Supplementary Material and Lab Documentation for Online Information

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Williamson Ether Synthesis

Ethers are compounds where an oxygen atom is bonded to two alkyl or aryl groups and have the general structure \( \text{R—O—R'} \), where \( \text{R} \) and \( \text{R'} \) are the alkyl or aryl groups. If the two groups, \( \text{R} \) and \( \text{R'} \), are identical the ether is symmetrical. When \( \text{R} \) and \( \text{R'} \) are not identical, the ether is called an unsymmetrical ether. Ethers are fairly inert compounds, they do not react with most of the reagents used by organic chemists. Their physical properties are unique because of the polarity of the carbon-oxygen bonds and the lone pairs of electrons on the oxygen atom. Their melting and boiling points are closer to those of a similar molecular weight hydrocarbon than to those of an isomeric alcohol because of their inability to form hydrogen bonds. For example, the boiling point of diethyl ether (35 °C) is virtually identical to n-pentane (36 °C) than to its isomer 1-butanol (117 °C) or even ethanol (78 °C). However, the oxygen of an ether can be a hydrogen bond acceptor. This results in an ether's solubility be comparable to that of an alcohol.

Diethyl ether was used as an anesthetic in medicine for quite some time. Unfortunately, ethers are very volatile and flammable; mixtures of air and ether can be explosive. Because of their inertness and in spite of their drawbacks, organic chemists frequently use ethers as solvents. They are nonpolar enough to dissolve many organic compounds and are good enough of Lewis bases to solublize alkali metal salts.

Ethers may be readily obtained in a substitution reaction between an alkoxide ion and alkyl halide. The reaction is called the Williamson Ether Synthesis. In this reaction, a primary alkyl halide reacts with the conjugate base of an alcohol, an alkoxide, in protic or aprotic solvent to give an ether via an \( \text{S}_2 \) mechanism (Equations 1 & 2). The alkoxide is generated by reacting the corresponding alcohol with a strong base, such as sodium hydride, in an aprotic medium, such as dimethylformamide (DMF) or tetrahydrofuran (THF). Unfortunately the nucleophile in this reaction is an alkoxide ion, which is also a very strong base. Because of its basicity, secondary and tertiary alkyl halides cannot be used in a Williamson Ether Synthesis because they undergo elimination reactions via an \( \text{E}_2 \) mechanism. Usually the reaction does not go to completion, a mixture of the product ether and starting alcohol is obtained. However, this mixture can be easily separated by acid-base extraction. Ethers do not react with bases and will remain in the organic phase while the alcohol may be extracted by a basic aqueous wash.
Experimental Procedure

Synthesis of 2-(10-Bromodecyloxymethyl)-15-crown-5 Ether:
To a 25 mL round bottom flask add 15 mL DMF and a stir bar. With stirring, add 0.42 g (9.3 mmol) NaH to the flask then add dropwise 4 mL of a 1 M solution of 2-(hydroxymethyl)-15-crown-5 ether in DMF. Then add via a 10 mL syringe 6 mL 1,10-Dibromodecane and stir the reaction mixture until the next lab period. Quench the reaction mixture with 25 mL of methanol and remove the solvent using a rotary evaporator. Dissolve the residue in 25 mL CH₂Cl₂, and wash sequentially once with 100 mL of water, twice with 100 mL of 3 M NaOH, and a final wash with 100 mL of water. Add MgSO₄ until there no further clumping of the drying agent is seen and let stand for 5 minutes. The drying agent is removed by gravity filtration using fluted filter paper and the organic solution collected in a 50 mL round bottom flask. Rinse the filter paper with 5 mL of CH₂Cl₂ and collect this rinse into the 50 mL round bottom flask. Remove
the solvent using a rotary evaporator. The oily residue is purified by dry-column flash chromatography. Pack 25-30 g dry silica gel inside a 4-cm diameter medium porosity sintered glass funnel (60 mL x 40 mm). Tap the funnel to settle the powder and place on a 250 mL Erlenmeyer flask using a vacuum adaptor and apply suction. Press down on the silica carefully with a rubber stopper leaving about 1 cm of head space. Prepare the column by carefully pouring 50 mL of hexane onto the bed with suction. Dissolve the sample mixture in 2-3 mL of hexane and pour the solution evenly onto the column. Elute the column with $2 \times 150 \text{ mL hexane}$ (waste) then $3 \times 200 \text{ mL 50\% hexane:50\% ethyl acetate}$ (save these fractions, your product is here). Combine the hexane:ethyl acetate fractions and remove the solvents using a rotary evaporator. Record the mass of your product, obtain an IR and $^1\text{H}$ & $^{13}\text{C}$ NMRs. Dispose of all organic waste into a waste container. Dispose of the silica gel waste into a waste bucket, not in the trash.

