CUMULATIVE EXAMINATION IN ANALYTICAL CHEMISTRY

Apr 18, 2009

After each individual exam is graded, five questions with the lowest score will be dropped. In other words, you only need to answer 5 questions out of 10 to earn a perfect total score.

One of important skills acquired in graduate school is the ability to read a research article – even on unfamiliar subject – and quickly grasp the concepts. Attached is the ‘truncated’ version of the Nature paper by Daniel Rugar and co-workers on detection of a single electron spin by force microscopy. Please, read the paper and answer the following questions.

1. The paper describes the detection of unpaired electron. Why is it impossible to detect paired electrons in the same fashion?

According to the Pauli principle, paired electrons normally have opposite spins (although there are exceptions to this rule such as \( \text{O}_2 \)) and thus no magnetic moment.

2. Briefly describe the principle of interferometry detection used in this experiment (see Fig. 1) as you imagine it.

For example, laser beam is channeled through the optic fiber. Part of it reflects from the glass/air interface at the cleaved end of the fiber. The rest goes through, hits the cantilever, reflects back and enters the same fiber. The interference (destructive or constructive) between the two beams carries the information about the distance (and by extension about the frequency of oscillation of the cantilever).

3. Estimated spin concentration in the sample was between \( 10^{13} \) and \( 10^{14} \) cm\(^{-3} \). What should be a minimum spatial resolution of the method to claim the detection of single spin in this sample?

Take worst-case scenario \( 10^{14} \) cm\(^{-3} \). This means one spin resides in a cube with the side of 200 nm. To make sure that we are detecting one spin and not more, we need a resolution that would be considerably better than this, i.e. in a way of an estimate <50 nm.

4. During each period of cantilever oscillation, the resonant slice (‘bowl’ in Fig. 1) hits the spin twice – on the way forth and on the way back. The spin gets inverted every time that it is hit by the ‘bowl’. In order to invert the spin it is necessary to expend some energy. What is the source of this energy?
Microwave irradiation from the coil (that's why it's the "resonant slice", the resonance conditions are fulfilled), but also the cantilever can be slowed down and loose energy to spins (negative frequency shift)

5. The method can detect spins that lie some 100 nm beneath the surface. Clearly, the depth of penetration is dictated by the size of 'bowl'. Suggest the method to increase the size of 'bowl' (and hence the penetration depth).

Put a little more ferromagnetic substance on the tip of the cantilever. Or increase the strength of external field (Fig. 3)

6. Eq. (2) in the paper contains the 'higher harmonics' terms. What is the origin of 'higher harmonics'? What are their characteristic frequencies?

The meander function such as shown in Fig. 2, bottom panel, produces harmonics from steep fronts with frequencies $2f_{sig}, 3f_{sig}$ etc.

7. Considering Eq. (2), the authors detect the first harmonic of the signal only. Technically, how does one get rid of higher harmonics?

Digital filters.

8. Focusing on the first harmonic in Eq. (2), the authors evaluated its amplitude square,

$$\sigma_{spin}^2 = \langle |\Delta f(t)|^2 \rangle = (4/\pi)^2 \langle |\delta f_c|^2 \rangle \langle |A(t)|^2 \rangle$$

or, given that $\langle |A(t)|^2 \rangle = 1$, simply

$$\sigma_{spin}^2 = (4/\pi)^2 |\delta f_c|^2$$

The result for $\sigma_{spin}^2$ shown in Fig. 3 is actually the main result of this paper, illustrating the detection of single electron spin. Please, suggest one or two negative control experiments to complement the measurement shown in Fig. 3.

Trying it on a different (diamagnetic) sample is not such a good idea – no guarantee that you can position the cantilever correctly, etc. Switching off microwave irradiation and observing the disappearance of the signal is a better approach. See also the original paper for other designs.

9. In the paper it is explained that the signal $\Delta f(t)$ is not perfectly periodic owing to extra random spin flips induced by the environment. These flips are modeled with a random 'telegraph function' $A(t)$ that takes on values $\pm1$ and obeys Poisson distribution. Why is it a Poisson distribution, rather than the Gaussian distribution commonly used to model random processes?

