Laboratory Manual

SMASH Chemistry Youth Adventure Program

July 25th – 29th, 2022

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Camp Overview

Did you ever wonder what happens to the molecules in a rock when Thor crashes his hammer, Mjollnir, into it? Or what happens when the Hulk smashes things together? It turns out, they aren't just breaking things, they are doing chemistry! When most people think about doing chemistry, they picture a scientist mixing solutions or heating things over a flame to cause them to react, but it turns out that another way to make molecules react is to crush them together. This type of chemistry is called mechanochemistry, where the application of mechanical force can be used to drive chemical reactions without adding heat, and without the use of toxic solvents, making it a cheaper, greener, and safer way to create new materials.

Figure 1. Figure adapted from Disney's Marvel.

In the Smash Chemistry YAP you will learn to "use the force" to make chemistry happen. You will gain hands on experience with the equipment used for carrying out and studying mechanochemical reactions, ranging from simple hammers and mechanical mills to advanced powder x-ray diffractometers and atomic force microscopes. You will also work with force responsive materials to see how molecules change when we "put the hammer down."

Throughout this camp you will learn to visualize the effects of force. First, you'll journey into the exciting area of mechanochemical reactions and examine two classical force driven phenomenon, the formation of thermite upon collision and the glow of triboluminescent compounds upon breakdown. Simultaneously, you will learn how force can be used to break down particles to fine scales for reactions. This will familiarize you with modern instrumentation and industrial practices. Then, you will use a non-Newtonian fluid to visualize the forces exerted on chemicals in a ball mill and you will synthesize a mechanochromophore, a material that changes color when mechanically distorted. Your newfound understanding of force, mechanochemical reactions, and mechanochemical instrumentation will be applied to the synthesis of organic drug compounds. Then , you will learn how to use the atomic force microscope, a classic tool for studying mechanochemistry at the atomic level, to draw at the nanoscale through nanolithography. You'll wrap up by using your skills to design a mechanochemical experiment to further determine the role of force in chemical reactions.

Safety

Please note that you will be working in active research labs, which require mature and responsible behavior to avoid potentially hazardous situations. The primary goal of this Smash Chemistry YAP is to create a safe and exciting learning environment, with experiences that lead to unique knowledge and expertise being gained. All rules, stated in this manual and given by instructors, must be followed at all times. Inability to do so will result in you not being allowed to continue the activity. Above all else, ***follow any instructions given by instructors***.

Rules:

I. You must come to lab dressed appropriately, this includes the following:
   - o Full length pants or long skirts which come all the way down to the ankles so that no parts of the legs or feet are exposed
   - o Shoes that cover all parts of the foot from the toe to the heel and cover the top and sides of the foot completely up to the ankle, i.e., tennis shoes.
   - o Long hair held in place to the back of your head (you are responsible for bringing the bands or clips to hold back your hair)
   - o *Contact lenses are NOT allowed.*
   - o Other personal protective equipment (PPE) will be provided, as needed (*i.e.,* gloves, safety glasses, and lab coats).

Figure 2. Adapted from https://www.pinterest.com/pin/390335492695103287/

II. The safety guidelines associated with individual experiments will be presented at the beginning of each experiment. The necessary personal protective equipment (PPE) for the experiment must be worn at all times when in designated lab areas.

III. Eating, drinking, and smoking are prohibited in the lab at all times. Chewing gum or tobacco is also prohibited.

IV. Change gloves when contaminated, glove integrity is compromised, or when otherwise necessary.

V. Remove gloves and wash hands when work with hazardous materials has been completed and before leaving the laboratory.
VI. Do not wash or reuse disposable gloves. Dispose of used gloves with other contaminated laboratory waste.
VII. Never handle unfamiliar chemicals.
VIII. All personal belongings must be placed in the back of the room and any food/drink should be inside a backpack.
IX. Always ask questions when you are unsure of anything.

Usage of masks.

To protect you and the course instructors and counselors, you are encouraged, but not required, to wear a face mask to help reduce the spread of COVID-19. All student instructors in this course will be wearing masks while working with you. Please be respectful of each other's choices.

Hazards

You will be working with a variety of chemicals in the following experiments, most of which are fairly benign and none of which has been identified as a known or anticipated carcinogen excepting the common laboratory solvent chloroform (usage: 200 μL-400 μL) the use of which will be monitored by instructors. Many of the chemicals that will be used in this lab are flammable, toxic if ingested or inhaled, and skin irritants. Appropriate attire (gloves and goggles) is sufficient for protection from these chemicals. Additionally, all syntheses must be performed in a fume hood or in a sealed plastic bag container to prevent accidental inhalation of solvents or powders.

Introduction to Mechanochemistry

Figure 3. Painting of an ancient alchemist using a mortar and pestle for mechanochemistry. Figure from Science History Institute's "Mechanochemistry: The Science of Crush" exhibit.

Mechanics study how objects react to forces like a push or a pull. That's why a lot of mechanics build machines that move things around. Meanwhile, chemists study the very tiny matter that makes up objects along with their structures and their properties. But chemists can be mechanics too, it's just on a much tinier scale. When we talk about mechanochemistry, we're looking at the intersection of mechanics and chemistry by trying to learn how forces affect molecules. Most of the mechanics that you know want their machines to convert chemical bond energy into mechanical force. For example, a car is a machine that takes the energy it gets from the chemicals in gasoline and uses it to move you from place to place. You're also like a machine that takes chemical energy from food and uses it to move your muscles. Mechanochemists generally like to study the opposite effect, converting mechanical energy into chemical bonds.[1] This is called a mechanochemical reaction.

Why should you care about these reactions? Well, that's a great question. Mechanochemical reactions have all sorts of applications. They can be used to make drug compounds, nanomaterials, energy-storage materials, semiconductors, perovskites, ceramics, polymers, and a host of other organic and inorganic compounds.[2] Mechanochemistry even opens up access to products we just can't make with traditional chemistry techniques. These materials are incorporated into all sorts of technology that runs our modern world. In fact, mechanochemistry was identified one of the top ten world changing technologies by the International Union of Pure and Applied Chemists in 2019.[3]

Mechanochemistry isn't just important for materials synthesis. It's also a critical part of making chemistry more environmentally friendly. Unlike most chemical reactions,

mechanochemical reactions use very little to no liquid solvent to make the reaction go. Solvents tend to be dangerous, toxic, and environmentally destructive. Without solvents, things get a whole lot safer and healthier. More importantly, mechanochemical reactions have increased product yield, fewer unwanted side reactions, lower energy demands, and simplified product processing.[1-5] This makes them very green compared to traditional chemistry.[4,5]

How green you ask? Well, according to the most recent literature remarkably so. Mack et al. set out to quantify the difference between a solution based synthesis and a mechanochemical one. They used a metric called the EcoScale rating to determine which synthesis was more environmentally friendly taking into account use of solvents, product yield, energy requirements, safety, and purification complexity. A higher EcoScale rating correlates to a better synthesis; the mechanochemical reaction had an EcoScale rating of 77 while the solution based reaction only earned a 35.[4] Moreover, Ardila-Fierro and Hernández have convincingly demonstrated that the literature mechanochemical syntheses fulfill all 12 principles of green chemistry, in contrast to most solution based methods.[5]

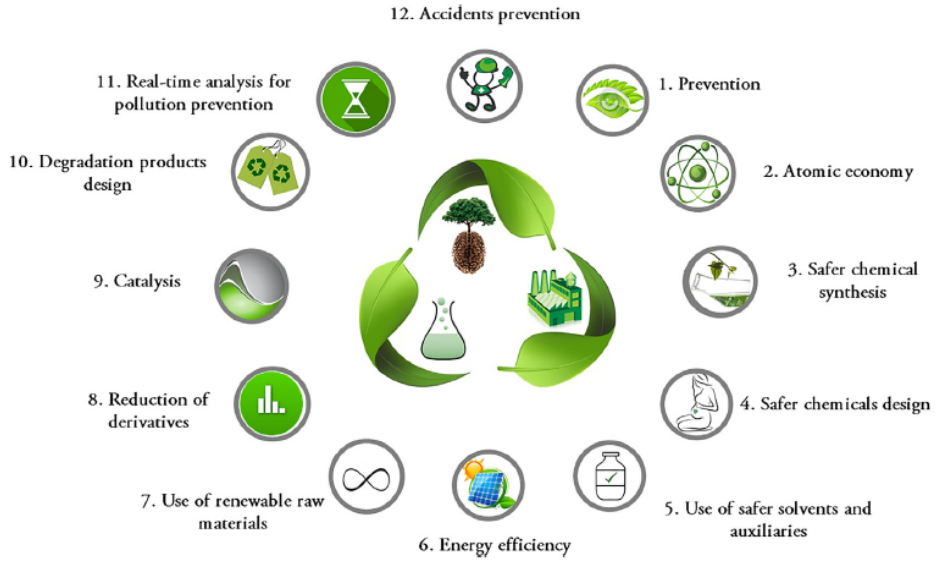


Figure 4. 12 Principles of Green Chemistry. Figure courtesy of Marco, B.; Rechelo, B.; Tótoli, E.; Kogawa, A.; Salgado, H. Evolution Of Green Chemistry And Its Multidimensional Impacts: A Review. Saudi Pharmaceutical Journal 2018, 27. DOI: 10.1016/j.jsps.2018.07.011.

So, if these reactions are so great why aren't we making all our chemicals this way? What's keeping this field back? The answer is knowledge. We don't know how to predict the products of these reactions like we do traditional solution based methods. We don't know how to tune the instruments to maximize product output. We also just haven't developed the wealth of analytical tools we need to properly study these reactions or the mathematical theory for modeling these systems. In short, chemists are still perfecting their Jedi skills just like you'll be doing in this YAP.

So, how do we do mechanochemistry? Well, it's as simple as mixing together two solids, either by vigorous shaking or by grinding with a mortar and pestle. However, these techniques aren't very repeatable since different people mix with different motions and different forces. So, we usually use mechanical devices to do the grinding for us in a careful and controlled manner. There are a variety of devices employed for this purpose including vibratory and planetary ball mills, twin screw extruders, and resonant acoustic mixers.

