Biochemistry Cumulative Exam Questions—October 2018

1. Describe the composition, structure, function and evidence for existence of lipid rafts (32 points).
   i. Composition- lipid rafts have elevated levels of glycosphingolipids, protein receptors, signaling molecules, cholesterol, flotillin or caveolin, and saturated sphingomyelin, and have reduced levels of phosphatidylcholine and unsaturated lipids.
   ii. Structure- lipid rafts are organized into membrane 5-200 nm microdomains that serve as organizing centers for the assembly of signaling molecules. They float freely in the membrane bilayer and may be thicker in width across the membrane than the rest of the plasma membrane. Because of their high structural organization, they appear to be more difficult to extract with non-ionic detergents such as Triton X-100. Flotillin-containing rafts are planar while caveolin-containing rafts are bowl shaped.
   iii. Function- lipid rafts are involved in the regulation of membrane fluidity, membrane protein trafficking, neural transmission, and signal transduction. They appear to be able to concentrate and organize specific signaling proteins into a separate patch of membrane.
   iv. Evidence for existence of lipid rafts- early studies demonstrated that there is a heterogeneity in the lifetime decay of the lipid probe, 1,6-diphenyl-1,3,5-hexatriene, which indicates that there are multiple phases in the lipid environment of the membrane. Lipid rafts can also sometimes be visualized using fluorescence microscopy, where for example, fluorophores conjugated to cholera-toxin B-subunit, which binds to the lipid raft constituent ganglioside GM1, are used to visualize the rafts. Alternatively lipophilic membrane dyes that partition preferentially into the lipid rafts can be used image their sizes and locations. Fluorescence resonance energy transfer studies have also used to demonstrate concentration of specific fluorescent dyes and rafts.

2. Define the role played by a plasma membrane potential in biology by answering the following: (24 points)
   i. Define a membrane potential across a mammalian plasma membrane.
      1. A plasma membrane potential is the electrical potential difference between the interior and exterior of a biological cell. For most mammalian cells this value ranges from -40 to -80 mV.
   ii. Explain specifically how a membrane potential is commonly generated across a plasma membrane in vivo.
      1. A membrane potential is primarily generated by the activity of the sodium/potassium pump (Na+/K+-ATPase), where three sodium ions are pumped out of a cell while two potassium ions are pumped into the cell. This asymmetric transport of cations creates a charge separation across the membrane that leaves the intracellular space electrostatically more negative than the extracellular space.
   iii. Summarize the uses of this plasma membrane potential in performing different biological functions.
      1. The plasma membrane potential can basically serve two general functions. First, it allows a cell to function as a battery, providing power to operate a variety of molecular devices (proteins) embedded in the
membrane. These proteins/devices can be exploited to transport calcium ions out of the cell for desirable solutes (e.g. glucose, K+, etc.) into the cell. Second, the plasma membrane potential and be used to transmit an electrical impulse along the cell such as a nerve cell.

iv. Describe the two major mechanisms by which a plasma membrane potential can be rapidly depolarized during neurotransmission.

1. There are two fundamental types of gated ion channels. One is a ligand-gated ion channel, whose opening is triggered by a ligand such as acetylcholine, dopamine, serotonin, or norepinephrine. The second is a voltage-gated ion channel, whose opening is triggered by a change in voltage, usually a depolarization of the cell. Both types of gated ion channels are involved in neurotransmission.

3. Define five distinct (nonoverlapping) functions of major membrane-spanning proteins and give a prominent example of each. (25 points)

   i. Transport- Na+/K+-ATPase
   ii. Enzymatic activity- 5'-nucleotidase, carbonic anhydrase IX
   iii. Signal transduction- EGF receptor
   iv. Cell-cell recognition- ICAM-1, integrins
   v. Anchorage of membrane to cytoskeleton- Band 3, integrins

4. Draw the structure of dioleylphosphatidylcholine (19 points)
Key - Inorganic Chemistry Cumulative Exam

1. (20) Derive the ground state term symbols for both Cr atom and Cr\(^{3+}\) ion.
   \[\text{Cr: } 4s^14p^6; \quad \text{Cr}^{3+}: 3d^5; \quad 4f^0\]

2. (10) Draw ferrocene in its staggered configuration and assign its point symmetry group. \(D_{5d}\)

3. (15) A ferrocene analogue (C, H and Fe only) was reported by Wilkinson in 1954 and its elemental analysis indicates the presence of 75.6% of carbon and 4.9% of hydrogen. Please derive the empirical formula (10 pt) and sketch its molecular structure (5 pt).

\[\text{C}_{18}\text{H}_{14}\text{Fe; Fe(indenyl)_2 (see JACS, 1954, p.2024)}\]

4. (20) An alloy of copper and gold has the cubic structure shown on right. Calculate the % composition of this unit cell. Given that the density of this alloy is 12.23 Mg/m\(^3\), what are the shortest Au-Au and Cu-Cu distances?

\[\text{AuCu}_3; \text{Au: } 50.8\%; \text{Cu: } 49.2\%; \quad a = 3.75 \text{ Å} = \text{Au-Au}; \quad \text{Cu-Cu} = a/\sqrt{2} = 2.65 \text{ Å}\]

6. (35) (a, 25) Considering Fe(CO)\(_3\) molecule. Determine the SALCs based on five C-O stretches expressed in terms of the internal coordinates, and identify the IR active stretch modes. (b, 10) The axial and equatorial carbonyls in Fe(CO)\(_3\) undergo fast exchange of their positions at room temperature through a non-dissociative process known as Berry pseudorotation (see p.567, Inorganic Chemistry, Shriver, 6e).

