

CHEMISTRY 5510

BIOLOGICAL CHEMISTRY I FALL 2025

Professor: David W. Christianson

Email: chris@sas.upenn.edu

Lectures: Tuesdays and Thursdays, 8:30 – 9:50.

Office Hours: Wednesdays 8:30-9:30 am and 4:30-5:30 pm (zoom).

Teaching Fellow: TBA.

Course Outline: This course will outline aspects of protein structure and stability, and then continue with a detailed analysis of protein structure-function relationships using specific examples from the primary literature. Topics to be addressed include protein structure-stability relationships, protein dynamics, protein function in the membrane, the molecular basis of anthrax infection, and the mechanisms of Ebola and influenza virus-cell recognition. Specific topics and readings for each lecture are outlined in the attached course schedule.

Textbook: There will be no textbook for the course; instead, research papers from the primary literature will be assigned as outlined in the course schedule.

Exams: Three 1.5-hour exams on Thursday 10/02, Thursday 11/06, and Thursday 12/04. *No final exam.*

Problem Sets: 8 graded problem sets will be distributed on most Thursdays and due the following Thursday as outlined in the course schedule.

Basis of

Final Grade:	Problem Sets	200 points
	Exams (best 2 out of 3)	300 points

Grade Cutoffs:

A's, 440 – 500 points
B's, 385 – 439 points
C's, 325 – 384 points
D's, 255 – 324 points
F's, 0 – 254 points

COURSE SCHEDULE

CHEMISTRY 5510 – BIOLOGICAL CHEMISTRY I

(* = required reading; † = recommended reading)

08/26 Lecture 1. Primary structure: chemical reactivity of amino acids, acid-base chemistry. Peptide bond geometry, *trans-cis* isomerization. Posttranslational modifications.

- *Genshaft et al. (2013) Energetically Unfavorable Amide Conformations for N6-Acetyllysine Side Chains in Refined Protein Structures. *Proteins: Struct., Funct., Bioinf.* 81, 1051.
Jorgensen & Gao (1988) Cis-Trans Energy Difference for the Peptide Bond in the Gas Phase and in Aqueous Solution. *J. Am. Chem. Soc.* 110, 4212.
Radzicka et al. (1988) Influences of Solvent Water on Protein Folding: Free Energies of Solvation of Cis and Trans Peptides are Nearly Equal. *Biochemistry* 27, 4538.
Tweedy et al. (1993) Structure and Energetics of a Non-Proline cis-Peptidyl Linkage in a Proline-202→Alanine Carbonic Anhydrase II Variant. *Biochemistry* 32, 10944.

08/28 Lecture 2. The hydrogen bond: molecular orbital description, geometry, energetics. The $n \rightarrow \sigma^*$ interaction. C-H hydrogen bonds

- *Arunan et al. (2011) Definition of the Hydrogen Bond (IUPAC Recommendations 2011). *Pure Appl. Chem.* 83, 1637.
Ippolito et al. (1990) Hydrogen Bond Stereochemistry in Protein Structure and Function. *J. Mol. Biol.* 215, 457.
Cleland (2000) Low-Barrier Hydrogen Bonds and Enzymatic Catalysis. *Arch. Biochem. Biophys.* 382, 1.
Steiner (2002) The Hydrogen Bond in the Solid State. *Angew Chem. Int. Ed.* 41, 48.
Pimentel (1951) The Bonding of Trihalide and Bifluoride Ions by the Molecular Orbital Method. *J. Chem. Phys.* 19, 446.
Derewenda & Derewenda (1995) The Occurrence of $\text{CH}\cdots\text{O}$ Hydrogen Bonds in Proteins. *J. Mol. Biol.* 252, 248.
Horowitz & Trievel (2012) Carbon-Oxygen Hydrogen Bonding in Biological Structure and Function. *J. Biol. Chem.* 287, 41576.

09/02 Lecture 3. Aquaporin: selective conduction of water into and out of cells.