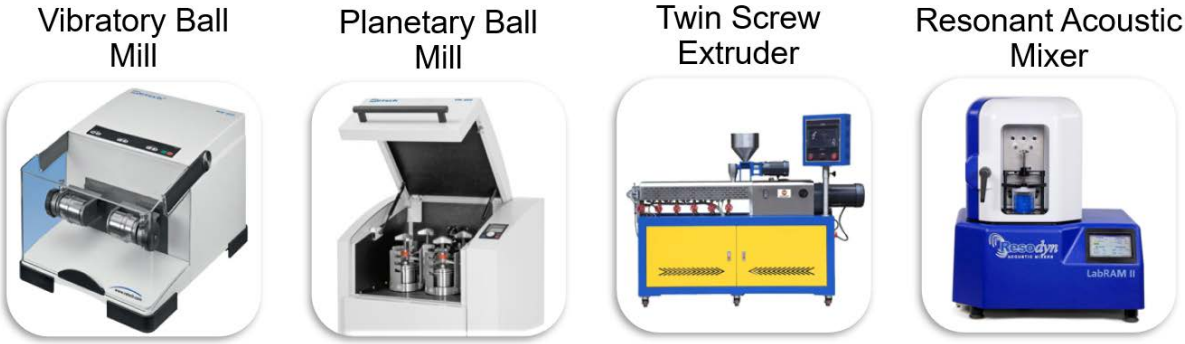


Figure 5. Tools of the mechanochemists. Images from coleparmer.com, certifiedmtp.com, fyitester.com, resodynmixers.com, all accessed April 19, 2022.

Over the course of the week, you will learn how to do mechanochemistry from the ground up by visualizing forces on materials and in mechanochemical reactors, driving mechanochemical reactions with your own two hands, and performing organic and inorganic mechanochemical syntheses with advanced ball milling equipment and simple hammers!

References

1. Michalchuk, A. A. L.; Boldyreva, E. V.; Belenguer, A. M.; Emmerling, F.; Boldyrev, V. V. Tribochemistry, Mechanical Alloying, Mechanochemistry: What is in a Name? Frontiers in Chemistry 2021, 9, Review. DOI: 10.3389/fchem.2021.685789.
2. James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; et al. Mechanochemistry: opportunities for new and cleaner synthesis. *Chemical Society Reviews* **2012**, *41* (1), 413-447, 10.1039/C1CS15171A. DOI: 10.1039/C1CS15171A.
3. Gomollón-Bel, F. Ten Chemical Innovations That Will Change Our World: IUPAC identifies emerging technologies in Chemistry with potential to make our planet more sustainable. Chemistry International 2019, 41 (2), 12-17. DOI: doi:10.1515/ci-2019-0203.
4. Denlinger, K.; Mack, A.; Mack, J. An EcoScale Comparison of Mechanochemistry and Solution Based Reactions. Vol. 1186; 2014; pp 129-137.
5. Ardila-Fierro, K. J.; Hernández, J. G. Sustainability Assessment of Mechanochemistry by Using the Twelve Principles of Green Chemistry. ChemSusChem 2021, 14 (10), 2145-2162. DOI: https://doi.org/10.1002/cssc.202100478.

Thermite Demo: Thermal vs. Mechanical

Instructors: Batteas & Felts

Introduction

In this demonstration you will observe how mechanical force can lower the activation energy for the thermite reaction, allowing it to proceed. Activation energy is the minimum energy required for a reaction to take place. Many reactions, like the thermite reaction you will observe today, do not have the required energy to proceed at room temperature. In the first demonstration this extra energy will be delivered in the form of heat, and in the second, mechanical force. Mechanical force lowers the activation energy, allowing for the reaction to proceed at room temperature.

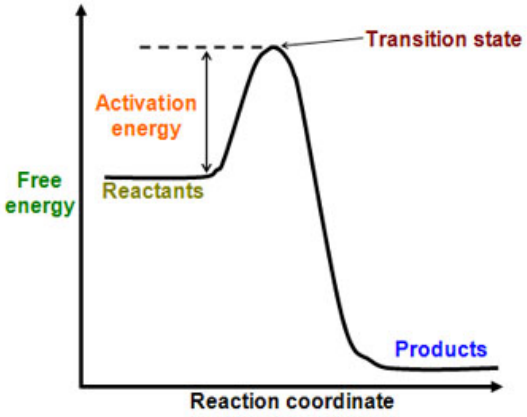


Figure 6. Figure reproduced from Kerem's Chemistry Notes IB.[6] Free energy diagram for an exothermic reaction. Reactants require activation energy for a reaction to proceed. This energy will be delivered in the form of heat (thermal energy) and force (mechanical energy).

As the iron oxide and aluminum-covered balls come together, the following reaction will occur:

$$Fe_2O_3 + 2Al_{(s)} \rightarrow Al_2O_3 + 2Fe_{(s)}$$

This reaction has an enthalpy change of around -850 kJ/mol – meaning that for every mole of reactant, 850 kJ of energy is released into the surrounding area! In your observations, think about how you can see the release of energy for this reaction.

Procedure

This will be performed by your instructor. You will observe two different ways of driving the formation of thermite, the thermal method and the mechanical method. Watch carefully and think about the activity questions.

Activity Questions

- In the first demonstration you may see molten iron is produced. Does this happen in the second demonstration? How do you know?
- Did you observe a reaction every time the reactants were brought into contact in the second demonstration? If not, what could explain the lack of reaction?
- What evidence did you see for the release of energy in this reaction?
- Describe where the energy released from the reaction would appear in the free energy diagram (Figure 6).

References

6. 6.1 Activation Energy – Kerem's Chemistry Notes IB. https://sites.google.com/site/keremschemistrynotesib2/chapter-6--kinematics/6-1-activation-energy (accessed 2022-6-28).

I. Particle Size Shakedown Challenge

Instructor: Emmanuel

Introduction

Reaction kinetics, the study of chemical reaction rate and factors that affect the rate of chemical reactions, is critical our understanding of mechanochemistry. According to the collision theory of reactivity, “reaction occurs when reactant molecules effectively collide” Factors such as temperature, concentration, surface area, and catalytic activity all influence the rate of chemical reactions. Efforts in mechanochemistry seek to understand how these chemical particles react under applied force and how chemical reaction rate is influenced.

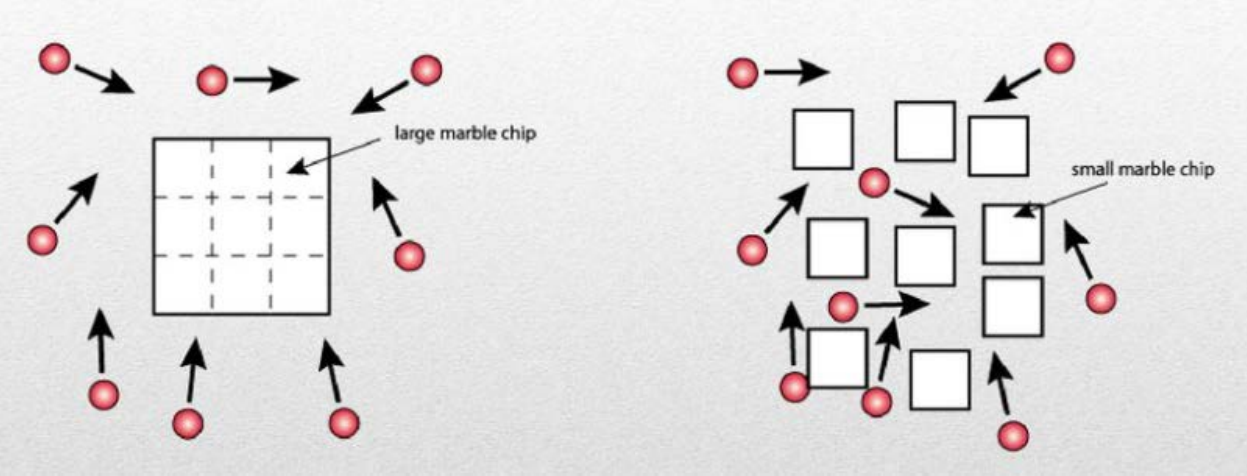


Figure 7. Visualization of particle size effect on rate of reaction. Figure adapted from https://slideplayer.com/slide/10876589/.[7]

One important factor that influences reaction rate is the surface area to volume ratio. As shown in Figure 7. for a given mass of a solid reactant, large lumps have smaller surface area to volume ratios than smaller lumps or powders. If a large lump is crushed into smaller pieces, the area of the exposed surface increases and the surface area to volume ratio increases, although total volume remains the same. More reactants particles are exposed at the surface due to an increased surface to volume ratio which in turn increases the frequency of particles collision thus increasing the rate of reaction. Mechanochemistry

provides us with the tools and techniques to understand how force influences the rate of reaction through particle size reduction.

Procedure

In this exercise, you will investigate the role of force in particle size reduction. This will be done by crushing some solid reactants (jaw breaker candy) with a hammer and sieving the granules to get a size distribution. For fun, this will be a competitive exercise and the winner of this exercise will be the student with the finest particles and best size distribution.

1. Weigh out 10g of jaw breaker candy as shown in Figure 9 and put into a plastic bag
2. Place the plastic bag on the slab provided and apply force using the hammer to crush “reactants” for 60s
3. Remove the crushed particles from the plastic bag and place into the sieve with the largest mesh size (#10) and stack sieve from largest to smallest mesh size.
4. Clamp down the sieves in the shaker and run the motorized shaker for 60 secs.
5. Remove the sieves, weigh the mass of particles on each sieve size and individually record the mass.
6. Use the spreadsheet provided to create a size distribution and report data.

Figure 8. Humboldt sieve shaker adapted from https://www.grainger.com/product/HUMBOLDT-Hand-Operated-Sieve-Shaker-5DPL2.

Figure 9. Jawbreakers in mini rainbow colors. Figure adapted from https://www.boydsretrocandy.com/jawbreakers-mini-rainbow-colors-1-4-1-lb/.

Activities Questions

1. How does surface area to volume ratio size affect the rate of chemical reactions?

References

1. Brian E. Hayden, “Particle Size and Support Effects in Electrocatalysis”, Accounts of Chemical Research 2013 46 (8), 1858-1866 DOI: 10.1021/ar400001n

2. Harold C. Helgeson, William M. Murphy, Per Aagaard, “Thermodynamic and kinetic constraints on reaction rates among minerals and aqueous solutions. II. Rate constants, effective surface area, and the hydrolysis of feldspar”, Geochimica et Cosmochimica Acta, Volume 48, Issue 12, 1984, Pages 2405-2432, ISSN 0016-7037.
3. “Rate of Reactions” Part of Chemistry (Single Science), Rate of chemical change and dynamic equilibrium https://www.bbc.co.uk/bitesize/guides/

II. Non-Newtonian Fluid in a Ball Mill

Instructor: Katie

Introduction

You might remember Newton as the “gravity guy”, but he also did a lot of work studying fluids and their behavior. We categorize fluids by their viscosity, or resistance to flow. You can think of this as the “thickness” of a liquid. Liquids like honey or syrup are highly viscous which is why they pour out so slowly. Meanwhile, liquids like water or milk have low viscosity. When we call something a Newtonian fluid, we mean that it’s viscosity stays the same even when you heat or cool the liquid or change the pressure acting on the liquid. This is true for most of the liquids you’re familiar with in the day to day, but a lot of industrially significant liquids like to break the rules. We call these non-Newtonian fluids because their viscosity changes with temperature and/or pressure.