**Results and Discussion**

Report your % yield for the reaction. Discuss the FTIR and NMR spectra you obtained. Identify the characteristic peaks for each spectrum. Do these confirm the identity of your expected product? Explain.
**Nucleophilic Substitution Reaction**

Alkyl halides may react with a variety of nucleophiles via a substitution reaction to produce several types of functional groups. This includes, but not limited to, nitriles, unsymmetrical ethers, thiols, thiolethers, and amines. Most nucleophiles are also bases, and may behave as such under certain conditions. When a nucleophile reacts with a tertiary halide instead of substitution, elimination occurs. Conversely, unhindered primary alkyl halides react cleanly and irreversibly with nucleophiles forming substituted products in high yields. The reactivity order for alkyl halides reflects the carbon-halogen bond strength, \( I > Br > Cl >> F \). Some hindered primary alkyl halides react very slowly with many nucleophiles, so prolonged reaction times and higher reaction temperatures may be necessary for reaction. Secondary alkyl halides that have \( \beta \)-hydrogens tend to react with nucleophiles giving mixtures of substitution and elimination products. Hindered nucleophiles that are also strong bases tend to form elimination products when reacting with secondary alkyl halides. Only strong nucleophiles from below the second row of the periodic table, such as thiolates (\( \text{SH}^- \) or \( \text{SR}^- \)) give good yields of substitution products with secondary alkyl halides.

In this experiment you will prepare a thiol by reacting the bromide from the previous experiment with a thiolate ion nucleophile. In this case, you may consider the hexamethyldisilathiane to produce \( S^2^- \), an extremely strong nucleophile. The reaction should give almost quantitative conversion of the bromide into the thiol.
Experimental Procedure

2-(10-Mercaptodecyloxymethyl)-15-crown-5 Ether:

An argon purged 25 mL flask containing 1.85 g (3.95 mmol) 2-(10-Bromodecyloxymethyl)-15-crown-5 Ether in 8 mL dry THF is cooled to -5 °C. Using a syringe for each, add 4.3 mL (4.3 mmol) 1 M tetrabutylammonium fluoride (in THF) and 1.0 mL (4.7 mmol) hexamethyldisilathiane. The solution should immediately turn green. Stir this mixture for 30 min, remove from the cold bath and stir an additional 2 h at room temperature. Add 20 mL methylene chloride and wash the reaction mixture once each (25 mL) with 1 M HCl, sat. NH₄Cl, and brine. Dry the organic layer over Na₂SO₄, gravity filter using fluted paper, and remove the solvent using a rotary evaporator. Record the mass of your product, obtain an IR and ¹H & ¹³C NMRs. Dispose of all organic waste into a waste container. Store the dark orange-yellow oil under argon in the freezer until it is to be used to modify the gold nanoparticles.