- King & Agre (1996) Pathophysiology of the Aquaporin Water Channels. *Ann. Rev. Physiol.* 58, 619.
†Kosinska Eriksson et al. (2013) Subangstrom Resolution X-ray Structure Details Aquaporin-Water Interactions. *Science* 340, 1346.

09/04 Lecture 4. Journal Club: Selective conduction of glycerol into and out of cells by GlpF.

- *Fu et al. (2000) Structure of a Glycerol-Conducting Channel and the Basis for its Selectivity. *Science* 290, 481.

Problem Set 1 posted

09/09 Lecture 5. The halogen bond: molecular orbital description, geometry, energetics. The $n \rightarrow \sigma^*$ interaction.

- *Auffinger et al. (2004) Halogen Bonds in Biological Molecules. *Proc. Natl. Acad. Sci. USA* 101, 16789.
Wolters & Bickelhaupt (2012) Halogen Bonding versus Hydrogen Bonding: A Molecular Orbital Perspective. *ChemistryOpen* 1, 96.

09/11 Lecture 6. Hierarchy of polar interactions in protein structure: charges, dipoles, quadrupoles; cation- π interactions. Metals in biology.

*Dougherty (1996) Cation-Pi Interactions in Chemistry and Biology: A New View of Benzene, Phe, Tyr, and Trp. *Science* 271, 163.

Burley & Petsko (1988) Weakly Polar Interactions in Proteins. *Adv. Prot. Chem.* 39, 125.

Problem Set 1 due; Problem Set 2 posted

09/16 Lecture 7. Hydrophobic effect, protein-protein interactions; quaternary structure.

*Chen et al. (2013) Protein-Protein Interactions: General Trends in the Relationship Between Binding Affinity and Interfacial Buried Surface Area. *Protein Sci.* 22, 510.

Spolar et al. (1989) Hydrophobic Effect in Protein Folding and Other Noncovalent Processes Involving Proteins. *Proc. Natl. Acad. Sci. USA* 86, 8382.

Horton & Lewis (1992) Calculation of the Free Energy of Association for Protein Complexes. *Protein Sci.* 1, 169.

Chandler (2005) Interfaces and the Driving Force of Hydrophobic Assembly. *Nature* 437, 640.

09/18 Lecture 8. Secondary Structure: α -helix structure-stability relationships. Sequence dependence, $n \rightarrow \pi^*$ interactions, side chain interactions. Coiled coils.

[†]Ghadiri & Choi (1990) Secondary Structure Nucleation in Peptides. Transition Metal Ion Stabilized α -Helices. *J. Am. Chem. Soc.* 112, 1630.

Huyghues-Despointes et al. (1995) Measuring the Strength of Side-Chain Hydrogen Bonds in Peptide Helices: The Gln•Asp ($i, i + 4$) Interaction. *Biochemistry* 34, 13267.

Newberry & Raines (2017) The $n \rightarrow \pi^*$ Interaction. *Acc. Chem. Res.* 50, 1838.

Lumb & Kim (1995) A Buried Polar Interaction Imparts Structural Uniqueness in a Designed Heterodimeric Coiled Coil. *Biochemistry* 34, 8642.

Schafmeister et al. (2000) An All-Hydrocarbon Cross-Linking System for Enhancing the Helicity and Metabolic Stability of Peptides. *J. Am. Chem. Soc.* 122, 5891.

[†]Hilinski et al. (2014) Stitched α -Helical Peptides via Bis Ring-Closing Metathesis. *J. Am. Chem. Soc.* 136, 12314.

Woolfson (2023) Understanding a protein fold: the physics, chemistry, and biology of α -helical coiled coils. *J. Biol. Chem.* 299, 104579.

Problem Set 2 due; Problem Set 3 posted

09/23 Lecture 9. Journal Club: Stapled helices in drug design.

*Chang et al. (2013) Stapled α -Helical Peptide Drug Development: a Potent Dual Inhibitor of MDM2 and MDMX for p53-Dependent Cancer Therapy. *Proc. Natl. Acad. Sci. USA* 110, E3445.