Poisson and Gaussian distribution are fundamentally equivalent in the limit of large number of observations (the difference is that Poisson distribution is formulated for discrete processes, so it fits the case of the flipping spin).
10. The paper suggests that $\langle A(t) \rangle = 0$. This is, in fact, an approximation – $\langle A(t) \rangle$ in this experiment is actually a very small, but non-zero number. Please, explain why $\langle A(t) \rangle \neq 0$.

Orientation of spin along the direction of external magnetic field is energetically more favorable than opposite to the field. Alternatively, you can argue that with a finite experimental time and a single spin probe the averaging is not perfect.
1. (24pts) Give the following information:
   a. The length of the C-C bond in benzene ring \(1.397 \text{Å}\)
   b. The boiling point of methylene chloride \(42 \text{C}\)
   c. The bond dissociation energy of the weakest bond in 1-butene \(78 \text{ kcal/mol}\)
   d. The IR stretching frequency of the strongest bond in acetone \(1720 \text{ cm}^{-1}\)
   e. The major peak in the electron impact mass spectrum of toluene \(91\)
   f. The time for the chair to chair inversion in cyclohexane at room temperature. \(10-5\) s

   g. The structure of S-alanine
   h. A graph showing the ionization states of p-aminobenzoic acid between pH 0 and 14
      see page 4

2. (26pts) Determine the structure of the unknown from the spectra shown. Briefly justify your choice.
   The Cl (butane) mass spectrum shows a major ion at 129 m/e.
3. (25 pts) The long standing problem of the origins of homochirality in amino acids and proteins has sparked a number of experiments. It was recently reported (Angew. Chem. Int. Ed. Vol.48, 590-594), that an initially partially enriched mixture of enantiomers could, with the appropriate catalyst, be deracemized into an enantiomerically pure crystalline product. The idea was put into practice with the following Mannich reaction. The kinetics of the process are shown in the Figure. There were several key observations.

i. Intermediate 2 was shown to be present during the conversion.

ii. The reaction was reversible and was close to thermodynamic equilibrium.

iii. The process was performed as a slurry not in solution with vigorous stirring (1300 rpm).

iv. Glass beads speed up the process.

v. The reaction led to the enhancement in the enantiomer that was in initial excess independent of the absolute chirality of that enrichment.

---

Scheme 1. Deracemization experiments with a Mannich type reaction carried out in toluene at room temperature with racemic or achiral catalysts. 4-Br-Bz=4-bromobenzoyl.

(a) Identify the intermediates A and 2 and write a mechanism for the formation of (S)-1 including the structure of the substituents, the stereochemical path and the role of the catalyst 4.

(b) Use your proposed mechanism to account for the difference between runs 1 and 3.

(c) One alternative pathway was excluded when it was discovered that deracemization did not occur when DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was used as a catalyst. Not only was there no deracemization, but 4-bromobenzoyl-hydrazine was found to be the product. Identify the alternative deracemization pathway and account for the formation of 4-bromobenzoyl-hydrazine.

(d) Explain why the reaction must be done as a slurry rather than a solution, the role of glass beads, and how the resolution process works.

---

Figure 1. Enantiomeric excess values versus time determined from the slurry for the Mannich product 1 in the deracemization process shown in Scheme 1 (runs 1 and 3 without glass beads; runs 2 and 4 with glass beads).
4. (25pts) The formation of double helices from random coils of oligoresorcinols of varying lengths has been studied. (JACS, 131, 4710-19, 2009). NMR and UV data for the 9-mer is shown below as the solvent is changed from water to methanol.

(a) The changes in the UV extinction coefficient of the 9-mer as a function of concentration were used to determine the equilibrium constant for binding. (See left plot). Write the expression for the K_a. The K_a values decreased as the volume of methanol increased. Suggest a reason for the sense of this change.

(b) A plot of ln K_a versus 10^3/T /K^-1 for dimerization of the 9-mer in water is shown below. Determine the binding enthalpy and entropy. Determine the free energy of binding at 25°C. Are these values consistent with your proposed dimerization model – explain.

