The role of peptide chemistry in understanding the chemical basis of protein function

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The total synthesis of proteins was one of the 'Grand Challenges' of 20th century chemistry. Despite decades of development by skilled organic chemists throughout the world, conventional synthetic methods were able to make only the smallest proteins. In 1992 we introduced the chemical ligation principle - the condensation of unprotected peptide segments by chemoselective reaction enabled by formation of an unnatural bond at the ligation site.[1] In 1994 we introduced native chemical ligation, the thiol ester-mediated condensation of unprotected peptide segments to give a native peptide bond at the ligation site.[2] In combination with peptide synthesis by state-of-the-art SPPS, modern chemical ligation methods enable the total chemical synthesis of proteins including enzymes.[3] Synthetic protein products are characterized by high resolution methods including LCMS, multidimensional NMR, and X-ray crystallography. Chemical protein synthesis gives precise, atom-by-atom control over the covalent structure of a protein molecule. Case studies of the application of chemical protein synthesis to the enzymes ribonuclease A and the HIV-1 protease will be described. The application of time-resolved FTIR spectroscopy to human insulin in which individual peptide bonds have been site-specifically isotope labelled with $^{13}C{=}^{18}O$ will also be presented.

References

1. Constructing proteins by dovetailing unprotected synthetic peptides: backbone engineered HIV protease. M. Schnölzer, S. Kent *Science*, **256**, 221-225 (1992).
2. Synthesis of proteins by native chemical ligation. Philip E. Dawson, Tom W. Muir, Ian Clark-Lewis, Stephen B.H. Kent, *Science*, **266**, 776-779 (1994).
3. Chemical protein synthesis: inventing synthetic methods to decipher how proteins work. Stephen B.H. Kent, *Bio Org Med Chem*., **25**, 4926-4937 (2017).