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Communication

Reversibly switching the conformation of short peptide through in-tether chiral sulfonium auxiliary

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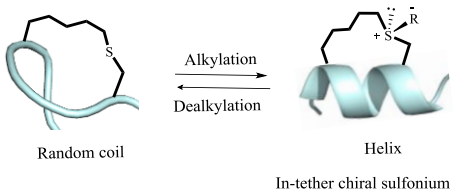
Graphical Abstract



A novel approach for reversibly switching the conformation of short constraint *α*-helical peptides through chemselective alkylation of the in-tether thioether and dealkylation of the chiral sulfonium was developed and it provides a valuable modifiable site to functionalize the peptides.

ABSTRACT
A chirality induced helicity method has been developed to modulate the peptide's biophysical and biochemical properties. We report herein a novel approach for reversibly switching the conformation of short constraint α-helical peptides through alkylation of the in-tether thioether and dealkylation of the chiral sulfonium. This traceless redox sensitive tagging strategy broadened our scope of CIH (chirality induced helicity) strategy and provided a valuable approach to functionalize the peptide tether.

Keywords: Cyclic peptide Sulfonium Chiral center α-Helix Reversible Tether modification

Protein-protein interactions (PPIs) play a central role in most biological processes and have been demonstrated to be important therapeutic targets in the past decades [1]. Synthetic peptides are suitable targeting candidates for PPIs as they are able to precisely mimic the topological features of target proteins and can be easily synthesized and modified [2]. Chemists have elaborated many efforts in order to stabilize these targeting epitopes into varies conformational elements, such as *α*-helix and *β*-hairpin [3]. Particularly, over 30% of protein secondary structure are helical in nature and over 50% of PPIs involve short *α*-helices according to a statistical analysis of protein data bank (PDB) [4]. As *α*-helix involved in a majority of PPIs, chemical methods, such as disulfide formation [3j], amide formation [3c], olefin/alkyne methathesis [3a], cysteine alkylation [3k] and perfluoroated arene incorportation [3l] have been utilized to confine peptides into helical structures.

Our group recently discovered a unique phenomenon [3d] that a precisely positioned chiral center in the tether of short peptides could dominantly induce helicity of the backbone peptides. This phenomenon could be extended to both a chiral sulfilimine center [5] and a chiral sulfoxide center [6] (Fig. 1), which provides a valuable modifiable site on the tether [7]. The absolute configuration of the in-tether chiral center was determined to be *R* for helicity inducement by peptide crystal structure.

Methionine alkylation is a facile and chemoselective approach for introducing functional groups into peptides [8]. Deming *et al.* reported a chemoselective tagging strategy for the modification of peptides in a reversible manner [9]. Met residues could be chemoselectively alkylated in quantitative yields under acidic condition with satisfying residue tolerances [10]. Inspired by the versatility of methionine alkylation on especially its great functional group tolerance even for residues like Lys and Cys, we propose a simple and versatile strategy for reversibly controlling the conformation of short *α*-helical peptides. A thioether tethered peptide could be facially synthesized *via* photo-induced intramolecular thiol-ene reaction but too flexible to induce peptide's helicity [11]. We could then functionalize this thioether tether to generate a sulfonium based chiral auxiliary by a facile alkylation of the tether with alkyl halides under acidic media of trifluoroacetic acid (TFA) [12]. We envision the newly-generated sulfonium chiral center could modulate the backbone peptides' secondary structure, similarly as the all-hydrocarbon, sulfilimine and sulfoxide chiral centers. More importantly,

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