

Role of sulfur-mediated chalcogen bonds in the structure and substrate specificity of proteins

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Abstract

Divalent sulfur (S) of methionine or cystine in proteins can interact with nucleophilic centers to form chalcogen bonds (Ch-bonds). Factors that determine the formation of chalcogen bond by S, or their relevance to protein structure and function are not well understood. Here, we show that the strength of the σ -holes on S, which are modulated by bonded substituents, primarily distinguish between H-bond and Ch-bond formation, respectively. Bioinformatics and computational analyses reveal that S-mediated chalcogen bonds can stabilize protein structures by various mechanisms, including capping α -helix termini, protecting free β -sheet edges by negative-design, and augmenting the stability of β -turns. Furthermore, we demonstrate the importance of Ch-bond in the enzyme specificity of methionyl-tRNA synthetase using a mutagenesis-based biophysical study. The importance of S-mediated interactions for protein structure and substrate specificity is highly relevant for protein structure prediction and design, and structure-based drug discovery.

Key words: Non-covalent interaction, chalcogen bond, σ -holes, protein structures, substrate specificity.