Department of Chemistry
Cumulative Examinations

April 5, 2014

You may choose to answer any exam from any area covered in the examination booklet. Each exam may contain multiple parts. You may answer more than one exam but each exam is scored separately and is treated as an individual examination result. Thus, answering parts of two exams with a score of 50% would not yield a 100% grade for this cumulative exam. Instead you would receive 50% on each examination attempted.

This booklet contains five examinations.

1) Analytical Cumulative Examination, Pages 1-2
2) Biochemistry Cumulative Examination, Pages 3-4
3) Inorganic Cumulative Examination, Pages 5-6
4) Organic Cumulative Examination, Pages 7-8
5) Physical Cumulative Examination, Pages 9-10

On your examination booklet:

1) Print your student ID number.
2) Print the Exam Booklet number.
3) Print the question number you are answering.
4) Print the Exam Date.

Do not write your name anywhere on the examination booklet. Each exam will be scored anonymously. If you attempt more than one exam, you must use a separate examination booklet for each examination.

When you complete the examination, return the examination and your answer booklet to the proctor. Exam results will be posted on bulletin board #2B on the north side of the hall near BRWN 2124.
Answer the following questions to demonstrate your knowledge on mass spectrometry. Each question is worth 10 pts.

1. Two commonly used evaporation/ionization methods are ESI and APCI. Please give the full names for these techniques. Explain how they both operate and illustrate this with a schematic in each case.

2. Which ones of below analytes would be best ionized by using ESI and which ones by using APCI? Justify.

3. Are there analytes above that would be difficult to deal with using either APCI or ESI? If so, which ones and why would they cause problems? What alternative technique could you try?
4. Mass spectrometers separate ions based on their m/z values. Describe how two of the mass spectrometers listed below separate ions. For each method, give figures of merit, such as resolution, scan rate, mass range, mass accuracy, and linear dynamic range.

   FT-ICR
   Quadrupole mass filter
   Magnet
   Orbitrap
   Time of flight
   Three-dimensional quadrupole ion trap
   Linear quadrupole ion trap

5. Most structural information in tandem mass spectrometry is obtained from dissociation reactions of mass-selected ions. Describe two different methods to activate ions in mass spectrometers in order to cause their dissociation. In your discussion, include the activation time, the average amount of energy after activation and the energy distribution typically deposited into the activated ion. Also please tell whether ion activation occurs in a single or several steps, and whether the activation is a vertical or adiabatic process.

6. Please show the most likely fragmentation pathway for each of the ions shown below:

   ![Chemical structures]

7. In the end of a mass spectrometry experiment, ions are detected. Describe the detection technique used in two of the below mass spectrometers, illustrating each with a diagram. Give each figures of merit for each, such as speed, resolution and mass accuracy, where applicable.

   FT-ICR, Orbitrap, Three-dimensional quadrupole ion trap, Quadrupole mass filter
CUMULATIVE EXAMINATION IN BIOCHEMISTRY
APRIL 5, 2014

1. Protein-ligand binding is often discussed in terms of two alternative mechanisms: "conformational selection" and "induced fit". Please explain in broad terms the meaning of these two models and the difference between the two.

2. It has been hypothesized that the cytoplasmic domain of protein MUC1 binds to the transcription factor STAT3. Please, suggest two different experiments that can prove or disprove the fact of binding. Please briefly explain the concept of each experiment.

3. When protein binding is controlled by diffusion, the corresponding rate constant is estimated to be \( k_{on} \approx 10^8 \text{ s}^{-1}\text{M}^{-1} \). In practice, however, the binding usually occurs more slowly (typically by several orders of magnitude). Please, explain why the actual rate is typically lower than the estimated rate.

4. When protein binding is controlled by diffusion, the corresponding rate constant is estimated to be \( k_{on} \approx 10^8 \text{ s}^{-1}\text{M}^{-1} \). In some (fairly rare) cases the binding actually occurs faster, with \( k_{on} \) reaching \( 10^{10} \text{ s}^{-1}\text{M}^{-1} \). What can be the reason for such unexpectedly high rate?