09/25 Lecture 10. Secondary Structure: β -sheet structure-stability relationships; context dependence, side chain interactions. β -Turns.

Minor & Kim (1994) Measurement of the β -Sheet-Forming Propensities of Amino Acids. *Nature* 367, 661.

Minor & Kim (1994) Context is a Major Determinant of β -Sheet Propensity. *Nature* 371, 264.

Zhang & Kim (2000) A Comprehensive Analysis of the Greek Key Motifs in Protein β -Barrels and β -Sandwiches. *Proteins: Struct., Funct. Genet.* 40, 409.

Problem Set 3 due

09/30 Exam #1 Review Session

10/02 Exam #1

10/07 Lecture 11. Cross- β spines in disease pathology.

[†]Tuttle et al. (2016) Solid-State NMR Structure of a Pathogenic Fibril of Full-Length Human α -Synuclein. *Nat. Struct. Mol. Biol.* 23, 409.

[†]Hsieh et al. (2018) Alpha Synuclein Fibrils Contain Multiple Binding Sites for Small Molecules. *ACS Neurosci.* 9, 2521.

Nelson et al. (2005) Structure of the Cross- β Spine of Amyloid-Like Fibrils. *Nature* 435, 773.

Sawaya et al. (2007) Atomic Structures of Amyloid Cross-Beta Spines Reveal Varied Steric Zippers. *Nature* 447, 453.

Gilbert et al. (2024) CryoET of β -amyloid and tau within postmortem Alzheimer's disease brain. *Nature* 631, 913.

Problem Set 4 posted

10/09 Fall Break

10/14 Lecture 12. Journal Club: Protein structure determination by cryo-electron diffraction.

*Rodriguez et al. (2015) Structure of the Toxic Core of α -Synuclein from Invisible Crystals. *Nature* 525, 486.

10/16 Lecture 13. Tertiary Structure: fold families, structural homology; AlphaFold; cavities and consequences for stability.

*Matthews & Liu (2009) A Review about Nothing: Are Apolar Cavities in Proteins Really Empty? *Protein Sci.* 18, 494.

Richardson (1981) The Anatomy and Taxonomy of Protein Structure. *Adv. Prot. Chem.* 34, 167.

Eriksson et al. (1992) A Cavity-Containing Mutant of T4 Lysozyme is Stabilized by Buried Benzene. *Nature* 355, 371.

Hubbard et al. (1994) Intramolecular Cavities in Globular Proteins. *Protein Eng.* 7, 613.

Williams et al. (1994) Buried Waters and Internal Cavities in Monomeric Proteins. *Protein Sci.* 3, 1224.

Problem Set 4 due; Problem Set 5 posted

10/21 Lecture 14. Membranes, membrane proteins.

Blobel (1980) Intracellular Protein Topogenesis. *Proc. Natl. Acad. Sci. USA* 77, 1496.

Lemmon et al. (1994) A Dimerization Motif for Transmembrane Alpha-Helices. *Nature Struct. Biol.* 1, 157.

Stams et al. (1996) Crystal Structure of the Secretory Form of Membrane-Associated Human Carbonic Anhydrase IV at 2.8 Å Resolution. *Proc. Natl. Acad. Sci. USA* 93, 13589.

Pautsch & Schulz (1998) Structure of the Outer Membrane Protein A Transmembrane Domain. *Nature Struct. Biol.* 5, 1013.

Russ & Engelman (2000) The GxxxG Motif: A Framework for Transmembrane Helix-Helix Association. *J. Mol. Biol.* 296, 911.

10/23 Lecture 15. β -Barrel pore-forming transmembrane toxins.

*Song et al. (1996) Structure of Staphylococcal α -Hemolysin, a Heptameric Transmembrane Pore. *Science* 274, 1859.

Olson et al. (1999) Crystal Structure of Staphylococcal LukF Delineates Conformational Changes Accompanying Formation of a Transmembrane Channel. *Nature Struct. Biol.* 6, 134.

