) with polypeptides is a subject of paramount importance, since it is a central feature to understand its deleterious effects in biological systems. Various drastic effects have been attributed to aluminum in its interaction with polypeptides and proteins. These interactions are thought to be established mainly through the binding of aluminum to phosphorylated and non-phosphorylated amino acid sidechains. However, a new structural paradigm has recently been proposed, in which aluminum interacts directly with the backbone of the proteins, provoking drastic changes in their secondary structure and leading ultimately to their denaturation. In the present paper, we use computational methods to discuss the possibility of aluminum to interact with the backbone of peptides and compare it with the known ability of aluminum to interact with amino acid sidechains. To do so, we compare the thermodynamics of formation of prototype aluminum-backbone structures with prototype aluminum-sidechain structures, and compare these results with previous data generated in our group in which aluminum interacts with various types of polypeptides and known aluminum biochelators. Our results clearly points to a preference of aluminum towards amino acid sidechains, rather than towards the peptide backbone. Thus, structures in which aluminum is interacting with the carbonyl group are only slightly exothermic, and they become even less favorable if the interaction implies additionally the peptide nitrogen. However, structures in which aluminum is interacting with negatively-charged sidechains like aspartic acid, or phosphorylated serines are highly favored thermodynamically.

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