Figure 10. An image of kids running across an oobleck pool. Adapted from https://thekidshouldseethis.com/post/oobleck-pool.

Today, we'll be making a non-Newtonian fluid called oobleck by mixing together the household ingredients water and cornstarch. Oobleck responds to pressure which is just force per unit area. This makes it a force responsive material. If you apply a lot of pressure it acts like a solid; whereas if you apply a little to no pressure it behaves like a liquid. This trait is usually used to let people pretend to "walk on water" or make slime, like in Figure 8, but today we'll use it to visualize force in a mechanochemical ball mill shown in Figure 9.

Figure 11. Retsch MM 400 ball mill used for performing mechanochemical reactions. Adapted from the Retsch MM 400 manual.

A ball mill is a simple device made to run chemical reactions in the solid state. Our ball mill is a Retsch MM400 and has four main parts: the hood, the display and operating unit, the milling cups, and the shaker arms. Chemicals are placed in the milling cups along with a hard ball to do the mixing and grinding, then the jars are screwed shut and slotted into the shaker arms. The plastic shield is lowered, and the desired frequency (or rate of shaking) and time are input. The machine shakes the chemicals together rapidly; driving the reaction until the time runs out. Then, the product can be removed directly from the milling cups.

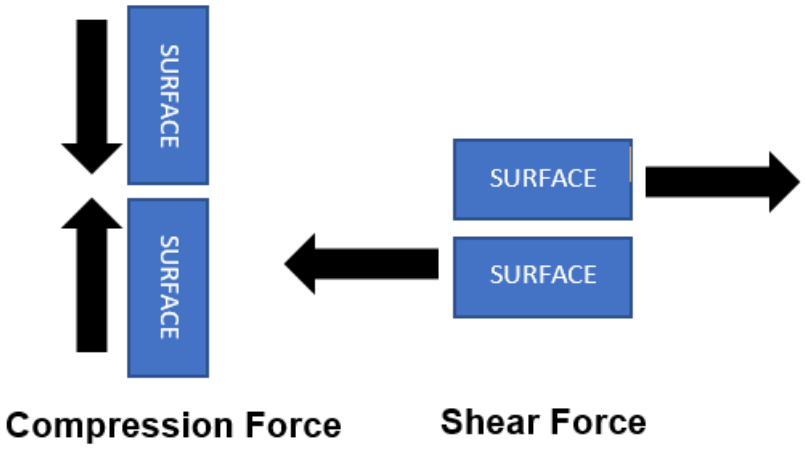


Figure 12. Simplified depiction of shearing and compressive force.

There are two main forces that the solid reactants experience inside the milling cups, shear forces from rubbing two surfaces together and compression forces from the head on impacts of the milling ball with the milling cup walls as shown in Figure 12. With the oobleck in the jars, we can see where force is applied by looking for where the oobleck is behaving more like a "solid". We'll also look at how the ball moves within the milling jars to figure out what regions experience more shear force and what regions experience more compression force. By making the oobleck glow in the dark using a fluorescent dye in our water, this will be easier to see.

Synthesis of Fluorescent Oobleck

We will be making a 50 µM solution of fluorescein in 100 mM sodium borate buffer to keep the fluorescein dye in it's brightest form. This solution will then be mixed with household cornstarch creating the oobleck.

1. Weigh out 0.0008 g of fluorescein, 0.5000 g of sodium hydroxide (~3 tablets), and 3.0915 g of boric acid and place them in a 50 mL volumetric flask.
2. Add distilled water to the flask about halfway up to the 50 mL marker line (~25 mL).
3. Cap the flask and shake until all the solids are dissolved.
    - Good Practice Tip: It is important to dissolve the solids before bringing it to volume so that you add the correct amount of liquid to get an accurate concentration. If you don't dissolve them first, the volume of liquid you add

will usually be under the actual amount you need since the components take up more space in the solid form than when dissolved.

4. Add distilled water up to the 50 mL flask.
5. Take the desired volume of 50 µM solution of fluorescein in 100 mM sodium borate buffer and place it in a suitably sized beaker.
6. Add 1 g of cornstarch per 1 mL of solution to the beaker.
7. Stir until well mixed. Note, as the oobleck forms it will be difficult to stir. Reduce the stirring speed to make mixing easier.
8. Ensure the oobleck is the right consistency (responds to force but flows relatively quickly) by adding excess fluorescein solution (loosener) or cornstarch (thickener) as needed.

Ball Mill Operation

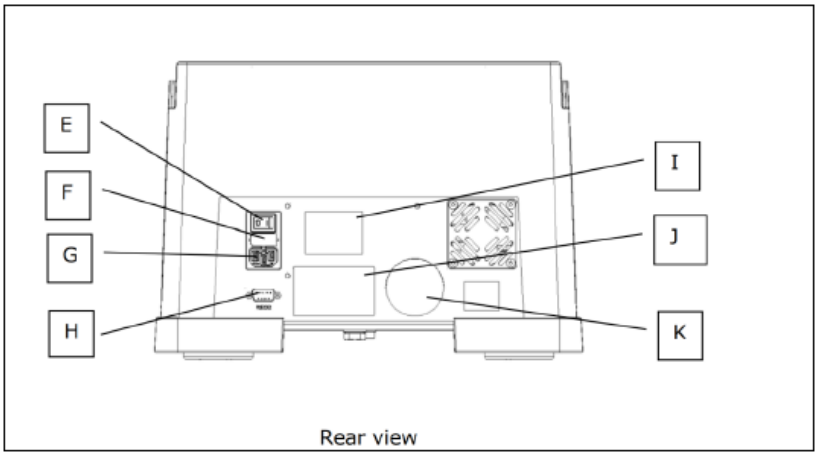


Figure 13. Diagram of the back of the Retsch MM 400 ball mill. Adapted from Retsch MM 400 operation manual.

Turning on the Mill

1. Ensure that the mill is plugged in to a working outlet.
2. Ensure that the power cable is securely docked inside socket G (see Figure 13).
3. Toggle the power button E above machine socket G (see Figure 13).

Preparing and Loading the Milling Cups

1. Ensure that the milling cups are clean and dry.

2. Insert a gasket into the cap end of the milling cup, ensure that it is fully seated below the threads.
3. Add one or two stainless steel balls to the milling cup.
4. Load the milling cup with materials to be milled –WARNING: sample quantity should not be less than 25% of the milling cup volume (Our milling cups are 25mL).
5. Shut the caps tightly. WARNING: Do not close the milling cup without a Teflon gasket, as this may damage the seal.
6. Insert the milling cups into the arms of the machine as described in Figure 14.

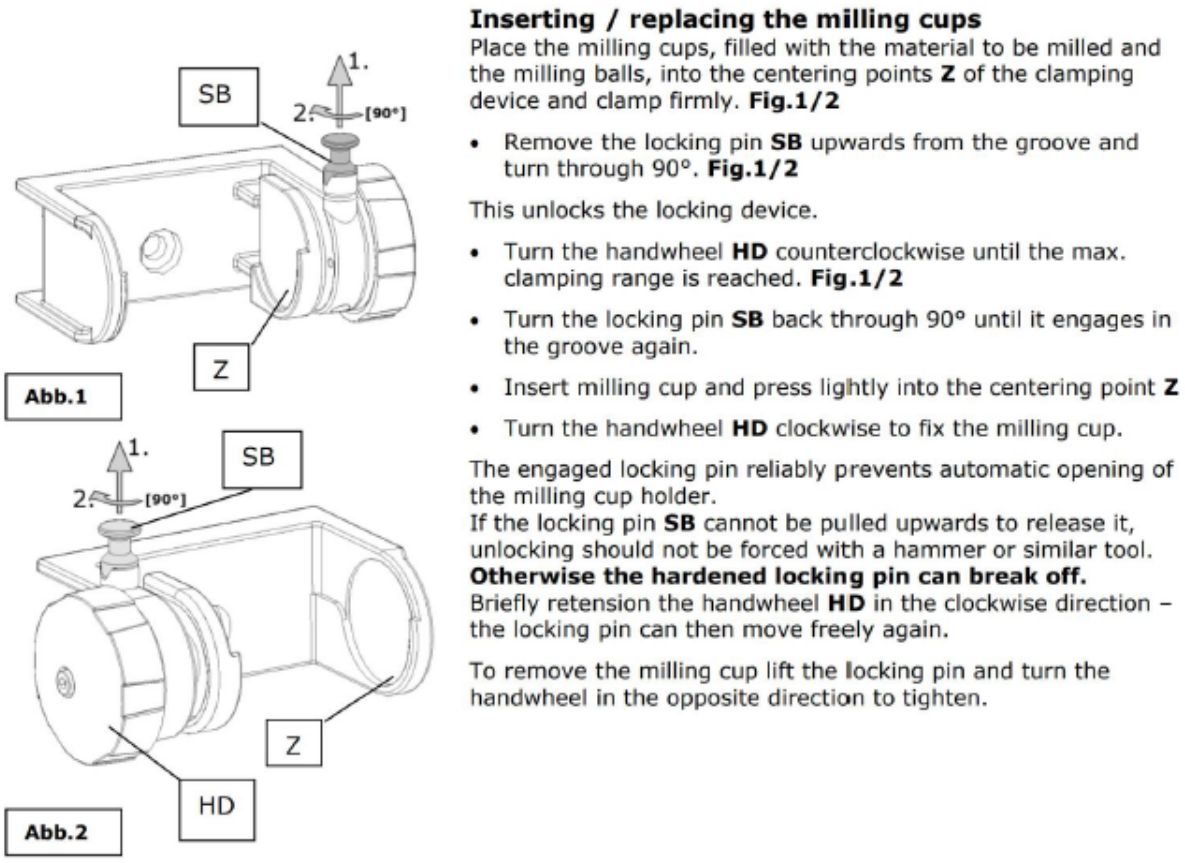


Figure 14. Diagram of milling cup shaker arms describing how to insert and remove the milling jars. Adapted from Retsch MM 400 operation manual.