Yamashita et al. (2011) Crystal Structure of the Octameric Pore of Staphylococcal γ -Hemolysin Reveals the β -Barrel Pore Formation Mechanism by Two Components. *Proc. Natl. Acad. Sci. USA* 108, 17314.

Problem Set 5 due; Problem Set 6 posted

10/28 Lecture 16. Journal Club: Mechanism of anthrax infection.

*Petosa et al. (1997) Crystal Structure of the Anthrax Toxin Protective Antigen. *Nature* 385, 833.

†Santelli et al. (2004) Crystal Structure of a Complex between Anthrax Toxin and its Host Cell Receptor. *Nature* 430, 905.

10/30 Lecture 17. β -Barrel pore-forming transmembrane toxins, continued. Transport of Fe^{3+} -siderophore complexes through the outer membrane by FepA and FhuA as powered by the ExbB₅ExbD₂TonB complex in the inner membrane of Gram-negative bacteria.

Ferguson et al. (1998) SiderophoreMediated Iron Transport: Crystal Structure of FhuA with Bound Lippolysaccharide. *Science* 282, 2215.

Buchanan et al. (1999) Crystal Structure of the Outer Membrane Active Transporter FepA from Escherichia coli. *Nat. Struct. Biol.* 6, 56.

Ratliff et al. (2022) The Ton Motor. *Front. Microbiol.* 13, 852955.

Problem Set 6 due

11/04 Exam #2 Review Session

11/06 Exam #2

11/11 Lecture 18. Journal Club: Structural basis of efflux mechanisms in Gram-negative bacteria.

*Koronakis et al. (2000) Crystal Structure of the Bacterial Membrane Protein TolC Central to Multidrug Efflux and Protein Export. *Nature* 405, 914.

Du et al. (2014) Structure of the AcrAB-TolC Multidrug Efflux Pump. *Nature* 509, 512.

Jang (2023) AcrAB-TolC, a Major Efflux Pump in Gram negative Bacteria: Toward Understanding Its Operation Mechanism. *BMB Rep.* 56, 326.

11/13 Lecture 19. Bacterial efflux mechanisms, continued.

Problem Set 7 posted

11/18 Lecture 20. Kinetically trapped folding intermediates.

Gettins (2002) Serpin Structure, Mechanism, and Function. *Chem. Rev.* 102, 4751.

Silvermann et al. (2001) The Serpins are an Expanding Superfamily of Structurally Similar but Functionally Diverse Proteins. *J. Biol. Chem.* 276, 33293.

11/20 Lecture 21. Journal Club: Mechanism of influenza virus infection: hemagglutinin.

*Bullough et al. (1994) Structure of Influenza Haemagglutinin at the pH of Membrane Fusion. *Nature* 371, 37.

Skehel & Wiley (2000) Receptor Binding and Membrane Fusion in Virus Entry: the Influenza Hemagglutinin. *Annu. Rev. Biochem.* 69, 531.

Harrison (2008) Viral Membrane Fusion. *Nature Struct. Mol. Biol.* 15, 690.

Ni et al. (2014) Structural Insights into the Membrane Fusion Mechanism Mediated by Influenza Virus Hemagglutinin. *Biochemistry* 53, 846.

Problem Set 7 due; Problem Set 8 posted

11/25 Lecture 22. Mechanism of influenza virus infection: neuraminidase, M2 channel protein.

Wang et al. (2011) Structure and Dynamic Mechanisms for the Function and Inhibition of the M2 Proton Channel from Influenza A Virus. *Curr. Opin. Struct. Biol.* 21, 68.

Jalily et al. (2020) Put a Cork In It: Plugging the M2 Viral Ion Channel to Sink Influenza. *Antiviral Res.* 178, 104780.

McAuley et al. (2019) Influenza Virus Neuraminidase Structure and Functions. *Front. Microbiol.* 10, 39.

Itzstein (2007) The War Against Influenza: Discovery and Development of Sialidase Inhibitors. *Nat. Rev. Drug Discov.* 6, 967.

11/27 Thanksgiving Holiday

12/02 Exam #3 Review Session

Problem Set 8 due

12/04 Exam #3