Note: in this discussion the temperature is presumed constant and equal to 37 °C.

5. Based on high-resolution structure of protein complexes, a number of parameters (descriptors) can be introduced to characterize protein interactions. Arguably, the most important parameter is the "hydrophobic surface area buried upon binding", \( A_{hs} \). As it turns out, this parameter can be used to predict binding affinity \( K_d \) with a certain degree of success. Please, surmise and explain the relationship between \( A_{hs} \) and \( K_d \).

6. The idea to develop drugs that would inhibit protein-protein interactions (PPI) have been around for some time. However, so far these efforts have met with little success. What is the main reason why this strategy has not been working?

7. The majority of protein-protein complexes are non-covalent. However, there are exceptions. What kind of intermolecular covalent linkages can be found in protein-protein complexes? Please describe two different types of such linkages.
8. A protein has two binding sites, BS1 and BS2, located close to each other on the surface. Small molecule M1 binds to BS1 with dissociation constant $K_d^{(1)}=0.1 \text{ mM}$. Small molecule M2 binds to BS2 with $K_d^{(2)}=1.0 \text{ mM}$.

We now make a construct where M1 and M2 are covalently linked through a tether (assume that the tether is sufficiently long and flexible and does not interact with the protein). This construct, M1-M2, binds to the protein such as shown in the figure (right portion). Estimate the dissociation constant of the construct, $K_d^{(2)}$, and briefly describe your reasoning.

9. Many proteins contain "standardized" domains that serve essentially as docking modules. Please name one such domain and describe its designated binding target.

10. Histones are small proteins that assemble into nucleosome, a spool-like structure around which the double-helix DNA is wrapped. As it turns out, histones tend to be highly basic (i.e. positively charged). Is there any connection between the fact that histones are basic and their biological function (DNA packaging)?
Inorganic Cume

1. (35 points.) The Figure below depicts a partial MO scheme for the triatomic molecule BeH₂.

A. Find and label any (all) missing MO(s) generated by the valence shell AO’s. Indicate where it (they) fits (fit) in the diagram, and add tie lines to show which AO’s connect to which MO’s.

B. Let the z-direction define the inter-nuclear axis. Where the amplitude is negative, shade the schematic contours i, ii, and iii, shown below, and identify each contour with a label from the diagram above. Indicate ALL participating AO(s) in each, and justify hydrogen or beryllium playing a bigger role.

C. Finally, estimate the ionization potential of the molecule in eV.

2. (35 points.) Solutions of hypophosphous acid and copper sulfate react to give a binary compound of copper, i.e., one with a formula of the type CuₙXₘ, where X is another element. The drawing below shows the unit cell which has sides of 2.89 Å and a height of 4.61 Å. The formula is the law of cosines.
2. Continued.
   A. What are the coordination numbers of X and Cu in the solid?

   B. Determine the identity of X if the density of the compound is 6.428 g cm$^{-3}$, and the unit cell volume is 33.34 Å$^3$. Show your reasoning. (AW(Cu): 63.54 g mol$^{-1}$.)

   C. Calculate the shortest Cu-X bond distance in Å.

3. (30 points.) Propose viable preparative routes to any three of the following compounds. Give one for the remaining compound for extra credit, but clearly designate that answer.

