Chemistry 351h: Bioinorganic Chemistry, Spring 2010

(www.haverford.edu/chem/351)

Description: This course will explore the inorganic chemistry behind the requirement of biological cells for metals such as zinc, iron, copper, manganese, and molybdenum. The course will begin with the principles of coordination chemistry and a survey of the abilities of various functional groups within proteins and nucleic acids to form coordination complexes with metal ions. The reactivity of coordination complexes of metal ions will be discussed in the context of the reaction mechanisms of specific metalloenzymes. A portion of the course will be devoted to medically-relevant topics such as mechanisms by which organisms obtain required metal ions from their environment, the toxicity of metals such as lead and mercury, and use of platinum-containing compunds in treating cancer.

Frequency: In recent years, this course has been offered once every academic year. It is scheduled to next be offered in Spring of 2011.

Prerequisites: Chemistry 221 (second semester Organic Chemistry) and 304 (first semester Physical Chemistry) or consent of the instructor. In addition, students should have completed either Chemistry 320g (Inorganic Chemistry) or Biology courses involving protein structure.

Instructor for Spring 2010: Professor Robert C. Scarrow, Koshland INSC East Wing, room 214a, (610) 896-1218, rscarrow@haverford.edu

Office Hours: My office is in KINSC E214A. Office hours are Tuesday, Wednesday and Thursdays 2:00 – 3:00. Feel free to ask me for help at other times when my office door is open, or call (610 896 1218) or e-mail me (rscarrow@haverford.edu) for an appointment (please suggest at least two possible times).

Required Textbook:

- **TEXT**: Bertini, I.; Gray, H. B.; Stiefel, E. I.; Valentine, J. S., editors. Biological Inorganic Chemistry (University Science Books, 2007). This a comprehensive textbook on bioinorganic chemistry designed for either an advanced undergraduate or graduate level course. Most reading assignments will be from this textbook.

Optional Textbooks and Reserve Readings:

The following books have been placed on reserve in the Science Library. This is pretty much all of textbooks that have been published in the last 15 years on the topic of Bioinorganic Chemistry. I urge you to familiarize yourself with these books; if you want to come by my office and browse through all of these books to learn about the style and content of each, that would be fine.

- **BGLV:** Bertini, I.; Gray, H. B.; Lippard, S. J.; Valentine, J. S. *Bioinorganic Chemistry* (University Science Books; Mill Valley, CA, 1994) – a graduate-level text composed of a collection of review articles on specific subject. Not as many topics are covered in **BGLV** compared with your required **TEXT,** but the articles in **BGLV** go into more detail (but at this point are somewhat dated).
- **C**: Cowan, J. A. *Inorganic Biochemistry: An Introduction* (Wiley-VCH: New York,

1997) – one of the standard textbooks for the field, with particular strengths in describing spectroscopic techniques and their use in revealing enzyme reaction mechanisms.

