From protein total synthesis to peptide transamidation and metathesis: Playing with the reversibility of N,S- or N,Se-acyl migration reactions

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Chemoselective amide bond forming reactions which proceed efficiently in water at neutral pH enable the sequential assembly of peptide segments and thus the total synthesis of large peptides or proteins.[1] These reactions are also useful tools for accessing to complex peptide scaffolds such as branched or cyclic peptides. The native chemical ligation (NCL) reaction is central to the field of protein total synthesis, but other amide bond forming reactions are emerging, which in combination with NCL can facilitate the access to large peptides or peptidic scaffolds. In particular, the *bis*(2-sulfanylethyl)amido (SEA) *N,S*-acyl shift system enabled the development of an array of useful chemical tools for peptide ligation[2] or peptide thioester[3-7] and thioacid[8] synthesis. SEA chemistry permitted also the development of N-to-C sequential peptide segment assembly methods for protein synthesis in solution[3,9,10] or on a solid-phase.[11] The lecture will present the main features of SEA chemistry as well as the potential of SEA and SeEA, i.e. the selenium analog of SEA group, for the synthesis of functional proteins derived from the hepatocyte growth factor (HGF) or peptide scaffolds. It will discuss also the potential of *N,Se*-acyl shift systems for designing native peptide metathesis reactions.[12]

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