   A. HCl(g) from Cl$_2$(g).

   B. B$_2$H$_6$(g) from BCl$_3$.

   C. H$_2$(g) from CH$_4$(g).

   D. NaH(s) from H$_2$(g).
Organic Cumulative Examination

April 5th, 2014

1. Garg and co-workers recently reported an elegant total synthesis of tubingensin A (J. Am. Chem. Soc. 2014, 136, 3036-3039). The following are the key steps in their synthesis.

\[ \text{18-crown-6, KF, THF, 35 °C} \]
\[ \text{b. mCPBA, CH₂Cl₂, -10 °C} \]

55% for 2 steps

Questions:

i) What’s the name of reagent A used in the transformation of 1 to 2?

ii) Provide a plausible reaction mechanism to account for the transformation of 1 to 2?

iii) Provide a plausible reaction mechanism to account for the transformation of 2 to 3?

iv) Provide a plausible reaction mechanism to account for the transformation of 3 to 4?

v) In the last step of their synthesis, reduction of the C19 ketone to give the desired stereochemistry turned out to be extremely challenging. Most of the hydride transferring reducing reagents gave the undesired stereochemical outcome. Explain why it’s so difficult to obtain the desired stereochemistry in the reduction step. Provide a plausible mechanism to account for their Na/i-PrOH reduction and explain why this condition was able to produce the desired product even though it’s obtained as the minor product.

2. Garg and co-workers recently reported another elegant work: total synthesis of picrinine (J. Am. Chem. Soc. 2014, asap). The following are the key steps involve in their synthesis.
Questions:

i) The transformation from 5 to 6 is called Fisher Indolization, which is a variation of the Fisher Indole synthesis (cf. 9 + 10 → 11). Provide a plausible mechanism for the following Fisher Indole synthesis. Which nitrogen atom, a or b, will end up in product 11? Explain your choice as well.

ii) Provide a plausible reaction mechanism to account for the transformation of 6 to 7?

iii) In their synthesis, nosyl protecting group (Ns) was used to protect one of the nitrogen atoms. Provide the structure of the Ns group.

iv) Provide a plausible reaction mechanism to account for the transformation of 8 to picrinine.
Physical Chemistry

The questions below are motivated by the paper "Origin of the Surprising Enhancement of Electrostatic Energies by Electron-Donating Substituents in Substituted Sandwich Benzene Dimers" by E. Hohenstein, J. Duan, and C.D. Sherrill (dx.doi.org/10.1021/ja204294q | J. Am. Chem. Soc. 2011, 133, 13244–13247).

1. (30 points) Symmetry adapted perturbation theory (SAPT) is a quantum-mechanical method to decompose the interaction energy of a molecular dimer into four main contributions: electrostatic, induction, dispersion, and exchange-repulsion.
   a) (10 points) Based on the results discussed in the paper, which SAPT terms are repulsive, attractive, or can be both repulsive and attractive?
   b) (5 points) Argon dimer is a weakly bound complex dominated by van der Waals interactions. Which SAPT terms will be significant in this dimer?
   c) (5 points) Water dimer is a complex with strong hydrogen bonding. Which SAPT terms will be significant in water dimer?
   d) (10 points) Interactions in liquids and biological systems can be modeled with classical force fields where non-covalent interaction energy between a pair of particles \( i \) and \( j \) is often computed by the following formula:

   \[ E_{\text{classic}} = \frac{q_i q_j}{R_{ij}} + 4 \varepsilon \left( \frac{\sigma}{R_{ij}} \right)^{12} - \left( \frac{\sigma}{R_{ij}} \right)^6 \]  

   (1)

   \( \varepsilon \) and \( \sigma \) are parameters specific for a pair of particles \( i \) and \( j \); \( q_i \) and \( q_j \) are partial charges on particles \( i \) and \( j \), and \( R_{ij} \) is a distance between these particles. Which SAPT terms correspond to each of the force field terms in eq. (1)? Which SAPT term is not accounted for in this formula?

2. (15 points) The paper discusses accuracy of the distributed multipole analysis (DMA) for modeling benzene-dimer interactions. DMA represents electronic density of a molecule by a set of multipole moments (charges, dipoles, quadrupoles, etc.).
   a) (5 points) Some force fields use DMA-based terms. Which term in eq. (1) would be substituted by the DMA-based terms?
   b) (5 points) The paper claims that DMA produces significant errors in interaction energies of substituted benzene dimers. What is the origin of this error?
   c) (5 points) If eq. (1) would be used to model these dimers, what is your expectation on the accuracy of the results? Briefly explain.

