

Solid-Phase Peptide Synthesis

June 5, 2013

- Solid-phase Fmoc-based peptide synthesis. The peptide antibiotic Temporin SHf as a case study for comparison with solution-phase methods.

Announcements

Quiz 4 is ready for pick-up after class. Stats: Average = 21.1/30, Std. Dev. = 6.7, High = 34/30. The key has been posted.

Final Exam Practice Problems and a Final Exam Review Sheet have been posted.

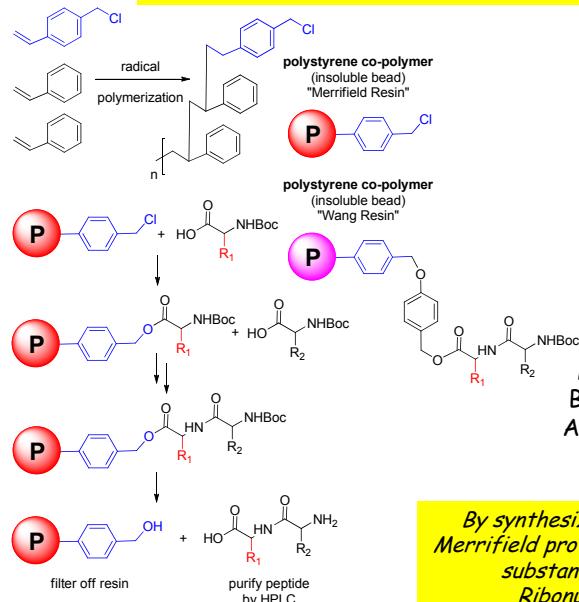
It's time to prepare for our final exam. The take-home final exam questions will focus primarily on 41c material, but material from earlier quarters is certainly fair game. You will be allowed to only use the following when working your final exam: a calculator, molecular models, Loudon's text & solutions manual, and any class notes associated with 41a-c. A final exam review session will take place on Friday, June 7th from 4:50 PM in Crenlin 151. The final will be distributed in Noyes 153 at 9:00 am on Monday June 10.

Be sure to provide course feedback via the Teaching Quality Feedback Report (TQFR) system, which is now open.

TA Office Hours during Finals Week: Ben Suslick (UTA) - Lloyd Lounge; Monday June 10 2-3 pm. If additional OH are required between now and then, please contact a TA or me and make an appointment.

Suggested Problems for Chapter 26: 26.42, 26.46, 26.48, 26.62(a-g), 26.66(a-d), 26.70.

Robert Bruce Merrifield: Inventor of SPPS



R. B. Merrifield
1921-2006
Montebello H.S. (Los Angeles)
B.S./Ph.D. UCLA (Biochemistry)
Academic Career: Rockefeller U.
1984 Chemistry Nobel Prize

By synthesizing peptides & small proteins, Merrifield proved the chemical nature of these substances (Oxytocin, Bradykinin, Ribonuclease A, among others)

Temporin-SHf
A peptide antibiotic isolated from Saharan frogs

The diagram shows the structure of Temporin-SHf, a cyclic peptide, at the top. Below it is a photograph of a green frog, *Pelophylax saharicus*. A schematic diagram illustrates the 'carpet model' for membrane permeation. It shows a lipid bilayer with blue and orange regions. Peptides (represented by orange and blue sticks) associate with the membrane. Stage A shows peptides binding to the anionic outer layer. Stage B shows the formation of pores in the membrane. Stage C shows the disintegration of the membrane.

Pelophylax saharicus

Ladram, et al. *J Biol Chem* 2010, 285, 16880.

A

B

C

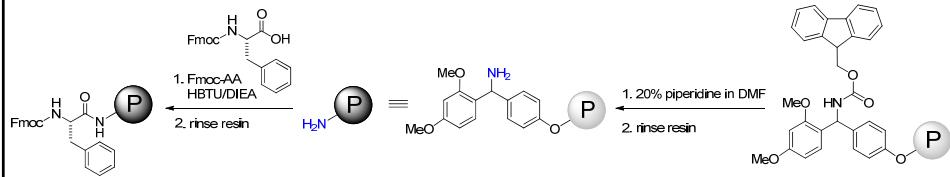
Figure 1. The carpet model for membrane permeation. Blue is the hydrophobic region and the orange is the hydrophilic region. The peptides associate to the membrane with their hydrophilic region to the anionic outer layer (A). When a certain concentration of the peptide has associated, the membrane can be permeated and pores will be created within the membrane (B). This process can also cause membrane disintegration (C). Source: *Biopolymers*, 2002, 66, 236.