Running the Mill

1. Turn on the mill and load the prepared milling cups.
2. Shut the Retch MM 400 hood

3. Set the desired frequency between 3 and 30 Hz with the +/- buttons labeled frequency. Short pressing of + and – adjusts the frequency in single steps. With longer pressing, the display changes the value faster. Record this value in your notebook.
4. Set the required milling time with the +/- buttons Short pressing of + and – adjusts the time by 1 sec or 1 min. With longer pressing, the display changes the value continuously. If 99.0 min is exceeded the display returns to 0.10 sec again. Record this value in your notebook.
5. Click the START button. The milling time is recorded and the time still remaining is shown in the display.
6. To stop the mill, press the STOP button. Pressing once will interrupt the milling process and pause the time. Repressing START will restart the milling at the remining time. Pressing STOP twice puts the machine in standby mode. Pressing the START button reactivates the display and milling time to the latest set values.
7. During milling, the time can be adjusted by pressing the +/- buttons.
8. When time has elapsed, remove the milling cups as described in Figure 14. CAUTION: Milling cups can get hot after long run times, use appropriate thermal gloves to remove hot cups.
9. Remove the sample from the milling cups.
10. Turn off the machine.

Oobleck Milling

1. Weigh 4.5 g of fluorescent oobleck into each milling cup and load cups into the machine.
2. Experiment with different milling frequencies at a 1 min run time and observe the ball motion.
3. Answer the activity questions.
4. Remove the milling cups.
5. Dispose of all oobleck in the appropriate waste containers.
6. Shut down the mill.

Activity Questions

- Where do you think shear forces are the most prevalent in the ball mill?
- Where do you think compression forces are the most prevalent in the ball mill?
- What is the motion of the ball in the ball mill and what role does the ball play in the mixing process?
- What happens to the oobleck and the milling as frequency changes?
- From what you observed, do you think material is well mixed together in the ball mill? Why or why not?

III. Triboluminescence

Instructor: Maya

Introduction

Triboluminescence is a fascinating phenomenon where light is emitted when certain crystalline compounds are fractured. We don't fully know why triboluminescence occurs, however one prominent theory is that when fracture occurs, a separation of positive and negative charges happens. These charges recombine, and release energy as light, which can be seen below in Figure 15. The compounds you will be investigating in this module emit light within the visible region (as in, the light human eyes can see) and you will use your own eyes and the cameras on your phone to observe this phenomenon.

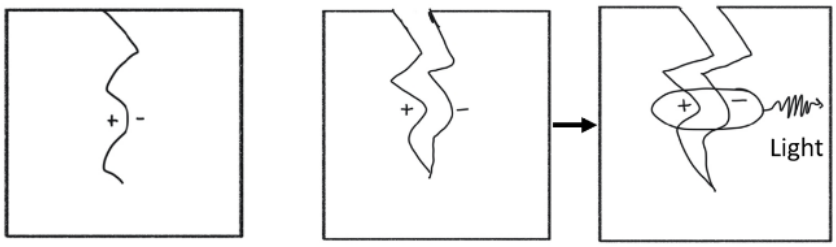


Figure 15. Charge separation along a fault line in a crystal. Opposite charges form along a fault line and recombine, releasing energy in the form of light.

Lifesaver Activity

1. Obtain a few (whole) lifesavers from your instructor. Observe them and record your observations in your lab notebook.
2. Take the lifesavers into the Witech room – This room is light-tight and will give you a better chance of seeing the effect!
3. You will have a variety of tools to choose from – pliers, hammers, and a mortar and pestle will all be available. Choose one of these tools to start with.
4. Smash your lifesaver using the chosen tool at the work area (denoted by a protective mat). Have at least one of your team members recording with a camera phone.
5. Record your observations in your lab notebook.

Synthesis of Blue Smash Crystals (aka. [Cu(NCS)(py)$_2$(PPh$_3$)])

1. Obtain a 25mL glass scintillation vial and a stir bar. Label your vial with the date, your initials and 'pyr' (It's always important to label chemicals in lab, this enables you and others in the lab to properly handle any chemical waste or spills!).
2. Into this vial add 0.121g copper thiocyanate (CuNCS), 0.262g triphenylphosphine (PPh$_3$). Bring your vial to the hood where your instructor will add 5mL of pyridine. Mark the level of the solvent on the side of your vial.
3. Place a small foil cover on top of your vial.
4. Place vial onto a hot plate at 70°C for 3 hours.
5. After the 3 hours have elapsed, turn off the hot plate and allow the vial to slowly cool on the hot plate.
6. Your solution will slowly cool until about half of the pyridine has evaporated – resulting in the precipitation of your crystals! When the solvent level reaches halfway to the original solvent line, record your observations in your notebook. What do the crystals look like, and what color are they? A ruler will be provided by your lab instructors so you can estimate the size of your crystals.
7. Clean your crystals: Your instructor will pipette out the dirty pyridine into a waste container. Wash the crystals with toluene and pipette the toluene into a waste container. Let the crystals dry for a few minutes in the hood.
8. Clean a spatula with Millipore water, then ethanol. Dry with a nitrogen gun.
9. Extract a few crystals onto a white paper towel.
10. Shine a UV light (365nm) onto the crystals. Record your observations in your lab notebook.
11. Transfer a few crystals into a clean, empty vial or glass beaker.
12. Smash the crystal against the side of the vial and record your observations.

Activity Questions

- The triboluminescent effects occur because when these materials are fractured, energy is emitted in the form of light. If you were unable to see this light, what might that mean about the light emitted?

IV. Medicinal Mechanochemistry

Instructor: Katie

Introduction

Historically, mechanochemists studied inorganic materials and reactions. In fact, mechanochemistry used to fall predominantly within the field of mechanical alloying. This focus changed rapidly in the twentieth century when it was discovered that mechanochemical conditions could be used to drive a variety of organic reactions; spurring a mechanochemical renaissance. Mechanochemistry shows great promise for creating greener and more efficient syntheses with ready scalability. It also opens up access to working with organic materials that have limited solubility.

Medicinal mechanochemistry is a subfield of mechanochemistry that applies mechanical techniques to the development of active pharmaceutical ingredients (APIs). By carrying out reactions in the solid state, drugs can be made in highly pure forms without the use of toxic chemicals. Mechanochemistry also shows particular promise for control of the polymorphism of the crystalized solid. Polymorphism occurs when a chemical compound crystallizes with different internal structures. The polymorphism of a drug impacts it's physical properties including flowability, tableting, dissolution rate, solubility, stability, and even performance (toxicity and efficacy).

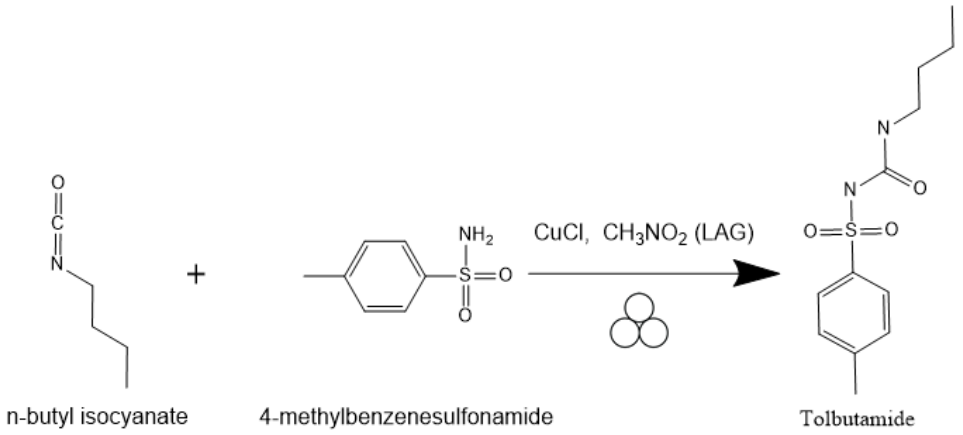


Figure 16. Scheme depicting the synthesis of tolbutamide in either neat or LAG conditions. Observe the common chemical symbol for ball milling conditions of three circles

Today, we'll practice our ball milling skills to synthesize the drug tolbutamide; which regulates high blood sugar in people with type 2 diabetes. Tolbutamide can be made in two polymorphic forms. One form results when you just mill the reactants together completely dry. This is known as neat grinding. The other polymorph results when you mill the reactants together with a very small amount of a liquid additive. This kind of milling is known as liquid assisted grinding (LAG).

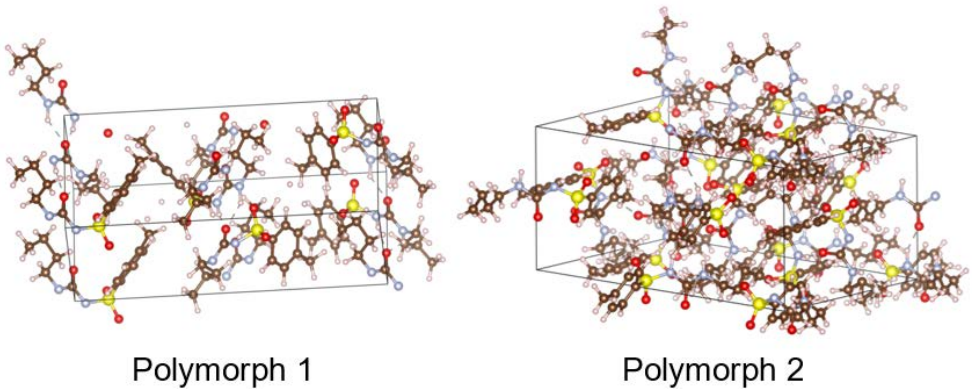


Figure 17. Polymorphs of the drug tolbutamide.

Liquid assisted grinding is often used when a reaction is proceeding either slowly or to a limited extent under neat conditions. Adding the small amount of liquid acts a bit like a lubricant and can prevent product clumping. However, in many cases the added liquid is more than just a lubricant. It can drastically shift the reaction rate and occasionally alter the reaction outcome as well. The ratio of liquid (in µL) to solid (in mg) in a mechanochemical reaction is defined by the parameter η. An η value of 0 indicates neat milling is being used. LAG conditions occur with η between 0–1 µL mg^{-1}. η values greater than 1 represent slurry reactions where the effects of reactant solubility on reactivity become noticeable.

