# TECHNICAL NOTE

## Automated Synthesis of Cyclic Peptides on the Pioneer™ Peptide Synthesis System

Cyclic peptides have been of interest to chemists and biologist since the late 1940s with the discovery that the antibiotic gramicidin S is a cyclic decapeptide.[1] Many other naturally occurring antibiotics and toxins have been discovered to have cyclic structures. Cyclic structures appear to exhibit enhanced metabolic activities, as well as increased stability. Synthesis of cyclic peptides has proven to be challenging due to the complexity of their structures.

### Classes of cyclic peptides

There are two general classes of cyclic peptides.

- **Homodetic Peptides**

Homodetic peptides are those in which the ring is formed through usual peptide (amide) linkages connecting amino and carboxyl functions.[2] The common forms are:

- Head to tail
- Side-chain to side-chain
- Side-chain to head (or tail)

While several methods have been developed for the formation of these lactam-cyclized peptides, the one most suitable to automation is that of allyl-based protection. Allyl-based protecting groups have been used extensively in organic synthesis and have recently been applied to DNA, carbohydrate, and peptide synthesis.[3] The mild conditions used to remove the allyl groups are compatible with classical Fmoc/*t*Bu methods for solid-phase peptide synthesis. [4,5]

For more information on the use of allyl-protection on the Pioneer™ for the formation of cyclic peptides, see the Technical Note entitled "Use of Allyl-based Protecting Groups for the Automated Synthesis of Cyclic and Branched-Chain Peptides on the Pioneer™ Peptide Synthesis System."

- **Heterodetic Peptides**

Heterodetic peptides are those in which the ring is formed *via* other functions, such as esters (lactones), thioesters, ethers or, most commonly, disulfides. Disulfide bridges play a crucial role in the folding and structural stabilization of many important extracellular peptide and protein molecules, including hormones, enzymes, growth factors, toxins, and immunoglobulins.[6]

Disulfide bonds are formed by the oxidation of the side-chain sulfhydryl of Cysteine residues. When more than two Cysteines are present, formation of the proper disulfide bonds can be directed by the use of alternate side-chain protection strategies.

For more information on the automated cyclization of disulfide-containing peptides on the Pioneer™, see the Technical Note entitled "Automated Disulfide Bond Formation on the Pioneer™ Peptide Synthesis System."

### References:


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3. Greene, T.W. and P.G.M. Wuts.1991. *Protective Groups in Organic Chemistry*, 2nd Ed., John Wiley and Sons, Inc., New York.

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