- **Cr:** Crighton, R. *Biological Inorganic Chemistry* (Elsevier: Amsterdam, 2008). A recent and short paperback textbook that stresses some of the more biological aspects of bioinorganic chemistry.
- **F:** Fenton, D. E. *Biocoordination Chemistry* (Oxford University Press, 1995) – part of Oxford's chemistry primer series – a good place to go for brief introductions to a variety of topics in chemistry.
- **FW:** Frausto da Silva, J. J. R. and Williams, R. J. P. *The Biological Chemistry of the Elements: the Inorganic Chemistry of Life* (2nd. edition, Oxford, 2001). This textbook contains a wealth of information as well as provocative speculations about "big questions" such as why certain elements and not others are used by biological organisms, and how biology and the surface geology of the earth have evolved together over time.
- **HS:** Housecroft, C. E. and Sharpe, A. G. "Inorganic Chemistry, Pearson/Prentice Hall", 2005 (2nd Edition). This book is the required textbook for Chemistry 320 this year, and one copy has been placed on reserve.
- **LB:** Lippard, S. J. and Berg, J. M. *Principles of Bioinorganic Chemistry* (University Science Books; Mill Valley, CA, 1994). Although the most dated of the available text, this is also the most readable and best organized introduction to the field written by a Haverford alum (Lippard) and the current head of the National Institute of General Medical Sciences (Berg). If you didn't take Chem 320, you should carefully read the chapter on basic coordination chemistry. If you have not taken a Biology course dealing with protein structure, you should carefully read the chapter on protein structure. Two copies will be placed on reserve.
- **KS**: Kaim, W. and Schwederski, B. *Bioinorganic chemistry : inorganic elements in the chemistry of life : an introduction and guide* (Wiley, 1994) - an interesting alternative textbook by a pair of German authors. The English translation is not always very clear, but the book has nice figures taken from the original literature.
- **M:** McCleverty, J. *Chemistry of the first-row transition metals* (Oxford) – another member of the Oxford chemistry primer series.
- **Q**: Que, L., Jr. ed. *Physical Methods in Bioinorganic Chemistry* (Univ. Sci. Books; Mill Valley, CA, 2000). A great resource for learning more about particular spectroscopic techniques used to study metal ions in biological (and model) systems.
- **R-M**: Roat-Malone, R. M. *Bioinorganic Chemistry: A Short Course* (Wiley, 2002). This textbook also has good introductory chapters and also provides a good introduction to the bioinorganic chemistry of nitrogenase.
- **SAL:** Shriver, D. F.; Atkins, P. and Langford, C *Inorganic Chemistry* (3rd edition) - another textbook that would be appropriate for the 320 inorganic course.
- **WW:** Wilkins, P. C.; Wilkins, R. G. *Inorganic Chemistry in Biology* (Oxford University Press: 1997) – another member of the Oxford chemistry primer series.

Order of Topics:

Below is an outline of the course. The instructor may omit or add topics in response to feedback from students and/or time constraints. An estimated schedule of topics is also given. The italicized items are suggestions for keywords for searching for focus articles.

Note: on Wednesday, March 17, 4:30 pm, Hilles 109, Haverford alumnus Matt Sazinsky '99 will give a talk as part of the Young Academic Alumni series sponsored by the Library. His talk title is not yet set but will certainly involve bioinorganic chemistry. Please put this talk on your calendar – attendance is expected for those enrolled in the class. If you absolutely cannot make the talk, let me know your reason and I will give you an alternative assignment.

1) Introductions (**TEXT**: Chapter I and Sections II.1, II.2 and II.3; pp. 5-16) **(week 1)**
   a) Fundamentals of Coordination Chemistry (**TEXT**: Tutorial II. pp. 695-712. Will be mostly review if you've taken Chemistry 320)
   b) Cell Biology, Biochemistry and Evolution (**TEXT**: Tutorial I, pp. 657-694, emphasizing sections T.1.4.2, pp. 675-680 on proteins and T.I.5, pp. 685-693 on metabolism. Will be mostly review if you've taken Biology 200. Also, take a look at the Glossary, pp. 717-725 – this may come in useful later)
   c) Physical Methods for Bioinorganic Chemistry (chapter 4 of **LB**).
2) Binding of Metal Ions to Proteins (**TEXT**: chapter III) **(week 2)**
   a) Metal-dependent lyases and hydrolases (**TEXT**: section IX.1)
      - *Carboxypeptidase A, Phosphatase, Purple Acid Phosphatase (metal-dependant), Carbonic Anhydrase*
   b) Zinc Binding domains (**TEXT**: section XIV.2)
      - *Zinc finger*
   c) Calcium and calcium-binding proteins (**TEXT**: section XIV.3)
      - *Calmodulin, Calbindin, Troponin, Calcium ATPase*
3) Transport and Storage of Metal Ions (**TEXT**: chapter V) **(week 3)**
   a) Transport and Storage of iron within organisms (**TEXT**: section VIII.1 and VIII.2)
      - *Transferrin, Lactoferrin, Ferritin*
   b) Obtaining iron from the environment (**TEXT**: section VIII.3)
      - *Siderophores, enterobactin, ferrioxamine*
4) Metals and Health (**TEXT**: chapter VII) **(week 4)**
   a) Metal-based drugs
      - *cis-platin, carboplatin, platinum anti-cancer drugs, technetium radiopharmaceuticals, gadolinium MRI contrast agents, auranofin,*
   b) Metal toxicity
      - *iron overload, mercuric ion reductase, lead and porphobilinogen synthase*
5) Oxygen metabolism **(weeks 5 and 6)**
   a) Reactivity of O_2 and its reduced forms (**TEXT**: section XI.1)
   b) Dioxygen carriers (**TEXT**: section XI.4; you may skim over or skip section XI.4.3 on cooperativity – this topic is often treated in protein biochemistry courses, so many of you