Your challenge will be to identify which tolbutamide polymorph is formed under neat conditions and which is formed under LAG conditions. To do this we will use a technique called powder x-ray diffraction (PXRD) to figure out the chemical structure of your solid product. PXRD works by shooting x-rays through a powder and collecting the pattern of the x-rays at a detector as the scatter off of the atoms in the structure. Think of this like throwing paint at someone standing in front of a wall. The paint is blocked when it hits the

person and doesn't show up at the other side. Once enough paint is thrown, you can use the silhouette that's left to figure out the height of that person or how they were standing. The PXRD spectra of the polymorphs is different because the atoms are arranged differently (aka. the person was standing in a different position). By comparing your spectra to the literature, you can determine which is which.

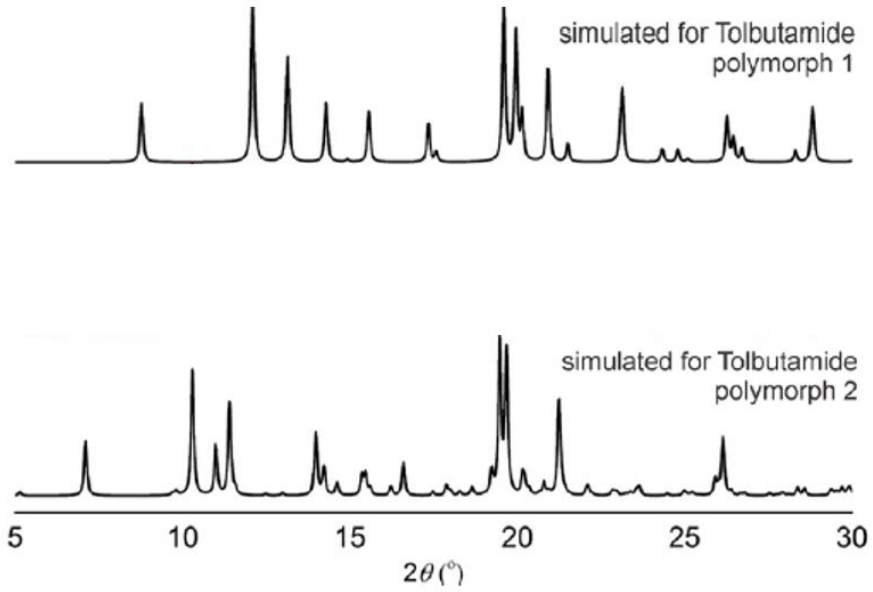


Figure 18. Simulated PXRD spectra for tolbutamide polymorphs 1 and 2. Figure adapted from Colacino, E. et al. Journal of Chemical Education 2019, 96 (4), 766-771.

Synthesis of Tolbutamide

1. Place 1 stainless steel ball (10 mm), 0.2140 g of 4-methylbenzenesulfonamide, 140.8 µL of n-butyl isocyanate, and 0.0062 g of CuCl in one 25 mL stainless steel milling cup. Seal the milling cup. Place 1 stainless steel ball (10 mm), 0.2140 g of 4-methylbenzenesulfonamide, 140.8 µL of n-butyl isocyanate, 0.0062 g of CuCl, and 86.03 µL of CH_3NO_2 in the remaining 25 mL stainless steel milling cup. Seal the milling cup. *NOTE*: keep careful track of which milling cup has your LAG reaction and which has your neat reaction.
2. Close the hood & set the Retsch MM400 to run for 1 hr at 30 Hz (will be 2 total).
3. Return at the end of the hour and set the Retsch MM 400 to run for 1 more hour at 30 Hz. At the end of the second hour, your product polymorphs should now be formed. Next, we will carry out a workup procedure to purify them.

4. Let the milling cups cool then remove the cups and add 0.05 g of $Na_2EDTA*2H_2O$ and 7.5 mL of distilled water to the milling cups and seal them. *REMEMBER*: keep track of which cup has your LAG and which has your neat grinding.
5. Close the hood and set the Retsch MM 400 to run for 10 min at 25 Hz.
6. Let the milling cups cool then remove the cups and pour each product through a vacuum filtration device (set up by the Instructor). Use water to rinse any remaining product out of the vials and through the vacuum filtration device. *REMEMBER*: keep your two polymorphs separate.
7. Remove the milling balls using a magnetic stir bar holder and rinse each solid with approximately 10 mL of distilled water.
8. Let the solid product polymorphs sit on the vacuum till they are as dry as possible.
9. Dry your product polymorphs in vacuo over P_4O_{10} until it's a constant weight (usually overnight). *REMEMBER*: keep your polymorphs separate.
10. Obtain PXRD spectra of your polymorphs from LAG and from neat grinding.

Activity Questions

- What polymorph do you get if you carry out the reaction under neat grinding?
- What polymorph do you get if you carry out the reaction under liquid assisted grinding (LAG)?

V. Mechanochromophore Sensors

Instructor: Maya

Introduction

Mechanochromic materials are a subset of mechanophores – materials which undergo a chemical change after the application of force. This response is due to mechanically induced changes in molecular structure, conformation, and on occasion even intermolecular reactions. In this activity, you will synthesize a chromo-mechanophore film from a polydiacetylene which changes color from blue to red in response to force.

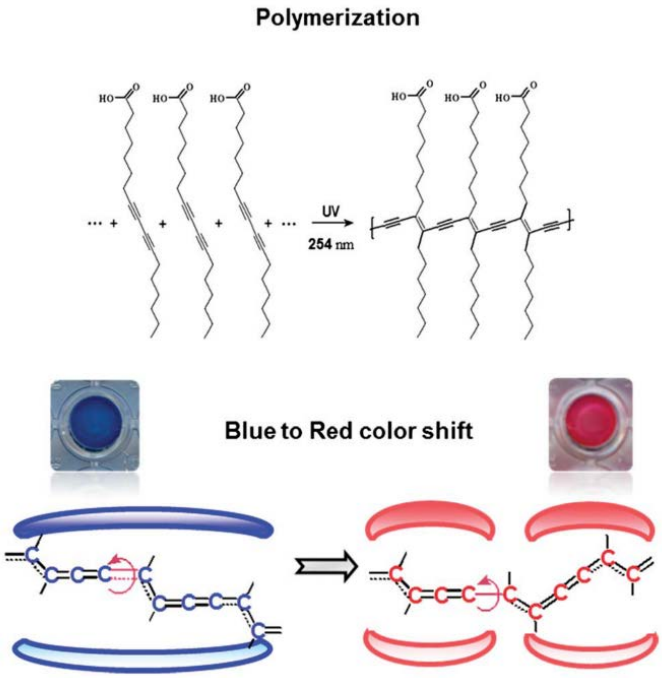


Figure 19. Reproduced from RSC Advances 2013, 3 (44), 21192-21201. This film will turn blue after irradiating with UV light – which causes individual molecules to join together – and slowly change to red as force is applied and these bonds are disrupted.

This makes chromo-mechanophores especially interesting as force sensors, as they allow for the detection of mechanical failure in polymers. When these polymers join together, or polymerize, as illustrated in Figure 19, they gain their characteristic blue color. When this connection is disrupted, they turn red. You will use this force sensor film to differentiate between hexane and dodecane, two colorless liquids, by naked eye. The unknowns you will be testing are known as Saturated Aliphatic Hydrocarbons, or SAHCs.

Hydrocarbons are simply chemicals made up of the elements carbon and hydrogen. Saturated Aliphatic Hydrocarbons are chains of carbon atoms which have the maximum number of allowed hydrogens (which means that they do not have any carbon-carbon double or triple bonds). Individual molecules of the SAHC surround the PDMS film, and as they are absorbed by the film they cause it to swell, distorting the geometry of the embedded mechanophore (PCDA) and inducing a color change. By soaking a strip of film into both unknowns for a set period of time, you will be able to differentiate which vial holds which hydrocarbon. Pentane is a shorter chain than heptane, and so a strip of your sensor film dipped into pentane should be redder, while a strip dipped into heptane will be bluer. You can see an image of this effect below.

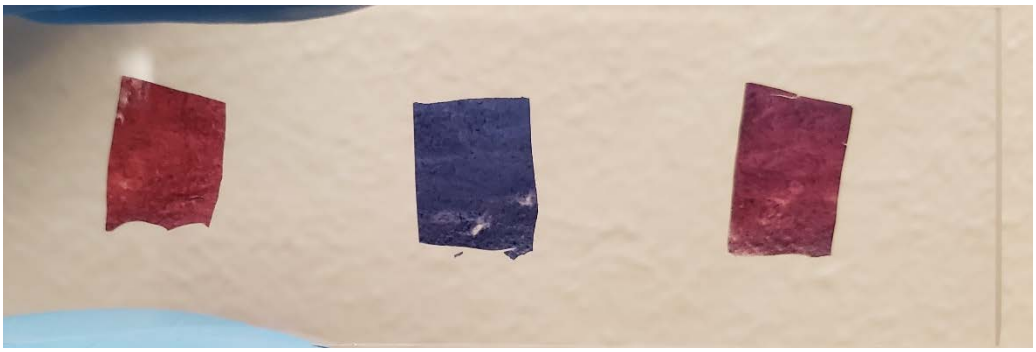


Figure 20. Mechanochromophore Films dipped into straight chain aliphatic hydrocarbons. The center film has not been exposed to solvent or mechanical force at all. The film on the left shows a greater progression towards red compared to the film on the right, allowing us to see that the inter-molecule bonds have been disrupted.

Functionalizing Glass Slides with C_{10}

This step may be performed by your lab instructor. If you have functionalized slides, move ahead to the procedure on fabricating films.

1. Pour 100 mL of toluene in a glass jar, position two slides in the jar leaning against each other so that both sides of each slide are exposed to the toluene.
2. Place your jar in the nitrogen tent and purge until the RH reading on the hygrometer reaches 0.1%. Add 13.1 µL of decyltrichlorosilane to the jar. Let stand two hours.
3. Remove the slides to a new, clean jar. Sonicate in fresh toluene for 10 min.
4. Remove toluene to waste jar, sonicate slides in fresh ethanol for 10 minutes.
5. Remove ethanol to waste jar, sonicate slides in fresh ethanol for 10 minutes.

6. Remove slides from jar, both sides of the slide should now be functionalized with C_{10}, which will allow us to remove our PDMS film from the surface after they've cured.