Results and Discussion

Report your % yield for the reaction. Discuss the FTIR and NMR spectra you obtained. Identify the characteristic peaks for each spectrum. Do these confirm the identity of your expected product? Explain.
Instructor Notes

Organic Chemistry-Williamson Ether Synthesis and Nucleophilic Substitution

- A 1 M solution of 2-(hydroxymethyl)-15-crown-5 ether may be prepared by dissolving 10 g of crown ether in 10 mL DMF
- Dry-column flash chromatography may be performed as follows: Pack 25-30 g dry silica gel inside a 4-cm diameter medium porosity sintered glass funnel (60 mL x 40 mm). Tap the funnel to settle the powder and place on a 250 mL Erlenmeyer flask using a vacuum adaptor and apply suction. Press down on the silica carefully with a rubber stopper leaving about 1 cm of head space. Prepare the column by carefully pouring 50 mL of hexane onto the bed with suction. Dissolve the sample mixture in 2-3 mL of hexane and pour the solution evenly onto the column. Then elute the column and collect the fractions in the Erlenmeyer flask.

- Students should obtain an IR and $^1$H & $^{13}$C NMRs and compare these to those of their starting materials.
- In the IR students should notice the loss of a broad OH stretch at 3400 cm$^{-1}$.

- Authentic FTIRs, $^1$H NMRs, & $^{13}$C NMRs of the starting materials and products are provided in the following pages. They are labeled with the structure of each molecule.

- **2-(10-Bromodecyloxymethyl)-15-crown-5 Ether**
  - $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.21-1.43 (m, 8H), 1.45-1.61 (m, 8H), 3.30-3.45 (m, 6H), 3.49-3.85 (m, 19H), $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 26.1-34.4 pendant alkyl CH$_2$ groups, 70.5-79.0, crown ether CH$_2$'s & CH group, CH$_2$'s attached to alky ether oxygen.

- **2-(10-Mercaptodecyloxymethyl)-15-crown-5 Ether**
  - $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.27-1.45 (m, 8H), 1.47-1.65 (m, 8H), 2.48 (q, 2H), 3.32-3.51 (m, 4H), 3.53-3.91 (m, 19H), $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 20.2-30.0 pendant alkyl CH$_2$ groups, 70.5-79.0, crown ether CH$_2$'s & CH group, CH$_2$'s attached to alky ether oxygen, and 59.5 CH$_2$ attached to thiol.
Student Handout: Analytical Chemistry

After synthesis and subsequent structural characterization the ionophoric behavior of the CE ligand may be verified using simple cyclic voltammetry diffusing experiments. Self-assembled monolayers (SAMs) of each of the synthesized thiolated crown ether ligands are formed on freshly Piranha-cleaned evaporated gold substrates. After allowing the SAM to form the electrochemistry (i.e., the cyclic voltammograms (CVs)) of a freely diffusing probe molecule, ruthenium hexamine (RuHex), will be examined in the presence and absence of sodium ions (Na+) for the CE-SAM modified substrates.

Experimental Procedure

Prepare 25 mL of a 5 mM solution of your crown ether thiol in toluene. Place this solution in a jar with a screw cap. Obtain a freshly cleaned gold slide from your instructor and place (carefully!) without touching the gold surface inside the jar, gold side up. Cap the jar and leave without disturbing overnight or until the next class period. During this time a self-assembled monolayer or SAM will form on the gold substrate.

While waiting for the SAM to form prepare a 10 mL aqueous solution of 1 mM ruthenium hexamine, RuHex (3.1 mg) with a supporting electrolyte of 100 mM tetraethylammonium chloride, TEAC (0.166 g). Label this flask as Solution A. Additionally, prepare 10 mL of a 1 mM RuHex solution (3.1 mg) with a supporting electrolyte of 80 mM TEAC (0.133 g) and 20 mM sodium chloride (11.7 mg). Label this flask as Solution B.

Obtain another freshly cleaned gold slide from your instructor. Use this gold substrate as a working electrode and place it along with a platinum counter electrode and an appropriate reference electrode (e.g., Ag/AgCl), in an electrochemical cell containing Solution A. Connect the electrodes to the potentiostat and run a cyclic voltammetry experiment at the bare gold electrode. Run the voltammetry with multiple cycles scanning between -0.7 and +0.2 V at a scan rate of 100 mV/sec. Record the voltammetric behavior of RuHex at a bare gold surface.