(c) Dimerization equilibria for the series of n-mers (like many other substrate – binding equilibria) are found to exhibit enthalpy/entropy compensation. In fact, a plot of free energy of binding versus the degree of oligomerization (n) is linear: ΔG = 0.50 - 0.94n for n = 3 - 11. For n > 11, the free energy is independent of n. Explain the concept of enthalpy/entropy compensation. How does the dependence of free energy on n fit the concept of enthalpy/entropy compensation.

(d) What species are present in the solution of the 9-mer that is 72 vol% D_2O. (Figure A) Note that NMR spectra of the random coil monomer and the dimer are only observed in the pure solvents. Account for the chemical shift and linewidth changes with solvent composition in the spectral series of Figure A.

1. (h)
(a) 

(b) The higher concentration of 4 increases the rate determining step of proton removal.

(c) DBU is a sufficiently strong and aprotic base that it could directly remove the proton alpha to the ester carbonyl. Reprotonation of the ester enolate from the opposite face would result in racemization.

(d) The solid enantiomerically pure form acts as a template to selectively remove the homochiral enantiomer from the mixture. If the reaction is run without template (i.e. in solution) it gives racemic product. The glass beads and high stirring break the precipitate up to increase the surface area and increase the rate of enantiomer deposition.
\[ 2 \text{mer} H \leftrightarrow (\text{mer} H)_2 \]

\[ K_a = \frac{[A_2]}{[A]^2} \]

Resorcinol polymer is aggregated by a combination of \( \pi \) stacking and hydrogen bonding. The monomer is more stable in methanol because of the unfavorable water-aromatic interaction.

(b) The plot of \( \ln K_a \) vs \( \frac{10^8}{T} \) has a slope of \( -\frac{\Delta H}{R} \) and intercept \( \frac{\Delta S}{R} \)

\[
\Delta G = \Delta H - T \Delta S = -RT \ln K_a
\]

From the graph slope \( \approx \frac{7}{0.6} \) and so \( \Delta H = -1987 \times 12 = -24 \text{ kcal/mol} \)

and \( \frac{\Delta S}{R} = 5.5 - \frac{7}{0.6} \times 3.0 = 29.5 \quad \therefore \frac{\Delta S}{R} = -80 \text{ cal/mol} \)

\[
\therefore \Delta G = -24 + 298 \times 60 = -6.5 \text{ kcal/mol}/e
\]

R.H. Graph shows \(-8 \text{ kcal/mol}\).

(c) Since \( \Delta H \) and \( \Delta S \) for association are both negative, association is favored enthalpically (bonding) but disfavored entropically. Consequently, these opposing effects compensate for each other and the free energy change is small overall. This shows that (a) \( \Delta G \approx 0 \) and only increases by \( \approx 1 \text{ kcal/mol} \) for each new pairing of resorcinol units.

(b) Once the limiting helix pair is made, at \( n = 10 \) additional resorcinol units do not provide further stabilization.

(d) At 72\% water the concentrations of monomer and dimer are about equal. Both the UV and NMR show this as the mid point of the equilibrium from monomer to dimer. Note that the monomer-dimer equilibrium is fast on the NMR time scale, so that the observed shift is the mole fraction average \( \delta_{obs} = Y_m \delta_m + (1 - Y_m) \delta_d \) for each proton.
The chemical shift of the dimer is to lower frequency because of the ring current effect of π stacking in the dimer.

The line broadening is from exchange broadening as the broadest lines occur around the 72% water composition. The width of the line is inversely related to the lifetime of each species.

\[ \lambda \mathbf{m} \xrightarrow{\text{d}} \frac{\mathbf{k}_f}{\mathbf{k}_b} \mathbf{m} \quad \text{and} \quad \mathbf{h}_f[m] = k[f][d] \]

and \[ K = \frac{k_f}{k_b} \]

The sequence is for a single proton.

\[ 0\% \text{H}_2\text{O} \]

\[ \sim 60\% \text{H}_2\text{O} \]

\[ 72\% \]

\[ 77\% \]

\[ 100\% \]

The dimer may also show additional broadening because of slower anisotropic tumbling.