will have seen it before)

- *myoglobin, hemerythrin, hemocyanin*

c) Enzymes that get rid of superoxide (**TEXT**: section XI.2)

- *Superoxide dismutase, Superoxide reductase*

d) Enzymes that utilize peroxides (**TEXT**: section XI.3)

- *Catalase, peroxidase*

e) Oxygen-activating enzymes (**TEXT**: section XI.5)

- *Cytochrome P-450$_{cam}$, methane monooxygenase, monooxygenase, dioxygenase*

f) Cytochrome c oxidase (**TEXT**: section XI.6)

- *Cytochrome c oxidase*

6) Special cofactors and metal clusters (**TEXT**: chapter IV) **(week 7)**

a) Electron transfer proteins (**TEXT**: section X.1)

- *Plastocyanin, Azurin, Blue-copper, Ferredoxin, Cytochrome c, Iron-sulfur*

b) Cobalamins (**TEXT**: section XIII.2)

- *Diol dehydrase, methylmalonyl-CoA Mutase, Methionine Synthase, adenosylcobalamin-dependent ribonucleotide reductase.*

c) Molybdenum-cofactor enzymes (**TEXT**: section XII.6, through the end of XII.6.3.2 [pp. 518-537])

- *Sulfite Oxidase, Nitrite Oxidase, Xanthine Oxidase, DMSO reductase*

The reading assigned above represents roughly half of the content of your textbook. There are a number of important topics that we will not be discussing in this seven-week course, and I encourage you to read the sections of the text and discuss these topics with me if you are interested. Among the topics that I would include if we had several more weeks would be biogeochemical cycles (**TEXT** chapter II), biomineralization (**TEXT** chapter VI), metalloregulatory proteins (**TEXT** section XIV.1), nitrogen metabolism (**TEXT** sections XII.3 and XII.4) and photosynthesis (**TEXT** sections X.3 and X.4).

Reading Assignments and Short Answer Questions

Before each class, you will be asked to read a certain chapter or section from **TEXT** and to answer several short answer questions (based on the reading) *via* an on-line submission system available through Blackboard. For full credit, submit the answers prior to 6 a.m. the day of the class (i.e. before you go to sleep the night before). This allows me to look at your answers and address common misperceptions in the class. If you submit your answers after 6 a.m. but before the 10 a.m. class time, your grade will be reduced by 5%; later than this the grade will be reduced by 20% (but no assignments may be turned in after 4 p.m. Friday April 30 without a dean's extension).

Focus article: Handout, Presentation, Questions and Term Paper.

During the first week of class, each student enrolled in the course will propose a focus article related to a bioinorganic topic for a class handout and presentation, as well as for a term paper. You must choose an article from a journal to which our library gives us on-line access; our library gives us access to the most important and well-respected journals in the field, and

conversely most article that require interlibrary loan to get are not the best papers. Suggestions for finding such a paper:

- Browse table of contents of bioinorganic journals listed in the back of your textbook. Note that the most important articles are often published in more general-audience journals – the *Journal of the American Chemical Society* and *Inorganic Chemistry* usually each have several bioinorganic-themed articles in each issue.
- Choose a keyword from the list above that sounds interesting and do a SciFinder, PubMed or Google Scholar search. Give preference to articles you find that are in major bioinorganic chemistry journals, as listed in the back of your book.