Synthesis of Mechanochromophore Film

We will prepare a solution of 10,12-pentacosdiynoic acid (PCDA) in polydimethylsiloxane (PDMS). We will then irradiate this solution and combine it with a curing agent before spreading it over glass slides and allowing it to cure for two days at room temperature. Then, we will use our chromo-mechanophore sensors to identify an unknown hydrocarbon. The following mechanochromophore film fabrication procedure was adapted from Park et al. 2014.

1. Put in base bath minimum 2 hours: short glass petri dish and watch glass. Wash with ethanol and Millipore water, dry in oven.
2. Purge N_2 tent until 0.1% RH. Remove PCDA.
3. Wash metal scoop and metal spatula with ethanol and Millipore water. Dry with N_2 gun.
4. Wash 2 glass slides with ethanol and Millipore water. Dry with N_2 gun.
5. Weigh 5.0 mg (0.005g) of PCDA onto weigh paper and add it to a 20 mL scintillation vial. Add 400 µL (0.4mL) of chloroform to vial, then cap and swirl until dissolved.
6. Place PCDA back in N_2 tent, purge until 0.1% RH. Open desiccator and replace PCDA.
7. Weigh out 2.0 g of PDMS elastomer base into separate 20 mL scintillation vial. Inject chloroform solution into base and mix.
8. Remove chloroform with vacuum for 15 minutes or until all bubbles have disappeared.
9. Spread mixture onto two functionalized glass slides placed inside a petri dish, using the tip of a glass pipette to get even coverage. Be very careful not to spill PDMS onto the bottom of the petri dish!

10. Irradiate with UV a 254 nm UV light for 1 min. Mixture should be blue at this point. Without scratching the bottom of the functionalized glass slide, ‘stir’ the wet PDMS on the top of the slide to evenly distribute the blue color.
11. Weigh out 0.2g of PDMS curing agent into a straight walled glass vial. Use a pipette to drop the curing agent onto functionalized glass slides, making sure to evenly distribute it between the two. Use the same pipette to ‘stir’ the mixture on the surface of the slide.
12. Degas your slides for 5-10 minutes under vacuum or until all gas bubbles are gone.
13. PCDA is sensitive to light, so be sure to cover your petri dish with aluminum foil when done. Your instructor will show you where to store your films while they cure at room temperature for two days.

Identifying Unknowns with Film Sensor

1. Wash a razors with Millipore water and ethanol. Dry with N_2 gun.
2. Place a white paper towel underneath the glass slide – observe the color of your film on the slide.
3. Obtain two vials from your instructors; one labeled Unknown 1 and one labeled Unknown 2.
4. Cut a 1x1 cm strip of the PDMS sensor film and gently peel from the slide with a pair of tweezers. This will be your ‘control’ film – you will not dip this into either chemical.
5. Record your observations of the film in your lab notebook. How big is it, and how would you describe its color?
6. Acquire a strip of aluminum foil from your instructor – this will be used as a drying ‘rack’ for your films.
7. Cut one more strip of film roughly the same size as your control strip. Measure it using the ruler provided by your instructor and record this in your lab notebook. Dip your film into the vial of Unknown #1 with your tweezers for 5 minutes. Remove and place onto the aluminum foil.
8. Remove your film from the vial and use a kimtech wipe to wick away the excess solvent. Observe how the film has changed and record your observations in your

notebook. What color is the film now and has it changed at all in size? Allow the film to dry for 5 minutes and record your observations again.

9. Repeat steps 7 and 8 with Unknown #2.
10. Identify your unknown. Bring your predictions to your lab instructor.

Activity Questions

- Why do you see less of a color change with the shorter-chain hydrocarbon?
- Over the course of submerging your sensor strip, it may appear purple. What would cause this?
- When the PDA comes out of the bottle it is blue, but when you add chloroform it turns red – why does this happen?

VI. Nanoscale Mechanochemical Tools

Instructor: Nathaniel Hawthorne

Introduction

An AFM instrument uses a piezoelectric scanner to move a cantilever attached to a nanoscopically-sharp tip (probe) across a surface (or, in an opposite configuration, the cantilever remains stationary while the sample is driven by the piezoelectric scanner). Laser light reflecting off the cantilever is sent to a detector, where these data are processed to give information about the height of the sample surface features and how strongly the probe interacts with the surface. The microscope will try to either drag the cantilever across the surface using a constant force or to oscillate the cantilever at a constant amplitude (wave height), and the movement of the laser beam position on the detector is fed back to the scanner to tell it to move up or down in order to maintain constant force or amplitude.

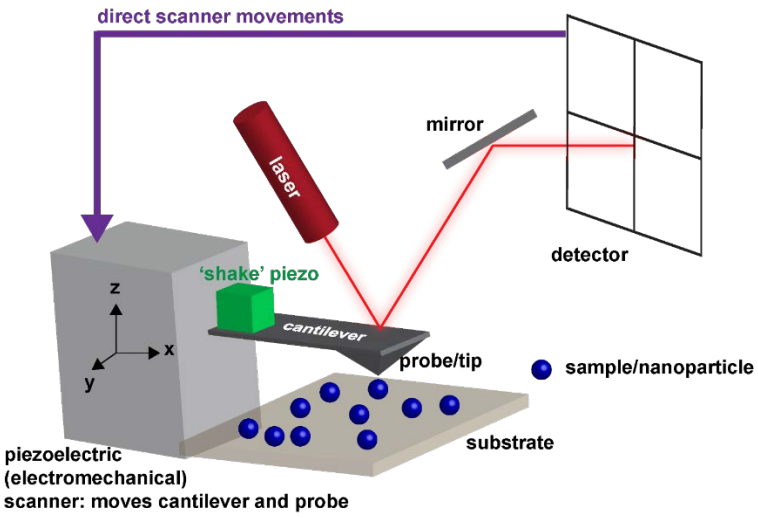


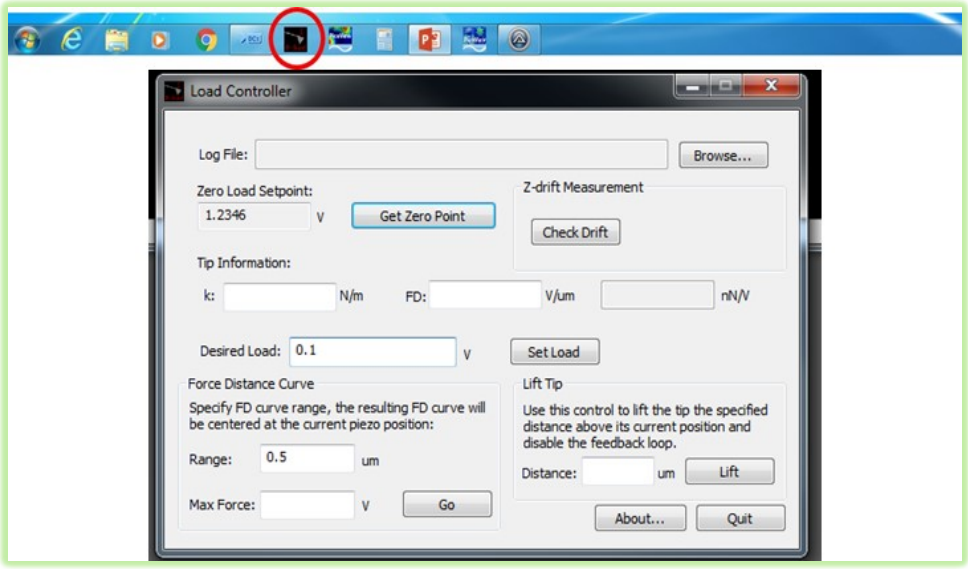
Figure 21. Simplified depiction of an atomic force microscope.

This week, we will use an AFM to manipulate atoms to "draw" on the nanoscale.

Basic operation of an AFM instrument

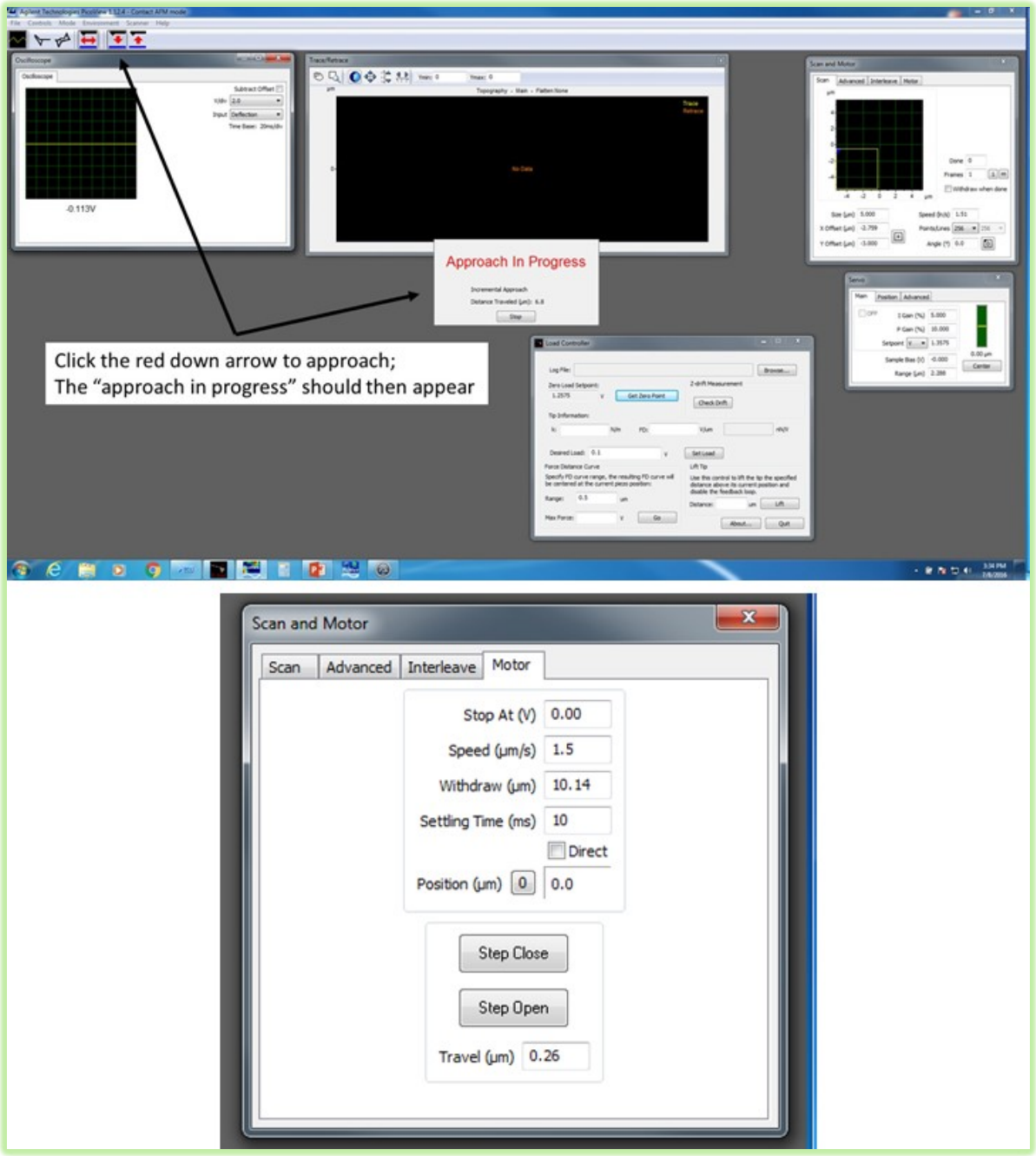
4. To approach the surface, specify where the "zero" is for the tip position when it is not interacting with anything. Do this by first opening the load controller, then clicking "get zero point" in the load controller window. Next, indicate the preferred

load for the tip force pressing into the surface. Do this by typing in “0.1 V” into the “desired load” box, then click “set load”.