3. (25 points) Charge penetration energy can be modeled as:

   \[ E_{\text{ch-pen}} = -2 \left( \frac{1}{-2 \ln |S_{ij}|} \right)^{1/2} \left( \frac{S^2_{ij}}{R_{ij}} \right) \]  

   (2)

   where \( R_{ij} \) is a distance between orbitals \( i \) and \( j \) on monomers \( A \) and \( B \), respectively, and \( S_{ij} \) is the orbital overlap that can be approximated as:

   \[ S_{ij} = n_x n_y (-\frac{1}{2} \alpha R_{ij}^2) \]  

   (3)

   where \( \alpha \) is a constant specific for a pair of orbitals \( i \) and \( j \).

   Using these formulas and eq. (1), estimate at which distances the charge penetration term becomes important. How does your estimate compare with the equilibrium distances in the substituted benzene dimers?

   [Take sample values of \( q_i = q_j = 0.1 \) and \( \alpha = 0.1 \). Eqs (1–3) use atomic units: charge of electron \( e = 1 \); atomic unit of distance 1 Bohr = 0.529 Angstroms.]
4. (30 points) The paper uses the Hammett parameter $\sigma_m$ to build qualitative correlation of dimer interaction energies.
   a) (5 points) What is the meaning of the Hammett parameter?
   b) (5 points) Which substituents considered in the paper (F, CN, OH, CH$_3$, NH$_2$) have positive Hammett parameter and which have negative Hammett parameter?
   c) (5 points) Electrostatic interactions in dimers with negative $\sigma_m$ substituents at long separations are (repulsive/attractive) because (briefly explain).
   d) (5 points) Electrostatic interactions in dimers with negative $\sigma_m$ substituents at short separations become (repulsive/attractive) because (briefly explain).
   e) (5 points) Electrostatic interactions in dimers with positive $\sigma_m$ substituents at long separations are (repulsive/attractive) because (briefly explain).
   f) (5 points) Electrostatic interactions in dimers with positive $\sigma_m$ substituents at short separations become (repulsive/attractive) because (briefly explain).
# Periodic Classification of the Elements

<table>
<thead>
<tr>
<th>Period</th>
<th>Group</th>
<th>Elements</th>
</tr>
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<tbody>
<tr>
<td>I A</td>
<td>1</td>
<td>H</td>
</tr>
<tr>
<td>II A</td>
<td>2</td>
<td>He</td>
</tr>
<tr>
<td>III B</td>
<td>3</td>
<td>Li, Be, Mg, Al, Si, P, S, Cl, Ar</td>
</tr>
<tr>
<td>III A</td>
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<td>B, C, N, O, Ne</td>
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<td>6</td>
<td>F, Ne, Se, Br, Kr</td>
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<tr>
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<td>7</td>
<td>Ne, Ar, Kr</td>
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<td>8</td>
<td>Br, Kr</td>
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</tr>
<tr>
<td>VIII</td>
<td>10</td>
<td>Ar, Kr</td>
</tr>
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</table>

*Lanthanides*:
- Ce (140.11)
- Pr (140.90)
- Nd (144.24)
- Pm (147.0)
- Sm (150.35)
- Eu (151.96)
- Gd (157.25)
- Tb (158.924)
- Dy (162.50)
- Ho (164.930)
- Er (161.26)
- Tm (168.934)
- Yb (173.04)
- Lu (174.97)

†Actinides:
- Th (232.038)
- U (238.03)
- Np (237.0)
- Pu (242.0)
- Am (243.0)
- Cm (247.0)
- Bk (247.0)
- Cf (249.0)
- Es (254.0)
- Fm (253.0)
- Md (256.0)
- No (256.0)
- Lw (257.0)

(Numbers in parentheses are the mass numbers of the most stable isotopes.)