To propose an article, please send me the complete literature reference (including title) along with a link that will get me to the pdf file of the article at the journal web site (if that doesn't work, attach a pdf file). Also, give me a one sentence summaries of the question the authors of the paper are attempting to answer (i.e. 2a below) and what techniques the authors are using that you will focus upon in your presentation and paper. Do this no later than Friday of the first week after spring break. Earlier submissions will be accepted, and you are more likely to get your first choice topic if you submit your proposal early.

The focus article must be approved by me, and I will schedule your class presentation so that it comes at an appropriate time to fit in with the overall course schedule. Thus use the schedule above (for the class presentation) and consider the timing of your other classes and activities in choosing your focus article. I will not approve the same article twice, and will not approve articles that are too similar to or focus on the same bioinorganic system as one already chosen by another student. Furthermore, presentations will be limited by general topic so that there are no more than three student presentations per week. Topics that "fill up" will be posted as Blackboard announcements.

All term papers will be due at the same time (the last day of classes). Because the purpose is to have you learn something new, please choose a topic you have not studied in a previous course (including research tutorial courses).

The **presentation** and **paper** may both start from the same outline, but because of the brief time allocated to your presentation, you will need to condense the background information (section 1) and omit other recent results (section 3) in your presentation.

1) **Background information** on the "system" that is being studied (in most cases this will be a metalloenzyme, but it could also be a small-molecule metal complex or a metal storage protein). *Note: you will need to be very careful to keep this section brief during your presentation, although you should expand this to two or three pages in your paper. For your presentation, assume that your colleagues have done the assigned reading from **TEXT**, and try to put your presentation in context with the assigned readings. I particular, do not extensively repeat information contained in the readings (a very brief review is OK).*
   a) What is the biological function and/or medical relevance of the system? In what species is this system found, and from which species is the system best characterized? If this a protein, is it part of a family of related proteins, and if so, what are some of the names of the similar proteins?
   b) What is the metal involved?
   c) What is the coordination environment of the metal?
   d) What is known and generally accepted about the chemical role of the metal and its

coordination environment in carrying out the function of the system?

2) **Summary of the focus article** you've chosen. *Aim for about three to five pages in your paper (not counting figures and tables you decide to include); this will be the section on which you will spend most of your time for your talk.*

   a) What previously unanswered question are the authors seeking to answer? *Note: in choosing the paper on which you focus, make sure that this question involves the structure or reactivity of the metal center – i.e. has a bioinorganic "flavor". If in doubt, please consult me.*

   b) What technique(s) are the authors using? If it is a long paper with multiple experiments and techniques, you may choose to focus on one of the more important techniques. What is the physical basis for this technique? *The books on reserve are good sources for learning about physical techniques used in bioinorganic chemistry. **Q** is devoted to this topic, with chapters on different methods, while **R-M**, **LB**, and **C** all contain one chapter devoted to methods, with sections on different methods. If you are presenting on a complicated method that hasn't been discussed before in the class, I may help out with a brief introduction to the technique prior to your presentation; if this would be useful, be sure to talk to me about it in advance.*

   c) In your presentation and paper, show at least one figure or table containing experimental data from your focus article, and explain how the data in the figure or table is interpreted and what is learned from it.

3) **Other recent results** on this system. *Paper only for this section; there is not time for this in your presentation. I'm looking for a couple paragraphs not a comprehensive literature review.* What other things are being learned about the system? Have there been any further studies that build on the studies of your focus article (try a citation search using either Web of Science or SciFinder)? What are some still unanswered questions that are motivating further research on the system that is the subject of your focus article?

PRESENTATION AND HANDOUT. The class presentation should be a 15-minute Powerpoint presentation or "chalk talk" accompanied by a **one-sheet** handout, which may also be projected as a pdf document if you don't use a Powerpoint presentation. If you wish me to take care of the photocopying, please turn it in by 4 p.m. the day prior to your talk. Also, please send me by email a copy of the handout and any Powerpoint presentation you use so that I may post them on the Blackboard site.