5. Start the approach by clicking the red down arrow. A box will appear stating “approach in progress” and will show the distance the tip has traveled towards the surface. You can check the motor speed (how fast the tip is moving towards the surface) by clicking the “motor” tab in the “scan and motor” window – it should be 1.5 µm/s.

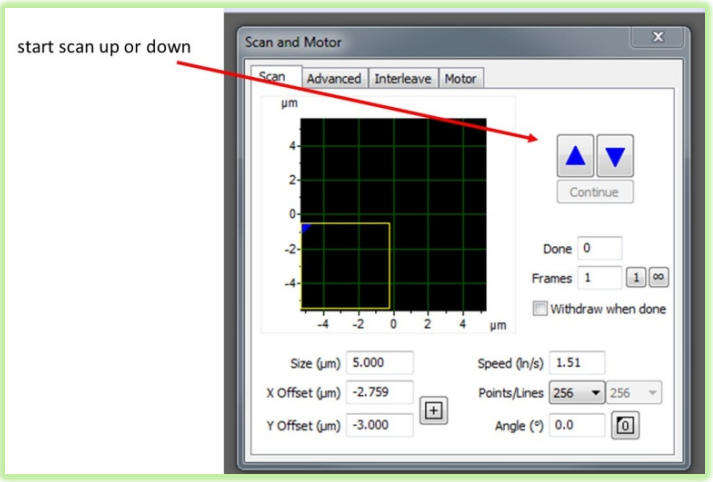
   ***note, follow steps 1 & 2 **<u>every time</u>** to approach the surface to scan



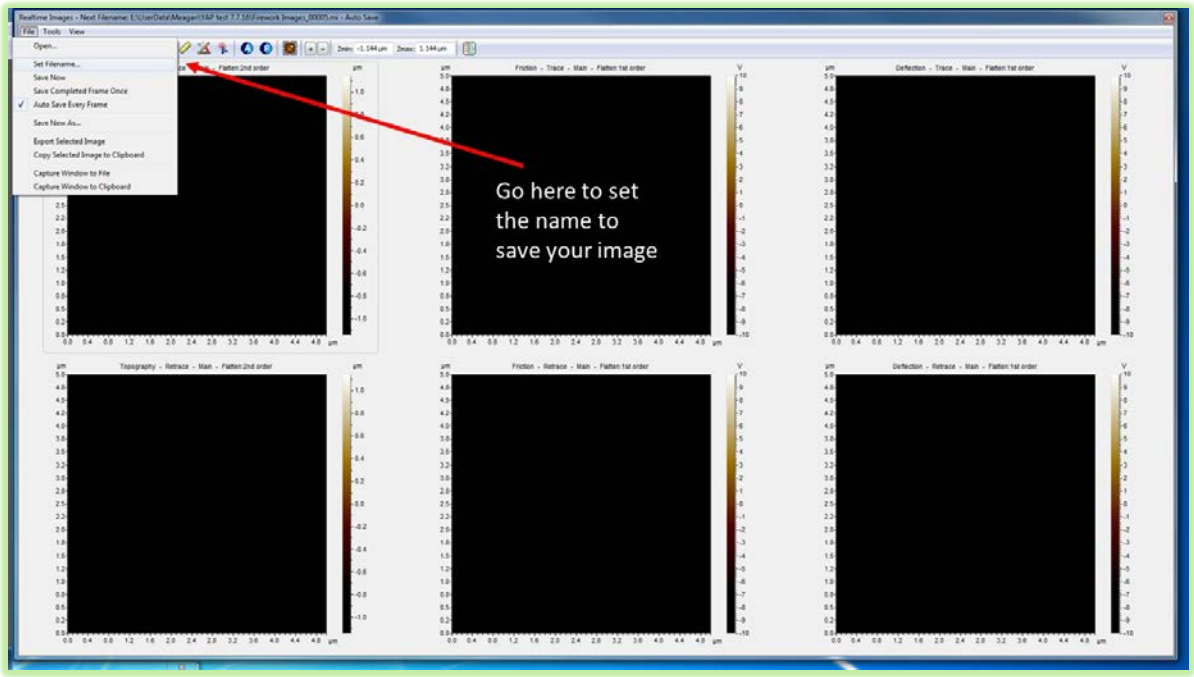
6. At the surface, BE VERY CAREFUL NOT TO BUMP THE MICROSCOPE TABLE to avoid jostling the set-up and breaking the tip.

7. Before starting a scan, set the desired parameters. A good starting point is a 5 x 5 µm scan with a speed of 1.5 lines/s (ln/s). Also, check that the gains are set to 5 % for the integral (I) gain & 10 % for the proportional (P) gain.

8. Start a scan by clicking either the blue up or down arrow.
   How does the scan look: clear or fuzzy? Do the trace/retrace lines agree?
   How can the scan be improved? (Scan faster or slower?)



9. While the scan is running, set the filename for the image.
   Do this before the scan finishes! (the program autosaves the image at the end of the scan)
   On the right monitor go to: file → set filename
   Save under: userdata → YAP 2021 → [create a new folder with your name/date]
   In that folder, set the filename you want for your image
   *Note: set a descriptive title to enable easy retrieval of the data

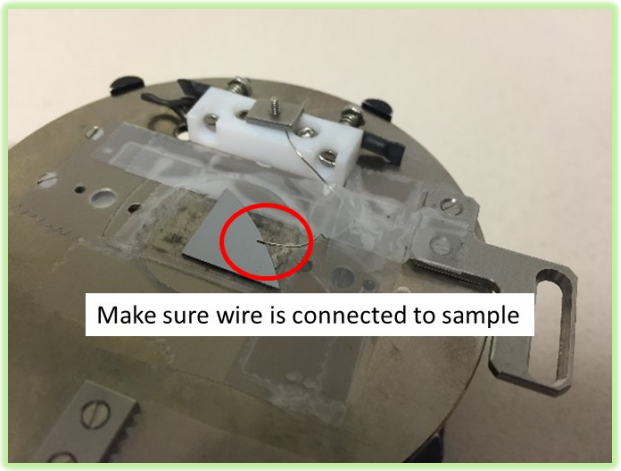


AFM Nanolithography

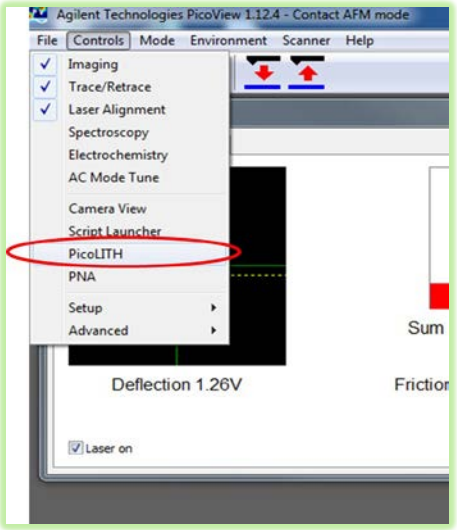
In nanolithography, a bias is applied between the tip and the sample to create an electric field that drives a chemical reaction. Water that condenses at the AFM tip reacts with the surface. For this experiment, the sample will be a Si(100) wafer.

> Why are we using Si(100) as the sample for nanolithography? (*hint:* what chemical reaction is taking place?) Can other materials be used?

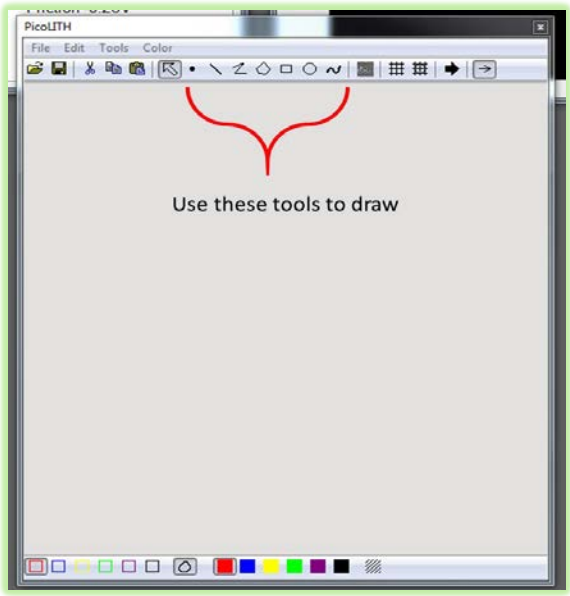
The AFM scanning set-up only requires a few changes for nanolithography. The AFM tip needs to be conductive and the sample plate needs additional electrical connections to complete a circuit. First, mount the sample on the conductive probe plate and connect the wire to the sample as shown in the picture below.