Describe the mechanism of this exchange by sketching the starting, intermediate and ending geometries with clear labels of COs being exchanged.

<table>
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<th>D(_{3h})</th>
<th>E</th>
<th>2C(_1)</th>
<th>3C(_2)</th>
<th>(\sigma_h)</th>
<th>2S(_3)</th>
<th>3(\sigma_v)</th>
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<td>-</td>
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<tr>
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<td>-1</td>
<td>-</td>
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</table>

SALCs: \(A'\) \(_1\): \((\Delta r_1 + \Delta r_2 + \Delta r_3); (\Delta r_4 + \Delta r_5)\); \(A'\) \(_2\): \((\Delta r_4 - \Delta r_5)\); IR active \((z)\)

\(E'\): \(E''\) \((2\Delta r_1 - \Delta r_2 - \Delta r_3); \Delta r_2 - \Delta r_3\); IR active, \((x,y)\)
1. Prior to the publication of this paper (Baran, P.S. et. al. J. Am. Chem. Soc. 2018, 140, 2072-2075), the most efficient way of forming the macrocycle in the arylomycins was via Suzuki-Miyaura coupling (Romesburg, F.E. et. al J. Am. Chem. Soc. 2007, 129, 15830-15838).

\[
\text{Boc-N}^+\text{H-N}^+\text{N-CO}_2\text{Me} \xrightarrow{\text{Pd(II)Cl}_2, \text{dpff, K}_2\text{CO}_3} \xrightarrow{\text{MeCN, 80°C, 18-22 h}} 49\% \text{isolated yield}
\]

a. Above is the Suzuki-Miyaura reaction that was previously performed. Draw the product and a mechanism for this reaction (20 pts).
b. In one to two sentences, describe the advantages of using the oxidative phenol coupling over the Suzuki-Miyaura coupling. (4 pts)

Suzuki requires extensive manipulation of starting materials to install requisite functional groups and protecting groups. It also has a high catalyst loading of the expensive Pd catalyst. Finally, there is a relatively high amount of protodeboronation byproducts.

2. To form the starting material for the oxidative phenol coupling (compound 2 in Scheme 1), the below reaction was performed. Propose a mechanism for the conversion of 1 to 2. (20 pts)
3. Baran et. al. decided to utilize oxidative phenol coupling to form the macrocycle using the below conditions:

![Chemical Reaction Diagram]

a. Name 4 aspects of this reaction that Baran and co-workers optimized. (4 pts)
   [Cu] source, ligand, oxidant, solvent

b. What is the chemical structure of TMEDA? What is its purpose in the reaction? (4 pts)

![Ligand for Copper]

Ligand for the copper

c. Compound 3 in Scheme 1 exists as a mixture of interconverting atropisomers. Define atropisomers. (2 pts)

Enantiomers that lack a chiral center and differ because of hindered rotation

d. The NMR for this molecule is very messy. How would you confirm that the messy NMR is due to the presence of atropisomers and not due to an impurity? (2 pts)

Variable temperature NMR; EXSY

e. A similar synthesis is used to access the compound BINOL (racemic mixture; structure below). What is BINOL typically used for in organic chemistry? (2 pts)

![BINOL Structures]

Chiral ligand for asymmetric synthesis

f. How might one make the synthesis of BINOL enantioselective? (2 pts)

Chiral amine in place of TMEDA
4. To access the molecules of interest from 3, the following transformations were performed. Give the structures of the intermediates A and B. (10 pts)

\[
\begin{align*}
\text{HO} & \quad \text{AcCl, MeOH} & \quad \text{PyAOP, DIPEA} & \quad \text{K}_2\text{CO}_3 \\
\text{Me} & \quad \text{NHMe} & \quad \text{NMe} & \quad \text{NHMe} \\
\text{Boc} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{AcCl, MeOH} & \quad \text{PyAOP, DIPEA} & \quad \text{K}_2\text{CO}_3 \\
\text{Me} & \quad \text{NHMe} & \quad \text{NMe} & \quad \text{NHMe} \\
\text{Boc} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

5. Recently, a derivative of arylomycin with improved potency and broader spectrum activity was reported (Heise, C.E. *Nature*, 2018, 561, 189-194). See below for the structure.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{O} & \quad \text{NMe} & \quad \text{O}
\end{align*}
\]

Starting with compound 3 in Scheme 1 of Baran's paper, the molecule below (T3), and other standard commercially available reagents, propose a synthetic route to G0775. (30 pts)
6. Bonus (5 pts). Give one advantage to using organic synthesis to access arylomycin and/or derivatives. Give one advantage to using the producing bacteria *Streptomyces* to produce arylomycin.

Organic synthesis = derivatives
Streptomyces = often (but not always) more efficient at producing molecules