Planning the SPPS of Temporin-SHf

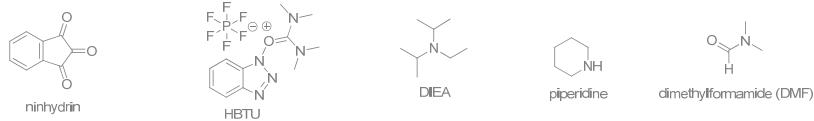
The diagram shows the structure of Temporin-SHf with annotations for synthesis planning:

- reactive N-terminus (protect)**: Points to the N-terminal amide group (H_3N^+) which is part of the peptide coupling step.
- peptide coupling (8th of 8)**: Points to the N-terminal amide group of the first repeat unit.
- reactive side chain (protect)**: Points to the side-chain amide groups ($\text{NH}-\text{CH}_2-\text{CO}-$) located on the backbone carbons of the repeating units.
- C-terminal amide (install from resin)**: Points to the C-terminal amide group ($-\text{NH}_2$) which is indicated as being installed from a resin.

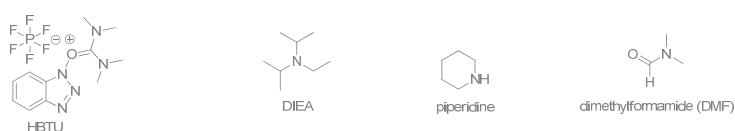
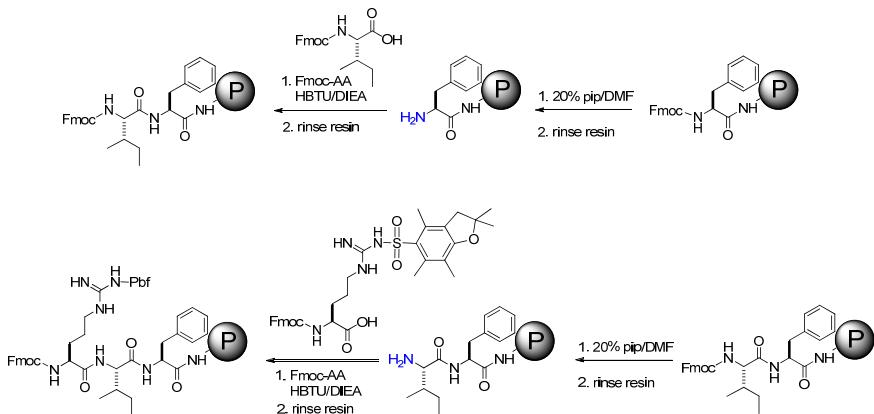
Installing the first Fmoc-amino acid



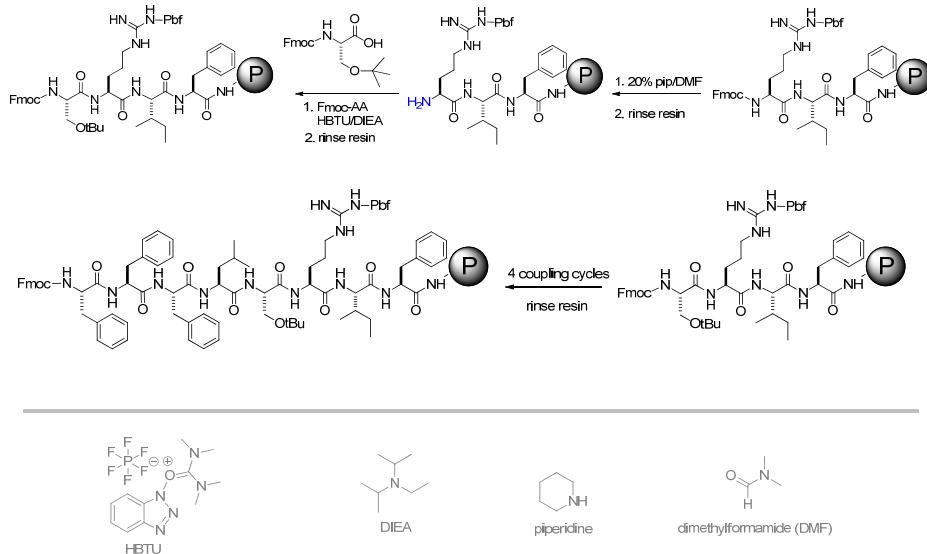
Kaiser Test: Ninhydrin-based assay for free amines:



Installing Ile and Arg



Installing Ser(OtBu) & Completing the On-Resin Peptide



Cleaving the Peptide from the Resin