After a SAM is formed on the immersed gold substrate, carefully remove the gold slide with forceps and rinse thoroughly with ethanol via a Pasteur pipette. Gently dry the substrate in a stream of nitrogen. As done previously in the preceding paragraph, immerse this substrate in Solution A as the working electrode and run the same cyclic voltammetry experiment under the
same conditions. Record the voltammetric behavior of RuHex at a CE-thiolate modified gold surface.

Remove the gold substrate from Solution A and thoroughly rinse with purified water and ethanol before gently drying it in a stream of nitrogen. Immerse the gold substrate in Solution B as the working electrode and repeat the entire procedure described above. Record the voltammetric behavior of RuHex at a CE-thiolate modified gold surface in the presence of sodium ions.

**Results and Discussion**

In your report include the CVs that you obtained for the unmodified gold surface and the crown ether modified surfaces in the absence and presence of Na\(^+\). Discuss the following: Justify to yourself what is responsible for the shape of the CV for RuHex at a bare gold substrate. How does the CV of RuHex at CE modified surface differ from that at an unmodified one? How does Na\(^+\) influence the CV? Identify the characteristic peaks for each spectrum. Do these confirm the identity of your expected product? Explain.
Instructor's Notes for Analytical Chemistry

- The gold slides were obtained from Evaporated Metal Films and are Cr/Au test slides, 50Å chromium, 2000Å gold, and are 1.7cm x 1.7cm x 1.5mm (0.062”).
- The toluene must be dried prior to use.
- Gold slides were prepared by cleaning in Piranha solution (2:1, sulfuric acid : hydrogen peroxide). Warning: Use extreme caution when working with Piranha solution; it reacts violently with organic materials.
- If a Ag/AgCl reference electrode is to be used, carefully monitor its internal standard solution level as it should be kept lower than that of the electrochemical cell’s solution level in order to minimize potassium ion leakage through the salt bridge during measurements. Once the electrodes are immersed in the solution, voltammetry should be run immediately to minimize these effects as well.
- Solution voltammetry of RuHex at a bare gold electrode should show a traditional diffusing and reversible cyclic voltammogram or “duck” corresponding to the RuHex$^{2+/3+}$ redox couple with a formal potential at approximately -0.15 V vs. Ag/AgCl. Adhering to Nerstian behavior for a one electron transfer couple, the peak splitting ($\Delta E_p$) should be approximately 60 mV.
- The positively charged RuHex molecules should exhibit characteristic diffusing behavior at the CE-SAMs in the absence of Na$^+$, indicating the molecule can easily access the electrode surface through defects in the monolayer. Students should note a slight increase in the $\Delta E_p$ with the addition of the SAM barrier at the surface. Once Na$^+$ ions are coordinated into the crown ether moieties the CE-SAM will retain a layer of positive charge on its periphery and is more effective at blocking the approach of the RuHex to the electrode surface, thereby eliminating or reducing the diffusion based electrochemistry.
Au Self-Assembled Monolayer
Current, mA vs E (V) vs Ag/AgCl

An Self-Assembled Monolayer

Na^+
The synthesis of the crown-ether functionalized monolayer-protected gold clusters will be accomplished in two steps. First you will prepare hexanethiolate capped MPCs, then perform a ligand exchange using the crown ether. After you have prepared this molecule, you will then obtain an UV-vis spectrum of the MPC in solution. You will then add a known amount of sodium chloride and obtain that UV-vis spectrum, then add increasing amounts of potassium chloride and record these spectra. There will be a shift in the plasmon band as the crown ethers coordinate to the metal ions. Plasmon emissions are the combination of the electromagnetic fields and the oscillating surface charge of a metal, in this case gold. By monitoring the position of the plasmon band and knowing that electromagnetic enhancement can exist over extended distances away from an enhancing surface, the spectral properties of aggregates of the crown ether capped MPCs can be probed. Lastly, you will prepare a solution of CE-MPCs in water and expose them to NaCl. Then you will add a known amount of KCl and monitor the change in absorbance as a function of time. You will then repeat using different concentrations of CE-MPCs and KCl. From these data you will calculate the rate constant for exchange and determine the ratio of Na\textsuperscript{+}:K\textsuperscript{+}. The reaction may be thought of as:

\[
p[M^+] + q[MPC] \rightarrow \text{aggregates (aq)} \rightarrow \text{aggregates (s)} \downarrow
\]

\[
\text{reaction rate} = -(1/q) \frac{d(MPC)}{dt} = -(1/p) \frac{d(M^+)}{dt} = k[M^+][MPC]
\]

By taking the log of both sides of Equation 2, this reduces to:

\[
\log(\text{reaction rate}) = \log k + p\log[M^+] + q\log[MPC]
\]

The apparent reaction rate is measured by monitoring the absorbance changes in the surface plasmon at 540 nm. The peak intensity of the surface plasmon band is proportional the MPC concentration, thus changes in the MPC concentration over time correspond to that species being consumed in the reaction and may be thought of as the reaction rate. In this reaction, the absorbance at 540 nm will initially increase followed by a gradual decrease. This curve corresponds to two different physical processes, the first being the exchange of Na\textsuperscript{+} for K\textsuperscript{+} and the particles beginning to form aggregates that are still soluble in solution. The second process is the sedimentation of aggregated MPCs whose sizes are too large to be soluble. The reaction orders, \(p\) and \(q\), as well as the rate constant for metal ion complexation, are determined by second-order kinetic methods. By plotting the log(reacti

Experimental Procedure

Hexanethiolate Capped Monolayer-Protected Clusters (MPC) Synthesis. To prepare the hexanethiolate capped MPC, add 0.34 g (0.8 mmol) of HAuCl₄ · 3H₂O in 25 mL of nanopure H₂O to a vigorously stirring solution of 1.5 g (2.7 mmol) of tetraoctyl ammonium bromide phase transfer reagent in 80 mL of toluene in a 250 mL Erlenmeyer flask. Stir this mixture an additional 30 min. The red/orange organic layer, containing the cluster in the toluene layer is separated from the water layer. Discard the aqueous layer. To the organic layer add via syringe 115 μL (0.8 mmol) of 1-hexanethiol (Aldrich). After the thiol is added, stir the solution ~30 min, until it becomes a light yellow color. Place this solution in an ice bath at 0°C for 20 minutes. At the same time, prepare a solution that contains 0.38 g (10 mmol) of NaBH₄ in 25 mL of nanopure water and chill in the ice bath. Add the reducing agent to the gold-thiol mixture over 10 s. The solution should turn a black color. Stir this mixture overnight at 0°C. Separate the black organic layer from the water layer into a 200 mL round-bottom flask. Remove the toluene by rotary evaporation keeping the temperature of the water bath below 50 °C. The remaining solid in the bottom of the flask is precipitated using 95% Methanol. Collect the precipitate by vacuum filtration using a 30 mL medium porosity glass frit and wash with 150 mL of acetonitrile. The product may be verified by characterizing the peripheral ligands using ¹H NMR after an oxidative decomposition or iodine “death” reaction. (See Pompano, R. R.; Wortley, P. G.; Moatz, L. M.; Tognarelli, D. J.; Kittredge, K. W.; Leopold, M. C. Thin Solid Films 2006, 510, 311-319 for details of how to perform this reaction)

Exchange of 15-crown- ether(CE) into the MPC core. Place 150 mg of the previously synthesized MPC in 75 mL of 99.9% anhydrous methylene chloride in a 200 mL round-bottom flask and stir. To this solution, add 15 mg of the CE ligand and briskly stir the solution for ~72 hours under argon. The methylene chloride is removed by rotary evaporation. The remaining solid in the bottom of the flask is precipitated using 95% Methanol. Collect the precipitate by vacuum filtration using a 30 mL medium porosity glass frit and wash with 150 mL of acetonitrile. The product may be verified using FTIR and ¹H NMR.