The one sheet handout may be single or double sided and must include the following information.

- Citation information for your focus article. You can get the authors and title by cut-and-paste from the article, but be sure to also include the journal name, volume, year and page range of the article. (URL's are often to long to be useful in a printed resource, but with the journal name you can get from the Science Library web site to the journal web site, and then with volume and page you can get the article.)
- Either an abstract, or if the article doesn't have an abstract (as in short communication articles), a concluding paragraph that summarizes the results of the paper. If the abstract is very long, you may condense it (or highlight certain parts) to concentrate on the part of the paper on which you are focusing.
- The figure or table with experimental data that you will be explaining.

If there is additional space on the one sheet handout, you may include additional figure(s) that explain the technique that is being used, show the metal coordination in your system, describe the generally-accepted mechanism, etc. If some of the figures are from a different source than your focus article, give proper attribution.

PRESENTATION HOMEWORKS Before you give your presentation, please send me three questions (two that are short answer, possibly involving the results of a calculation, and one that might require several sentences to answer) that would be reasonable to ask other students in the class to assess whether they understood the technique and experiment described in your focus paper. The questions should focus on important points, and may require that students look at the focus paper or your handout to see the original data. These questions will be given to your colleagues after your presentation, and you should not give pointed hints in your presentation that your listeners should pay particular attention to one point (if you do this I will ask you to redo the questions). There is an art to creating assessment questions that are not to difficult and not too easy, and also that focus on important points rather than minor details, and I may send your initial round of questions back to you for revision before sending it out to the class.

I will approve your questions or make suggestions for modifications. If I suggest modifications, please make them within a day, so that I can post the questions on Blackboard no more than two days after you make your presentation. You should not include answers with your questions, If your colleagues ask you for clarification, you may give it to them, but you should not give out the answer. Instead, you may point your colleagues to appropriate readings tat will help them find the answer).

The answers to the presentation homeworks should be turned in at the beginning of class the Thursday of the week following the presentation. You must turn in answers to the questions from your own presentation and (unless there are errors – hopefully not) I will use your answers for an answer key to be posted online. The homeworks from the presentations given the last week of class will be due at the same time – 10:00 am on Thursday, May 6. This is the only assignment you will have due during finals period.

TERM PAPER. The outline for the term paper was already given above. Overall it will be about six to ten double-spaced pages, not counting figures, tables and references. **Please follow the "Writing Guidelines" available on the Haverford Chemistry Department web site,** but include outline numbers ((1a), (1b) etc.) to correspond to the recommended outline shown above. Use a reference style found in chemistry journals. For your paper, avoid citations to web sites unless you cannot find the information in a refereed journal article (and in such a case make sure it is a trusted web site such as one of those suggested by **TEXT**). If you find a pdf of a journal article using an on-line search, you do not need to include the URL and accession information (just the normal journal citation information). I will be looking for citations to at least three journal articles (including your focus article) in sections 2 and 3. It is OK to refer to review articles and/or book chapters, especially in section 1.

Grading and Due dates

The following weights will be used in determining the final course grade:

- Answers to on-line reading assignment questions (20%)
    - These are due 6 a.m. the day of each class
- Presentation proposal, well-thought out and completed in a timely manner (5%)
    - This is due 4 p.m. Friday, March 19

- Presentation, including quality of handouts and questions (10%)
- Presentation homeworks (30 %).
    - These will be due at 10 a.m. on Thursdays between April 1 and May 7.
- Paper on focus article (35%)
    - This is due 4 p.m. Friday, April 30
- Class participation (attendance and participation in discussions) (5%)

My scheme for assigning "letter" grades is as follows, based on percentage scores: 90-100 (4.0), 86-90 (3.7), 81-86 (3.3), 76-81 (3.0), 72-76 (2.7), 68-72 (2.3), 63-68 (2.0).