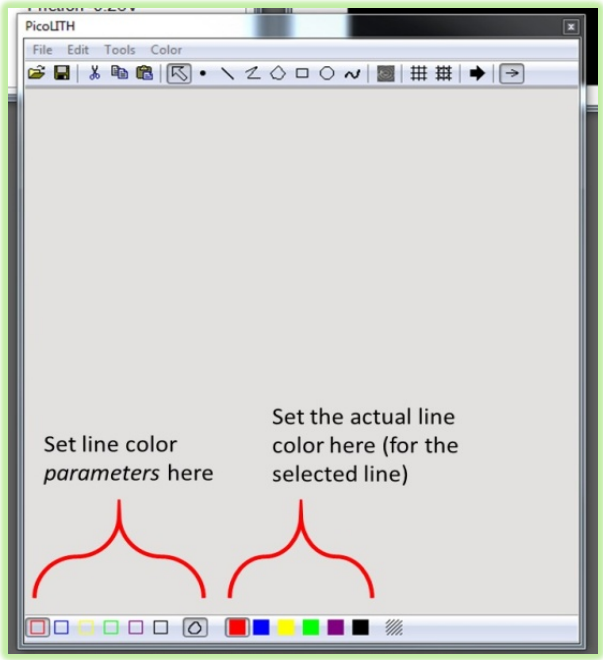
1. To draw an oxide pattern on the surface, open the PicoLith window under controls.



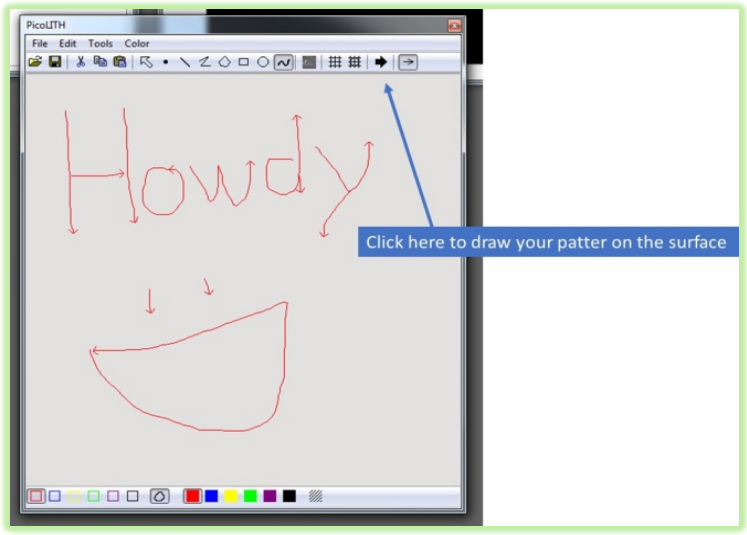
2. In the drawing window, you can choose to draw with straight lines, circles, dots, *etc*., or to use “free hand” with the computer mouse. A grid is available as a guide.



3. At the bottom of the screen, you can select different line colors – each color is used to represent different parameters for the oxidation reaction (*i.e*.: applied bias, speed); note that the colors do NOT represent the “color” of the line drawn on the surface. The lines added to the surface are a build-up of material as Si is oxidized to SiO_2.



4. To have the AFM draw your pattern on the surface, click the solid black arrow. You can watch it trace your design until it is done; then, to see your newly drawn pattern, take another AFM image by clicking the blue up or down arrow (step 13 in basic AFM operation).



VII. Hammer Challenge

Instructor: Katie

Introduction

So far in this camp, we've learned that force *can be* used to induce chemical reactions in the solid state. We first saw this in the thermite demo. However, we have not yet learned fundamentally what factors affect forces. How do materials respond to shear versus impact forces? What affects the strength of the exerted force? How does the reaction rate scale with force? In short, we need to know just what "the force" is in order to exploit it. That's what we're going to explore in this experiment.

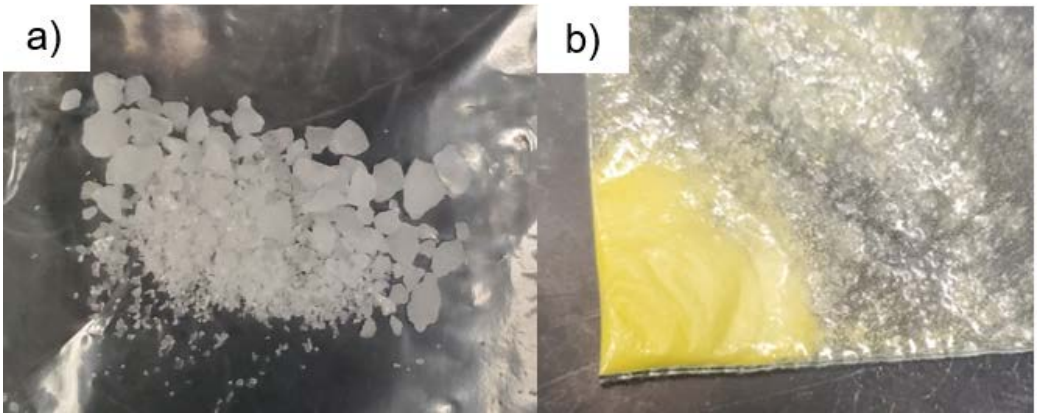


Figure 22. The reaction between lead nitrate and potassium iodide a) before hammering and b) after hammering.

You will be using a variety of hammers and blocks to drive the following chemical reaction:

$$Pb(NO_3)_2\ (white\ solid) + 2KI(white\ solid) \rightarrow 2KNO_3(\ white\ solid) + PbI_2(yellow\ solid)$$

The reaction progress is easy to see with your naked eye because the mixture will turn yellow as the PbI_2 product forms. You will attempt to figure out how to influence reaction progress by changing the experimental setup. There are a variety of tools and devices that you may use in your experimental plans. These are depicted in Figures 23-25.

Figure 23. Blocks of marble tile, countertop, foam, and wood that slide together.

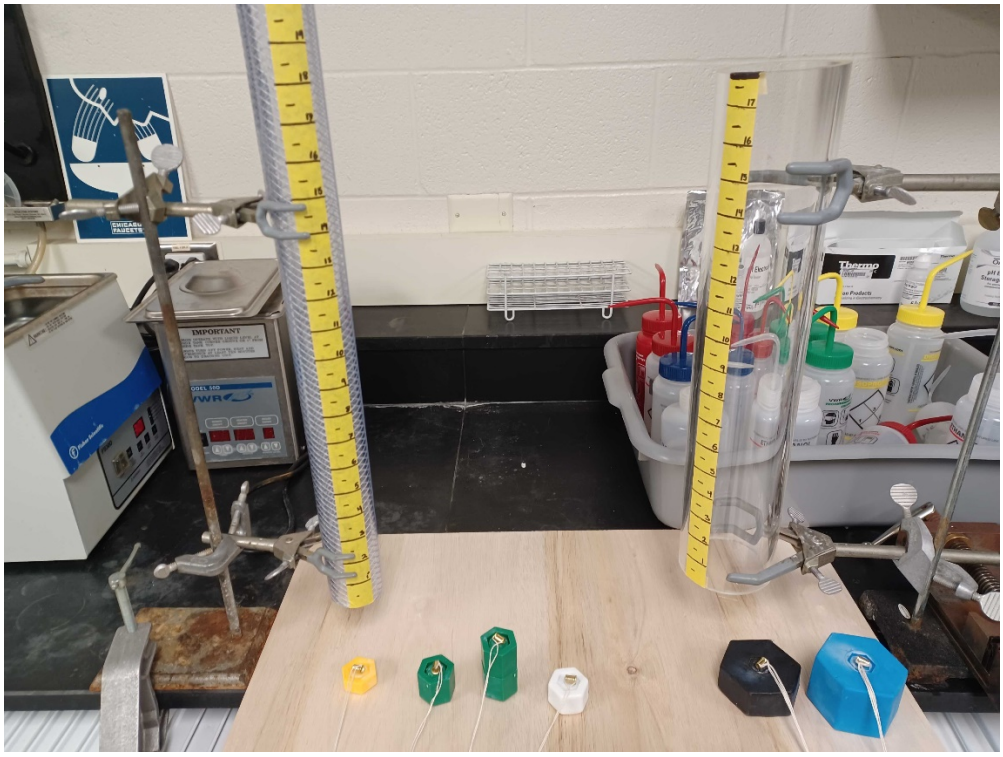


Figure 24. Weights ranging from 5 to 1000 g and corresponding measured sliding tubes for alteration of drop force.

Figure 25. Hammers with wood, steel, and rubber faces along with a loosely controlled arm swinger for more repeatable motion.

So, start forming your hypotheses and put the hammer down!

Procedure

1. Develop an experiment to test a hypothesis that will help us learn about how we can use force to influence the reaction progress. You may be allowed to work independently or be collaborating in a group depending on the number of YAP students. This will be described by the instructor at the beginning of the lesson.
    a. A simple starting hypothesis is to develop an "if/then statement". For example, one hypothesis could be "if I make my hammer material harder, then the reaction will be faster". This is a good first plan, but make sure your hypothesis is testable. Our example hypothesis is pretty vague … we don't know how to measure "go faster". It would be better if we wrote something like "if I make my hammer material harder, then the reaction will be complete in fewer hammer hits" because now we can just count hammer hits to figure out if our hypothesis is true or false.
    b. When developing an experiment, you want to figure out what your variables are. You will have an independent variable (what you are changing in each

test, a dependent variable (what you expect to be changed by each test), and control variables (what will be the same in each test). In our example, our independent variable will be the material type, the dependent variable will be the number of hammer hits, and control variables would include the person hammering, the method of hammering, the temperature, and the humidity.

c. Figure out how many tests you need to prove/ disprove your hypothesis and plan what you will do for each.

1. Weigh out ~0.5 g of lead nitrate (aka. $Pb(NO_3)_2$) into a weigh boat. Carefully dump your solid from the weigh boat into one corner of a plastic bag.
2. Weigh out ~0.5 g of potassium (aka. KI) into a weigh boat. Carefully dump your solid from the weigh boat into the opposite corner of your plastic bag. Make sure that the compounds don't mix! We don't want to start the reaction prematurely and throw off our results.
3. Mix your compounds together in one corner of the bag and begin applying your force (either hammering or sliding the bag between blocks) and collecting your data. Make sure you do this in a fume hood because the powders are toxic if you inhale them.
4. Collect your data and see whether your hypothesis was correct or not.
5. Reveal your results to the class, how does the independent variable you examined impact the reaction progress?
6. Broaden your perspective and use the class results to start figuring out how force can be exploited in mechanochemical reactors by answering the activity questions.

Activity Questions

- Would a mechanochemical reaction that needs a lot of force have a higher product yield if run in a hard stainless steel milling cup or in a soft Teflon milling cup?
- When we increase the frequency of the Retsch MM 400, will the mechanochemical reaction have a greater yield or a smaller yield? Why?

- Do you think a vibratory ball mill (where reagents are shaken side to side) or a planetary ball mill (where reagents rotate continuously in a drum) be better for a shear driven reaction? Why?