UV-vis spectra and kinetics of metal ion complexation. Prepare a 20 nM CE-MPC stock solution by weighing out 10 mg of CE-MPC then placing it into a 10 mL volumetric flask and
filling with distilled water. Mix this flask well to get an evenly dispersed solution. Take 2.0 mL of this stock solution and place into a quartz cuvette. Record the UV-vis spectrum of this solution from 300-900 nm. Add 10 μL of 0.5 M NaCl (2.5 mM Na\(^+\)), note the color of the solution and again record the UV-vis spectrum. Add 20 μL of 0.01 M KCl (100 μM K\(^+\)), mix carefully, and wait until there is a visible color change. Record the UV-vis spectrum. Repeat this process but now record the change in absorbance at 540 nm as a function of time. Monitor the kinetics for 900 seconds taking a data point every second. Make sure that you start the kinetics as quickly as possible so as to not miss the early reaction. Obtain kinetic runs by varying the amount of KCl (i.e. 5 μL and 10 μL, 25 μM and 50 μM K\(^+\), respectively). Repeat but this time varying the concentration of CE-MPC by using 1.0 mL of stock solution and diluting with 1.0 mL of distilled water (10 nM CE-MPC) and 0.5 mL of stock solution and diluting with 1.5 mL of distilled water (5 nM CE-MPC). The concentration of K\(^+\) ion should be 100 μM. Save your raw data in *.txt format and analyze your kinetic runs using Origin.

**Results and Discussion:** Discuss ligand exchange and identify if successful by NMR, UV-Vis discuss plasmon band emissions for solutions of hexanethiolate capped MPCs, CE-capped MPCs, w/ added Na\(^+\), w/ added K\(^+\). Discuss color of solutions. Discuss the kinetics of complexation and the exponential factors \(p\) and \(q\). What is the ratio of Na\(^+\):K\(^+\)? Show how you determined these ratios.
Instructor's Notes for Physical Chemistry

- The glassware must be cleaned with aqua regia before use, we suggest the instructor prepare a bath of this solution, have students put their necessary glassware into it the week prior to the experiment.
- The iodine oxidative decomposition reaction is not necessary to confirm that ligands are present on the MPCs, it is included only as a possible extension for the experiment.
- The "molecular mass" for the CE-MPC is based on a molecular formula of $\text{Au}_{140}(\text{CE})_{45}(\text{C}_6)_8$ and is approximately 47,500 g/mol.
- The kinetics may be monitored by any UV-vis spectrophotometer and data analyzed by any software package. We use Origin but Kaleidagraph, SigmaPlot, or Excel will suffice. Data from the spectrophotometer should be saved in a format compatible with the analysis software, commonly we use *.dx or *.txt format.
- The reaction rate may be found by curve-fitting the data to the following equation:

\[
\text{Reaction Rate} = \left( \frac{A}{\tau_1} \right) e^{-t/\tau_1} + \left( \frac{A}{\tau_2} \right) e^{-t/\tau_2}
\]

where $A$ is the absorbance for the pre-exponential factors and $\tau_1$ and $\tau_2$ are the relaxation times for the aggregation and sedimentation processes, respectively.
- Students are given this equation to curve-fit their data, and generally they are quite capable of determining the individual kinetic parameters.
- The coefficients $p$ and $q$ are approximately 0.6 and 1.2, respectively and the second-order rate constant is $6.0 \times 10^6 \text{ M}^{-2}\text{s}^{-1}$.
$^1$H NMR spectra of hexanethiolate capped MPCs and crown ether capped MPCs after ligand exchange.

Prior to CE exchange

Following CE exchange

CE peaks
CE-MPCs after iodine death
UV-vis spectra of metal ion complexed crown ethers